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

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Joint FAO/WHO Expert Committee on Food Additives

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Members*

Professor Junshi Chen, Institute of Nutrition and Food Hygiene, Chinese Academy of Preventive Medicine, Beijing, China (*Joint Vice-Chairman*)

Professor S.M. Dagher, Department of Biology, American University of Beirut, Beirut, Lebanon

Dr C.E. Fisher, Head, Risk Analysis and International Coordination Branch, Ministry of Agriculture, Fisheries and Food, London, England

Professor W. Grunow, Head, Food Toxicology Division, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Dr D.G. Hattan, Director, Division of Health Effects Evaluation, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*Joint Rapporteur*)

Dr Y. Kawamura, Section Chief, Division of Food Additives, National Institute of Health Sciences, Tokyo, Japan

Dr A.G.A.C. Knaap, Centre for Substances and Risk Assessment, National Institute of Public Health and the Environment, Bilthoven, Netherlands

Dr P.M. Kuznesof, Acting Deputy Director, Division of Product Manufacture and Use, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*Chairman*)

Dr J.C. Larsen, Head, Department of Biochemical and Molecular Toxicology, Institute of Food Safety and Toxicology, Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark

Mrs I. Meyland, Senior Scientific Adviser, Institute of Food Research and Nutrition, Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark (*Joint Rapporteur*)

Dr G. Pascal, Chairman, Scientific Steering Committee of the European Union, National Institute for Agricultural Research, Paris, France

Mrs M. Riordan, Team Leader (Food Standards), Food and Nutrition Section, Ministry of Health, Wellington, New Zealand

Professor R. Walker, Emeritus Professor of Food Science, School of Biological Sciences, University of Surrey, Guildford, Surrey, England (*Joint Vice-Chairman*)

Dr J.D. Wilson, St Louis, Missouri, USA

Secretariat

Dr P.J. Abbott, Australia New Zealand Food Authority, Canberra, Australia (*WHO Temporary Adviser*)

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* Unable to attend: Mrs J. Baines, Senior Nutritionist, Australia New Zealand Food Authority, Canberra, Australia; Ms J. Mutamba, Deputy Director, Department of Nutrition, Ministry of Health, Harare, Zimbabwe.

Mrs D. Akkelidou, Director, State General Laboratory, Ministry of Health, Nicosia, Cyprus (*FAO Consultant*)

Dr D.C. Bellinger, Associate Professor of Neurology, Harvard Medical School, Children's Hospital Neuroepidemiology Unit, Boston, MA, USA (*WHO Temporary Adviser*)

Dr M. Bolger, Contaminants Branch, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr C. Carrington, Contaminants Branch, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser*)

Dr E. Dewailly, Director, Public Health Centre of Quebec, Environmental Health Service, Beauport, Quebec, Canada (*WHO Temporary Adviser*)

Dr M. DiNovi, Division of Product Manufacture and Use, Office of Premarket Approval, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC, USA (*WHO Temporary Adviser, Joint Rapporteur*)

Mr G.S. Eriksen, Department of Animal Nutrition and Management, Swedish University of Agricultural Sciences, Uppsala, Sweden (*WHO Temporary Adviser*)

Dr J. Greig, Joint Food Safety and Standards Group, Department of Health, London, England (*WHO Temporary Adviser*)

Mr E.F.F. Hecker, Chairman, Codex Committee on Food Additives and Contaminants, Risk, Substances and Nutrition Division, Department of Environmental Quality and Health, Ministry of Agriculture, Nature Management and Fisheries, The Hague, Netherlands (*WHO Temporary Adviser*)

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

Professor J.H. Hotchkiss, Food Safety, Toxicology and Packaging, Department of Food Science, Cornell University, Ithaca, NY, USA (*FAO Consultant*)

Dr C. Madsen, Institute of Food Safety and Toxicology, Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark (*WHO Temporary Adviser*)

Dr L.P.A. Magos, TNO BIBRA International Ltd, Carshalton, Surrey, England (*WHO Temporary Adviser*)

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

Dr G. Moy, Programme of Food Safety, WHO, Geneva, Switzerland

Dr I.C. Munro, President, CanTox Health Sciences International, Mississauga, Ontario, Canada (*WHO Temporary Adviser*)

Dr A. Nishikawa, Division of Pathology, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr J.A. Pennington, Research Nutritionist, Division of Nutrition Research Coordination, National Institutes of Health, Bethesda, MD, USA (*FAO Consultant*)

Dr B. Petersen, President, Novigen Sciences Inc., Washington, DC, USA (*WHO Temporary Adviser*)

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

Professor S. Resnik, Food Technology, Department of Industry, Faculty of Exact and Natural Science, University Campus, Buenos Aires, Argentina (*FAO Consultant*)

Dr J. Schlatter, Federal Office of Public Health, Institute of Veterinary Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland (*WHO Temporary Adviser*)

Professor G.I. Sipes, Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ, USA (*WHO Temporary Adviser*)

Dr G.J.A. Speijers, Head, Centre for Substances and Risk Assessment, National Institute of Public Health and Environmental Protection, Bilthoven, Netherlands (*WHO Temporary Adviser*)

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

Dr P.J.P. Verger, President, Observatory of Food Consumption, National Centre for Study and Research on Nutrition and Food, Paris, France (*FAO Consultant*)

Professor R. Vilu, Department of Biochemistry, Tallinn Technical University, Tallinn, Estonia (*FAO Consultant*)

Mrs H. Wallin, Senior Food Control Officer, National Food Administration, Helsinki, Finland (*FAO Consultant*)

Dr J. Weatherwax, Consultant, Food Quality and Standards Service, Food and Nutrition Division, FAO, Rome, Italy (*Joint Secretary*)

Dr D.B. Whitehouse, Food Regulatory Affairs, Bowden, Cheshire, England (*FAO Consultant*)

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

Safety evaluation of certain food additives and contaminants. WHO Food Additives Series, No. 44, 2000.

Specifications are issued separately by FAO under the title:

Compendium of food additive specifications, addendum 7. FAO Food and Nutrition Paper, No. 52, Add. 7, 1999.

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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

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

1. Introduction

The Joint FAO/WHO Expert Committee on Food Additives met in Rome from 1 to 10 June 1999. The meeting was opened by Mr G. Orriss, Chief, Food Quality and Standards Service, Food and Nutrition Division, FAO, on behalf of the Directors-General of the Food and Agriculture Organization of the United Nations and the World Health Organization. Mr Orriss noted the large number of substances to be evaluated by the Committee during its meeting and expressed the appreciation of the sponsoring Organizations for the work done before the meeting and that which would be done during the meeting by the participants. The advice and scientific expertise of experts in safety and risk assessments were the cornerstones of the evaluation process. He further noted that the Codex Alimentarius Commission had established principles relating the role of risk assessments of foods to their standard-setting activities. He also noted that the Codex Committee on Food Additives and Contaminants had recently prepared a paper on the application of the principles of risk analysis for food additives and contaminants. As the principal scientific advisory body to that Committee, the Expert Committee was therefore asked to consider and comment on the paper. Mr Orriss stressed the importance of this advisory role to the Codex Alimentarius Commission and asked the Expert Committee to review the paper in detail at the present meeting.

2. General considerations

As a result of the recommendations of the first Joint FAO/WHO Conference on Food Additives, held in September 1955 (*1*), there have been fifty-two previous meetings of the Expert Committee (Annex 1). The present meeting was convened on the basis of the recommendation made at the fifty-first meeting (Annex 1, reference *137*).

The tasks before the Committee were:

— to elaborate further principles for evaluating the safety of food additives and contaminants (section 2.2);
— to undertake toxicological evaluations of certain food additives, flavouring agents and contaminants (sections 3, 4 and 6 and Annex 2);
— to assess the potential allergenicity of refined oils (section 5 and Annexes 2 and 4);
— to assess the intake of certain food additives and contaminants (sections 6 and 7 and Annex 2); and
— to review and prepare specifications for selected food additives (sections 3 and 8 and Annex 2).

2.1 Modification of the agenda

Hydrogenated poly-1-decene was added to the agenda at the request of the manufacturer. Montanic acid esters were removed from the agenda because no data were submitted. Argon, helium and oxygen were not evaluated toxicologically as no data were submitted. Calcium metabisulfite, calcium sulfite and potassium hydrogen sulfite had been on the agenda for the establishment of specifications only but were removed as no data were received and there was no indication that they were used in food.

On the basis of comments received by the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*2*), the following substances were added to the agenda for the review of the specifications only: α-acetolactate decarboxylase from *Bacillus brevis* expressed in *B. subtilis*, maltogenic amylase from *B. stearothermophilus* expressed in *B. subtilis*, carob bean gum, guar gum, xanthan gum, carotenes (algal and vegetable), nitrogen, riboflavin from *B. subtilis* and sucrose esters of fatty acids.

2.2 The role of the Committee in risk analysis

2.2.1 *Background*

Risk analysis in the context of the Codex system has been considered at three recent FAO/WHO consultations (*3–5*). These consultations outlined the responsibilities of advisory committees such as the Joint FAO/WHO Expert Committee on Food Additives and of committees of the Codex Alimentarius Commission dealing with general subjects, such as the Codex Committee on Food Additives and Contaminants, and clarified their role in the three components of risk analysis: risk assessment, risk management and risk communication.

Risk assessment as outlined in the FAO/WHO consultations consists of four steps: (i) hazard identification; (ii) hazard characterization (dose–response assessment); (iii) exposure assessment; and (iv) risk characterization on the basis of the hazard characterization and exposure assessment. Scientific committees, which are composed of experts serving in their individual capacities as scientists, are responsible for assessing risks whereas Codex committees dealing with general subjects, which consist of government delegates, are responsible for making recommendations for the management of risk. All participants in the risk analysis process together with other interested parties are involved in the communication of information on risk.

Although the FAO/WHO consultations have indicated that risk management should be functionally separate from risk assessment, risk assessors and risk managers (e.g. scientific committees and Codex

committees, respectively) must be able to communicate effectively to ensure that the questions asked by the risk managers are understood and addressed by the Expert Committee, that the risk assessments are clearly described and that the process operates efficiently.

The Joint FAO/WHO Consultation on Risk Management and Food Safety (*4*) concluded that ". . . in the process of assessing substances scientific committees continually need to select and utilize various scientific assumptions", including the following:

— reliance on animal models to establish potential effects on humans;
— scaling of body weights for comparisons between species;
— use of a 100-fold safety or uncertainty factor to account for likely differences in susceptibility between and within species, with guidelines for situations in which deviations from the Acceptable Daily Intake (ADI) are permitted;
— permitting the presence of contaminants at levels "as low as reasonably achievable" (ALARA); and
— establishing temporary ADIs for additives and residues of veterinary drugs where the available data have been incomplete and specific data have been requested for consideration by the Committee at a future meeting.

The Consultation recommended that the Codex Alimentarius Commission define the role of its committees in providing clear, unequivocal guidance for risk assessment to scientific committees. Such guidance should acknowledge the prerogative of scientific committees to make choices in risk assessment, but should provide guidelines for the value judgements and policy choices that may be required, including the choice of safety (uncertainty) factors at specific stages in the risk assessment process. The Codex Alimentarius Commission recommended at its Twenty-second Session that the Codex Committee on Food Additives and Contaminants, in consultation with the Joint FAO/WHO Expert Committee on Food Additives, propose a policy statement on risk assessment that provides such guidelines (*6*).

At its Thirty-first Session the Codex Committee on Food Additives and Contaminants considered a paper on its role in relation to that of the Expert Committee in the risk analysis process (*7*). The paper included a discussion of priorities for work and principles for risk assessment policy and the outcome of risk assessment. It included a number of recommendations to both the Codex Committee and the Expert Committee. The Expert Committee was invited by the Codex Committee to consider the paper; its comments are summarized below.

2.2.2 *Comments of the Committee*

Any request to the Expert Committee for scientific advice must clearly state the reason for the request and outline the probable options for risk management. Clear communication between risk assessors and risk managers is particularly important at the initial stage because of the long delays between meetings of the Codex Committee and the Expert Committee. At its present meeting, the Expert Committee agreed that the outcome of its own assessments and the basis for its recommendations should be clearly documented and should include descriptions of any uncertainties. Clearer communication between the Codex Committee and the Expert Committee would obviate the need for several rounds of communication and increase the value of the advice provided. Procedures should be developed to enhance communication between meetings of the two Committees.

Characterization of risk

The Expert Committee characterizes risk in one of two ways: (i) by quantifying the dose (or range of doses, usually from zero upwards) at or below which there is judged to be no appreciable risk; or (ii) by describing the relationship between intake and the probability of an adverse response in humans. The former process, usually referred to as a "safety assessment", is used by the Expert Committee when allocating ADIs to food additives and tolerable intakes (expressed on either a weekly or a daily basis) to contaminants. The Expert Committee considered that this process constitutes risk assessment: although the ADI and tolerable weekly or daily intake do not represent quantitative estimates of risk, they represent levels of intake at which there is "no appreciable risk" and are used as measures of the safety of a substance when consumed at that level. Hazard is identified and characterized in the process of establishing ADIs and tolerable intakes, and risk is characterized as being not appreciable when intake does not exceed those values. Uncertainty is incorporated into the value by the magnitude of the safety factor.

The information available to the Expert Committee on toxicological and related aspects (such as pharmacokinetics and pharmacodynamics in animals and humans, and information on dose–response relationships) is generally as complete as that available to national governments. In consequence, the hazards, dose–response relationships, no-observed-effect levels (NOELs) and derived ADIs and tolerable intakes characterized by the Committee are applicable internationally. If detailed information on the intake of a substance by various population groups is available, the Committee can charac-

terize the risks for those groups. Such risk characterizations can serve as examples for detailed risk assessments by governments.

Potential intake is an integral component of the Procedure for the Safety Assessment of Flavouring Agents adopted by the Committee at its forty-sixth meeting (Annex 1, reference *122*). When the Committee establishes an ADI "not specified" for a food additive, the potential intake of the additive is also considered to ensure that consumers are unlikely to be exposed to concentrations greater than that associated with no appreciable risk when the additive is used in accordance with good manufacturing practice for its technological function. Potential intake is determined on the basis of the probable use of the food additive at the time of assessment, which may change subsequently. As stated in section 2.2.4 of the report of the thirty-ninth meeting of the Committee (Annex 1, reference *101*), a food additive should be referred to the Committee for re-evaluation when new uses that would significantly increase its intake are envisaged. It is critical that the uses on which the ADI "not specified" is based be well documented by the scientific committee concerned.

Specifications of identity and purity are integral to assessing the risk associated with the use of food additives. Such specifications make it possible to define the product that was tested toxicologically; they also include requirements for the identity and purity of the additive. Specifications proposed by the Expert Committee are considered by the Codex Committee for adoption as "Codex Advisory Specifications", which are used in risk management to ensure the appropriate purity of the product in commerce.

The assessments of food additives and of contaminants differ fundamentally, primarily because food additives, which generally show little toxicity, are deliberately added to food to confer specific benefits, whereas contaminants (except for micronutrients) are of no benefit. Food additives can be controlled easily, while the elimination of contaminants from foods often incurs costs which may result in a reduction in the availability and/or affordability of foods. Thus, different terms are used for the two, the word "tolerable" being considered more appropriate for the intake of contaminants that are unavoidably associated with the consumption of otherwise wholesome, nutritious foods (Annex 1, reference *76*).

Conservative assumptions are made in establishing ADIs to ensure that intake up to the maximum value of the ADI represents no appreciable risk. This process is described in *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*). In those rare instances in which long-term intake

exceeds the ADI, the risk may not be negligible, but it is difficult to quantify since the available data on adverse effects in humans are usually not sufficient to define a dose–response relationship.

Risk assessments of contaminants

The Expert Committee agreed that the relationship between the intake of contaminants and the probability of an adverse response in humans should ideally be identified in the risk assessment process. If the risk is adequately documented and explained, risk managers can use the assessment to decide on the appropriate degree of protection that can reasonably be achieved for the population of concern on the basis of the levels of intake and a comparison of the risks and of the risks in relation to the benefits. The Expert Committee used this approach at its forty-ninth meeting (Annex 1, reference *131*), when it estimated the carcinogenic potency of aflatoxins in individuals infected with hepatitis B virus and in uninfected persons. The risks for the population were calculated on the basis of the available information on the intake of aflatoxins and hypothetical standards. The calculations were presented as examples. In regard to those examples, risk managers should base national standards for aflatoxin contamination on the patterns of consumption and contamination of foods and the incidence of hepatitis B viral infection in their countries, and on the Expert Committee's estimates of carcinogenic potency. They should keep in mind that the population risks calculated in the report are only indicative of the range of potential risks.

Although the relationship between intake and the probability of an adverse response should be determined for contaminants, this is usually difficult in practice because of the paucity of quantitative data on the relationship between intake and the incidence of effects in humans, which are necessary to provide confidence in any observed association between intake and response. For this reason, the Expert Committee will probably continue to establish tolerable intakes for some contaminants for the foreseeable future, as was done for zearalenone at the present meeting. Adherence to a defined tolerable intake may not always be feasible, for instance because it results in removing a major, nutritious food item from the local diet. Risk managers must therefore closely consult the results of the Expert Committee's evaluations in order to appreciate the risks associated with high levels of intake.

The Expert Committee sometimes recommends an "irreducible level" for a food contaminant, which it has defined as "that concentration of a substance which cannot be eliminated from a food without

involving the discarding of that food altogether, severely compromising the ultimate availability of food supplies" (Annex 1, reference *76*). The Joint FAO/WHO Expert Consultation on Application of Risk Analysis to Food Standards Issues (*3*) referred to this concentration as ALARA (as low as reasonably achievable). Although the risk is not quantified, the general nature and, when possible, the magnitude of the potential risks for toxic effects due to intake are described in the report of the Expert Committee evaluating such substances. Possible control measures are often given, which are among those that risk managers should consider in establishing standards. When providing such qualitative information on toxicity and possible control options, the Expert Committee performs a risk assessment function.

The acceptable or tolerable intake is an indication of both the magnitude and the duration of acceptable intake. Unless otherwise indicated, the ADI refers to the average daily intake over the lifetime of an individual. Tolerable intakes are expressed on a weekly basis (provisional tolerable weekly intake or PTWI) for contaminants that accumulate in the body and whose toxicity is associated with long-term intake, whereas they are expressed on a daily basis (provisional maximum tolerable daily intake or PMTDI) for contaminants that are not known to accumulate in the body and which are of concern when consumed in high quantities over a short period. These end-points should be compared with the results of surveys of intake of appropriate duration in the assessment of risk.

Risk assessment policy

The Expert Committee agreed with the Codex Committee on Food Additives and Contaminants that risk assessment policy is an important component of risk analysis. Such policies should be reviewed to ensure that they serve the needs of the Codex Alimentarius Commission. All parties should be aware that this is particularly difficult at the international level because the Expert Committee responds to requests for evaluation not only from the Codex Alimentarius Commission but also directly from FAO and WHO and from their Member States.

The Expert Committee considered that most of the risk assessment policies identified by the Joint FAO/WHO Consultation on Risk Management and Food Safety (*4*) represent principles that should be established by risk assessors. For example, the Expert Committee considered that the magnitude of safety factors is a matter of scientific judgement. The safety factors most appropriate for meeting the Committee's goal of establishing levels of intake that represent no appreciable risk vary, depending on the quality and quantity of the

available toxicological data and data on chemical analysis and intake. Application in the risk assessment process of an additional, non-scientific factor to protect infants and children, for example, would override the use of scientific judgement based on the available data. An implicit risk assessment policy that has been in effect with regard to food additives for many years is that the Expert Committee should establish ADIs that represent no appreciable risk over a lifetime. The Expert Committee is responsible for deciding on the appropriate safety factor in order to accomplish that goal.

2.3 Principles governing the toxicological evaluation of compounds on the agenda

In making recommendations on the safety of food additives, food ingredients, flavouring agents and contaminants, the Expert Committee took into consideration the principles established and contained in Environmental Health Criteria, No. 70, *Principles for the safety assessment of food additives and contaminants in food* (Annex 1, reference *76*) as well as the principles elaborated subsequently at meetings of the Committee (Annex 1, references *77*, *83*, *88*, *94*, *101*, *107*, *116*, *122*, *131* and *137*), including the present one. Environmental Health Criteria, No. 70 (Annex 1, reference *76*) embraces the major observations, comments and recommendations on the safety assessment of food additives and contaminants contained, up to the time of its publication, in the reports of the Committee and other associated bodies. The Committee noted that the document reaffirms the validity of recommendations that are still appropriate and points out the problems associated with those that are no longer valid in the light of modern technical advances.

2.4 Food allergies

The primary role of the Committee is to evaluate the safety and assess the risks associated with consumption of food additives and contaminants, and it has elaborated principles and guidelines for that purpose (Annex 1, reference *76*). In general, it has not evaluated specific foods or commodities and has not developed general principles to do so. The Expert Committee was, however, asked by the Codex Committee on Food Labelling at its Twenty-sixth Session in 1998 to consider draft recommendations for the labelling of foods that can elicit hypersensitivity reactions (*8*).

In response, WHO convened an ad hoc Panel on Food Allergens in February 1999 that considered and prepared recommendations on the following points:

- the identification of criteria for adding foodstuffs to the list of common allergenic foods developed by the Codex Committee on Food Labelling, if found to be necessary;
- the development of criteria for identifying products of foodstuffs on the Codex Committee's list for which labelling of the food source is unnecessary; and
- consideration of ways in which FAO and WHO could provide continued guidance in this area to the Expert Committee.

The report of the Panel is attached as Annex 4.

The Expert Committee considered the Panel's report and recommendations and concluded that the scientific criteria given for adding foodstuffs to the Codex Committee's list of common allergenic foods and for identifying food products to be excluded from the list form a suitable basis for addressing the allergenicity of food and food products. The Expert Committee agreed that advice from specialists would be essential in addressing future requests of this nature.

The Expert Committee noted that the report of the Panel addresses issues of both risk assessment and risk management, but it considered that only the former was in its purview. Therefore, once the Expert Committee has evaluated the allergenic risk, it is for the Codex Committee to determine the appropriate risk management.

2.5 Principles governing assessments of the intake of contaminants

Assessments of the dietary intake of contaminants may form part of an estimate of total exposure that would include contributions from water and non-dietary sources as well as intake from food. Because an intake assessment is required in order to characterize the risk associated with consumption of contaminants in foods, the Expert Committee established the following principles for assessing intake as part of an assessment of risk. These principles complement the general principles governing intake assessment developed by the Committee at its forty-ninth and fifty-first meetings (Annex 1, references *131* and *137*). The report of the Joint FAO/WHO Expert Consultation on Food Consumption and Exposure Assessment of Chemicals (*9*) contains additional information on the estimation of intake.

The Committee may assess intake over different periods, depending on the toxicological profile of the contaminant being evaluated. An assessment of acute intake refers to intake on a single occasion or a single day. An assessment of chronic intake refers to intake over longer periods.

2.5.1 *Acute intake*

An assessment of the intake of a contaminant that has an adverse effect after a single exposure should also provide a realistic estimate of the intake of a consumer who ingests large amounts of the contaminant, i.e. in the high-percentile range of consumption. Statistically, the combination of data on consumers in the high-percentile range and high concentrations of the contaminant would yield a point estimate of intake that would be higher than that for the whole population. A more realistic assessment can be obtained by making a detailed simulation that includes the entire distribution of short-term food consumption and the concentrations of the contaminant in the foods consumed. In practice, the available data are often inadequate for such an analysis, particularly at the international level, and the objective of the assessment may not require such a detailed evaluation. When a detailed analysis is not appropriate, food consumption by a consumer in the high-percentile range should be combined with a high-percentile concentration of the contaminant in the foods consumed. For assessments of acute exposure to pesticides, for example, use of the 97.5th percentile for both food consumption and residue concentrations has been recommended (*9*). The Committee will determine the most appropriate approach on a case-by-case basis, taking into consideration the objective of the assessment and the available data.

2.5.2 *Chronic intake*

An assessment of the intake of a contaminant that has an adverse effect after long-term consumption should take into account the distribution of long-term food consumption in the population and the mean (average) concentration of the contaminant in the foods consumed. The resulting intake represents the probable lifetime exposure to the contaminant. This principle reflects the likelihood that no consumer of a contaminant would be exposed continually to a higher-than-average concentration of the contaminant throughout the food supply over a lifetime.

A measure of the national intake of a contaminant is derived from national data on food consumption and the concentration of the contaminant. National total diet studies, in which foods that represent the diet of the whole population or of subpopulations at risk are analysed for a contaminant, allow estimates of the intake of contaminants. Mean food consumption in regional diets (such as those described in the WHO Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food)) can be used with representative concentrations of contaminants to derive estimates of intake for broad groups of countries.

Estimates of intake can be adjusted to reflect the proportion of the food supply that is affected and the effects of processing or cooking on the concentrations of residues.

The Committee receives estimates of intake of contaminants and further data relevant for making risk assessments from national governments and other interested parties. The Committee recommended that such submissions include the following:

- a description of the specific chemical form of the contaminant;
- complete descriptions of the foods that contain the contaminant;
- the concentrations of the contaminant in foods as consumed; and
- an explicit description of the values used in an assessment when the concentrations of the contaminant are below the limit of quantification.

2.6 Principles governing the establishment and revision of specifications

2.6.1 *Residual ethanol*

Ethanol is one of several extraction solvents used in the production of various food additives. The specifications for such additives usually include limits for the residues of the solvents. The Committee was requested to consider whether it would be necessary to define a limit for ethanol in such cases. It concluded that from the point of view of good manufacturing practice ethanol should be considered no differently from other extraction solvents, and it reaffirmed the requirement for a limit for residues of all solvents, including ethanol. The Committee noted, for instance, that the existing specifications for two substances, cochineal extract and xanthan gum, indicate that ethanol is used as a solvent in their production but do not include limits for residual ethanol. The specifications for xanthan gum were revised at the present meeting. The Committee decided to postpone its review of the specifications for cochineal extract until its fifty-fifth meeting, to be held in 2000.

2.6.2 *Limit test for heavy metals*

The Committee agreed to implement the decision taken at its forty-ninth and fifty-first meetings (Annex 1, references *131* and *137*) to review and replace the limit test for heavy metals with, as appropriate, limits for individual metals of concern in all existing specifications. In order to accomplish this, the Committee decided to review the existing specifications on the basis of functional use (e.g. antioxidant, preservative), and set a target of 5 years for completion of the task.

The Committee decided to begin by reviewing the limits for heavy metals in emulsifiers at its fifty-fifth meeting, to be held in 2000. The call for data for that meeting will include requests for suggestions about limits for individual heavy metals and supporting data. Once the Expert Committee has considered the submissions, proposals will be submitted for consideration by the Codex Committee on Food Additives and Contaminants for eventual adoption by the Codex Alimentarius Commission.

The Expert Committee reaffirmed its earlier conclusions that it would establish a maximum level of 2 mg/kg for lead and 1 mg/kg for cadmium and for mercury, except when there were good reasons for establishing a lower or higher maximum level. The Committee also reaffirmed its earlier decision to include limits for arsenic only when the source from which the additive is prepared or the nature of the manufacturing method indicated that such a limit was necessary.

The Committee reiterated that replacement of the test for heavy metals by specific limits is intended to ensure that the concentrations of those elements that are likely to be of concern are limited.

2.6.3 *Citation of microbial strains*

At its fifty-first meeting (Annex 1, reference *137*), the Committee revised an addendum to the "General specifications for enzyme preparations used in food processing," which was originally published in Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*).

At its present meeting, the Committee further reviewed the specifications for numbering of microbial strains in the light of comments received by the Codex Committee on Food Additives and Contaminants at its Thirty-first Session (*2*).

The Expert Committee reaffirmed that the requirement for identification of a microbial strain by number in the source section of specifications monographs on enzymes prepared from genetically modified organisms might impose unnecessary constraints on the development of organisms for food-grade enzymes. The Committee concluded that the source section of monographs on enzymes derived from non-pathogenic, non-toxicogenic strains that belong to species that include pathogenic and toxicogenic strains should

include the statement that "the strain is non-pathogenic and non-toxicogenic", and a suitable strain number could be included as an example.

The Committee therefore amended the requirement for microbial strain numbers in the specifications section of Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) as follows, and decided that this amendment should be published as an annex to the *Compendium of food additive specifications, addendum 7* (*10*).

> *Microbial strain numbers* — Any microbial strain that meets the considerations described above should be a safe and suitable host for the introduced DNA. Citation in the monograph of the genus and species of the host organism is usually adequate for those that have been determined to be safe and suitable. Identification at the strain level may impose unnecessary constraints on the development of production microorganisms used to produce food-grade enzymes. In the case of a non-pathogenic, non-toxicogenic strain that belongs to a species that includes pathogenic and toxicogenic strains (e.g. *Escherichia coli*), there should be a requirement in the monograph that the strain be non-pathogenic and non-toxicogenic. Citation of a suitable strain number may be included by way of example.

The Committee further decided that lack of pathogenicity and toxicogenicity was a general requirement that should apply to all microorganisms used to produce food-grade enzymes. It therefore also agreed to the addition of the following text to the end of the section on source materials of Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*):

> When a non-pathogenic, non-toxicogenic strain belongs to a species that includes pathogenic and toxicogenic strains, the source section of the monograph for the enzyme should include a requirement that the strain be non-pathogenic and non-toxicogenic. Citation of a suitable strain number may be included by way of example.

The Committee further agreed that the above-mentioned requirement should be extended to all food additives that have been prepared from microorganisms that belong to species that include pathogenic and toxicogenic strains.

2.6.4 *Tentative specifications for food additives*

The Committee noted that many of the older specifications for food additives (other than flavouring agents) published in the

Compendium of food additive specifications (Annex 1, references *96*, *103*, *109*, *118*, *124*, *133* and *139*) are designated as "tentative", indicating that some information or data were missing or incomplete at the time the specifications were prepared. Some of these specifications have been designated as "tentative" for more than 30 years, and often no reason is given for this designation. Newer specifications include the reasons.

The Committee prepared two lists of the existing tentative specifications for food additives, excluding flavouring agents. The first list comprises specifications that do not include the reasons for the "tentative" designation, while the second contains the remaining tentative specifications, with the reasons for the designation.

The lists will be included with the call for data for the fifty-fifth meeting of the Committee, to be held in 2000. Technical data and information on the present uses of the additives in foods will be requested. If no data are received or if the substance is no longer used in foods, the tentative specifications will be withdrawn. Technical data and information on the reasons for all tentative designations will also be requested.

2.6.5 *Tentative specifications for flavouring agents*

At its forty-sixth, forty-ninth and fifty-first meetings (Annex 1, references *122*, *131* and *137*), the Committee developed specifications for the purity of over 400 flavouring agents, of which about one-quarter were designated as "tentative" because certain necessary information was lacking. In making these designations, the Committee relied on its judgement rather than on a carefully defined system. At its present meeting, the Committee agreed that it was important to be consistent in applying tentative designations and agreed that specifications submitted for consideration should be designated as "tentative" if information had not been provided on:

- chemical formula and relative molecular mass, identity test, and the minimum amount that can be determined (minimum assay value);
- the additional criteria related to purity, including boiling-point (for liquids), melting-point (for solids), refractive index (for liquids) and specific gravity (for liquids).

The Committee will, however, consider attributing full specifications when the absence of one or more of the additional criteria related to purity can be justified.

In order to ensure consistency, the Committee agreed that the specifications for the flavouring agents evaluated at its forty-sixth, forty-ninth and fifty-first meetings should be re-examined by the same approach. As a result, the tentative designation for the specifications for one of the flavouring agents (no. 8, allyl sorbate) was removed, and the specifications for over 50 other flavouring agents were given "tentative" designations. Although some of these flavouring agents, such as acetaldehyde and acetic acid, are well characterized, they were given tentative designations because not all of the information required to satisfy the criteria set out above regarding their use as flavouring agents was included in the material submitted. Overall, about one-third of the specifications for flavouring agents developed at the previous three meetings were designated as "tentative". The Committee agreed that flavouring agents submitted for evaluation at future meetings would not be considered for specifications unless the minimum information set out above was provided.

The Committee concluded that its first priority was to seek further information on the tentative specifications; however, it will also re-examine specifications that are not designated as "tentative" but for which the minimum assay values are less than 95%, and these will be included in future calls for data. The Committee further agreed that the relevant data should be sought in time for review at its fifty-fifth meeting to be held in 2000, and the flavouring agents on which data are sought will be included in the call for data for that meeting. If these data are not supplied, the specifications will be withdrawn.

2.7 Evaluation of substances as food additives that are also food ingredients or natural constituents of food

The Committee noted that some substances can be used both as ingredients of food and as food additives (e.g. polyols and turmeric), and that some substances used as food additives occur naturally in foods (e.g. carotenes and some flavouring agents). The Committee reaffirmed that its risk assessments clearly identify whether a substance is being evaluated only as a food additive or for additional uses, such as a food ingredient, and that the relative contribution of use as a food additive to total intake is identified when possible. When other food uses of the substance are known the assessment will clearly state whether all routes of intake have been evaluated. The Committee noted that numerical ADIs refer to exposure from all sources.

3. Specific food additives and substances used in food fortification

The Committee evaluated three food additives for the first time and re-evaluated two food additives and one substance used in food fortification programmes considered at previous meetings. Information on the evaluations and on specifications is summarized in Annex 2. Details of further information required for certain substances are given in Annex 3.

3.1 Glazing agent: hydrogenated poly-1-decene

Hydrogenated poly-1-decene is a mixture of synthetic branched-chain hydrocarbons (isoparaffins) which are produced by oligomerization of 1-decene to the tri-, tetra- and penta-decene molecules, followed by hydrogenation to full saturation of the oligomer. Hydrogenated poly-1-decene has been proposed for use in foods as a substitute for white mineral oil when it is used as a glazing or polishing agent for dried fruits and certain sugar confectionery, such as fruit gums and jellies. Hydrogenated poly-1-decene is also used as a release ("non-stick") coating in bread tins, as a lubricant in dough-dividing machines, as an anti-dusting and anti-foaming agent and as a plasticizer in films that come into contact with food.

Since hydrogenated poly-1-decene is a synthetic product, its composition is well defined. The oligomer distribution of the product is 16–35% trimers, 42–61% tetramers, 12–23% pentamers and 1–9% hexamers; the dimer concentration is less than 1%.

Hydrogenated poly-1-decene was previously evaluated by the Committee at its forty-ninth meeting (Annex 1, reference *131*), when the data available from two studies of 28 and 90 days' duration in rats given repeated doses were reviewed and considered to be inadequate to support the use of this product as a food additive. In view of the potentially high intake of this compound, the Committee concluded that adequate data were required to establish that the oily coats observed in rats fed hydrogenated poly-1-decene were not the result of systemic absorption. It also requested data that clearly demonstrate the lack of absorption of this substance in humans. In the absence of these data, the Committee noted that the results of long-term toxicity and reproductive toxicity studies and information on the metabolism, distribution and excretion of hydrogenated poly-1-decene would be required. The only study submitted to the Committee at its present meeting was an investigation of the distribution and excretion of hydrogenated poly-1-decene and of the origin of the oily coats in rats

in the 90-day study. All relevant data, including those reviewed at the forty-ninth meeting, were evaluated at the present meeting.

[^{3}H]Hydrogenated poly-1-decene (97% radiochemical purity), administered as a single oral dose of 30, 210 or 1500mg/kg of body weight to rats, was eliminated almost entirely in the faeces, with 0.2%, 0.05% and 0.6% of the dose, respectively, excreted in the urine. In rats treated with 210mg/kg of body weight per day for 14 days, 0.07% of the dose was eliminated in the urine. Negligible amounts were detected in the bile of all treated animals. The very low concentrations of radiolabel in plasma and tissues did not increase in direct proportion to the dose, suggesting that absorption was limited at high doses. At 8 hours after dosing, 60–80% of the radiolabel in plasma was present as $[^3H]_2O$ (tritiated water), indicating that the label had a half-life of 80–90 hours. The ratio of the concentration of the radiolabel in the liver or lymph nodes (site unspecified) to that in plasma was approximately 5, which suggested that the material in these tissues was not simply $[^3H]_2O$ and that the material had been absorbed from the gastrointestinal tract through the lymphatic system. The absorbed radiolabel was not characterized further, and the results of administration of an intravenous dose did not provide useful information on the disposition of the parent compound through the circulation. The study indicated very little absorption of hydrogenated poly-1-decene in rats after oral administration but was uninformative with regard to the disposition of the compound. The Committee concluded that the oiliness of the fur observed within 1–6 hours of dosing was associated with radiolabelled material originating from the anal region which was spread by grooming activity.

In the 90-day study, rats of each sex received diets containing hydrogenated poly-1-decene at 1, 7 or 50g/kg of feed; some animals were maintained on a control diet for a 4-week recovery period. Both males and females in the highest-dose group had ungroomed coats during the second week of treatment and then oily coats from the third week of treatment to the first week of the recovery period. Animals in all treatment groups showed hair loss during treatment; this effect persisted in animals in the highest-dose group throughout the recovery period. Some marginal effects on haematological parameters were noted. Males in the highest-dose group showed a significant, but reversible, reduction in liver weight, which was not associated with any unusual histological appearance. Females in the highest-dose group showed no effect on liver weights, but histological examination revealed necrosis of individual hepatocytes and a decrease in the fat content of hepatocytes. In the 28-day study, a dose-related decrease in the weights of mandibular lymph nodes was noted, which reached

statistical significance in females at the highest concentration tested, 50 g/kg of feed, but was not associated with histopathological changes. This parameter was not evaluated in the 90-day study. Accumulation of saturated hydrocarbons was not observed in lymphoid, gastrointestinal, hepatic or splenic tissue.

No genotoxicity studies have been conducted with hydrogenated poly-1-decene; however, the results of genotoxicity tests on related isoparaffins of lower relative molecular mass showed that they had no effect on a variety of end-points. Consequently, the Committee concluded that genotoxicity tests on hydrogenated poly-1-decene were not required.

Patch tests on human skin with the same related isoparaffins did not indicate sensitization.

The Committee noted that the study of the disposition of hydrogenated poly-1-decene did not allow clear definition of the fate or deposition of any absorbed material. It was therefore unable to establish an ADI. Before reviewing this substance again, the Committee would wish to see an adequate study of the absorption and deposition of hydrogenated poly-1-decene in order to determine whether further studies were required.

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

3.2 Sweetening agent: erythritol

Erythritol is a four-carbon sugar alcohol (*meso*-1,2,3,4-butanetetrol) with a sweetness that is 60–80% that of sucrose. It is intended for use as a low-calorie sweetener. It is manufactured from glucose or sucrose by fermentation with *Trichosporonoides megachiliensis* or *Moniliella pollinis*, which are non-pathogenic, non-toxicogenic yeasts. Erythritol also occurs naturally in fruits and mushrooms and is present in various fermented products, including wine, *sake* and soy sauce, generally at low concentrations (700–1300 mg/kg), but in the exceptional case of a single species of mushroom, at 34 g/kg. It is often detected in human and animal tissues and body fluids, including the lens, cerebrospinal fluid, serum, semen and urine.

Erythritol has not been previously evaluated by the Committee. Its technical characteristics, such as its cooling effect and low hygroscopicity, are more similar to those of xylitol than those of sorbitol, which together account for a large proportion of sweetening agents on the market. If erythritol were to be used to replace xylitol (which accounts for 20% of all polyol use), the projected mean intake would be

1 g/day and the intake in the 90th percentile, based on the estimated intake of diabetic patients, would be 4 g/day; if it were used to replace all polyols, the mean intake would be 4–5 g/day and the intake in the 90th percentile would be 20 g/day.

Studies in mice, rats, dogs and humans showed that erythritol is rapidly and extensively absorbed after oral ingestion and rapidly excreted unchanged in the urine. Excretion in the faeces was a minor route after dietary administration to mice, rats and dogs; no data were available for humans. The small but significant proportion of the administered dose recovered in expired carbon dioxide after oral administration was probably the result of fermentation of erythritol in the lower gastrointestinal tract; the proportion increased in a dose-related manner. In contrast, the major route of excretion of orally administered glycerol, lactitol and mannitol was expired carbon dioxide, negligible amounts being excreted unchanged in the urine and faeces. These findings indicate the importance of gastrointestinal fermentation in the disposition of these polyols. There was no evidence of fermentation of erythritol by the gastrointestinal flora in humans who had not been exposed to it previously.

Erythritol showed little toxicity when administered orally to mice, rats and dogs as a single dose. The symptoms observed in animals that subsequently died were considered to be nonspecific effects resulting from the absorption of a large volume of a hypertonic solution.

Toxicity studies were conducted in mice given erythritol in the diet for 13 weeks, in rats treated for 28 days in the diet (two studies) or for 13 weeks in the diet or by gavage, and in dogs treated by gavage for 13 weeks or in the diet for 1 year. In all of these studies, concentrations of up to 200 g/kg of diet were used. In both male and female rodents, administration of erythritol was accompanied by dose-related increases in water consumption and urine volume. Urine density and osmotic pressure were increased at the lower doses and decreased at the higher doses, reflecting the competing factors of high concentrations of erythritol and its effects on diuresis. Urinary excretion of electrolytes, particularly sodium, potassium and calcium (measured only after dietary administration), and of protein was also increased in rats and mice. Increased kidney weights were observed in rats but not in mice. In the study in which erythritol was administered for 28 days in the diet of rats that had undergone partial nephrectomy, no difference in response was seen between sham-operated and nephrectomized animals. Other effects related to diuresis were seen in response to erythritol only in the 13-week study in rats treated by gavage; these included increased blood urea nitrogen concentration,

decreased serum concentrations of sodium and chloride, an increased incidence of slight dilatation of the renal tubules, and increased adrenal weights accompanied by dilatation of the sinusoids of the adrenal cortex. These effects were no longer seen after a 4-week recovery period. The results of an additional study to investigate these effects suggested that the increase in blood urea nitrogen concentration was a compensatory homeostatic response to serum hyponatraemia. The more extensive effects noted after administration by gavage were probably related to the higher maximum plasma concentrations of erythritol after a bolus dose than after gradual intake in the diet.

Gastrointestinal effects were seen in all of the studies in which erythritol was administered orally. These included transient laxation and soft stools in rats and increased caecal weights in both rats and mice. The decrease in caecal pH in the 13-week study in rats treated in the diet would have promoted increased absorption of calcium and might therefore account for the increased urinary excretion of calcium. Serum alkaline phosphatase activity was increased by treatment in these studies. Since the main source of circulating alkaline phosphatase in rats is the intestine, the increase in plasma activity may have resulted from the intestinal effects of erythritol.

In dogs, transient clinical effects (salivation, vomiting, reddening of the epidermal and mucous membranes, laxation and soft stools) were seen after treatment by gavage but not after dietary administration. These effects, with the exception of that on faecal consistency, were attributed to increased plasma osmolality. As in the rodents, water consumption and urine volume were increased in both studies, with increased osmotic pressure and specific gravity of the urine observed at the lower doses and decreases in these parameters at the higher doses. Renal function, as assessed by clearance of phenosulfonphthalein after treatment by gavage, was not affected. In the 1-year study, some histopathological changes were seen in the kidneys of 2 of the 3 dogs at the highest dose, which regressed during the 4-week recovery period and were considered to be a transient, functional osmotic response. Changes observed in the prostate were considered not to be toxicologically relevant.

All of the effects seen in these short-term studies in rodents and dogs were considered to be physiological or adaptive responses to the osmotic diuretic effects of absorbed erythritol or (in rodents) the effect of gastrointestinal fermentation of unabsorbed erythritol. All of these effects were reversed when feeding of erythritol was stopped. Intravenous administration of erythritol to rats resulted in physiological changes that were qualitatively similar to those observed after

administration in the diet or by gavage but were more marked. The NOEL in the feeding studies was 50 g/kg of feed, equivalent to 7.5 g/kg of body weight per day in the 13-week study in mice, 2.5 g/kg of body weight per day in the 13-week study in rats and 1.7 g/kg of body weight per day in the 1-year study in dogs. The NOELs in the studies in which erythritol was given by gavage for 13 weeks were 2 g/kg of body weight per day in rats and 1.2 g/kg of body weight per day in dogs.

Erythritol was not carcinogenic in rats treated in the diet for 78 or 104 weeks; no long-term toxicity studies in mice were available. Effects similar to those seen in the short-term studies were observed in the rats, with the addition of earlier onset of nephrosis in males at the highest dose. The NOELs for physiological responses to erythritol were 30 g/kg of feed (equal to 1.4 g/kg of body weight per day) in the 78-week study and 20 g/kg of feed (equal to 0.9 g/kg of body weight per day) in the 104-week study.

Erythritol did not exhibit mutagenic or clastogenic activity in vitro.

No reproductive or developmental toxicological effects were observed at doses of up to 8 g/kg of body weight per day in mice given by gavage or at doses representing up to 100 g/kg of feed in rats.

The gastrointestinal and renal effects of erythritol and its effects on glucose control have also been studied in volunteers. When single doses of 30–75 g of erythritol were administered in solution or jelly to healthy adults in three studies, the NOEL for induction of laxation was 0.46–0.66 g/kg of body weight in men and 0.76–0.80 g/kg of body weight in women. The dose that induced laxation in 50% of the subjects was estimated to be 1.1 g/kg of body weight in men and 1.6 g/kg of body weight in women. Although women appeared to be less sensitive to erythritol-induced laxation than men, they reported gastrointestinal symptoms, including nausea, more frequently. When a divided dose of 40 g of erythritol in solution was ingested by healthy individuals daily for 5 days or divided doses of 60–68 g/day were ingested in tea or coffee for 3 days, no laxation occurred at doses of up to 0.91 g/kg of body weight per day in men and 0.74 g/kg of body weight per day in women. Single doses of 0.3 and 1 g/kg of body weight of erythritol in aqueous solution given to healthy adults had no effect on plasma glucose or insulin concentrations, and neither urine volume nor urinary excretion of sodium, chloride or potassium was affected by the lower dose.

No gastrointestinal symptoms were seen when single doses of 0.4 or 0.8 g/kg of body weight were given in food, or when repeated doses of 1 g/kg of body weight per day were ingested in a variety of foods

throughout the day for 5 days by healthy individuals. The osmolality of urine was increased by erythritol treatment in a dose-related manner in both of these studies. After single doses of erythritol, no changes in measured plasma osmolality were observed, and there was no effect on water consumption, urine volume or 24-hour excretion of electrolytes or *N*-acetyl-glucosaminidase. Plasma glucose levels were not affected.

In subjects with non-insulin-dependent diabetes, a 20-g dose of erythritol in solution consumed on a single occasion or on 14 consecutive days did not induce laxation and had no effect on blood glucose concentrations.

The NOELs for physiological responses to orally administered erythritol in animals were generally between 1 and 2 g/kg of body weight per day. Since the observed effects of erythritol in animals are a physiological response to an osmotically active substance, application of a safety factor to the NOELs observed in studies in experimental animals was considered inappropriate. In humans, a dose of 1 g/kg of body weight per day consumed in a variety of foods for 5 days had no effect, although the same (and lower doses) consumed in aqueous solution as a bolus dose after fasting resulted in laxation. The Committee established an ADI "not specified"[1] for erythritol for use as a sweetening agent.

A toxicological monograph and new specifications were prepared.

3.3 Thickening agent: curdlan

Curdlan is a linear polymer consisting of β-(1→3)-linked glucose residues, which is derived by fermentation from the bacterium *Alcaligenes faecalis* var. *myxogenes*. It has not been previously reviewed by the Committee. At its present meeting, the Committee considered use of curdlan in food as a formulation aid, processing aid, stabilizer and thickener or texturizer.

Information on the current per capita intake of curdlan in Japan was submitted, together with intake data based on the levels of use of the additive and on food consumption in the USA. However, the

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

Committee considered this information inadequate for making a complete assessment of intake, because no data were provided on the maximum levels of use and the distribution of intake of foods that might contain the additive in different regions of the world.

In two studies, rats given [^{14}C]curdlan at a dose of 20mg/kg of body weight orally excreted about 80% and 40% of the radiolabel as [^{14}C]carbon dioxide within 24 hours, respectively. In these studies, excretion in urine represented about 3% and 1.5% of the dose and excretion in faeces about 8% and 34%, respectively. After 48 hours, 100% and 80% of the radiolabel was recovered from carbon dioxide, urine and faeces combined in the two studies, respectively. When tetracycline was given concomitantly in the drinking-water, excretion as carbon dioxide decreased by one-third, whereas excretion in faeces was increased, indicating that intestinal microflora may be responsible for the metabolism of this compound. Excretion of the radiolabel as carbon dioxide also decreased with increasing dose of curdlan, indicating that metabolism was more limited at higher doses. In humans, the faeces appeared to be the main pathway for excretion, except for a portion that was fully metabolized to carbon dioxide. The extent of metabolism to carbon dioxide in humans also appeared to reflect the action of intestinal bacteria: when the bacterial microflora were suppressed by pretreatment with antibiotics, very limited production of [^{14}C]carbon dioxide was seen.

Curdlan given to rats at concentrations of 10, 50 or 150g/kg of feed had no effect on the bioavailability of calcium, magnesium, iron, zinc, copper or manganese.

The LD_{50} value in mice and rats treated orally was >10g/kg of body weight, and no abnormalities were seen at autopsy.

In short-term and long-term studies in experimental animals, the only effects of orally administered curdlan were soft stools and/or laxation, reduced body-weight gain and increased weights of full and empty caeca due to the presence of high concentrations of undigested curdlan. In an 8-week study in mice and a 4-week study in rats given curdlan at concentrations of up to 300g/kg of feed, the only effects were large faecal pellets, soft stools and/or laxation and increased weights of full and empty caeca.

In a 3-month study in rats, the NOEL was the lowest concentration tested, 50g/kg of feed. Growth was inhibited at the highest level, 200g/kg of feed, even though food intake was increased. Soft stools, enlarged large intestines when full and increased weights of full and empty caeca appeared to be the major effects at 100 and 200g/kg of feed. Dose-related decreases in platelet counts and protein and

globulin concentrations and dose-related increases in serum alkaline phosphatase activity, absolute carcass weight and the relative weights of adrenal glands and submaxillary glands were seen in males at 100 and 200 g/kg of feed. In addition, males in the highest-dose group had decreased serum calcium and cholesterol concentrations, while females had decreased relative pituitary weights and increased relative uterine weights. At necropsy, decreased deposition of adipose tissue was seen in the abdominal cavity in females at all doses and in males at the highest dose.

In a 1-year study in dogs, animals treated with curdlan at a concentration of 150 g/kg of feed or given gelled curdlan at a concentration of 40 g/kg of feed had blood-tinged, mucoid, soft stools. Increases in the weights of full and empty caeca were also observed at 150 g/kg of feed. The petaechial haemorrhages and mucosal ecchymosis occasionally observed in the small intestinal mucosa of dogs at all doses were considered to be unrelated to treatment with curdlan.

In a lifetime carcinogenicity study in mice, addition of gelled curdlan at a concentration of 400 g/kg of feed or of curdlan at concentrations of up to 150 g/kg of feed did not cause any significant abnormalities, although decreased food consumption was seen with curdlan and increased food consumption with gelled curdlan. No changes in tumour incidence were observed.

In a 2-year study in rats, the highest concentration of curdlan (150 g/kg of feed) decreased growth and food consumption and increased the weights of full and empty caeca. Gelled curdlan at 400 g/kg of feed had no effect. A further 2-year study was conducted at the same laboratory, using rats of the same strain. Animals exposed in utero to curdlan at 150 g/kg of feed showed inhibited growth and a slight decrease in food consumption. Increased empty caecal weights were seen in males given curdlan at 50 g/kg of feed and in females at 150 g/kg of feed or given gelled curdlan at 400 g/kg of feed. Clinical chemical analyses during treatment showed increased aspartate aminotransferase and serum alkaline phosphatase activities in animals given curdlan at 150 g/kg of feed or gelled curdlan. Gross and microscopic examination revealed a significantly increased incidence of benign uterine polyps in rats exposed to curdlan at 150 g/kg of feed. The authors reported that benign uterine polyps were seen infrequently in control animals; the incidences in historical controls were not available.

In a three-generation study of reproductive toxicity in rats, with two litters per generation, no effect was seen on fertility, gestation or the viability of the pups. Parents given curdlan at 150 g/kg of feed or gelled curdlan at 400 g/kg of feed showed slight growth inhibition.

Food consumption was slightly decreased in parents given gelled curdlan at 400 g/kg of feed. Furthermore, F_2 dams given curdlan or gelled curdlan had increased full and empty caecal weights. The weights of the pups in most litters of dams given curdlan were significantly decreased during lactation: in F_{1a} and F_{1b} litters at 14 and 21 days of age; in F_{2a} litters at 4, 7, 10, 14, 17 and 21 days of age; in F_{2b} litters at day 4 of age; in F_{3a} litters at 4, 7, 10, 14, 17 and 21 days of age; and in F_{3b} litters at day 21 of age. The NOEL for both maternal toxicity and embryotoxicity was 50 g/kg of feed. Although the authors suggested that the decrease in the weight gain of pups during lactation was due to consumption of the dams' feed, it could have been a treatment-related effect or a combination of consumption of the treated feed and an effect via the milk. In order to investigate these possibilities, a number of single-generation studies (two litters per generation) were performed in which the offspring of treated dams were nursed by untreated dams and the offspring of untreated dams were nursed by treated dams. Another single-generation study was conducted in which rats were given cellulose at 50 or 150 g/kg of feed. Both curdlan and cellulose significantly decreased pup weight gain during lactation at 150 g/kg of feed; this effect was decreased in pups transferred from treated to control dams during lactation. When treatment of the dams with curdlan during lactation was withdrawn, the weights of the pups of treated dams during lactation were comparable to those of the pups of control dams.

The three-generation study of reproductive toxicity included a teratogenicity study in the F_{2c} litters. No embryotoxic or teratogenic effects were observed at any concentration of curdlan up to 150 g/kg of feed or of gelled curdlan up to 400 g/kg of feed. In a teratogenicity study in rabbits treated orally by gavage at up to 5 g/kg of body weight per day, no teratogenic effects were seen.

Curdlan had no effects in in vitro assays for gene mutation in bacteria or mouse lymphoma cells, and the results of chromosomal aberration tests in hamster ovary cells were negative. It did not induce micronucleus formation in mice treated in vivo.

No pathogenic effects were observed in mice that received live or dead cells of the producing microorganism, *Alcaligenes faecalis* var. *myxogenes*, strain NTK-u, IFO 13140, orally or in mice that received intravenous, intraperitoneal or intracerebral injection of live organisms. This curdlan-producing strain was not cytotoxic to HeLa cells.

Curdlan was not immunotoxic in mice or rats. It did not induce skin sensitization in a study in humans, although the study was of limited value.

In a 4-week study in which six volunteers each consumed up to 50 g of curdlan daily, increased flatulence was observed. One subject who consumed 50 g of curdlan per day had some diarrhoea. No evidence of toxicity was seen.

In summary, curdlan did not induce genotoxic, carcinogenic or teratogenic effects or effects on reproduction. At high doses, it decreased growth and/or food consumption and increased the weights of full and/or empty caeca. These effects are commonly observed after the consumption of large amounts of indigestible bulking materials.

The Committee noted the significant increase in the incidence of benign uterine polyps in rats exposed in utero to curdlan at a concentration of 150 g/kg of feed. The effect appeared to be dose-related; however, uterine polyps were not observed in the lifetime study in mice or in the 2-year study in rats of the same strain from the same laboratory that were not exposed in utero. These benign growths are known to occur naturally in older rats at incidences of 1–20%, depending on the study and strain. Taking into consideration the lack of genotoxicity of curdlan and its structure and metabolism, the Committee allocated a temporary ADI "not specified"[1] to curdlan for use as a food additive. The ADI was made temporary, pending the provision of the following information:

- information on the use of curdlan, including the maximum and typical levels expected to occur in the food categories proposed in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants;
- data on the consumption of foodstuffs that might contain curdlan in different regions of the world, to permit assessment of the intake.

This information is required for evaluation in 2001.

A toxicological monograph, including information on intake, and new specifications were prepared.

3.4 Miscellaneous substances

3.4.1 *γ-Cyclodextrin*

γ-Cyclodextrin is a ring-shaped molecule made up of eight glucose units linked by α-1,4-bonds. The circular structure of γ-cyclodextrin provides a hydrophobic cavity that allows incorporation and solubilization of a variety of organic molecules, while the hydrophilic outer surface makes it water-soluble. γ-Cyclodextrin is used as a carrier for flavours, sweeteners and colours. It is also proposed for use as a

[1] See footnote on page 22.

carrier for vitamins and polyunsaturated fatty acids and as a flavour modifier.

γ-Cyclodextrin was previously evaluated by the Committee at its fifty-first meeting (Annex 1, reference *137*). At that meeting, the Committee concluded that there were sufficient data to allocate a temporary ADI "not specified", but that the results of a study of human tolerance known to have been conducted should be reviewed in order to confirm the absence of adverse effects on the gastrointestinal tract at normal levels of intake. The results were required for evaluation in 1999. At its present meeting, the Committee reviewed the results of that study and of a 12-month study of toxicity in rats treated orally, which had also become available.

In the latter study, rats were given γ-cyclodextrin at concentrations of up to 200 g/kg of feed. Minimal changes were seen at the highest dose, probably as a result of the presence of a large amount of an osmotically active substance in the large intestine. These changes were considered to be transient and not of toxicological significance.

The study of adverse effects in humans indicated that γ-cyclodextrin did not cause symptoms of gastrointestinal discomfort when ingested at levels of up to 8 g per serving (equal to 0.11 g/kg of body weight in males and 0.13 g/kg of body weight in females).

The estimated 3-day average daily per capita intake of γ-cyclodextrin when used at a maximum level in 19 foods was 4 g, and the intake by consumers in the 90th percentile was 7.5 g.

On the basis of the above studies, and the information reviewed at its fifty-first meeting, the Committee allocated an ADI "not specified"[1] to γ-cyclodextrin.

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

3.4.2 *Sodium iron EDTA*

Sodium iron(III) EDTA (ethylenediamine tetraacetate or edetic acid) was previously evaluated by the Committee at its forty-first meeting (Annex 1, reference *107*), when it provisionally concluded that use of sodium iron EDTA meeting the tentative specifications prepared at the meeting would not present a safety problem in supervised food fortification programmes in iron-deficient populations. The Committee requested that additional studies be conducted to assess the site of deposition of iron administered in this form and to

[1] See footnote on page 22.

assess the metabolic fate of sodium iron EDTA after long-term administration. The Committee emphasized that its evaluation applied only to the use of sodium iron EDTA as a dietary supplement to be used under supervision, and expressed its concern about the potential for over-fortification of food because of the enhanced bioavailability of iron in this form.

Several studies were submitted in response to the Committee's request, which were reviewed at the present meeting. One study that was specifically designed to address the Committee's concerns involved feeding male rats diets containing iron in two forms, ferrous sulfate and sodium iron EDTA, for 62 days. The dietary concentrations provided iron intakes of 2.8, 5.7 and 12 mg/kg of body weight per day from ferrous sulfate, and 2.8, 5.7 and 11 mg/kg of body weight per day from sodium iron EDTA. There was a dose-related increase in the amount of non-haem iron stored in the liver, spleen and kidney, which was more pronounced in the animals fed diets containing ferrous sulfate. There was no evidence that the total iron-binding capacity of the blood plasma was altered by treatment with sodium iron EDTA. The Committee therefore concluded that there was no evidence that administration of iron in the form of sodium iron EDTA would result in greater uptake of iron than that from an equivalent dietary concentration of ferrous sulfate once the nutritional requirement for iron is satisfied. There was no evidence of adverse effects at the highest daily intake of iron from sodium iron EDTA, i.e. 11 mg/kg of body weight, which is 55 times the proposed daily human intake of 0.2 mg/kg of body weight in food fortification programmes.

Short-term studies in rats and humans have shown no adverse effects of dietary intake of sodium iron EDTA on the concentrations of other minerals such as calcium, copper, manganese and zinc. The results of an intervention study in iron-deficient populations in Guatemala demonstrated the efficacy of a diet supplemented with sodium iron EDTA in reducing the prevalence of iron deficiency. The Committee therefore considered that the data submitted satisfied its concerns about the use of sodium iron EDTA in food fortification programmes.

The Committee was aware of the results of acute toxicity, mutagenicity, teratogenicity and 90-day toxicity studies in rats given sodium iron EDTA. Full reports of these studies were not available to the Committee, but the information was considered unnecessary for evaluating the safety of this compound. The Committee also received an assessment of the potential intake of sodium iron EDTA by consumers in the United States that would result from fortification of foodstuffs. The Committee was of the view that this assessment was

not relevant to any proposed use of sodium iron EDTA as a food fortifier in areas of iron deficiency.

The Committee concluded that sodium iron EDTA could be considered safe when used in supervised food fortification programmes in response to a need for iron supplementation in a population as determined by public health officials. Such programmes would provide a daily iron intake of approximately 0.2mg/kg of body weight.

An addendum to the toxicological monograph was prepared. The existing specifications were revised to include an identification test for sodium, a method for the analysis of nitrilotriacetic acid and a modified method of assay for sodium iron EDTA.

3.4.3 *Sodium sulfate*

Sodium sulfate has not been evaluated previously by the Committee. The sulfate anion was evaluated at the twenty-ninth meeting (Annex 1, reference *70*), when an ADI "not specified" was established, on the basis that sulfate is a natural constituent of food and is a product of sulfur metabolism in animals. Sodium sulfate was not specifically included in that ADI because no information was available to indicate that it was being manufactured or used as a food-grade material. It was evaluated at the present meeting at the request of the Codex Committee on Food Additives and Contaminants because it is included in the draft General Standard for Food Additives.

The Committee was unaware of any data on the dietary intake of sodium sulfate in human populations.

The Committee considered that the results of the published studies in experimental animals did not raise any concern about the toxicity of sodium sulfate. The compound has a laxative action, which is the basis for its clinical use. The minor adverse effects reported after ingestion of purgative preparations containing sodium sulfate may not be due to the sodium sulfate itself.

In the absence of any evidence of toxicity, the Committee allocated a temporary ADI "not specified"[1] to sodium sulfate in accordance with the principles established at its twenty-ninth meeting.

A toxicological monograph and new specifications were prepared. The new specifications were designated as "tentative", pending the submission of information on the functional effect and actual uses of sodium sulfate in foods. This information is required for evaluation in 2001.

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[1] See footnote on page 22.

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

Two groups of flavouring agents were evaluated using the Procedure for the Safety Evaluation of Flavouring Agents as outlined in Fig. 1 (Annex 1, references *116*, *122*, *131* and *137*).

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

- Class I. Substances that have simple chemical structures and efficient modes of metabolism which would suggest a low order of toxicity when given by the oral route.
- Class II. Substances that have structural features that are less innocuous than those of substances in Class I, but are not suggestive of toxicity. Substances in this class may contain reactive functional groups.
- Class III. Substances that have structural features that permit no strong initial presumption of safety, or may even suggest significant toxicity.

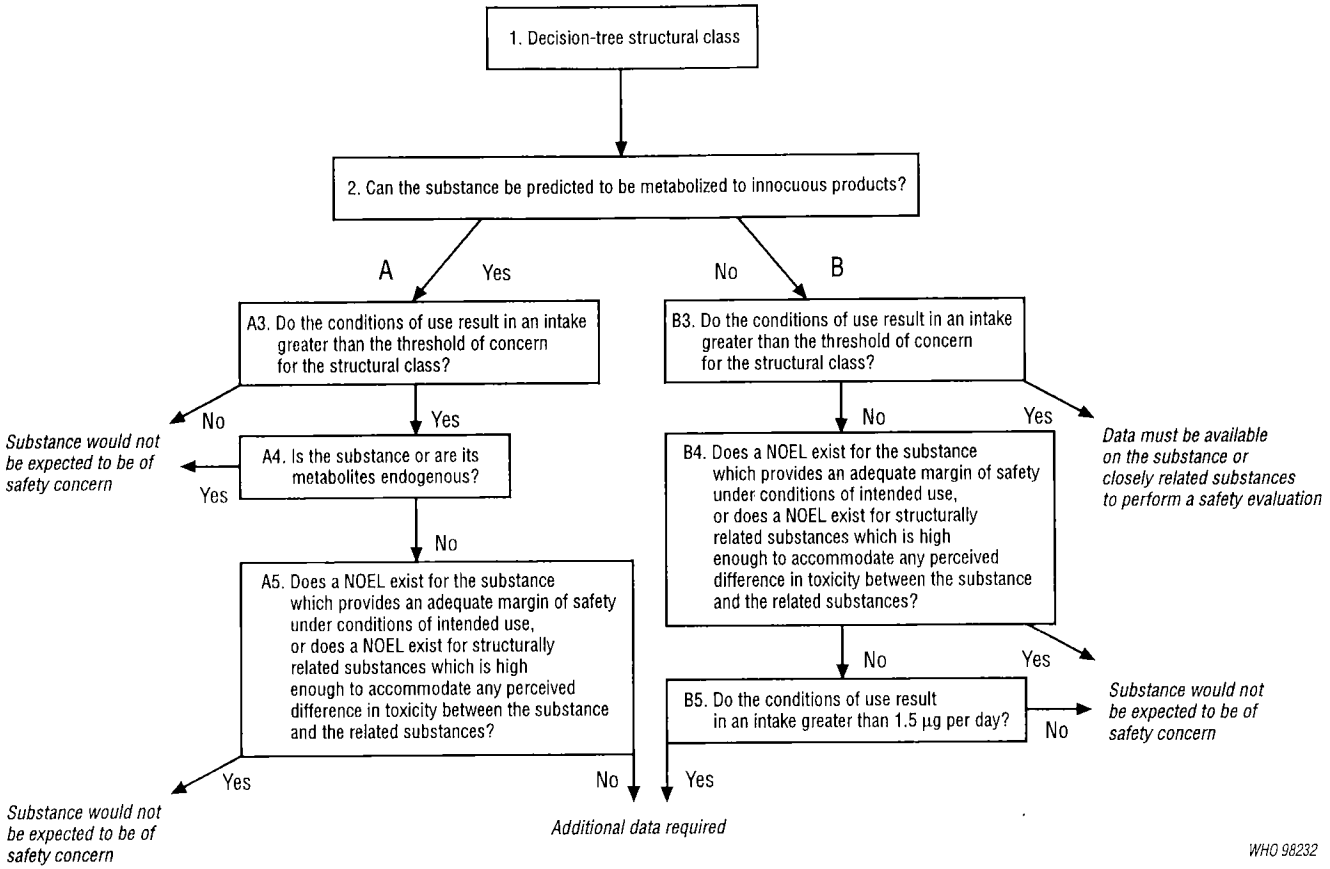
A key element of the Procedure involves determining whether a flavouring agent and the product(s) of its metabolism are innocuous and/or endogenous substances. For the purpose of the evaluations, the Committee used the following definitions, adapted from the report of its forty-sixth meeting (Annex 1, reference *122*):

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.

Estimates of the intake of flavouring agents by populations typically involve the acquisition of data on the amounts used in food. These 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

Figure 1
Procedure for the Safety Evaluation of Flavouring Agents



the European Union during the previous year. 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 Research Council of the National Academy of Sciences (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 maximum levels at which each substance was added to a number of broad food categories.

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

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

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

In applying the Procedure, the Committee compared the estimated intakes with the thresholds for human intake for the respective structural classes. These are 1800 µg per day per person for class I, 540 µg per day per person for class II and 90 µg per day per person for class III.

4.1 Simple aliphatic and aromatic sulfides and thiols

The Committee evaluated a group of 137 flavouring agents that includes aliphatic and aromatic sulfides and thiols, with and without an additional oxygenated functional group (Table 1), using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1). The Committee had not previously evaluated any member of the group.

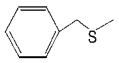
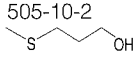
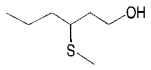
4.1.1 *Intake data*

The total annual volume of production of the 137 simple aliphatic and aromatic sulfides and thiols in this group destined for use as flavouring agents is approximately 6 tonnes in Europe and 5.3 tonnes in the USA. Methyl sulfide (no. 452) accounts for 51% of the total annual volume of production in Europe and 52% of the total annual volume of production in the USA. The estimated daily intake of methyl sulfide by consumers of this substance is 10 µg/kg of body weight in Europe and 9 µg/kg of body weight in the USA. The estimated daily intakes of the remaining substances in this group are much lower, the next highest values being 2 µg/kg of body weight

Table 1
Summary of the results of safety evaluations of 137 aliphatic and aromatic sulfides and thiols[a]

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup i — simple sulfides (thioethers)						
Structural class I						
Methyl sulfide	452	75-18-3	No Europe: 590 USA: 527	Yes, a NOEL of 250 mg/kg of body weight per day was reported in a 14-week study in rats treated by gavage at multiple doses	NR	No safety concern
Methyl ethyl sulfide (ethyl methyl sulfide)	453	624-89-5 	No Europe: ND USA: 2	Yes, related substance no. 452	NR	
Diethyl sulfide	454	352-93-2	No Europe: ND USA: 13	Yes, related substance no. 452	NR	
Butyl sulfide	455	544-40-1 	No Europe: 4 USA: 0.1	Yes, related substance no. 452	NR	
(1-Buten-1-yl)methyl sulfide	457	32951-19-2	No Europe: ND USA: 0.1	Yes, related substance no. 452	NR	
bis(Methylthio)methane	533	1618-26-4 	No Europe: ND USA: 94	Yes, related substance no. 452	NR	
Structural class II						
Allyl sulfide	458	592-88-1	No Europe: ND USA: 0.4	No, related substance no. 521, subgroup iv, is not predicted to be a metabolite of allyl sulfide	No	No safety concern

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup i — continued						
Structural class II (continued)						
Methyl phenyl sulfide	459	100-68-5 	No Europe: ND USA: 0.4	No	No	No safety concern
Benzyl methyl sulfide	460	766-92-7 	No Europe: 0.2 USA: 0.02	No	No	
Subgroup ii — acyclic sulfides with oxidized side-chains						
Structural class I						
3-(Methylthio)propanol	461	505-10-2 	No Europe: 4 USA: 1	Yes, related substance no. 505; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern
4-(Methylthio)butanol	462	20582-85-8 	No Europe: 0.02 USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
3-(Methylthio)-1-hexanol	463	51755-66-9 	No Europe: 5 USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	

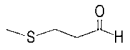
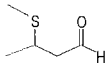
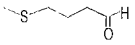
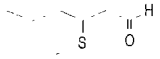
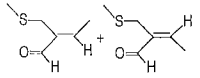
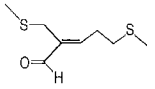
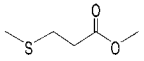
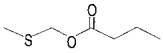
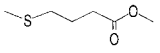
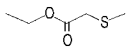
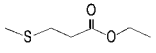
2-(Methylthio)acetaldehyde ((methylthio)acetaldehyde)	465	23328-62-3 	No Europe: ND USA: 1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern
3-(Methylthio)propionaldehyde	466	3268-49-3 	No Europe: 45 USA: 25	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
3-(Methylthio)butanal	467	16630-52-7 	No Europe: 0.1 USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
4-(Methylthio)butanal	468	42919-64-2 	No Europe: ND USA: 0.02	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
3-(Methylthio)hexanal	469	38433-74-8 	No Europe: ND USA: 1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
2-[(Methylthio)methyl]-2-butenal	470	40878-72-6 	No Europe: 0.04 USA: 0.1	No	No	
2,8-Dithianon-4-ene-4-carboxaldehyde (5-(methylthio)-2[(methylthio)methyl]-2-pentenal)	471	59902-01-1 	No Europe: 0.01 USA: 0.1	No	No	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup ii — continued						
Structural class I (continued)						
Methyl 3-(methylthio)propionate	472	13532-18-8 	No Europe: 146 USA: 9	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain; the simple side-chain acid and ester would be predicted to be of low toxicity	NR	No safety concern
(Methylthio)methyl butyrate	473	74758-93-3 	No Europe: ND USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Methyl 4-(methylthio)butyrate	474	53053-51-3 	No Europe: 0.1 USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Ethyl 2-(methylthio)acetate (ethyl(methylthio)acetate)	475	4455-13-4 	No Europe: ND USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Ethyl 3-(methylthio)propionate	476	13327-56-5 	No Europe: 37 USA: 2	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	

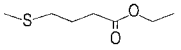
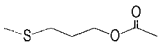
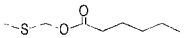
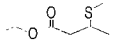
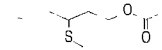
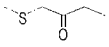
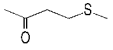
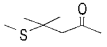
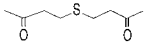
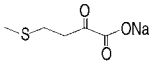
Ethyl 4-(methylthio)butyrate	477	22014-48-8 	No Europe: ND USA: 2	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern
3-(Methylthio)propyl acetate	478	16630-55-0 	No Europe: ND USA: 11	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
(Methylthio)methyl hexanoate	479	74758-91-1 	No Europe: ND USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Ethyl 3-(methylthio)butyrate	480	Pending 	No Europe: ND USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
3-(Methylthio)hexyl acetate (3-(methylthio)-1-hexanol acetate)	481	51755-85-2 	No Europe: 0.1 USA: 9	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
1-(Methylthio)-2-propanone	495	14109-72-9 	No Europe: ND USA: 0.2	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
1-(Methylthio)-2-butanone	496	13678-58-5 	No Europe: 0.01 USA: 0.02	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup ii — continued						
Structural class I (continued)						
4-(Methylthio)-2-butanone	497	34047-39-7 	No Europe: 0.02 USA: 0.4	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern
4-(Methylthio)-4-methyl-2-pentanone (4-methyl-4-(methylthio)-2-pentanone)	500	23550-40-5 	No Europe: 0.04 USA: 0.1	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Di(butan-3-one-1-yl) sulfide (4,4′-thiobis-2-butanone)	502	40790-04-3 	No Europe: ND USA: 0.02	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	
Structural class II						
o-(Methylthio)phenol	503	1073-29-6 	No Europe: 1 USA: 1	Yes, related substance nos 461 and 505; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern
Structural class III						
Sodium 4-(methylthio)-2-oxobutanoate	501	— 	No Europe: ND USA: 0.2	Yes, related substance no. 461; data for substance no. 452, subgroup i, are relevant to compounds with a simple oxidized side-chain	NR	No safety concern

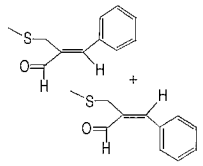
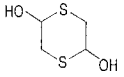
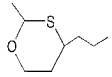
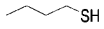
2-(Methylthiomethyl)-3-phenylpropenal (2-[(methylthio) methyl]-3-phenyl-2-propenal)	505	65887-08-3 	No Europe: ND USA: 2	Yes, a NOEL of 1.4 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
Subgroup iii — cyclic sulfides ***Structural class I***						
2,5-Dimethyl-2,5-dihydroxy-1,4-dithiane (2,5-dimethyl-1,4-dithiane-2,5-diol)	562	55704-78-4 	No Europe: 0.2 USA: 0.2	Yes, a NOEL of 3.1 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
2,5-Dihydroxy-1,4-dithiane (1,4-dithiane-2,5-diol)	550	40018-26-6 	No Europe: ND USA: 0.1	Yes, related substance no. 562	NR	
Structural class II						
2-Methyl-4-propyl-1,3-oxathiane	464	67715-80-4 	No Europe: 2 USA: 1	Yes, a NOEL of 0.44 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
4,5-Dihydro-3(2*H*)-thiophenone (dihydro-3(2*H*)-thiophenone)	498	1003-04-9 	No Europe: 1 USA: 2	Yes, a NOEL of 9.2 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
2-Methyltetrahydrothiophen-3-one (dihydro-2-methyl-3(2*H*)-thiophenone)	499	13679-85-1 	No Europe: 19 USA: 0.1	Yes, related substance no. 498	NR	
1,4-Dithiane	456	505-29-3 	No Europe: ND USA: 0.1	Yes, related substance nos 464, 534 and 543	NR	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup iii — continued						
Structural class II (continued)						
2-Methyl-1,3-dithiolane	534	5616-51-3 	No Europe: 0.1 USA: 4	Yes, a NOEL of 7 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
2,2,4,4,6,6-Hexamethyl-1,3,5-trithiane	543	828-26-2 	No Europe: 2 USA: 0.4	Yes, a NOEL of 0.21 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
Subgroup iv — simple thiols						
Structural class I						
Methyl mercaptan (methanethiol)	508	74-93-1 	No Europe: 83 USA: 0.2	Yes, related substance no. 516	NR	No safety concern
1-Propanethiol	509	107-03-9 	No Europe: 3 USA: 7	Yes, related substance no. 516	NR	
2-Propanethiol	510	75-33-2 	No Europe: ND USA: 0.004	Yes, related substance no. 516	NR	
1-Butanethiol	511	109-79-5 	No Europe: 0.5 USA: 0.04	Yes, related substance no. 516	NR	
2-Methyl-1-propanethiol	512	513-44-0 	No Europe: ND USA: 1.3	Yes, related substance no. 516	NR	

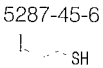
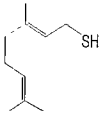
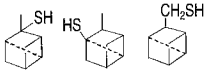
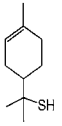
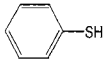
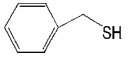
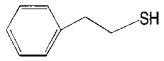
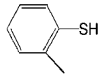
3-Methyl-1-butanethiol	513	541-31-1 	No Europe: ND USA: 0.01	Yes, related substance no. 516	NR	No safety concern
Pentane-2-thiol	514	2084-19-7 	No Europe: 2 USA: 2	Yes, related substance no. 516	NR	
2-Methyl-1-butanethiol	515	1878-18-8 	No Europe: 0.5 USA: 0.02	Yes, related substance no. 516	NR	
3-Methyl-2-butanethiol	517	2084-18-6 	No Europe: 0.02 USA: 0.02	Yes, related substance no. 516	NR	
1-Hexanethiol	518	111-31-9 	No Europe: ND USA: 0.01	Yes, related substance no. 516	NR	
2-Ethylhexane-1-thiol	519	7341-17-5 	No Europe: ND USA: 0.01	Yes, related substance no. 516	NR	
Prenylthiol (3-methyl-2-butene-1-thiol)	522	5287-45-6 	No Europe: ND USA: 0.2	Yes, related substance no. 516; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	
Thiogeraniol (3,7-dimethyl-2(*E*), 6-octadiene-1-thiol)	524	39067-80-6 	No Europe: 2 USA: 0.02	Yes, related substance no. 516; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	
Structural class II						
Cyclopentanethiol	516	1679-07-8 	No Europe: ND USA: 1	Yes, a NOEL of 0.56 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup iv — continued ***Structural class II (continued)***						
Mixture of 2-,3- and 10-mercaptopinane (mixture of 2,6,6-trimethyl-bicyclo(3.1.1) heptane-2-,3- and 10-thiols)	520	23832-18-0 	No Europe: 0.1 USA: 10	Yes, related substance nos 516, 528, 530 and 531; a NOEL of 0.06 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
Allyl mercaptan (2-propene-1-thiol)	521	870-23-5 	No Europe: 0.2 USA: 2	Yes, related substance no. 516; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	
1-*p*-Menthene-8-thiol (α,α-4-trimethyl-3-cyclohexene-1-methanethiol)	523	71159-90-5 	No Europe: 1 USA: 1	Yes, related substance no. 516; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	
Benzenethiol	525	108-98-5 	No Europe: 1 USA: 30	Yes, related substance nos 528, 530 and 531	NR	
Benzyl mercaptan (benzene-methanethiol)	526	100-53-8 	No Europe: 2 USA: 0.4	Yes, related substance nos 528, 530 and 531	NR	
Phenylethyl mercaptan (2-phenyl-ethanethiol)	527	4410-99-5 	No Europe: ND USA: 0.2	Yes, related substance nos 528, 530 and 531	NR	
o-Toluenethiol	528	137-06-4 	No Europe: 27 USA: 0.2	Yes, a NOEL of 0.52 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	

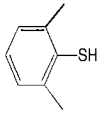
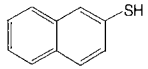
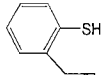
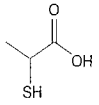
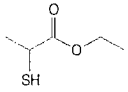
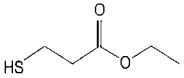
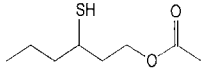
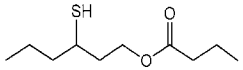
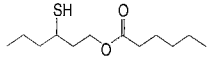
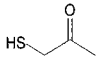
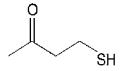
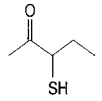
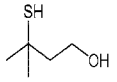
2,6-Dimethylthiophenol (2,6-dimethylbenzenethiol)	530	118-72-9 	No Europe: 2 USA: 0.02	Yes, a NOEL of 0.43 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
2-Naphthalenethiol	531	91-60-1 	No Europe: ND USA: 0.1	Yes, a NOEL of 3.4 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
Structural class III						
2-Ethylthiophenol (2-ethylbenzenethiol)	529	4500-58-7 	No Europe: 0.0002 USA: 0.1	Yes, related substance nos 528, 530 and 531	NR	No safety concern
Subgroup v — thiols with oxidized side-chains						
Structural class I						
2-Mercaptopropionic acid	551	79-42-5 	No Europe: 3 USA: 84	Yes, related substance nos 546, 547 and 560	NR	No safety concern
Ethyl 2-mercaptopropionate	552	19788-49-9 	No Europe: 0.5 USA: 0.4	Yes, related substance nos 546, 547 and 560	NR	
Ethyl 3-mercaptopropionate	553	5466-06-8 	No Europe: 0.1 USA: 43	Yes, related substance nos 546, 547 and 560	NR	
3-Mercaptohexyl acetate	554	136954-20-6 	No Europe: ND USA: 0.2	Yes, related substance nos 546, 547 and 560	NR	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup v — continued						
Structural class I (continued)						
3-Mercaptohexyl butyrate	555	136954-21-7 	No Europe: ND USA: 0.2	Yes, related substance nos 546, 547 and 560	NR	No safety concern
3-Mercaptohexyl hexanoate	556	136954-22-8 	No Europe: ND USA: 0.2	Yes, related substance nos 546, 547 and 560	NR	
1-Mercapto-2-propanone	557	24653-75-6 	No Europe: ND USA: 0.09	Yes, related substance nos 546, 547 and 560	NR	
3-Mercapto-2-butanone	558	40789-98-8 	No Europe: 5 USA: 0.04	Yes, related substance nos 546, 547 and 560	NR	
2-Keto-4-butanethiol (4-mercapto-2-butanone)	559	34619-12-0 	No Europe: ND USA: 0.1	Yes, related substance nos 546, 547 and 560	NR	
3-Mercapto-2-pentanone	560	67633-97-0 	No Europe: ND USA: 0.1	Yes, a NOEL of 1.9 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
3-Mercapto-3-methyl-1-butanol	544	34300-94-2 	No Europe: ND USA: 2	Yes, related substance nos 546, 547 and 560	NR	

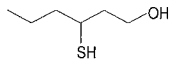
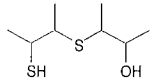
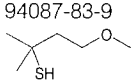
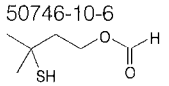
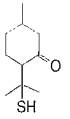
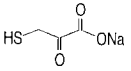
3-Mercaptohexanol	545	51755-83-0 	No Europe: ND USA: 1	Yes, related substance nos 546, 547 and 560	NR	
2-Mercapto-3-butanol ((*R*,*S*)-3-mercaptobutan-2-ol)	546	37887-04-0 	No Europe: 6 USA: 0.1	Yes, a NOEL of 1.9 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
α-Methyl-β-hydroxypropyl α-methyl-β-mercaptopropyl sulfide (3-[(2-mercapto-1-methylpropyl)thio]-2-butanol)	547	54957-02-7 	No Europe: ND USA: 1	Yes, a NOEL of 2.8 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
4-Methoxy-2-methyl-2-butanethiol	548	94087-83-9 	No Europe: ND USA: 0.8	Yes, related substance nos 546, 547 and 560	NR	
3-Mercapto-3-methylbutyl formate	549	50746-10-6 	No Europe: ND USA: 0.1	Yes, related substance nos 546, 547 and 560	NR	
Structural class II						
p-Mentha-8-thiol-3-one (2-(1-mercapto-1-methylethyl)-5-methylcyclohexanone)	561	38462-22-5 	No Europe: 16 USA: 2	Yes, related substance nos 546, 547 and 560	NR	No safety concern
Structural class III						
Sodium 3-mercapto-oxopropionate (sodium 3-mercaptopyruvate)	563	10255-67-1 	No Europe: ND USA: 0.2	Yes, related substance nos 546, 547 and 560; see related substance no. 452, subgroup i, for the sulfur moiety; the oxopropionate moiety would be predicted to be of low toxicity	NR	No safety concern

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup vi — dithiols						
Structural class I						
1,2-Ethanedithiol	532	540-63-6	No Europe: 0.002 USA: 0.9	Yes, related substance nos 539 and 541	NR	No safety concern
1,3-Propanedithiol	535	109-80-8	No Europe: 1 USA: 0.9	Yes, related substance nos 539 and 541	NR	
1,2-Propanedithiol	536	814-67-5	No Europe: ND USA: 0.9	Yes, related substance nos 539 and 541	NR	
1,2-Butanedithiol	537	16128-68-0	No Europe: ND USA: 0.2	Yes, related substance nos 539 and 541	NR	
1,3-Butanedithiol (butane-1,3-dithiol)	538	24330-52-7 	No Europe: ND USA: 0.9	Yes, related substance nos 539 and 541	NR	
2,3-Butanedithiol	539	4532-64-3	No Europe: 0.1 USA: 0.2	Yes, a NOEL of 0.7 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
1,6-Hexanedithiol (hexane-1,6-dithiol)	540	1191-43-1 	No Europe: 2.5 USA: 0.1	Yes, related substance nos 539 and 541	NR	

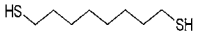
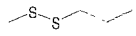
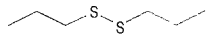
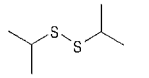
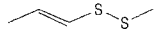
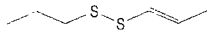
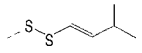
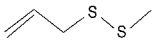
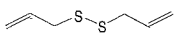
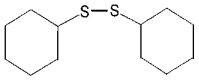
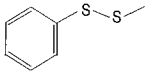
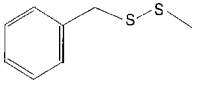
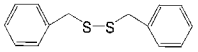
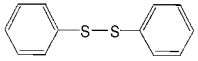
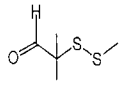
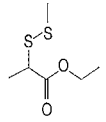
1,8-Octanedithiol (octane-1,8-dithiol)	541	1191-62-4 	No Europe: 3 USA: 0.9	Yes, a NOEL of 0.7 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
1,9-Nonanedithiol	542	3489-28-9 	No Europe: 0.002 USA: 0.9	Yes, related substance nos 539 and 541	NR	
Subgroup vii — simple disulfides ***Structural class I***						
Dimethyl disulfide	564	624-92-0 	No Europe: 11 USA: 2	Yes, related substance no. 566	NR	
Methyl propyl disulfide	565	2179-60-4 	No Europe: 6 USA: 0.02	Yes, related substance no. 566	NR	
Propyl disulfide	566	629-19-6 	No Europe: 5 USA: 0.1	Yes, a NOEL of 7.3 mg/kg of body weight per day was reported in a 90-day study in rats treated at multiple doses	NR	
Diisopropyl disulfide	567	4253-89-8 	No Europe: ND USA: 8	Yes, related substance nos 566 and 575	NR	No safety concern
Methyl 1-propenyl disulfide	569	5905-47-5 	No Europe: ND USA: 1	Yes, related substance no. 566	NR	
1-Propenyl propyl disulfide	570	5905-46-4 	No Europe: ND USA: 8	Yes, related substance no. 566	NR	
Methyl 3-methyl-1-butenyl disulfide	571	Pending 	No Europe: ND USA: 0.1	Yes, related substance no. 566	NR	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup vii — continued						
Structural class II						
Allyl methyl disulfide	568	2179-58-0 	No Europe: 0.002 USA: 0.02	Yes, related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl mercaptan	NR	
Allyl disulfide	572	2179-57-9 	No Europe: 92 USA: 8	Yes, related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl mercaptan	NR	
Dicyclohexyl disulfide	575	2550-40-5 	No Europe: 0.02 USA: 0.2	Yes, a NOEL of 0.23 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
Methyl phenyl disulfide	576	14173-25-2 	No Europe: ND USA: 0.2	Yes, related substance no. 531, subgroup iv, which is predicted to be rapidly reduced to thiophenol	NR	No safety concern
Benzyl methyl disulfide	577	699-10-5 	No Europe: 0.02 USA: 0.1	Yes, a NOEL of 1.2 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
Benzyl disulfide	579	150-60-7 	No Europe: 0.01 USA: 0.1	Yes, related substance no. 577	NR	
Structural class III						
Phenyl disulfide	578	882-33-7 	No Europe: ND USA: 0.04	Yes, related substance no. 531, subgroup iv, which is predicted to be rapidly reduced to thiophenol	NR	No safety concern

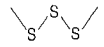
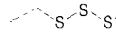
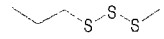
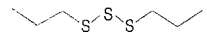
Subgroup viii — disulfides with oxidized side-chains

Structural class I

2-Methyl-2-(methyldithio)propanal	580	67952-60-7 	No Europe: ND USA: 2	Yes, related substance nos 566, 575 and 577, subgroup vii, and no. 560, subgroup v; see related substance no. 516, subgroup iv, for the thiol products of reduction	NR	No safety concern
Ethyl 2-(methyldithio)propionate	581	23747-43-5 	No Europe: ND USA: 0.1	Yes, related substance nos 566, 575 and 577, subgroup vii, and no. 560, subgroup v; see related substance no. 516, subgroup iv, for the thiol products of reduction	NR	

Subgroup ix — trisulfides and polysulfides

Structural class I

Dimethyl trisulfide	582	3658-80-8 	No Europe: 2 USA: 0.02	Yes, related substance no. 585	NR	No safety concern
Ethyl methyl trisulfide	583	31499-71-5 	No Europe: ND USA: 1	Yes, related substance no. 585	NR	
Methyl propyl trisulfide	584	17619-36-2 	No Europe: 0.3 USA: 0.1	Yes, related substance no. 585	NR	
Dipropyl trisulfide	585	6028-61-1 	No Europe: 11 USA: 1	Yes, a NOEL of 4.8 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	

Structural class II

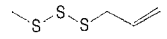
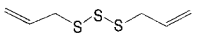
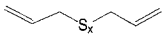
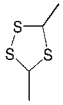
Allyl methyl trisulfide	586	34135-85-8 	No Europe: ND USA: 0.9	Yes, related substance no. 587	NR	No safety concern

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup ix — continued						
Structural class II (continued)						
Diallyl trisulfide	587	2050-87-5 	No Europe: 6 USA: 0.02	Yes, a NOEL of 4.6 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
Diallyl polysulfide	588	72869-75-1  x=2,3,4 or 5	No Europe: 2 USA: 0.02	Yes, related substance no. 587	NR	
Subgroup x — heterocyclic disulfides						
Structural class II						
3,5-Dimethyl-1,2,4-trithiolane	573	23654-92-4 	No Europe: 0.04 USA: 0.1	Yes, a NOEL of 1.9 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
3-Methyl-1,2,4-trithiane	574	43040-01-3 	No Europe: 0.1 USA: 43	Yes, related substance no. 573; a NOEL of 0.3 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	
Subgroup xi — thioesters						
Structural class I						
Methyl thioacetate	482	1534-08-3 	No Europe: ND USA: 0.002	Yes, related substance nos 483 and 484	NR	No safety concern

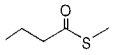
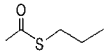
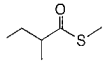
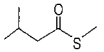
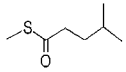
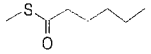
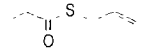
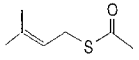
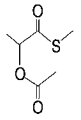
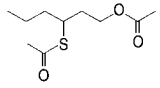
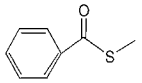
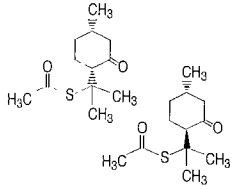
Ethyl thioacetate (*S*-ethyl ethanethioate)	483	625-60-5 	No Europe: 0.02 USA: 0.02	Yes, a NOEL of 6.5 mg/kg of body weight per day was reported in a 90-day study in rats treated at only that dose	NR	No safety concern
Methyl thiobutyrate (*S*-methyl butanethioate)	484	2432-51-1 	No Europe: 5 USA: 5	Yes, a NOEL of 1000 mg/kg of body weight per day was reported in a 90-day study in rats treated at multiple doses	NR	
Propyl thioacetate (*S*-propyl thioacetate)	485	2307-10-0 	No Europe: 0.4 USA: 0.02	Yes, related substance nos 483 and 484	NR	
S-Methyl 2-methylbutanethioate	486	42075-45-6 	No Europe: 0.2 USA: 0.1	Yes, related substance nos 483 and 484	NR	
S-Methyl 3-methylbutanethioate	487	23747-45-7 	No Europe: ND USA: 0.2	Yes, related substance nos 483 and 484	NR	
S-Methyl 4-methylpentanethioate	488	61122-71-2 	No Europe: ND USA: 0.001	Yes, related substance nos 483 and 484	NR	
S-Methyl hexanethioate	489	2432-77-1 	No Europe: ND USA: 0.1	Yes, related substance nos 483 and 484	NR	
Allyl thiopropionate (*S*-2-propenyl propanethioate)	490	41820-22-8 	No Europe: ND USA: 0.1	Yes, related substance nos 483 and 484; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	
Prenyl thioacetate	491	33049-93-3 	No Europe: ND USA: 0.2	Yes, related substance nos 483 and 484; related substance no. 587, subgroup ix, which is predicted to be metabolized to allyl disulfide and allyl mercaptan	NR	

Table 1 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step B3*[c] Does intake exceed the threshold for human intake?	*Step B4* Adequate NOEL for substance or structurally related substance?	*Step B5* Intake >1.5 µg/day?	Conclusion based on current intake
Subgroup xi — continued						
Structural class I (continued)						
Methylthio 2-(acetyloxy)propionate (1-[(methylthio)methyl]ethyl acetate)	492	74586-09-7 	No Europe: ND USA: 9	Yes, related substance nos 483 and 484	NR	No safety concern
Methylthio 2-(propionyloxy) propionate (*S*-methyl 2-(propionyloxy)propanethioate)	493	— 	No Europe: ND USA: 9	Yes, related substance nos 483 and 484	NR	
3-(Acetylmercapto)hexyl acetate	494	136954-25-1 	No Europe: ND USA: 0.4	Yes, related substance nos 483 and 484	NR	

Structural class II						
S-Methyl benzothioate (*S*-methyl thiobenzoate)	504	5925-68-8 	No Europe: ND USA: 0.001	Yes, related substance nos 483 and 484	NR	No safety concern
cis- and *trans*-Menthone-8-thioacetate (*S*-[1-methyl-1-(4-methyl-2-oxocyclohexyl)ethyl] ethanethioate)	506	94293-57-9 	No Europe: ND USA: 0.4	Yes, related substance nos 483 and 484	NR	
Subgroup xii — sulfoxides						
Structural class III						
Methylsulfinylmethane (dimethyl sulfoxide)	507	67-68-5 	No Europe: ND USA: 0.001	Yes, a NOEL of 3000 mg/kg of body weight per day was reported in a study in monkeys treated by gavage at multiple doses for 74–87 weeks; data in support of the NOEL were reported from studies in rats, dogs and humans	NR	No safety concern

CAS: Chemical Abstracts Service; ND: no intake data reported; NR: not required for evaluation because an adequate NOEL for the substance or a related substance was identified at step B4 of the Procedure.

[a] None of the substances in this group are predicted to be metabolized to innocuous products. They were placed in subgroups i–xii on the basis of the position of the sulfur atom.

[b] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 7, 1999). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.

[c] The thresholds for human intake of classes I, II and III are 1800, 540 and 90 μg per day, respectively. All intake values are expressed in μg per day.

for methyl 3-(methylthio)propionate (no. 472) in Europe and for bis(methylthio)methane (no. 533) in the USA and 0.0003–0.2 μg/kg of body weight for 3-(methylthio)propionaldehyde (no. 466), ethyl 3-(methylthio)propionate (no. 476), methyl mercaptan (methanethiol; no. 508) and allyl disulfide (no. 572) in Europe and benzenethiol (no. 525) and 3-methyl-1,2,4-trithiane (no. 574) in the USA. The intake of each substance in the group in μg per day per person in Europe and the USA is reported in Table 1.

Simple aliphatic and aromatic sulfides and thiols have been detected in a variety of foods and beverages, including onion, garlic, cabbage, tea, coffee and beer. Of the 137 substances in this group, 106 have been reported to occur naturally in foods. Quantitative data on the natural occurrence of 19 substances in the group demonstrate that they are consumed predominantly in traditional foods, with the exception of methyl 3-(methylthio)propionate (no. 472) and ethyl 3-(methylthio)propionate (no. 476).

4.1.2 *Absorption, metabolism and elimination*

The group of 137 flavouring agents considered at this meeting was divided into 12 subgroups on the basis of the position of the sulfur atom, to facilitate assessment of their metabolism and toxicity. The subgroups are:

- Subgroup i — simple sulfides (thioethers), in which the sulfur is located between two unoxidized alkyl or aryl side-chains (nos 452–455, 457–460 and 533).
- Subgroup ii — acyclic sulfides with oxidized side-chains, in which an alcohol, aldehyde, ketone, ester, carboxylic acid or phenol group is present (nos 461–463, 465–481, 495–497, 500–503 and 505).
- Subgroup iii — cyclic sulfides (nos 456, 464, 498, 499, 534, 543, 550 and 562).
- Subgroup iv — simple thiols with unoxidized aliphatic or aromatic side-chains (nos 508–531).
- Subgroup v — thiols with oxidized side-chains, in which an alcohol, aldehyde, ketone, ester or carboxylic acid group is present (nos 544–549, 551–561 and 563).
- Subgroup vi — dithiols (nos 532 and 535–542).
- Subgroup vii — simple disulfides (nos 564–572 and 575–579).
- Subgroup viii — disulfides with oxidized side-chains (nos 580 and 581).
- Subgroup ix — trisulfides and polysulfides (nos 582–588).
- Subgroup x — heterocyclic disulfides (nos 573 and 574).
- Subgroup xi — thioesters (nos 482–494, 504, 506a and 506b).
- Subgroup xii — sulfoxides (no. 507).

All of the sulfur substances considered are of low relative molecular mass and are sufficiently lipophilic to be absorbed from the intestine. These flavouring agents would be metabolized via many different pathways. As metabolism would usually result in increased polarity and a greater likelihood of excretion, these substances would not be expected to accumulate in the body. Many substances, such as thiols and disulfides, would be able to form disulfide bonds with endogenous thiols. Disulfides formed with cysteine could be excreted in the urine as the xenobiotic cysteine disulfide, whereas formation of disulfides with endogenous macromolecules would delay elimination and could result in effects such as enzyme inhibition.

Potential toxicity can be deduced by comparison with structural analogues on the basis of metabolic similarities. In the absence of information on the toxicity of structural analogues, however, it is not possible to conclude a priori that the substances are metabolized to innocuous products.

Subgroup i — simple sulfides (thioethers)

Once alkyl and aromatic thioethers, commonly called "sulfides", enter the systemic circulation, they are rapidly oxidized to sulfoxides and, depending on the structure of the sulfide, may be further oxidized to sulfones. Sulfoxides and sulfones are the major urinary metabolites of simple sulfides. Aliphatic sulfides (nos 452–455, 457, 458 and 533) and sulfides containing an aromatic ring (nos 459 and 460) yield mixtures of sulfoxide and sulfone metabolites. Enzymes of the cytochrome P450 superfamily and flavin-containing monooxygenases catalyse the oxidation of sulfides to sulfoxides. Oxidation of sulfoxides to the corresponding sulfones occurs both in tissues and in aerobic microorganisms and is an irreversible metabolic reaction in mammals. Sulfoxides may also be converted back to the corresponding sulfides by aldehyde oxidase, by thioredoxin and thioredoxin reductase, and by the anaerobic microflora in the lower bowel.

The methyl aromatic sulfides (nos 459 and 460) are predicted to be major metabolites of the corresponding aromatic thiols (nos 525 and 526, subgroup iv) and would be oxidized to sulfoxides and sulfones, which would be excreted.

Subgroup ii — acyclic sulfides with oxidized side-chains

The presence of other functional groups, such as alcohols (nos 461–463), aldehydes (nos 465–471 and 505), esters (nos 472–481), acids (no. 501), β-ketones (nos 495–497, 500 and 502) and phenols (no. 503), provides centres of greater polarity and additional sites for the biotransformation of sulfides. The presence of these polar groups

would also result in increased renal excretion. The biotransformation of oxygenated, carbon-containing, functional groups is well characterized and has been described for groups of flavouring agents previously evaluated by the Committee. Concurrent metabolism of various substrates at both sulfur and oxygenated functional groups has been reported, and sulfoxide formation usually predominates as the major metabolic pathway of detoxification. Experiments in vitro suggest that hydrolysis of carboxyl esters occurs in the presence of thioether (sulfide) groups. In consequence, sulfides with oxidized side-chains would be expected to be eliminated more rapidly than simple sulfides.

Subgroup iii — cyclic sulfides

Oxidation of unsubstituted and methyl-substituted cyclic sulfides by the cytochrome P450 superfamily produces the corresponding sulfoxides. The mono-sulfoxides are predicted to be the main urinary metabolites of simple cyclic sulfides (nos 456, 534 and 543). The metabolism of cyclic sulfides containing oxidized carbon atoms (nos 464, 498, 499, 550 and 562) has not been studied but would be predicted to involve extensive *S*-oxidation and possibly oxidation or conjugation of alcohol groups. The polarity of the hydroxy thioethers (nos 550 and 562) may allow their elimination unchanged.

Subgroup iv — simple thiols

The simple thiol flavouring agents considered were alkyl and alicyclic thiols (nos 508–524, 526 and 527) and aromatic thiols (thiophenols; nos 525 and 528–531). These substances can be metabolized via several pathways. Simple aliphatic and aromatic thiols undergo *S*-methylation in mammals to produce the corresponding methyl thioether or sulfide. *S*-Methylation is catalysed by thiopurine *S*-methyltransferase in the cytosol and thiol *S*-methyltransferase in microsomes; both reactions require *S*-adenosyl-L-methionine as a methyl group donor. Thiopurine *S*-methyltransferase is present in human liver, kidney and erythrocytes, and its preferred substrates include aromatic and heterocyclic thiols. *S*-Methylation of aliphatic thiols is catalysed by microsomal thiol *S*-methyltransferase, and the resulting methyl thioether (sulfide) metabolite undergoes *S*-oxidation to give the corresponding methyl sulfoxide and methyl sulfone analogues, which are excreted in the urine.

Thiols may react with glutathione and other endogenous thiol substances to form mixed disulfides. Both microsomal and cytosolic thioltransferases have been reported to catalyse the formation of mixed disulfides. The resulting mixed disulfides can undergo

reduction back to thiols, oxidative desulfuration or oxidation to the corresponding sulfonic acid via the intermediate thiosulfinate and sulfinic acid. The principal form in the circulation would probably be a mixed disulfide formed with albumin.

S-Glucuronidation of aromatic thiols has been reported, and this may be a pathway for the metabolism of aromatic thiols (thiophenols; nos 525 and 528–531) and simple aromatic disulfides (nos 576 and 578; subgroup vii) after their reduction (see below). Glucuronyl transferases behave similarly towards hydroxyl and sulfhydryl functional groups, and the two activities have the same subcellular location and optimal pH.

Thiols may be oxidized to form sulfenic acids (RSOH), which are unstable and readily undergo further oxidation to sulfinic (RSO_2H) and sulfonic (RSO_3H) acids or combine with nucleophiles. The sulfonic acid group is highly polar and renders molecules very soluble in water. In general, sulfonic acids are not extensively metabolized.

Alkyl thiols of low relative molecular mass undergo oxidative desulfuration in vivo to yield carbon dioxide and sulfate. This reaction has been shown to occur, for example, with methyl mercaptan (no. 508). Whereas the carbon atoms from thiols may be used in the biosynthesis of amino acids, the sulfur atoms are not used significantly in the synthesis of sulfur-containing amino acids.

Subgroup v — thiols with oxidized side-chains

Although alkyl thiols with oxidized side-chains (nos 544–549, 551–561 and 563) comprise a significant proportion of the flavouring agents evaluated, their metabolic fate has not been studied. Their metabolism is predicted to involve a combination of the pathways described above for simple thiols and further oxidation or conjugation of the oxidized side-chain. The compound that is in structural class III, sodium 3-mercapto-oxopropionate (sodium 3-mercaptopyruvate; no. 563), would be expected to be eliminated very rapidly after metabolism at both the thiol and keto-acid groups.

Subgroup vi — dithiols

The metabolism of the simple aliphatic dithiols (nos 532 and 535–542) is predicted to involve the pathways described above for simple thiols. Urinary metabolites could result from *S*-methylation, *S*-oxidation of one sulfur atom to yield a polar sulfonate or the formation of mixed disulfides of low relative molecular mass such as cysteine, an endogenous thiol. The longer, linear dithiols (nos 540–542) could form intramolecular disulfide bonds, with interconversion between the dithiol and cyclic disulfide forms.

Subgroup vii — simple disulfides

The reduction of xenobiotic disulfides is believed to be extensive, and the reaction may be catalysed enzymatically by thioltransferases and chemically by exchange with glutathione, thioredoxin, cysteine and other endogenous thiols. Reduction of the non-cyclic disulfides considered in the group (nos 564–572 and 575–579) would result in the formation of thiols of low relative molecular mass, which would then be metabolized by the various pathways described above for simple thiols.

Subgroup viii — disulfides with oxidized side-chains

As discussed above for acyclic sulfides with oxidized side-chains and cyclic sulfides (subgroups ii and iii), the presence of additional sites of carbon oxidation would result in greater polarity and further oxidation or conjugation of the flavouring agents evaluated (nos 580 and 581). By analogy to thiols with oxidized side-chains (subgroup v), the oxidized side-chains in this group are susceptible to reductive cleavage, which would be expected to be the initial metabolic reaction. The polarity of the side-chains would primarily affect elimination of the thiol fragments.

Subgroup ix — trisulfides and polysulfides

The trisulfide of glutathione is labile and readily converted to the disulfide, the sulfur being released as hydrogen sulfide. The trisulfides and polysulfide in this subgroup (nos 582–587 and no. 588) are predicted to be converted rapidly to the corresponding disulfides and reduced to thiols, which would then be metabolized via the pathways described above for simple thiols. The potential toxicity of trisulfides and polysulfides is probably related to their metabolic lability and to the nature of the resultant thiol (e.g. allyl thiol).

Subgroup x — heterocyclic disulfides

The heterocyclic disulfides (nos 573 and 574) are five- and six-carbon rings which also contain a cyclic thioether bond. A related substance, lipoic acid, which is endogenous, undergoes rapid redox cycling between the ring disulfide and open dithiol forms. On the basis of the known metabolism of lipoic acid, the principal metabolic pathways of the substances in this group are predicted to be reduction of the disulfide with opening of the ring to produce a dithiol, and *S*-oxidation of the cyclic thioether.

Subgroup xi — thioesters

Thioester groups (—S—CO—) are present in a number of the flavouring agents in this subgroup (nos 482–494, 504 and 506). The hydrolysis of esters has been considered previously by the Committee, but not that of thioesters. Thioesters are hydrolysed by lipase and

esterases, and the rate of hydrolysis increases with increasing length of the carbon chain of the carboxylic acid fragment and decreases with increasing oxygenation of the carbon chain in the thiol moiety.

The thioesters in this subgroup are predicted to be hydrolysed to the corresponding thioic acid and alcohol, or the corresponding carboxylic acid and thiol (the metabolic fates of which are outlined above). Data on dithioic acids and esters indicate that the esters of monothioic acids would be poor substrates for oxidation, but the monothioic acid released by hydrolysis would be oxidized to the corresponding dioxo acid. Other possibilities for elimination in vivo include urinary excretion of thiocarboxylic acid. The substances evaluated (with the exceptions of prenyl thioacetate (no. 491) and allyl thiopropionate (*S*-2-propenyl propanethioate; no. 490)) are simple linear alkyl compounds, branched-chain alkyl compounds or their side-chain hydroxyester analogues, so that their toxicity can reasonably be compared.

Subgroup xii — sulfoxides

The sulfoxides are predicted to be metabolized via the same pathways as thioethers (subgroup i). The only sulfoxide flavouring agent evaluated was methylsulfinylmethane (dimethyl sulfoxide; no. 507), since data were available on both its metabolism and its toxicity in experimental animals and humans. Methylsulfinylmethane is readily absorbed and excreted in urine as the parent sulfoxide and dimethyl sulfone.

4.1.3 *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 aliphatic and aromatic sulfides and thiols, the Committee assigned 97 of the 137 substances (nos 452–455, 457, 461–463, 465–497, 500, 502, 508–515, 517–519, 522, 524, 532, 533, 535–542, 544–560, 562, 564–567, 569–571 and 580–585) to structural class I. These substances are simple aliphatic thiols and sulfides, which may or may not contain an additional oxygenated functional group, and have the lowest toxic potential. The Committee assigned 34 of the 137 substances to structural class II because they are aromatic sulfides or thiols (nos 459, 460, 503, 504, 525–528, 530, 531, 576, 577 and 579), alicyclic substances (nos 506, 516, 520, 523, 561 and 575), heterocyclic substances (nos 456, 464, 498, 499, 534, 543, 573 and 574) or allyl mercaptan (2-propene-1-thiol) or sulfides (nos 458, 521, 568, 572 and 586–588), which are common components of food. The Committee assigned aromatic thiols or sulfides that are not common components

of food (nos 505, 529 and 578) to structural class III. The remaining three substances were also assigned to structural class III by virtue of the fact that they are aliphatic thiols or sulfides containing more than three functional groups (nos 501 and 563) or do not contain divalent sulfur (no. 507).

Step 2

None of the 137 substances in this group can be predicted to be metabolized to innocuous products. The evaluation of these substances therefore proceeded via the right-hand side of the decision tree (Fig. 1).

Step B3

The estimated daily per capita intakes of the substances in this group for which data were available were below the thresholds for the structural classes to which they were assigned (1800μg for class I, 540μg for class II and 90μg for class III).

Step B4

The Committee considered the results of toxicity studies of at least 90 days' duration in rodents or monkeys for 27 substances in this group of flavouring agents (nos 452, 464, 483, 484, 498, 505, 507, 516, 520, 528, 530, 531, 534, 539, 541, 543, 546, 547, 560, 562, 566, 573–575, 577, 585 and 587).

The Committee noted that the single or multiple doses of the flavouring agents tested in a number of such studies had no effect in rats and that the NOELs were consequently derived from the results of studies that did not show toxic effects. The results of long-term studies in rats, dogs and monkeys were considered for one substance, methylsulfinylmethane (no. 507). To facilitate comparisons of the toxicity of structurally related substances, the flavouring agents were considered in 12 subgroups, as defined above (see Tables 1 and 2). Toxicity was compared within and across subgroups, with no restriction on the basis of structural class assignment.

Subgroup i — simple sulfides (thioethers). This subgroup comprises nine simple thioethers. The NOEL for methyl sulfide (no. 452) in a 14-week study in rats treated with multiple doses by gavage was 250mg/kg of body weight per day. This NOEL provided an adequate basis for evaluating the toxicity of five structurally and metabolically related substances (nos 453–455, 457 and 533). However, the Committee considered it inappropriate for the evaluation of allyl sulfide (no. 458) and two aromatic sulfides, methyl phenyl sulfide (no. 459) and benzyl methyl sulfide (no. 460). The evaluation of these three substances therefore proceeded to step B5.

Table 2
Comparison of the toxicity and intake data used in the safety evaluation of 137 aliphatic and aromatic sulfides and thiols, by subgroup[a]

Subgroup	Adequate NOEL for substance[b]	Adequate NOEL for structurally related substance[b]	No adequate NOEL for substance or related substance, but intake <1.5 µg/day[c]
(i) Simple sulfides (thioethers)	no. 452	nos 453–455, 457, 533	nos 458–460
(ii) Acyclic sulfides with oxidized side-chains	no. 505	nos 461–463, 465–469, 472–481, 495–497, 500–503	nos 470, 471
(iii) Cyclic sulfides	nos 464, 498, 534, 543, 562	nos 456, 499, 550	—
(iv) Thiols	nos 516, 520, 528, 530, 531	nos 508–515, 517–519, 521–527, 529	—
(v) Thiols with oxidized side-chains	nos 546, 547, 560	nos 544, 545, 548, 549, 551–559, 561, 563	—
(vi) Dithiols	nos 539, 541	nos 532, 535–538, 540, 542	—
(vii) Simple disulfides	nos 566, 575, 577	nos 564, 565, 567–572, 576, 578, 579	—
(viii) Disulfides with oxidized side-chains	—	nos 580, 581	—
(ix) Trisulfides and polysulfides	nos 585, 587	nos 582–584, 586, 588	—
(x) Heterocyclic disulfides	no. 573	no. 574	—
(xi) Thioesters	nos 483, 484	nos 482, 485–494, 504, 506	—
(xii) Sulfoxides	no. 507	—	—

[a] See Table 1 for further details of the evaluations.
[b] See Fig. 1, step B4 and pages 60–65 for further information.
[c] See Fig. 1, step B5 and page 65 for further information.

Subgroup ii — acyclic sulfides with oxidized side-chains. This subgroup comprises 28 acyclic thioethers with oxidized side-chains. The NOEL for 2-(methylthiomethyl)-3-phenylpropenal (2-[(methylthio)methyl]-3-phenyl-2-propenal; no. 505) in a 90-day study in rats treated with a single dose was 1.4 mg/kg of body weight per day.

This substance is an aromatic compound with a sulfide group in an unsaturated side-chain; it was assigned to structural class III because it is not a common component of food.

Data for methyl sulfide (no. 452; subgroup i) were also considered relevant for assessing the toxicity of compounds with simple side-chains (e.g. nos 461–463, 465–469, 472–481, 495–497 and 500–503).

Although 2-(methylthiomethyl)-3-phenylpropenal (no. 505) is not an aryl thioether, the safety margin between its NOEL and the intake of *o*-(methylthio)phenol (no. 503) was considered to be adequate. The NOEL for 2-(methylthiomethyl)-3-phenylpropenal (no. 505) did not provide an adequate margin of safety for methyl 3-(methylthio)propionate (no. 472) at the current estimated level of intake, but the simple side-chain acid and ester were predicted to be of low toxicity and the NOEL for methyl sulfide (no. 452; subgroup i) was considered to provide an adequate safety margin. The NOELs for 2-(methylthiomethyl)-3-phenylpropenal (no. 505) and methyl sulfide (no. 452; subgroup i) were considered inappropriate for evaluating the toxicity of two α, β-unsaturated carbonyls (nos 470 and 471) because the latter substances are potentially more reactive and toxic. The evaluation of the two α, β-unsaturated carbonyls (nos 470 and 471) therefore proceeded to step B5.

Subgroup iii — cyclic sulfides. This subgroup comprises eight cyclic thioethers. NOELs of 0.44 mg/kg of body weight per day for 2-methyl-4-propyl-1,3-oxathiane (no. 464), 9.2 mg/kg of body weight per day for 4,5-dihydro-3(2*H*)-thiophenone (dihydro-3(2*H*)-thiophenone; no. 498), 7 mg/kg of body weight per day for 2-methyl-1,3-dithiolane (no. 534), 0.21 mg/kg of body weight per day for 2,2,4,4,6,6-hexamethyl-1,3,5-trithiane (no. 543) and 3.1 mg/kg of body weight per day for 2,5-dimethyl-2,5-dihydroxy-1,4-dithiane (2,5-dimethyl-1,4-dithiane-2,5-diol; no. 562) were reported. These values were considered to provide an adequate margin of safety for evaluating the toxicity of substance nos 456, 499 and 550.

Subgroup iv — simple thiols. This subgroup comprises 24 simple thiols. NOELs of 0.56 mg/kg of body weight per day for cyclopentanethiol (no. 516), 0.06 mg/kg of body weight per day for a mixture of 2-, 3- and 10-mercaptopinane (mixture of 2,6,6-trimethylbicyclo(3.1.1)heptane-2-, 3- and 10-thiols; no. 520), 0.52 mg/kg of body weight per day for *o*-toluenethiol (no. 528), 0.43 mg/kg of body weight per day for 2,6-dimethylthiophenol (2,6-dimethylbenzenethiol; no. 530) and 3.4 mg/kg of body weight per day for 2-naphthalenethiol (no. 531) were reported. These values were considered to provide an adequate margin of safety for the individual substances and for the other structurally related thiols in subgroup iv (nos 508–515, 517–519,

521–527, 529) in relation to current estimates of intake, with the exception of the mixture of 2-, 3- and 10-mercaptopinane (no. 520). A margin of safety of about 300 (based on an estimated per capita intake of 0.2μg/kg of body weight per day in the USA) was obtained from the results of a 90-day study in which a single dose of 0.06mg/kg of body weight per day was tested. This substance was therefore also evaluated by comparison with other substances in this subgroup (nos 516, 528, 530 and 531), for which there was an adequate margin of safety. The Committee noted that nos 521–524 are unsaturated thiols. Of these, allyl mercaptan (no. 521) would be predicted to be more toxic than thiols that have double bonds in different positions (by analogy with their oxygenated analogues). Although no data were available on the toxicity of allyl mercaptan (no. 521), the NOEL for diallyl trisulfide (no. 587; subgroup ix), which would be converted to allyl mercaptan after reduction to allyl disulfide, was 4.6mg/kg of body weight per day in a 90-day study in rats. This NOEL was considered to provide an adequate margin of safety for substance nos 521–524.

Subgroup v — thiols with oxidized side-chains. This subgroup comprises 18 thiols with oxygenated side-chains. NOELs of 1.9mg/kg of body weight per day for 2-mercapto-3-butanol ((*R*,*S*)-3-mercaptobutan-2-ol; no. 546) and 3-mercapto-2-pentanone (no. 560), and 2.8mg/kg of body weight per day for α-methyl-β-hydroxypropyl α-methyl-β-mercaptopropyl sulfide (3-[(2-mercapto-1-methylpropyl)thio]-2-butanol; no. 547) were reported. These levels were considered to provide an adequate margin of safety for the other flavouring agents in this subgroup (nos 544, 545, 548, 549, 551–559, 561, 563), including the one substance in structural class III, sodium 3-mercapto-oxopropionate (no. 563). Although the latter compound has more than three functional groups, the oxopropionate moiety would have little toxic potential, and the NOELs for substance nos 546, 547 and 560 were considered to provide an adequate margin of safety.

Subgroup vi — dithiols. This subgroup comprises nine dithiols. The NOEL for both 2,3-butanedithiol (no. 539) and 1,8-octanedithiol (octane-1,8-dithiol; no. 541) was 0.7mg/kg of body weight per day, which was considered to provide an adequate margin of safety for the other substances in the subgroup (nos 532, 535–538, 540, 542).

Subgroup vii — simple disulfides. This subgroup comprises 14 disulfides. The major metabolites of the unsaturated disulfides in this subgroup would be thiols. The NOELs were 7.3mg/kg of body weight per day for propyl disulfide (no. 566), 0.23mg/kg of body weight per day for dicyclohexyl disulfide (no. 575) and 1.2mg/kg of body weight per day for benzyl methyl disulfide (no. 577). These values provide an adequate margin of safety for these substances as well as for seven

structurally related substances (nos 564, 565, 567, 569–571 and 579) at currently estimated levels of intake. NOELs were not available for the unsaturated or aryl disulfides in this subgroup, but the aryl disulfides, methyl phenyl disulfide (no. 576) and phenyl disulfide (no. 578), would be rapidly reduced to thiophenol, and the NOEL of 3.4 mg/kg of body weight per day for 2-naphthalenethiol (no. 531; subgroup iv) was considered to provide an adequate margin of safety for these agents.

The Committee was aware that propenyl disulfides can cause haemolytic anaemia in certain species after short-term exposure. This effect would be of concern to susceptible individuals. Substance nos 568 and 572 would be metabolized to allyl mercaptan (no. 521; subgroup iv). The Committee noted that the NOEL for diallyl trisulfide (no. 587; subgroup ix) in a 90-day study in rats given a single dose was 4.6 mg/kg of body weight per day, and considered that this would provide an adequate margin of safety for the allyl thiol produced on reduction of substance nos 568 and 572. A closely related substance, di(1-propenyl) disulfide, was about four times as potent as allyl disulfide (no. 572) and about 20 times as potent as propyl disulfide (no. 566). The intakes of the related propenyl and butenyl disulfides (nos 569–571) gave safety margins of greater than 50000 in comparison with the NOEL for propyl disulfide (no. 566), and this was considered to be adequate to allow for the differences in potency.

Subgroup viii — disulfides with oxidized side-chains. This subgroup consists of two disulfides with oxidized side-chains, 2-methyl-2-(methyldithio)propanal (no. 580) and ethyl 2-(methyldithio)propionate (no. 581). Since the toxicity of these agents has not been studied, the Committee compared these substances with the simple disulfides (subgroup vii) and concluded that adequate margins of safety were available, given their greater polarity and the presence of thiols with and without oxidized side-chains, i.e. subgroups iv and v.

Subgroup ix — trisulfides and polysulfides. This subgroup consists of six trisulfides and one polysulfide. NOELs of 4.8 mg/kg of body weight per day for dipropyl trisulfide (no. 585) and 4.6 mg/kg of body weight per day for diallyl trisulfide (no. 587) were reported, which gave an adequate margin of safety for these and the other substances in this subgroup (nos 582–584, 586 and 588).

Subgroup x — heterocyclic disulfides. This subgroup comprises two heterocyclic disulfides. The NOEL of 1.9 mg/kg of body weight per day for 3,5-dimethyl-1,2,4-trithiolane (no. 573) provides an adequate margin of safety for this substance at current levels of use. 3-Methyl-1,2,4-trithiane (no. 574) was reported to have no effect at the single dose of 0.3 mg/kg of body weight per day in a 90-day study. This dose provides

a margin of safety of only 100 in relation to the estimated per capita intake level of 1 μg/kg of body weight per day in the USA, but the NOEL for the closely related compound 3,5-dimethyl-1,2,4-trithiolane (no. 573) provides a margin of safety greater than 1000.

Subgroup xi — thioesters. This subgroup consists of 15 thioesters. The NOELs of 6.5 mg/kg of body weight per day for ethyl thioacetate (*S*-ethyl ethanethioate; no. 483) and 1000 mg/kg of body weight per day for methyl thiobutyrate (*S*-methyl butanethioate; no. 484) were considered to provide an adequate margin of safety for all other esters in this group. The Committee concluded that the current intake levels of allyl thiopropionate (*S*-2-propenyl propanethioate; no. 490) and prenyl thioacetate (no. 491) are safe on the basis of the NOEL of 4.6 mg/kg of body weight per day for diallyl trisulfide (no. 587; subgroup ix), which is predicted to be metabolized initially to allyl disulfide and then to allyl mercaptan.

Subgroup xii — sulfoxides. This subgroup consists of only one sulfoxide, methylsulfinylmethane (no. 507). The NOEL in monkeys given methylsulfinylmethane by gavage for 74–87 weeks was 3000 mg/kg of body weight per day. The Committee concluded that this NOEL and other data from studies in rats, dogs and humans provide an adequate margin of safety for the use of methylsulfinylmethane as a flavouring agent at the estimated daily per capita intake of 0.00001 μg/kg of body weight per day in the USA.

Step B5

Five substances, allyl sulfide (no. 458), methyl phenyl sulfide (no. 459), benzyl methyl sulfide (no. 460), 2-[(methylthio)methyl]-2-butenal (no. 470) and 2,8-dithianon-4-ene-4-carboxaldehyde (5-methylthio-2[(methylthio)methyl]-2-pentenal; no. 471), were evaluated at this step of the Procedure. The daily per capita intake of all five substances is less than 1.5 μg per day in both Europe and the USA. The Committee applied the criteria for step B5 outlined in Annex 5 of the safety evaluation of its forty-ninth meeting (Annex 1, reference *132*) and concluded that use of these substances at their current levels of intake raises no concern about safety.

Summary

In summary, for 100 agents in subgroups iii–xii, a NOEL was available for the substance, a closely related substance or a predicted major metabolite which provided an adequate margin of safety (>1000). For six of nine agents in subgroup i and 26 of 28 agents in subgroup ii, a NOEL was available for the substance or a closely related substance that provided a margin of safety >1000. Therefore, the Committee determined at step B4 of the Procedure that the safety of these 132

substances would not be expected to be a concern when they were used at their current estimated levels of daily intake. The evaluation of the remaining five substances (nos 458–460 in subgroup i and nos 470 and 471 in subgroup ii) proceeded to step B5 of the Procedure. The Committee concluded that use of these substances at their current levels of intake raises no concern about safety. The comparisons of toxicity and the data on intake for each subgroup which were used to apply steps B4 and B5 of the Procedure to the evaluation of individual substances in this group of flavouring agents are summarized in Tables 1 and 2.

4.1.4 *Consideration of combined intakes*

In the unlikely event that foods containing all 97 aliphatic and aromatic sulfides and thiols in structural class I were to be consumed simultaneously on a daily basis, the estimated total daily per capita intake would not exceed the threshold for human intake for substances in class I (1800μg). In the unlikely event that foods containing all 34 aliphatic and aromatic sulfides in structural class II and all six aliphatic and aromatic sulfides in structural class III were to be consumed simultaneously on a daily basis, the estimated total daily per capita intake would not exceed the threshold for human intake for flavouring agents in classes II and III (540μg and 90μg, respectively). The Committee noted that the powerful aroma of these substances limits the level of their use in foods.

4.1.5 *Conclusions*

The Committee concluded that the 137 flavouring agents comprising aliphatic and aromatic sulfides and thiols evaluated at the present meeting could not be predicted to be metabolized to innocuous products. According to the Procedure, data on toxicity were needed to evaluate the safety of this group of flavouring agents. The primary data that were used in the evaluations consisted of 27 short-term studies (lasting at least 90 days) in rats or monkeys for 25 of the substances and a short-term study in dogs and a long-term study in rats for one substance (no. 507, methylsulfinylmethane). Most of these studies were conducted using single or multiple doses which had no effects. The NOELs were therefore derived from studies in which no toxic effects were seen.

On the basis of the available toxicity data on representative substances in each subgroup and on their metabolism, the Committee concluded that 132 of the flavouring agents are of no safety concern when used at their current levels of estimated intake. The remaining five substances were considered to be of no safety concern at intake levels of < 1.5μg per day.

Other toxicity data, including the results of short-term toxicity tests and developmental toxicity and genotoxicity studies, were consistent with the results of the evaluation conducted using the Procedure. A monograph summarizing the safety data on this group of flavouring agents was prepared.

4.2 Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups

The Committee evaluated a group of 47 flavouring agents that included aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (Table 3) using the Procedure for the Safety Evaluation of Flavouring Agents (see Fig. 1).

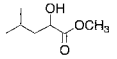
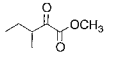
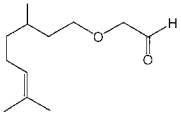
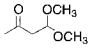
Eight of these substances (nos 589, 591, 603 and 631–635) are α-keto acids, esters or related substances; five (nos 590 and 619–622) are α-hydroxy acids, esters or related substances; 14 (nos 592–602, 604, 614 and 615) are β-keto or β-hydroxy alcohols, aldehydes, carboxylic acids or their related acetals or esters; five (nos 605–609) are γ-keto acids, esters or related substances; four (nos 610–613) are ω-substituted alcohols, aldehydes or acetals; and 18 (nos 614–631) are simple, aliphatic di- or tricarboxylic acids or their esters.

The Committee had evaluated three members of this group previously for other functional uses. Fumaric acid ((2*E*)-2-butenedioic acid; no. 618) was first considered by the Committee at its tenth meeting (Annex 1, reference *13*); at its thirty-fifth meeting (Annex 1, reference *88*), the Committee established a group ADI "not specified"[1] for fumaric acid and its salts. Triethyl citrate (triethyl 2-hydroxy-1,2,3-propanetricarboxylate; no. 629) was first considered by the Committee at its twenty-third meeting (Annex 1, reference *50*); at its twenty-eighth meeting (Annex 1, reference *66*), the Committee established an ADI of 0–20 mg/kg of body weight. Diethyl tartrate (diethyl 2,3-dihydroxybutanedioate; no. 622) was first considered by the Committee at its twenty-third meeting (Annex 1, reference *50*), when it determined that an evaluation was not possible on the basis of the data available at that time. As no additional data were available to the Committee at its twenty-fifth meeting (Annex 1, reference *56*), no ADI was allocated. The Committee also evaluated terpenoid flavouring agents related to this group, including linalool, linalyl acetate, citronellol, citral and geranyl acetate, at its twenty-third meeting and established a group ADI of 0–0.5 mg/kg of body weight, expressed as citral (Annex 1, reference *50*).

[1] See page 22.

Table 3

Summary of the results of the safety evaluation of 47 aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups[a]

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
2-Oxobutyric acid (2-oxobutanoic acid)	589	600-18-0 	No Europe: 0.03 USA: 2	NR	NR	No safety concern
Methyl 2-hydroxy-4-methyl-pentanoate (methyl 2-hydroxy-4-methylvalerate)	590	40348-72-9 	No Europe: ND USA: 0.8	NR	NR	
Methyl 2-oxo-3-methyl-pentanoate (methyl 3-methyl-2-oxo-pentanoate)	591	3682-42-6 	No Europe: ND USA: 19	NR	NR	
Citronelloxyacetaldehyde ([(3,7-dimethyl-6-octenyl) oxy]-acetaldehyde)	592	7492-67-3 	No Europe: 34 USA: 0.1	NR	NR	
3-Oxobutanal dimethyl acetal (4,4-dimethoxy-2-butanone)	593	5436-21-5 	No Europe: 0.01 USA: 0.1	NR	NR	
Ethyl 3-hydroxybutyrate	594	5405-41-4 	No Europe: 12 USA: 29	NR	NR	

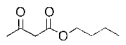
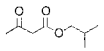
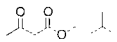
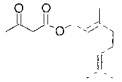
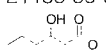
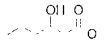
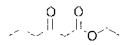
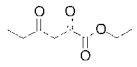
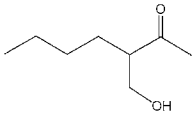
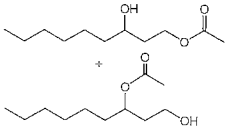
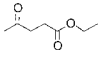
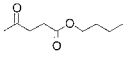
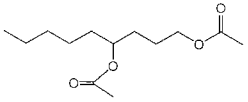
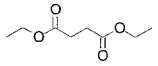
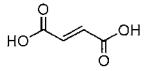
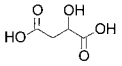
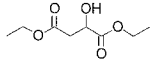
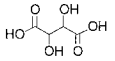
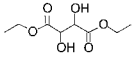
Ethyl acetoacetate	595	141-97-9 	Yes Europe: 1900 USA: 3900	Yes[d]	NR	No safety concern
Butyl acetoacetate	596	591-60-6 	No Europe: 98 USA: 6	NR	NR	
Isobutyl acetoacetate	597	7779-75-1 	No Europe: ND USA: 4	NR	NR	
Isoamyl acetoacetate (isopentyl acetoacetate)	598	2308-18-1 	No Europe: ND USA: 11	NR	NR	
Geranyl acetoacetate (3,7-dimethyl-2,6-octadienyl acetoacetate)	599	10032-00-5 	No Europe: ND USA: 0.04	NR	NR	
Methyl 3-hydroxyhexanoate	600	21188-58-9 	No Europe: 1 USA: 1	NR	NR	
Ethyl 3-hydroxyhexanoate	601	2305-25-1 	No Europe: 93 USA: 0.1	NR	NR	
Ethyl 3-oxohexanoate	602	3249-68-1 	No Europe: 0.04 USA: 1	NR	NR	
Ethyl 2,4-dioxohexanoate	603	13246-52-1 	No Europe: ND USA: 0.02	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
3-(Hydroxymethyl)-2-heptanone	604	65405-68-7 	No Europe: 38 USA: 8	NR	NR	No safety concern
1,3-Nonanediol acetate (mixed esters) (1,3-nonanediol monoacetate)	605	1322-17-4 	No Europe: 15 USA: 8	NR	NR	
Levulinic acid (4-oxopentanoic acid)	606	123-76-2 	No Europe: 1600 USA: 1200	NR	NR	
Ethyl levulinate (ethyl 4-oxopentanoate)	607	539-88-8 	No Europe: 740 USA: 84	NR	NR	
Butyl levulinate (butyl 4-oxopentanoate)	608	2052-15-5 	No Europe: ND USA: 3	NR	NR	
1,4-Nonanediol diacetate	609	67715-81-5 	No Europe: 0.06 USA: 0.4	NR	NR	

Hydroxycitronellol (3,7-dimethyloctane-1,7-diol)	610	107-74-4 	No Europe: 11 USA: 6	NR	NR	No safety concern
Hydroxycitronellal (7-hydroxy-3,7-dimethyloctanal)	611	107-75-5 	No Europe: 28 USA: 30	NR	NR	
Hydroxycitronellal dimethyl acetal (8,8-dimethoxy-2,6-dimethyl-2-octanol)	612	141-92-4 	No Europe: 0.04 USA: 0.8	NR	NR	
Hydroxycitronellal diethyl acetal (8,8-diethoxy-2,6-dimethyloctan-2-ol)	613	7779-94-4 	No Europe: 0.01 USA: 2	NR	NR	
Diethyl malonate (diethyl propanedioate)	614	105-53-3 	No Europe: 760 USA: 370	NR	NR	
Butyl ethyl malonate (butyl ethyl propanedioate)	615	17373-84-1 	No Europe: ND USA: 0.1	NR	NR	
Dimethyl succinate (dimethyl butanedioate)	616	106-65-0 	No Europe: 78 USA: 120	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
Diethyl succinate (diethyl butanedioate)	617	123-25-1 	No Europe: 150 USA: 180	NR	NR	No safety concern
Fumaric acid[e] ((2*E*)-2-butenedioic acid)	618	110-17-8 	Yes Europe: 920 USA: 220000	Yes[f]	NR	
(–)-Malic acid ((2*S*)-hydroxybutanedioic acid)	619	97-67-6 	Yes Europe: 16000 USA: 58000	Yes[e]	NR	
Diethyl malate (diethyl hydroxybutanedioate)	620	7554-12-3 	No Europe: 5 USA: 34	NR	NR	
Mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (mixture of (+)-, (–)-, (+/–)- and meso-2,3-dihydroxybutanedioic acid)	621	87-69-4 	Yes Europe: 4400 USA: 14000	No	Yes; the NOEL of 1200 mg/kg of body weight per day reported in a 2-year study in rats is >1000 times the daily per capita intake	
Diethyl tartrate (diethyl 2,3-dihydroxybutanedioate)	622	87-91-2 	No Europe: 17 USA: 0.02	NR	NR	

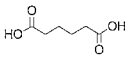
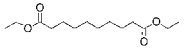
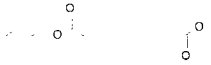
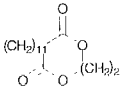
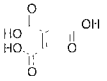
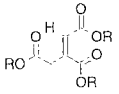
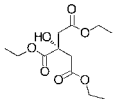
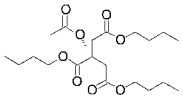
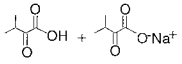
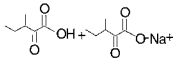
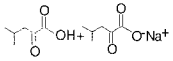
Adipic acid (hexanedioic acid)	623	124-04-9 	Yes Europe: 12 USA: 18000	No	Yes; the NOEL of 6200 mg/kg of body weight per day reported for the structurally related substance, dibutyl sebacate, in a 2-year study in rats is >10000 times the daily per capita intake	No safety concern
Diethyl sebacate (diethyl decanedioate)	624	110-40-7 	No Europe: 135 USA: 76	NR	NR	
Dibutyl sebacate (dibutyl decanedioate)	625	109-43-3 	No Europe: ND USA: 0.08	NR	NR	
Ethylene brassylate (1,4-dioxacycloheptadecane-5,17-dione)	626	105-95-3 	No Europe: 4 USA: 0.8	NR	NR	
Aconitic acid (1-propene-1,2,3-tricarboxylic acid)	627	499-12-7 	No Europe: 0.01 USA: 0.02	NR	NR	
Ethyl aconitate (mixed esters) (ethyl 1-propene-1,2,3-tricarboxylate)	628	1321-30-8  R = C_2H_5	No Europe: ND USA: 4	NR	NR	

Table 3 (*continued*)

Substance[b]	No.	CAS no. and structure	*Step A3*[c] Does intake exceed the threshold for human intake?	*Step A4* Is the substance or are its metabolites endogenous?	*Step A5* Adequate NOEL for substance or related substance?	Conclusion based on current intake
Triethyl citrate[e] (triethyl 2-hydroxy-1,2,3-propanetricarboxylate)	629	77-93-0 	Yes Europe: 3400 USA: 2400	Yes[f]	NR	No safety concern
Tributyl acetylcitrate (tributyl 2-(acetyloxy)-1,2,3-propanetricarboxylate)	630	77-90-7 	No Europe: ND USA: 0.4	NR	NR	
3-Methyl-2-oxobutanoic acid and its sodium salt	631	759-05-7 and 3715-29-5 	No Europe: 0.01 USA: 0.2	NR	NR	
3-Methyl-2-oxopentanoic acid and its sodium salt	632	1460-34-0 and 66872-74-0 	No Europe: ND USA: 0.2	NR	NR	

4-Methyl-2-oxopentanoic acid and its sodium salt	633	816-66-0 and 4502-00-5 	No Europe: ND USA: 0.2	NR	NR	No safety concern
2-Oxopentanedioic acid	634	328-50-7 	No Europe: ND USA: 0.2	NR	NR	
3-Hydroxy-2-oxopropionic acid	635	1113-60-6 	No Europe: ND USA: 0.2	NR	NR	

CAS: Chemical Abstracts Service; ND: no data available; NR: not required for evaluation because an adequate NOEL for the substance or a related substance was identified at step A3 or A4 of the Procedure.

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

[b] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 7, 1999). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.

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

[d] Ethyl acetoacetate is expected to be hydrolysed to acetoacetic acid, which is endogenous in humans.

[e] The ADI for this substance was maintained.

[f] Fumaric acid, (–)-malic acid and triethyl citrate are components of the tricarboxylic acid cycle.

4.2.1 *Intake data*

The total annual volume of production of the 47 substances in this group destined for use as flavouring agents is approximately 200 tonnes in Europe and 1700 tonnes in the USA. On the basis of the reported annual volumes of production, the estimated total daily per capita intakes of these substances resulting from their use as flavouring agents is 28mg in Europe and 300mg in the USA.

Fumaric acid (no. 618) and (–)-malic acid ((2*S*)hydroxybutanedioic acid; no. 619) account for approximately 59% of the total daily per capita intake of these 47 substances in Europe and 88% in the USA. The estimated daily per capita intake of fumaric acid resulting from its use as a flavouring agent is approximately 0.9mg in Europe and 219mg in the USA. The estimated daily per capita intake of (–)-malic acid resulting from its use as a flavouring agent is about 16mg in Europe and 58mg in the USA. The intake of each substance in the group in μg per day in Europe and the USA is reported in Table 3.

Of the 47 substances evaluated, 25 have been detected as natural components of traditional foods.

4.2.2 *Absorption, metabolism and elimination*

Studies on the absorption, metabolism and elimination of aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters with additional oxygenated functional groups show that these substances are readily hydrolysed and absorbed and are completely metabolized. Many of these substances or their metabolites are endogenous in humans.

The majority of the substances in this group are esters or diesters and are expected to undergo hydrolysis to their corresponding saturated linear or branched-chain aliphatic primary alcohols or branched-chain hydroxy or keto alcohols. The presence of a second oxygenated functional group has little, if any, effect on the hydrolysis of these esters. β-Keto acids and derivatives such as acetoacetic acid readily undergo decarboxylation and, together with α-keto and α-hydroxyacids, yield breakdown products which are incorporated into normal biochemical pathways. The γ-keto acids and related substances may undergo complete or partial β-oxidation to yield metabolites, which are eliminated in the urine. The ω-substituted derivatives are readily oxidized and/or excreted in the urine. The simple aliphatic di- and tricarboxylic acids either occur endogenously in humans or are structurally related to endogenous substances. They are metabolized through the fatty acid β-oxidation pathway or the tricarboxylic acid cycle.

4.2.3 *Application of the Procedure for the Safety Evaluation of Flavouring Agents*

Step 1

In applying the Procedure for the Safety Evaluation of Flavouring Agents (Fig. 1) to the above-mentioned aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups, the Committee assigned all 47 substances to structural class I.

Step 2

Metabolic data on individual members of the group are limited, but the common structural features and common pathways of metabolism allow some general conclusions to be drawn about the likely metabolic fate of these agents. Of the 47 substances in this group, 14 occur endogenously in humans, and 28 are esters or diesters that would be expected to be metabolized to innocuous products. There was evidence that the remaining substances in the group, including acetals, derivatives of β-keto and β-hydroxy acids, γ-keto and γ-hydroxy acids and aliphatic di- and tricarboxylic acids, are also metabolized to innocuous products. The evaluation of all of the substances in this group therefore proceeded via the left-hand side of the decision-tree.

Step A3

The estimated daily per capita intakes of 41 of the 47 substances in this group were below the threshold for substances in class I (1800μg), indicating that they are of no safety concern when used at current levels of intake. The estimated daily per capita intakes of the remaining six substances, ethyl acetoacetate (no. 595), fumaric acid (no. 618), (–)-malic acid (no. 619), a mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (mixture of (+)-, (–)-, (+/–)- and meso-2,3-dihydroxybutanedioic acid; no. 621), adipic acid (hexanedioic acid; no. 623) and triethyl citrate (triethyl 2-hydroxy-1,2,3-propanetricarboxylate; no. 629) were above the threshold for class I. The evaluation of these six substances therefore proceeded to step A4.

Step A4

Four of the six substances for which the intake exceeded the threshold of concern for class I are endogenous in humans. Three of these four substances, namely, fumaric acid (no. 618), (–)-malic acid (no. 619) and triethyl citrate (no. 629), are components of the tricarboxylic acid cycle. The fourth substance, ethyl acetoacetate (no. 595), is expected to be hydrolysed to acetoacetic acid, which is endogenous in humans and is formed from the condensation of two acetyl CoA units in the fatty acid pathway.

The remaining two substances, the mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (no. 621) and adipic acid (no. 623), are not endogenous and are not predicted to be metabolized to endogenous products. The evaluation of these substances therefore proceeded to step A5.

Step A5

The NOEL for tartaric acid (no. 621) in a 2-year toxicity study in rats was 1200 mg/kg of body weight per day, the highest dose tested, which provides an adequate margin of safety (>10000 in Europe and >1000 in the USA) when compared with the current levels of estimated intake of this substance. A NOEL was not available for adipic acid (no. 623), but the NOEL for a structurally related substance, dibutyl sebacate (dibutyl decanedioate; no. 625), in a 2-year study in rats was 6200 mg/kg of body weight per day, which provides an adequate margin of safety (>1×10^7 in Europe and >10000 in the USA), when compared with the current levels of estimated intake of adipic acid. Therefore, these substances were determined to be of no safety concern when used at current levels of estimated intake.

Table 3 summarizes the stepwise evaluation of the 47 aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups used as flavouring agents.

4.2.4 *Consideration of combined intakes*

In the unlikely event that foods containing all 47 aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups were consumed simultaneously on a daily basis, the estimated total daily per capita intake of these substances in Europe and the USA would exceed the threshold for flavouring agents in class I. All of these substances are expected to be efficiently metabolized via well known biochemical pathways to innocuous metabolic and/or endogenous substances; in the opinion of the Committee, the endogenous levels of these metabolites would not give rise to perturbations outside the physiological range. Accordingly, even a combined theoretical intake would be of no safety concern.

4.2.5 *Conclusions*

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

No toxicity data were required for application of the Procedure to 45 of the 47 substances in this group. For the remaining two substances, the mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (no. 621) and

adipic acid (no. 623), the toxicity data were consistent with the results of the safety evaluation using the Procedure.

The ADIs for fumaric acid (no. 618) and its salts and for triethyl citrate (no. 629) were maintained at the present meeting.

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

5. Peanut oil and soya bean oil

The allergenicity of foodstuffs has not previously been considered by the Expert Committee. Allergens in food have been considered by the Codex Committee on Food Labelling on a number of occasions since 1993, and that Committee has issued a list of foods and food ingredients known to cause allergy. The list, with modifications, was revised at an FAO Technical Consultation in 1995 (*11*). After debate in the Codex Committee (*8*), the list was forwarded at step 8 for adoption by the Codex Alimentarius Commission. The Joint FAO/WHO Expert Committee on Food Additives was asked by the Codex Committee on Food Labelling (*8*) to provide scientific advice on this issue and to develop criteria for identifying food products on the list for which labelling of the food source is unnecessary (see section 2.4). An ad hoc Panel on Food Allergens was convened for this purpose; its report is attached as Annex 4.

The criteria identified by the Panel included:

- evidence from a double-blind clinical study that challenge with the specific product does not elicit allergic reactions in a group of patients with clinical allergy to the parent foodstuff, and
- the existence of specifications for the product and its manufacturing process that ensure that the process yields a consistently safe product.

The Panel identified only two foodstuffs that it considered may currently fulfil the criteria for inclusion in a list of products for which labelling of the allergen-containing food source is not necessary: refined peanut oil and refined soya bean oil. The Panel recommended that these substances be considered by the Committee at its present meeting.

The Committee recognized that the allergenicity of vegetable oils is heavily dependent on the processes used to extract and refine the oils. It was aware that several steps are involved in the refining process and that different producers may use variations of the basic procedures. In addition, in clinical trials of the oils, the mode of administration, the

allergic sensitivity of the subjects to the source material and the use of double-blind protocols can affect the outcome.

The Committee was aware of a number of studies conducted using the double-blind procedure in which people sensitive to peanuts had been challenged with various grades of peanut oil. In a study from the USA, all 10 male and female patients with known sensitivity to peanuts gave a positive reaction in skin-prick tests with peanut extracts and were found to have elevated serum titres of antibodies to peanut allergens. A cross-over challenge with commercial peanut oil and olive oil did not elicit adverse reactions, although the Committee noted that the use of gelatin capsules to administer the oils may have masked reactions of the lips and oral cavity.

In a double-blind study in France, 11 children with symptoms possibly due to allergies were found to react to skin-prick tests with peanut or peanut protein extracts. Four of the patients reacted to an oral challenge with peanut oil. The origin and grade of the peanut oil used were not defined, and the Committee recognized that it may have been obtained before adoption of a revised code of practice for the refining of vegetable oils by the food industry in continental Europe. Earlier studies of infants in France had suggested that peanut oils used as a vitamin carrier or in infant formulas may have contained allergenic proteins.

The results of a randomized, double-blind, cross-over challenge study involving a group of 62 patients from the United Kingdom who had reacted to skin-prick tests with peanut extracts were reviewed. None of the subjects reacted to challenge with refined peanut oil, although six reacted to challenge with crude peanut oil. Of the 62 patients, 60 also reacted to an oral challenge with peanuts. The Committee considered that the study was well designed, with adequate statistical power, and recognized the value of confirming the sensitivity of the subjects to peanuts after the double-blind challenge had been completed. Nevertheless, although the study provided adequate evidence for a lack of allergenicity of the oil used, appropriate descriptions of the manufacturing process and the consequent specifications of the oil were not provided and the results cannot be extrapolated to other oils.

The Committee also reviewed the results of a double-blind, cross-over challenge study of the allergenicity of soya bean oils involving seven individuals who had experienced allergic reactions up to 10 years previously. All the individuals had positive reactions to a skin-prick test with soya bean extract. The titres of serum immunoglobulin E (IgE) binding to soya bean proteins were increased in six of the seven patients. None of the subjects reacted to increasing volumes of

hydrogenated, partially hydrogenated or cold-pressed soya bean oils, although the Committee noted that the use of gelatin capsules to administer the oils may have masked reactions of the lips and oral cavity. Although the study provided some evidence that the oils used were not allergenic, appropriate descriptions of the manufacturing process and the consequent specifications of the oils were not provided, and the results cannot be extrapolated to other oils.

The Committee noted the absence of clear descriptions of the processes that had been used to refine the peanut and soya bean oils tested. Additionally, comparable data on the protein content of those oils that were clinically tested were not available. Furthermore, the Committee expressed reservations about the quality and the lack of validation of the analytical methods used to determine the concentration of residual protein in the oils. In view of these considerations, the Committee concluded that refining processes that would consistently yield safe products have not been defined.

The Committee therefore concluded that the results of studies of immunological tolerance to representative refined peanut and soya bean oils would be required for a full evaluation. Such studies should provide extensive information on a wide range of oils, representing refining procedures used throughout the world. Full descriptions of the refining processes used and evidence for a lack of allergenicity of the oils as determined by appropriately designed clinical studies should be provided. Information on the nature and quantity of protein in the oils would be essential for defining the level of refinement of the oils tested, with a view to identifying representative oils.

6. Contaminants

The Committee evaluated one contaminant for the first time and re-evaluated two contaminants considered at previous meetings. The results of the evaluations are summarized in Annex 2.

6.1 Lead

The Committee first evaluated lead at its sixteenth meeting (Annex 1, reference *30*), when a provisional tolerable weekly intake (PTWI) of 3mg per person, equivalent to 50μg/kg of body weight, was established. This PTWI was reconfirmed at the twenty-second meeting (Annex 1, reference *47*). At its thirtieth meeting (Annex 1, reference *73*), the Committee assessed the health risks of lead to infants and children and established a PTWI of 25μg/kg of body weight for this population group. The Committee again evaluated lead at its forty-

first meeting (Annex 1, reference *107*), when the previous PTWI of 50μg/kg of body weight for adults was withdrawn and the existing PTWI of 25μg/kg of body weight for infants and children was reconfirmed and extended to all age groups. The review of the health effects of lead at the forty-first meeting was based on an assessment of lead that had been performed by an IPCS Task Group, which was published as Environmental Health Criteria, No. 165 (*12*).

At its present meeting, the Committee was requested to assess the health risks of dietary exposure of infants and children to lead, with special emphasis on the most critical effect, which was considered to be impaired neurobehavioural development. The Committee considered several models that had been developed to define the relationship between the effects of current levels of exposure to lead and the impact on health that might be anticipated from a reduction in exposure. The PTWI was not reconsidered and was maintained at its present value.

The most widely used biomarker of exposure to lead is the concentration in blood (blood lead concentration, measured in μg/dl). The most critical effect of lead at low concentrations is reduced cognitive development and intellectual performance in children. A number of studies in which various tests of behavioural performance were used have shown an association between blood lead concentration and reduced intelligence quotient (IQ) in children exposed pre- and postnatally. The effects of confounding variables and limits to the precision of analytical and psychometric measurements increase the uncertainty of any estimate of the effect of blood lead concentrations below 10–15μg/dl. If a threshold does exist, it is unlikely to be detected because of these limitations; nevertheless, there was some evidence of an association between cognitive deficits and blood lead concentrations below 10μg/dl.

6.1.1 *Exposure*

Exposure to lead can occur as a result of ingestion of lead in foodstuffs and water and from other sources, such as air. All these sources make important contributions. Although the assessment reported here was limited to dietary intake, a complete analysis would require the inclusion of all sources of lead.

The Committee reviewed data on lead intake in 25 countries and assessed several diets on the basis of the assumption that the Global Environment Monitoring System–Food Contamination Monitoring and Assessment Programme (GEMS/Food) regional diets contain "typical" levels of lead in the food categories for which limits have

been proposed by the Codex Committee on Food Additives and Contaminants. The GEMS/Food diets have been used by the Codex Committee on Pesticide Residues and other committees to estimate intakes of pesticides and contaminants since 1987. At its present meeting, the Expert Committee also used the regional diets to estimate lead intake under three sets of assumptions:

- All foods contain lead at the limits proposed by the Codex Committee on Food Additives and Contaminants.
- All foods contain lead at a "typical" average concentration.
- All foods contain lead at "typical" high levels.

When levels at the limits proposed by the Codex Committee on Food Additives and Contaminants were used in the assessment, the estimated intakes were 13–20 μg/kg of body weight per week. The "typical" average and high levels were derived from monitoring studies in the USA and were similar to those reported in other countries. The intakes ranged from 1 to 2 μg/kg of body weight per week for "typical" lead levels and from 2 to 4 μg/kg of body weight per week for "typical high" levels. The narrow ranges in estimated intake reflect the fact that the data submitted to the Expert Committee did not include foodstuffs that contained particularly high levels of lead, and no food group predominated. Virtually no data were submitted on foods containing levels above the limit proposed by the Codex Committee. The Expert Committee noted that similar intakes were estimated on the basis of the three sets of assumptions for the five GEMS/Food regional diets.

The Expert Committee consulted the GEMS/Food database and found that foods that were sampled in the 1980s contained much higher concentrations of lead than those measured recently and decided to base its conclusions on current data.

The potential intake of lead by children was reported by seven countries in which the general food supply, infant formulas and other foods commonly consumed by children had been monitored. Several countries provided information on consumption of foods by children. On the basis of this information, the estimated range of intake of lead by children was 0.6–30 μg/kg of body weight per week, which was generally two to three times the intake by adults in the same country when evaluated on the basis of body weight.

Tap water is a significant potential source of lead intake, particularly for bottle-fed infants, but the data submitted were inadequate to permit estimation of the range of levels found.

6.1.2 *Quantitative risk assessment*

Exposure assessment

Several simulation models were developed to estimate the distributions of dietary lead intake in regional diets. The first involved a scenario in which the regional populations covered by the GEMS/Food database consumed food with lead concentrations corresponding to those found in a survey conducted in the USA. The second was designed to evaluate the impact of inclusion of a food commodity from a source with a much higher distribution of lead superimposed on the background of other regional dietary and non-dietary exposures. In a third simulation, the effects of several theoretical regulatory interventions on dietary intake were evaluated.

Estimates of the blood lead concentrations from dietary intake

In order to predict the biological effects of lead intake, the Committee used simple empirical models to relate the concentration of lead in the diet to changes in the biomarker, the concentration of lead in blood. Most of the older data refer to relatively constant exposure to lead, usually as a consequence of contamination of drinking-water by lead plumbing. These data have limited predictive value for levels of exposure that result in blood lead concentrations higher than 25 µg/dl. In addition, other dietary components or atypical physiological states may alter the rate of absorption of lead from the intestine to the blood.

In order to infer a relationship between ingestion of lead and an increase in the blood lead concentration of infants and young children, data from studies of bottle-fed infants were fitted into several models. Reasonable fits required the assumption that a lead concentration in drinking-water of zero corresponds roughly to a blood lead concentration of 15 µg/dl, perhaps reflecting exposure from the environment or in utero. The results attributable to dietary intake of lead by infants correspond roughly to a change in blood lead concentration of 0.05–0.1 µg/dl per µg of lead intake per kg of body weight per day. For a 10-kg infant, this corresponds to a blood lead concentration of 0.5–1.0 µg/dl per µg of lead in the diet per day.

The Committee used data from another study to calculate the relationship between the blood lead concentration of pregnant women and intake of lead from drinking-water. The sample size was large enough to allow characterization of variation in the population. When the raw data were introduced into several simple models, all showed poor fits. When concentrations of lead in drinking-water below 300 µg/l were fitted separately, a linear model with a lognormal population distribution produced a very good fit. A background blood lead

concentration of roughly 9μg/dl was obtained, probably reflecting exposure from sources other than drinking-water. The model yielded a blood lead concentration of 0.035μg/dl per μg of lead in 1 litre of drinking-water. Because of uncertainty about the amount of water consumed by the individuals in the study, the values covered a wide range, from 0.023 to 0.07μg/dl per μg of lead intake per kg of body weight per day. For a 60-kg person, this corresponds to a range of 1.4–4.2μg/dl per μg of lead in drinking-water per day.

Dose–response assessments of neurobehavioural effects of lead in children

The Committee noted a number of limitations of the available data on the effects of lead on neurobehavioural development in children. One limitation was the lack of raw data for use in risk assessments and in evaluating mathematical models of the relationship between exposure to lead and performance in behavioural tests. Another limitation was that somewhat disparate results were obtained. Furthermore, it was difficult to compare the results of large epidemiological studies that included many potential confounding variables in different models, and it was uncertain whether any observed effect was due to lead or to some other variable. A further limitation was that the same tests were not used in all of the studies, so that different end-points were measured. (Measures of cognitive and motor performance might be preferable to a general measure of IQ.) Finally, most of the analyses were based on tests of statistical significance between groups with high and low levels of exposure to lead, and did not include critical evaluations of the dose–response relationship.

The analysis that had the fewest of these potential flaws showed a decrease of 1 IQ point for every 2–4μg/dl increase in blood lead concentration, with a greater effect at higher blood lead concentrations than at lower ones. A meta-analysis of seven studies showed that an increase in the blood lead concentration from 10 to 20μg/dl would result in a decrease of approximately 2.5 IQ points.

This analysis did not include the possibility that the relationship between blood lead concentration and IQ is non-linear, although there is some evidence that this is so. Furthermore, no expression of either population variation or uncertainty was included in the dose–response relationship. In order to address these concerns, statistical distributions and probability trees were included in the dose–response relationship. Because raw data were not available, the values for the magnitude of the variation and uncertainty were chosen so as to be generally consistent with those available in the literature on the health effects of lead. To illustrate the behaviour of the composite

Table 4
Decreases in intelligent quotient (IQ) associated with the concentration of lead in blood

Concentration of lead in blood (μg/dl)	Median decrement in IQ (95% confidence interval)
5	0.4 (0.0–1.5)
10	1.7 (0.5–3.1)
15	3.4 (1.1–5.0)
20	5.5 (1.6–6.9)

dose–response function generated, Table 4 shows the estimated net decreases in IQ for the median population at four values of blood lead concentration, with a range of uncertainty for each estimate.

Dose–response simulation

A simulation model was developed in which a dose–response component was added to the model of exposure described previously. This model was used to illustrate the net benefit of imposing limits on the levels of lead in food with respect to neurobehavioural development of children exposed to lead from dietary sources.

The studies that have associated exposure to lead with performance in behavioural tests were conducted in populations whose exposure to lead was relatively constant. In order to gauge the relative importance of shorter exposures, it was presumed that the net lifetime effect of lead on intellectual status (adult IQ) after a limited prenatal or postnatal exposure can be scaled relative to a period of 5–15 years, where the range represents the uncertainty associated with the adjustment.

The model was based on consumption patterns from a GEMS/Food Middle Eastern diet, assuming that the lead concentrations in food were typical of those in the USA and that non-dietary exposure roughly corresponded to that in the USA. In this hypothetical scenario, a decrement in IQ of 0.006 points (range of 0–0.06 points) was estimated for the population mean of children as a result of maternal exposure for 9 months. The procedure described above was used to adjust for the period of exposure. In a scenario in which the cereal grains in a regional diet contained 10 times higher lead levels than those used in the first model, the estimated decrement in IQ points attributable to exposure to lead was 0.02 points (range 0–0.1 points). A hypothetical intervention leading to a 50% reduction in the lead concentration of grain was estimated to reduce the decrement in IQ points to 0.011 points (range 0–0.08 points). Given the similarity in the

estimates of exposure from the different regional diets, similar results would be anticipated if other GEMS/Food regional diets were used in the scenario.

The Committee also estimated the effect on blood lead concentrations of long-term exposure to lead in the three models of regional diets, to illustrate the ranges of intake of lead under various assumptions. Long-term exposure was assumed to include that occurring in utero and for the first 10 years of life. As a conservative estimate, the Committee assumed that a dietary intake of 1 μg/kg of body weight per day would result in an increase in blood lead concentration of 1 μg/dl, this being the upper estimate for infants, and that this relationship was valid during the long-term exposure period. This would correspond to an increase in blood lead concentration of 0.14 μg/dl per μg of lead per kg of body weight per week. Using this assumption in combination with the ranges of values for high estimated dietary intake, the Expert Committee calculated that consumption of a diet containing lead at the limits proposed by the Codex Committee on Food Additives and Contaminants would result in an increase in blood lead concentration of 3 μg/dl. Consumption of diets containing lead at "typical" average or high concentrations would result in increases in blood lead concentrations of 0.3 and 0.6 μg/dl, respectively. The results shown in Table 4 provide confidence that the levels of lead that are found currently in foods would have negligible effects on the neurobehavioural development of infants and children. Nevertheless, the Committee stressed that a full risk assessment of dietary intake of lead should take into account other sources of exposure.

6.1.3 *Conclusions*

The Committee concluded that, overall, the concentrations of lead found currently in food would have negligible effects on intellectual development, but noted that foods with high lead content remain in commerce. The simulation model presented here could be used to evaluate the effects of any proposed regulatory interventions to reduce exposure to lead.

A toxicological monograph was prepared.

6.2 Methylmercury

The Committee first evaluated methylmercury at its sixteenth meeting (Annex 1, reference *30*), when it established a PTWI of 300 μg of total mercury per person, of which no more than 200 μg should be present as methylmercury. At its twenty-second and thirty-third meetings (Annex 1, references *47* and *83*), the Committee confirmed the PTWI of 200 μg of methylmercury (3.3 μg/kg of body weight) for the general

population. At its thirty-third meeting, the Committee noted that pregnant women and nursing mothers may be at greater risk than the general population from the adverse effects of methylmercury. The Committee considered the available data insufficient for it to recommend a specific methylmercury intake for this population group and recommended that more detailed studies be undertaken.

At its present meeting, the Committee reviewed information that had become available since the previous evaluation in order to estimate the risk associated with various levels of exposure. The PTWI was not reconsidered and was maintained at its present value.

6.2.1 *Intake*

Although methylmercury can occur in other foods, it is found primarily in fish. In other foods, mercury is present mainly as elemental mercury. The Committee noted the variation in levels of methylmercury in fish, both within and between species and also noted that fish from polluted waters usually have higher mercury levels than those from unpolluted waters. When intakes of total mercury were provided, the Committee assumed conservatively that all of the mercury was present as methylmercury.

A "typical" level of methylmercury must be established to permit estimation of intake from the GEMS/Food regional diets. A "typical" level should correspond to the average levels of intake by consumers and should therefore represent the usual levels in commonly consumed species of fish. The Committee concluded that levels based on estuarine fish, tuna or flake fillet would be appropriate for this purpose. For these analyses, the average concentrations found in tinned tuna and flake fillet were used to derive a range of estimates of regional intakes of methylmercury.

Data on the levels of mercury residues in food and/or assessments of mercury intake were submitted to the Committee by 25 countries representing the major regions of the world. The Committee used these data, together with the estimates of fish consumption in each of five regional GEMS/Food diets, to estimate typical methylmercury intakes of 0.3–1.1 μg/kg of body weight per week, depending on the region. These values are based on the assumption that all fish and shellfish contain methylmercury at a concentration of 200 μg/kg. If all fish and shellfish that are consumed contain methylmercury at a concentration of 330 μg/kg, the intake would range from 0.5 to 1.8 μg/kg of body weight per week.

The methylmercury intake of consumers in Australia, who were considered to have a high fish intake was estimated on the assumption

Table 5
Estimated intake of methylmercury from fish by consumers in the 95th percentile and comparison of the impact of three theoretical residue limits on intake levels[a]

Residue limit (μg/kg of fish)	Estimated intake of methylmercury (μg/kg of body weight per week)		
	Children (2–5 years)	Women	Total
None	1.5	0.8	0.9
1000	1.4	0.7	0.9
500	1.4	0.6	0.8
200	0.8	0.4	0.5

[a] Based on data from the USA.

that the fish contained methylmercury at a concentration of 200 or 640μg/kg. The estimated intakes for consumers in the 95th percentile were 2.1 and 5.6μg/kg of body weight per week, respectively. As these values are based on the assumption that all fish contain methylmercury at these levels, they are highly conservative estimates of extreme levels of intake.

A probability analysis was conducted in the USA to provide a more realistic estimate of the intake of methylmercury by consumers in the 95th percentile, by taking into account the variation in both fish consumption and residue levels in the fish that are consumed. The analysis covered the entire distribution of fish consumption and methylmercury residues in fish. An estimate was also provided from a simulation model of the potential impact of establishing limits on intake of methylmercury, by repeating the analysis after excluding residue levels that exceeded theoretical regulatory limits of 1000, 500 or 200μg/kg of fish. The results of the analysis are presented in Table 5 for consumers in the 95th percentile in three population groups. These results suggest that the intake of the adult populations would be below the PTWI, providing individuals consumed fish containing "typical" levels of methylmercury.

The Committee also specifically evaluated the potential intake of children and infants. The GEMS/Food regional diets do not include separate estimates for children, but several countries provided estimates of the intake of mercury by children and infants. Comparison of the intake by adults and children in each country shows that children consume two to three times more mercury than adults per unit body weight. Nevertheless, the concentrations of mercury in the hair of children are similar to those in adult hair, indicating that children have similar body burdens to those of adults. Therefore, the higher

intakes of children would not necessarily result in an equivalent increase in risk, and, if children are no more sensitive than adults to methylmercury, the PTWI would be appropriate for both adults and children. In simulations conducted in the USA, children were found to have intakes below the PTWI. Although data were not available to permit equivalent analyses for other countries, the results can be expected to be similar, providing the methylmercury concentrations in fish and the levels of fish consumption are comparable to those in the USA.

6.2.2 *Pharmacokinetic data*

Studies of the kinetics of methylmercury showed that its distribution in tissues after ingestion is more homogeneous than that of other mercury compounds, with the exception of elemental mercury. The most important features of the distribution pattern of methylmercury are high blood concentrations, a high ratio of the concentrations in plasma to those in erythrocytes and high levels of deposition in the brain. Another important characteristic is slow demethylation, which is a critical detoxification step. Methylmercury and other mercury compounds have a strong affinity for sulfur and selenium. Although selenium has been suggested to provide protection against the toxic effects of methylmercury, no such effect has been demonstrated.

6.2.3 *Toxicity data*

A variety of effects have been observed in animals treated with toxic doses of methylmercury. Some of these, such as renal damage and anorexia, have not been observed in humans exposed to high doses. The primary tissues of concern in humans are those of the central nervous system, particularly the developing brain, and these have been the focus of epidemiological studies.

Methylmercury induces neurotoxicity in small rodents such as mice and rats at doses that usually also affect other organ systems. Moreover, the maternal dose that causes neurotoxic effects in offspring exposed in utero also results in maternal toxicity. The main neurotoxic effects are impairment of coordination and pathological changes in selected areas of the brain and spinal cord. Similar effects are seen in domestic animals. In cats, no difference in toxicity was observed between methylmercury naturally present in fish and methylmercury added to the diet.

Similar effects of methylmercury were observed in 4-year studies in non-human primates, in which the techniques used to detect neuronal damage included pathological and behavioural tests and investigations of the visual and auditory systems. Although the number of

animals included in these experiments was small, the NOEL was 10μg/kg of body weight per day (expressed as mercury and corresponding to a steady-state blood concentration of 0.4μg/l).

The clearance, half-life and blood concentrations of methylmercury at steady-state depend on the body surface area. On the basis of body weight, small animals are much less sensitive to methylmercury than are humans, while the sensitivity of non-human primates is similar to that of humans.

The two biomarkers used most frequently for quantifying the burden of methylmercury in the human body are blood and hair concentrations. Establishment of a quantitative relationship between exposure (daily intake) and concentrations in blood and hair began with a study of the effects of accidental consumption of grain treated with methylmercury fungicide in Iraq. Although the weight of evidence suggested that every 1μg/l increase in the blood concentration of methylmercury results in an increase in the hair concentration of 140–370μg/kg, in six of ten studies, the ratio of the hair:blood concentrations was 230–280. The Committee concluded that a ratio of 250 is a reasonable estimate of the ratio of the hair:blood concentrations. The approximate relationships between weekly intake and blood concentration of mercury at steady state indicate that intake of 1μg of mercury per kg of body weight per week in the form of methylmercury corresponds to a concentration of mercury of 10μg/l of blood and 2.5mg/kg of hair.

Since the Committee's previous consideration of methylmercury, a considerable amount of data have become available on the possible neurobehavioural effects of prenatal and postnatal exposure. The most relevant data are from two large prospective epidemiological cohort studies conducted in the Faroe Islands and the Seychelles, where large amounts of seafood are consumed. The prenatal exposure of the two cohorts to mercury appears to have been similar. The geometric mean concentration of mercury in the hair of mothers during pregnancy was 4.3μg/g (interquartile range 3–8μg/g) in the Faroe Islands and 6.8μg/g (interquartile range 0.5–27μg/g) in the Seychelles. In the Faroe Islands, the geometric mean concentration in umbilical cord blood was 23μg/l (interquartile range 13–41μg/l). In the study in the Faroe Islands, no association was seen between the extent of prenatal exposure to methylmercury and performance in clinical or neurophysiological tests, although significant decrements were observed in the children's scores in tests of functions such as fine motor skills, attention, language, visual–spatial skills and memory. Most of these associations were still apparent when the children whose mothers had had hair concentrations of mercury greater than 10μg/g were excluded from the analyses (representing 15% of the

total). No adverse effects associated with exposure to mercury were reported in the study in the Seychelles.

Several differences between the studies may have contributed to the apparent discrepancy between the findings. First, the children were evaluated for neurobehavioural end-points at different ages and using different tests. In the Faroe Islands, the first neurobehavioural evaluation was conducted when the children were 84 months (7 years) of age, whereas in the Seychelles, the children were assessed at 6, 19, 29 and 66 months of age. As the capabilities of young children change rapidly, the scores at different ages may reflect performance in qualitatively different types of tasks, and scores achieved by children of different ages cannot be compared easily. In addition, although early childhood development was assessed in both studies, different batteries of tests were used. In the Faroe Islands, the battery of tests focused on specific aspects of language, memory, fine motor function, attention and visual–spatial skills. In the Seychelles, the main test was a general test of development that included performance in many aspects of neurological function, although general tests of language, visual–spatial skills and academic achievement were also used. Even though some types of neurological function were assessed in both studies (e.g. language and memory), the differences in the specific tests used make the findings difficult to compare.

Secondly, the two study cohorts may differ with regard to exposure to other factors that can affect the neurobehavioural development of children. In the Faroe Islands, many potential confounding factors were addressed in the analysis, including exposure to polychlorinated biphenyls (PCBs). Pilot whale is the major source of both methylmercury and PCBs in this population, and PCBs are thought to adversely affect the neurodevelopment of children exposed prenatally. When PCBs were measured in samples of umbilical cord tissue (blood and plasma were not available) from one-half of the Faroe Islands cohort, the average PCB concentration in cord tissue lipids was lower than the concentration previously reported in breast milk lipids in the same population, indicating that cord tissue concentration may not be an appropriate indicator of the burden of PCBs. In the Seychelles, potential confounding exposures were not addressed, but it has been suggested that the finding that a higher intake of mercury was associated with higher scores in some tests of development is a result of nutritional factors or mitigating substances present in fish.

Thirdly, the intake patterns of the two cohorts may have differed. Most of the methylmercury consumed in the Faroe Islands is from pilot whale, which is eaten less frequently than fish but contains more mercury per serving. In contrast, the source of methylmercury in the

Seychelles is fish, which is consumed almost daily. Therefore, the intake of methylmercury in the Faroe Islands may be episodic, with high peak levels of intake. Although the effect of methylmercury on neurobehavioural development has generally been presumed to be a function of cumulative intake, short-term peak intake may also be important.

Further follow-up of these cohorts, with greater coordination between the study organizers, would be helpful for addressing some of the issues of assessment. For example, the cohort in the Seychelles was evaluated at 96 months with many of the same tests as were used in the Faroe Islands, and the results are expected to become available in the near future.

The Environmental Health Criteria monograph on methylmercury (*13*) cited the need "for epidemiological studies on children exposed in utero to levels of methylmercury that result in peak maternal hair mercury levels below 20μg/g, in order to screen for those effects only detectable by available psychological and behavioural tests". This proposal arose from an evaluation of data from the study in Iraq, which implied that adverse effects were associated with peak levels of 10–20μg/g of maternal hair.

6.2.4 *Conclusions*

The studies in the Faroe Islands and the Seychelles that were evaluated by the Committee did not provide consistent evidence of neurodevelopmental effects in the children of mothers whose intake of methylmercury yielded hair burdens of 20μg/g or less. The Committee could not evaluate the risks for the complex and subtle neurological end-points used in these studies that would be associated with lower intakes. In the absence of any clear indication of a consistent risk in these recent studies, the Committee recommended that methylmercury be re-evaluated in 2002, when the 96-month evaluation of the Seychelles cohort and other relevant data that may become available can be considered. The Committee noted that fish makes an important contribution to nutrition, especially in certain regional and ethnic diets, and recommended that its nutritional benefits be weighed against the possibility of harm when limits on methylmercury concentrations in fish or on fish consumption are being considered.

A toxicological monograph was prepared.

6.3 Zearalenone

Zearalenone is a heat-stable, non-steroidal estrogenic mycotoxin produced by several species of *Fusarium*. It has been implicated in

numerous incidents of mycotoxicosis in farm animals, especially in pigs. It is found worldwide in a number of cereal crops. Zearalenone has not been evaluated previously by the Committee. However, a mammalian metabolite of zearalenone, α-zearalanol (zeranol), was considered by the Committee at its twenty-sixth, twenty-seventh and thirty-second meetings (Annex 1, references *59, 62* and *80*) for use as a veterinary drug; at the latter meeting, the Committee allocated an ADI of 0–0.5μg/kg of body weight.

6.3.1 *Intake*

The average dietary intakes of zearalenone from cereals and legumes in two of the five GEMS/Food regional diets were estimated to be 1.5μg/day in the European diet and 3.5μg/day in the Middle Eastern diet. If a mean body mass of 60kg is assumed, these intakes correspond to 0.03 and 0.06μg/kg of body weight per day, respectively. The average dietary intakes of zearalenone estimated from individual dietary records are 0.98μg/day (0.02μg/kg of body weight per day) in Canada, 1.2μg/day (0.02μg/kg of body weight per day) in Denmark, 1.1μg/day (0.02μg/kg of body weight per day) in Norway and 2.1μg/day (0.03μg/kg of body weight per day) in the USA.

The theoretical maximum daily intake of α-zearalanol when used as a veterinary drug was calculated to be 1.6μg/day (0.02μg/kg of body weight per day) on the basis of the recommended maximum residue limits of 10μg/kg in cattle liver and 2μg/kg in cattle muscle (Annex 1, reference *80*).

6.3.2 *Pharmacokinetic data*

Studies of the pharmacokinetics and metabolism of zearalenone indicate that it is extensively metabolized by intestinal tissue in pigs (and possibly in humans) during its absorption, with the formation of α- and β-zearalenol and α- and β-zearalanol, which are subsequently conjugated with glucuronic acid. The existence of this pathway limits the value of studies conducted using parenteral administration for assessing the risk associated with dietary intake. Biliary excretion with enterohepatic circulation occurs in rats and mice, while urinary excretion predominates in rabbits. Urinary excretion is also the main route of elimination in pigs in spite of the demonstrated enterohepatic circulation of zearalenone, owing to a high degree of reabsorption in the gut. The very limited data in humans (one individual) suggest that urinary excretion is also significant. Differences between species in the metabolism of zearalenone were found: a higher proportion of the administered zearalenone was metabolized to α-zearalenol in pigs than in rats or cattle. In the one human subject, as in pigs, zearalenone

was found mainly in urine as glucuronide conjugates of the parent compound and α-zearalenol.

6.3.3 *Toxicity data*

Zearalenone has little toxicity after administration as single oral or intraperitoneal doses. In studies in which the drug was administered orally for up to 90 days, the effects appeared to be dependent on the estrogenic activity of zearalenone and/or its metabolites. Pigs and sheep were more sensitive than rodents; in controlled studies with well-defined exposure to multiple doses, the NOEL in pigs was 40μg/kg of body weight per day on the basis of estrogenic effects in responsive tissues and reproductive performance, while the NOEL in rats was 3mg/kg of body weight per day.

Zearalenone has been tested for genotoxicity in a variety of test systems covering several end-points, including point mutations, unscheduled DNA synthesis and chromosomal aberrations. The results were negative, except for the induction of chromosomal aberrations after exposure of mammalian cells in vitro to very high concentrations of zearalenone. Evidence that zearalenone modifies DNA was obtained with a [^{32}P]-postlabelling assay. However, the Committee concluded that these results do not unequivocally demonstrate covalent binding of zearalenone and/or its metabolites to DNA but probably reflect oxidative damage to DNA, since the DNA damage was greatly reduced by coadministration of the antioxidant α-tocopherol.

Hepatocellular adenomas and pituitary tumours were observed in a long-term toxicity and carcinogenicity study in mice given zearalenone at 8–9mg/kg of body weight per day, which is greatly in excess of the concentration that has hormonal effects. The Committee concluded that these tumours were a consequence of the estrogenic effects of zearalenone. A similar conclusion was drawn by the Committee in evaluating α-zearalanol at its thirty-second meeting (Annex 1, reference *80*). No treatment-related increase in the incidence of tumours was seen in rats given zearalenone at 1–3mg/kg of body weight per day.

6.3.4 *Conclusions*

The Committee concluded that the safety of zearalenone could be evaluated on the basis of the dose that had no hormonal effect in pigs, the most sensitive species. Using a safety factor of approximately 100, the Committee established a provisional maximum tolerable daily intake (PMTDI) for zearalenone of 0.5μg/kg of body weight. This decision was based on the NOEL of 40μg/kg of body weight per day in a 15-day study in pigs. The Committee also took into account the

lowest-observed-effect level of 200μg/kg of body weight per day in this study and the previously established ADI of 0–0.5μg/kg of body weight for the metabolite α-zearalanol, evaluated as a veterinary drug. The Committee recommended that the total intake of zearalenone and its metabolites (including α-zearalanol) should not exceed this value.

A toxicological monograph was prepared.

7. Intake assessments of specific food additives

In response to a request by the Codex Committee on Food Additives and Contaminants at its Thirtieth Session (*14*), the Expert Committee assessed the intake of four food additives. The Expert Committee's conclusions are summarized in Annex 2.

7.1 Annatto extracts

Annatto extracts, which are food additives used to impart a yellow colour to food, were previously evaluated by the Committee at its twenty-sixth meeting (Annex 1, reference *59*), when it allocated an ADI of 0–0.065 mg/kg of body weight, expressed as bixin (the primary chemical colouring agent). At its present meeting, the Committee assessed the intake of annatto extracts, although national authorizations are also generally expressed in terms of bixin. Maximum limits have been proposed for use in a wide range of solid foods in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants.

Seven Member States provided information on the intake of annatto extracts: Australia, Brazil, Canada, France, the Netherlands, the United Kingdom and the USA. The assessments were conducted on the basis of a variety of assumptions about the potential concentrations of annatto extracts and for various patterns of consumption. The Expert Committee concluded that the intake of annatto extracts would exceed the ADI for bixin if all foods contained annatto extracts at the maximum levels proposed in the draft General Standard for Food Additives. However, intake assessments based on national permitted levels would not exceed the ADI for most population groups.

Since estimates of intake based on the assumption that all foods in a specific category are coloured by the same additive at the maximum level are overestimates, the Expert Committee recognized that the ADI for bixin is unlikely to be exceeded as a result of the use of annatto extracts. Information from Brazil indicated, however, that

about 44 million people (28% of the population) consume annatto seeds directly as a condiment and have done so for many years, at a level of consumption that is approximately 150% of the ADI.

Although the results of studies in humans normally take precedence over those in experimental animals, the submitted reports were of only limited value. In order to ensure that all of the relevant data on annatto extracts have been reviewed, the Expert Committee recommended their re-evaluation in 2001. The Expert Committee also recommended that populations that have a high intake of annatto extracts continue to be monitored.

7.2 Canthaxanthin

Canthaxanthin, a food additive used to colour foods both directly and also indirectly through its use in animal feeds, was previously evaluated by the Committee at its tenth, eighteenth, thirty-first, thirty-fifth and forty-fourth meetings (Annex 1, references *13*, *35*, *77*, *88* and *116*). The Committee established an ADI of 0–25 mg/kg of body weight at its eighteenth meeting, which it changed to a temporary ADI of 0–0.05 mg/kg of body weight at its thirty-first meeting. This temporary ADI was not extended by the Committee at its thirty-fifth meeting. At its forty-fourth meeting, the Committee established an ADI of 0–0.03 mg/kg of body weight. At its present meeting, the Committee assessed the intake of canthaxanthin. Maximum limits have been proposed for its use in a variety of solid foods and beverages in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants.

Five Member States provided information on the intake of canthaxanthin: Australia, France, New Zealand, the United Kingdom and the USA. A joint assessment was submitted by Australia and New Zealand. Information was also provided by a manufacturer of canthaxanthin. The intake assessments were based on "poundage" data, model diets and individual dietary records.

The Expert Committee noted that estimates of intake based on the assumption that all foods contain canthaxanthin at the maximum levels proposed in the draft General Standard for Food Additives greatly exceed the ADI, as the range of foods in which its use is proposed is much broader than in those countries in which canthaxanthin is used. Intake assessed on the basis of national permitted levels did not exceed the ADI. The data submitted by the manufacturer indicated that indirect exposure through the use of canthaxanthin as a colourant in animal feeds is the major source of canthaxanthin in food.

The Expert Committee concluded that long-term intake of canthaxanthin is unlikely to exceed the ADI.

7.3 Erythrosine

Erythrosine, a food additive used to impart a red colour to food, was previously evaluated by the Committee at its thirty-seventh meeting (Annex 1, reference *94*), when it established an ADI of 0–0.1 mg/kg of body weight. At its present meeting, the Committee assessed the intake of erythrosine. Maximum limits have been proposed for its use in a wide range of solid foods and non-alcoholic and alcoholic beverages in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants.

Information on the intake of erythrosine was received from seven Member States: Australia, Brazil, Canada, Japan, New Zealand, the United Kingdom and the USA. All of the national estimates of erythrosine intake were below the ADI. In assessing the risk of exceeding the ADI, the Expert Committee noted that non-food sources of erythrosine, such as pharmaceutical products, should also be considered as they may make a significant contribution to the total intake if consumed over a long period. The Expert Committee also noted that the ADI could be exceeded if the maximum limits proposed in the draft General Standard for Food Additives are widely adopted at the national level. However, models based on the maximum limits proposed in the draft General Standard give overestimates of actual intake, because erythrosine would be used in only a limited number of foods. The Expert Committee therefore concluded that it is unlikely that long-term intake of erythrosine would exceed the ADI.

7.4 Iron oxides

Iron oxides were previously evaluated by the Committee at its eighteenth, twenty-second and twenty-third meetings (Annex 1, references *35*, *47* and *50*); at the latter meeting, the Committee established an ADI of 0–0.5 mg/kg of body weight. At its present meeting, the Committee assessed the intake of iron oxides.

Iron oxides are permitted for use in foods in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants, their use being limited only by good manufacturing practice. At its present meeting, the Expert Committee assessed national estimates of intake of iron oxides used as additives for colouring food. Use of iron oxides is permitted in most countries. Data were submitted by four Member States: Australia, Canada, the United Kingdom and the USA.

The current use of iron oxides as a food colour is limited, and the estimated intakes based on national permitted levels do not exceed the ADI. The Committee therefore concluded that it is unlikely that intake of iron oxides would exceed the ADI.

8. Specifications for certain food additives

A total of 36 substances were examined for specifications only (see Annex 2). New specifications were prepared for four substances and the existing specifications for 29 were revised. The existing specifications for two substances were maintained and the specifications for one were deleted.

New specifications were prepared for argon, helium and oxygen gas.

No information was received on actual uses of calcium hydrogen sulfite in food, and all existing data indicated that the substance is not used as a food additive. The Committee therefore decided to withdraw the existing specifications.

The information on the level of selenium in potassium metabisulfite, potassium sulfite, sodium hydrogen sulfite, sodium metabisulfite, sodium sulfite and sodium thiosulfate that had been requested at the fifty-first meeting (Annex 1, reference *137*) was received. The existing tentative specifications were revised and the "tentative" designation was removed.

The existing tentative specifications for ferrous sulfate were revised in the light of new information about the presence of mercury as a contaminant and the "tentative" designation was deleted. The Committee was informed of the existence of a dried product of ferrous sulfate and prepared new specifications for "ferrous sulfate, dried".

The existing tentative specifications for citric acid were revised on the basis of new data on the need for a test for oxalate and a suitable limit for this impurity and the "tentative" designation was deleted.

The existing tentative specifications for ferrous gluconate were revised and the "tentative" designation was deleted. The limits for mercury and oxalate were considered unnecessary and were therefore deleted.

The existing tentative specifications for magnesium gluconate were revised and the "tentative" designation was deleted. Microbiological criteria were considered unnecessary, and the requirement was therefore deleted.

The existing tentative specifications for thaumatin were revised. As the specific identification test that had been requested at the fifty-first

meeting (Annex 1, reference *137*) had been submitted, this test was included and the "tentative" designation was deleted.

The Committee revised the specifications for two enzyme preparations produced from genetically modified organisms: α-acetolactate decarboxylase from *Bacillus brevis* expressed in *B. subtilis* and maltogenic amylase from *B. stearothermophilus* expressed in *B. subtilis.* The source descriptions of the specifications were amended in accordance with the Committee's decision on the citation of microbial strains (see section 2.6.3).

The existing tentative specifications for five other enzyme preparations prepared from genetically modified microorganisms (α-amylase from *B. stearothermophilus* expressed in *B. subtilis*, α-amylase from *B. megaterium* expressed in *B. subtilis*, chymosin A from *Escherichia coli* K-12 containing the prochymosin A gene, chymosin B from *Aspergillus niger* var. *awamori* containing the prochymosin B gene and chymosin B from *Kluyveromyces lactis* containing the prochymosin B gene) were also revised to align the descriptions of the source strains with Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms) to Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*; see section 2.6.3). The "tentative" designation was deleted since the Committee deleted the "tentative" designation in Appendix B to Annex 1 at its fifty-first meeting (Annex 1, reference *137*).

The existing specifications for carob bean gum were revised. The methods for microbiological criteria were changed in the light of comments that the existing procedures were inadequate.

The existing specifications for carotenes (algae) and carotenes (vegetable) were reviewed in response to a request to consider whether a limit for residual ethanol was required (see section 2.6.1). The Committee decided to maintain the existing specifications.

The existing specifications for xanthan gum were revised to include a limit for residual ethanol.

The existing specifications for sucrose esters of fatty acids were revised, with minor changes.

The existing specifications for guar gum were revised to reflect the use of ethanol and isopropanol in the manufacturing process, and the methods for meeting microbiological criteria were changed in the light of comments that the existing procedures were inadequate.

The existing specifications for nitrogen were revised to include improved methods for determining oxygen, carbon monoxide and nitrogen.

The existing specifications for riboflavin derived from *B. subtilis* were revised to reflect the existence of new products on the market.

The existing specifications for adipic acid, fumaric acid, DL-malic acid, DL-tartaric acid and L-tartaric acid were revised to include uses other than as flavouring agents.

9. Future work

1. The Committee considered that Annex 1 (General specifications for enzyme preparations used in food processing) of the *Compendium of food additive specifications* (Annex 1, reference *96*) should be reviewed and revised at a future meeting. Annex 1 requires updating in the light of technological developments and to ensure consistency and coherence with the appendices, including Appendix B (General considerations and specifications for enzymes from genetically manipulated microorganisms).
2. The Committee noted that the data available on some of the flavouring agents were inadequate to allow the appropriate specifications to be established. The Committee considered that this could have implications for the safety evaluation of these substances, which should be clarified at a future meeting.

10. Recommendations

1. In view of the large number of food additives, food ingredients and contaminants requiring evaluation or re-evaluation, the important role that the recommendations of the Committee play in the development of international food standards and of regulations in many countries, and the need for maintaining consistency and continuity within the Committee, it is strongly recommended that meetings of the Joint FAO/WHO Expert Committee on Food Additives continue to be held at least once yearly to evaluate these substances.
2. The usefulness of the Committee's recommendations depends heavily on its understanding of the needs of those who request and will use its recommendations. The Committee found that a lack of clear understanding of the task to be performed hindered its work in some instances. The Committee therefore recommended that the Codex Alimentarius Commission and other bodies that seek advice ensure that their requests are clearly formulated and are placed in the appropriate context.

3. Assessments of dietary intake are an important component of the evaluations performed by the Committee of the risk posed by food additives and contaminants. As the necessary expertise and capacity to perform such assessments has not yet been developed in many countries, the Committee recommended that FAO and WHO assist countries and regions to develop national capacity and expertise in conducting food consumption surveys and in determining the concentrations of food additives and contaminants in food products.
4. In view of the international importance of its evaluations, the Committee recommended that FAO and WHO take steps to improve communication with all parties interested in its work. Improvement in communication will allow for more timely responses to calls for data and dissemination of its reports and evaluations. The suggested actions include:
   - publication of reports and evaluations in searchable CD-ROM format;
   - development of a searchable electronic database of the work of organizations interested in the Committee's work, including Member States, commercial enterprises, trade organizations and consumer groups; and
   - continued use of the FAO and WHO web sites (www.fao.org and www.who.int) as a means of disseminating current information in a timely fashion. The existence of the two sites should be publicized more widely.

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Annex 1
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133. *Compendium of food additive specifications, addendum 5.* FAO Food and Nutrition Paper, No. 52, Add. 5, 1997.
134. *Evaluation of certain veterinary drug residues in food* (Fiftieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 888, 1999, and corrigendum.
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.
137. *Evaluation of certain food additives* (Fifty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 891, 2000.

138. *Safety evaluation of certain food additives*. WHO Food Additives Series, No. 42, 1999.
139. *Compendium of food additive specifications, addendum 6*. FAO Food and Nutrition Paper, No. 52, Add. 6, 1998.
140. *Evaluation of certain veterinary drug residues in food* (Fifty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, 2000.
141. *Toxicological evaluation of certain veterinary drug residues in food*. WHO Food Additives Series, No. 43, 2000.
142. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, No. 41/12, 2000.

Annex 2

Acceptable Daily Intakes, other toxicological information and information on specifications

Specific food additives and substances used in food fortification

Substance	Specifications[a]	Acceptable Daily Intake (ADI) in mg/kg of body weight and other toxicological recommendations
Glazing agent		
Hydrogenated poly-1-decene	R	No ADI allocated[b]
Sweetening agent		
Erythritol	N	ADI "not specified"[c]
Thickening agent		
Curdlan	N	ADI "not specified" (temporary)[c-e]
Miscellaneous substances		
γ-Cyclodextrin	R	ADI "not specified"[c]
Sodium iron EDTA	R	Considered to be safe when used in supervised food fortification programmes[f]
Sodium sulfate	N,T	ADI "not specified" (temporary)[c,g]

[a] N, New specifications prepared; R, existing specifications revised; T, the existing, new or revised specifications are tentative and comments are invited.
[b] Data were insufficient for establishing an ADI.
[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 arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for reasons stated in individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.
[d] Applies to food additive uses.
[e] See Annex 3.
[f] The Committee concluded that sodium iron EDTA (ethylene diamine tetraacetate) could be considered to be safe when used in supervised food fortification programmes in response to a need for iron supplementation of the diet of a population as determined by public health officials. Such programmes would provide a daily iron intake of approximately 0.2mg/kg of body weight.
[g] Temporary ADI pending consideration of the "tentative" qualification of the specifications (see Annex 3).

Flavouring agents

The substances listed here were evaluated using the Procedure for the Evaluation of Flavouring Agents. For further details, see section 4 of the main report.

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic and aromatic sulfides and thiols			
Subgroup i — simple sulfides (thioethers)			
Structural class I			
Methyl sulfide	452	N	No safety concern
Methyl ethyl sulfide (ethyl methyl sulfide)	453	N	
Diethyl sulfide	454	N	
Butyl sulfide	455	N	
(1-Buten-1-yl)methyl sulfide	457	N,T	
bis(Methylthio)methane	533	N,T	
Structural class II			
Allyl sulfide	458	N,T	No safety concern
Methyl phenyl sulfide	459	N	
Benzyl methyl sulfide	460	N	
Subgroup ii — acyclic sulfides with oxidized side-chains			
Structural class I			
3-(Methylthio)propanol	461	N,T	No safety concern
4-(Methylthio)butanol	462	N,T	
3-(Methylthio)-1-hexanol	463	N	
2-(Methylthio)acetaldehyde ((methylthio)-acetaldehyde)	465	N,T	
3-(Methylthio)propionaldehyde	466	N,T	
3-(Methylthio)butanal	467	N,T	
4-(Methylthio)butanal	468	N,T	
3-(Methylthio)hexanal	469	N	
2-[(Methylthio)methyl]-2-butenal	470	N,T	
2,8-Dithianon-4-ene-4-carboxaldehyde (5-(methylthio)-2-[(methylthio)methyl]-2-pentenal)	471	N,T	
Methyl 3-(methylthio)propionate	472	N	
(Methylthio)methyl butyrate	473	N,T	
Methyl 4-(methylthio)butyrate	474	N	
Ethyl 2-(methylthio)acetate (ethyl(methylthio)acetate)	475	N,T	
Ethyl 3-(methylthio)propionate	476	N	
Ethyl 4-(methylthio)butyrate	477	N	
3-(Methylthio)propyl acetate	478	N,T	
(Methylthio)methyl hexanoate	479	N,T	
Ethyl 3-(methylthio)butyrate	480	N,T	
3-(Methylthio)hexyl acetate (3-(methylthio)-1-hexanol acetate)	481	N,T	
1-(Methylthio)-2-propanone	495	N,T	
1-(Methylthio)-2-butanone	496	N	
4-(Methylthio)-2-butanone	497	N,T	
4-(Methylthio)-4-methyl-2-pentanone (4-methyl-4-(methylthio)-2-pentanone)	500	N,T	
Di(butan-3-one-1-yl) sulfide (4,4′-thiobis-2-butanone)	502	N,T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic and aromatic sulfides and thiols (*continued*)			
Subgroup ii — acyclic sulfides with oxidized side-chains (*continued*)			
Structural class II			
o-(Methylthio)phenol	503	N,T	No safety concern
Structural class III			
Sodium 4-(methylthio)-2-oxobutanoate	501	N	No safety concern
2-(Methylthiomethyl)-3-phenylpropenal (2-[(methylthio)methyl]-3-phenyl-2-propenal)	505	N	
Subgroup iii — cyclic sulfides			
Structural class I			
2,5-Dimethyl-2,5-dihydroxy-1,4-dithiane (2,5-dimethyl-1,4-dithiane-2,5-diol)	562	N,T	No safety concern
2,5-Dihydroxy-1,4-dithiane (1,4-dithiane-2,5-diol)	550	N	
Structural class II			
2-Methyl-4-propyl-1,3-oxathiane	464	N,T	No safety concern
4,5-Dihydro-3(2*H*)-thiophenone (dihydro-3(2*H*)-thiophenone)	498	N,T	
2-Methyltetrahydrothiophen-3-one (dihydro-2-methyl-3(2*H*)-thiophenone)	499	N,T	
1,4-Dithiane	456	N,T	
2-Methyl-1,3-dithiolane	534	N	
2,2,4,4,6,6-Hexamethyl-1,3,5-trithiane	543	N,T	
Subgroup iv — simple thiols			
Structural class I			
Methyl mercaptan (methanethiol)	508	N,T	No safety concern
1-Propanethiol	509	N,T	
2-Propanethiol	510	N,T	
1-Butanethiol	511	N	
2-Methyl-1-propanethiol	512	N,T	
3-Methyl-1-butanethiol	513	N,T	
Pentane-2-thiol	514	N,T	
2-Methyl-1-butanethiol	515	N	
3-Methyl-2-butanethiol	517	N	
1-Hexanethiol	518	N,T	
2-Ethylhexane-1-thiol	519	N,T	
Prenylthiol (3-methyl-2-butene-1-thiol)	522	N	
Thiogeraniol (3,7-dimethyl-2(*E*),6-octadiene-1-thiol)	524	N,T	
Structural class II			
Cyclopentanethiol	516	N,T	No safety concern
Mixture of 2-, 3- and 10-mercaptopinane (mixture of 2,6,6-trimethyl-bicyclo(3.1.1)-heptane-2-, 3- and 10-thiols)	520	N,T	
Allyl mercaptan (2-propene-1-thiol)	521	N,T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic and aromatic sulfides and thiols (*continued*)			
Subgroup iv — simple thiols (*continued*)			
Structural class II (*continued*)			
1-*p*-Menthene-8-thiol (α,α-4-trimethyl-3-cyclohexene-1-methanethiol)	523	N,T	No safety concern
Benzenethiol	525	N	
Benzyl mercaptan (benzenemethanethiol)	526	N	
Phenylethyl mercaptan (2-phenylethanethiol)	527	N	
o-Toluenethiol	528	N,T	
2,6-Dimethylthiophenol (2,6-dimethylbenzenethiol)	530	N	
2-Naphthalenethiol	531	N,T	
Structural class III			
2-Ethylthiophenol (2-ethylbenzenethiol)	529	N,T	No safety concern
Subgroup v — thiols with oxidized side-chains			
Structural class I			
2-Mercaptopropionic acid	551	N	No safety concern
Ethyl 2-mercaptopropionate	552	N,T	
Ethyl 3-mercaptopropionate	553	N	
3-Mercaptohexyl acetate	554	N	
3-Mercaptohexyl butyrate	555	N	
3-Mercaptohexyl hexanoate	556	N,T	
1-Mercapto-2-propanone	557	N,T	
3-Mercapto-2-butanone	558	N,T	
2-Keto-4-butanethiol (4-mercapto-2-butanone)	559	N,T	
3-Mercapto-2-pentanone	560	N,T	
3-Mercapto-3-methyl-1-butanol	544	N,T	
3-Mercaptohexanol	545	N	
2-Mercapto-3-butanol ((*R,S*)-3-mercaptobutan-2-ol)	546	N,T	
α-Methyl-β-hydroxypropyl α-methyl-β-mercaptopropyl sulfide (3-[(2-mercapto-1-methylpropyl)thio]-2-butanol)	547	N	
4-Methoxy-2-methyl-2-butanethiol	548	N,T	
3-Mercapto-3-methylbutyl formate	549	N	
Structural class II			
p-Mentha-8-thiol-3-one (2-(1-mercapto-1-methylethyl)-5-methylcyclohexanone)	561	N,T	No safety concern
Structural class III			
Sodium 3-mercapto-oxopropionate (sodium 3-mercaptopyruvate)	563	N	No safety concern
Subgroup vi — dithiols			
Structural class I			
1,2-Ethanedithiol	532	N	No safety concern
1,3-Propanedithiol	535	N	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic and aromatic sulfides and thiols (*continued*)			
Subgroup vi — dithiols (*continued*)			
Structural class I (*continued*)			
1,2-Propanedithiol	536	N,T	No safety concern
1,2-Butanedithiol	537	N	
1,3-Butanedithiol (butane-1,3-dithiol)	538	N	
2,3-Butanedithiol	539	N	
1,6-Hexanedithiol (hexane-1,6-dithiol)	540	N	
1,8-Octanedithiol (octane-1,8-dithiol)	541	N	
1,9-Nonanedithiol	542	N	
Subgroup vii — simple disulfides			
Structural class I			
Dimethyl disulfide	564	N	No safety concern
Methyl propyl disulfide	565	N,T	
Propyl disulfide	566	N	
Diisopropyl disulfide	567	N	
Methyl 1-propenyl disulfide	569	N,T	
1-Propenyl propyl disulfide	570	N,T	
Methyl 3-methyl-1-butenyl disulfide	571	N,T	
Structural class II			
Allyl methyl disulfide	568	N,T	No safety concern
Allyl disulfide	572	N,T	
Dicyclohexyl disulfide	575	N,T	
Methyl phenyl disulfide	576	N	
Benzyl methyl disulfide	577	N	
Benzyl disulfide	579	N,T	
Structural class III			
Phenyl disulfide	578	N	No safety concern
Subgroup viii — disulfides with oxidized side-chains			
Structural class I			
2-Methyl-2-(methyldithio)propanal	580	N,T	No safety concern
Ethyl 2-(methyldithio)propionate	581	N,T	
Subgroup ix — trisulfides and polysulfides			
Structural class I			
Dimethyl trisulfide	582	N,T	No safety concern
Ethyl methyl trisulfide	583	N,T	
Methyl propyl trisulfide	584	N,T	
Dipropyl trisulfide	585	N,T	
Structural class II			
Allyl methyl trisulfide	586	N,T	No safety concern
Diallyl trisulfide	587	N,T	
Diallyl polysulfide	588	N,T	
Subgroup x — heterocyclic disulfides			
Structural class II			
3,5-Dimethyl-1,2,4-trithiolane	573	N,T	No safety concern
3-Methyl-1,2,4-trithiane	574	N,T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic and aromatic sulfides and thiols (*continued*)			
Subgroup xi — thioesters			
Structural class I			
Methyl thioacetate	482	N,T	No safety concern
Ethyl thioacetate (*S*-ethyl ethanethioate)	483	N	
Methyl thiobutyrate (*S*-methyl butanethioate)	484	N,T	
Propyl thioacetate (*S*-propyl thioacetate)	485	N	
S-Methyl 2-methylbutanethioate	486	N,T	
S-Methyl 3-methylbutanethioate	487	N,T	
S-Methyl 4-methylpentanethioate	488	N,T	
S-Methyl hexanethioate	489	N,T	
Allyl thiopropionate (*S*-2-propenyl propanethioate)	490	N,T	
Prenyl thioacetate	491	N	
Methylthio 2-(acetyloxy)propionate (1-[(methylthio)methyl]ethyl acetate)	492	N	
Methylthio 2-(propionyloxy)propionate (*S*-methyl 2-(propionyloxy)-propanethioate)	493	N	
3-(Acetylmercapto)hexyl acetate	494	N	
Structural class II			
S-Methyl benzothioate (*S*-methyl thiobenzoate)	504	N,T	No safety concern
cis- and *trans*-Menthone-8-thioacetate (*S*-[1-methyl-1-(4-methyl-2-oxocyclohexyl)ethyl]ethanethioate)	506	N	
Subgroup xii — sulfoxides			
Methylsulfinylmethane (dimethyl sulfoxide)	507	N,T	No safety concern
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups			
Structural class I			
2-Oxobutyric acid (2-oxobutanoic acid)	589	N,T	No safety concern
Methyl 2-hydroxy-4-methylpentanoate (methyl 2-hydroxy-4-methylvalerate)	590	N,T	
Methyl 2-oxo-3-methylpentanoate (methyl 3-methyl-2-oxo-pentanoate)	591	N,T	
Citronelloxyacetaldehyde ([(3,7-dimethyl-6-octenyl)oxy]-acetaldehyde	592	N,T	
3-Oxobutanal dimethyl acetal (4,4-dimethoxy-2-butanone)	593	N	
Ethyl 3-hydroxybutyrate	594	N,T	
Ethyl acetoacetate	595	N	
Butyl acetoacetate	596	N,T	
Isobutyl acetoacetate	597	N,T	
Isoamyl acetoacetate (isopentyl acetoacetate)	598	N,T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (*continued*)			
Structural class I (*continued*)			
Geranyl acetoacetate (3,7-dimethyl-2,6-octadienyl acetoacetate)	599	N,T	No safety concern
Methyl 3-hydroxyhexanoate	600	N,T	
Ethyl 3-hydroxyhexanoate	601	N	
Ethyl 3-oxohexanoate	602	N	
Ethyl 2,4-dioxohexanoate	603	N,T	
3-(Hydroxymethyl)-2-heptanone	604	N,T	
1,3-Nonanediol acetate (mixed esters) (1,3-nonanediol monoacetate)	605	N,T	
Levulinic acid (4-oxopentanoic acid)	606	N	
Ethyl levulinate (ethyl 4-oxopentanoate)	607	N	
Butyl levulinate (butyl 4-oxopentanoate)	608	N	
1,4-Nonanediol diacetate	609	N,T	
Hydroxycitronellol (3,7-dimethyloctane-1,7-diol)	610	N,T	
Hydroxycitronellal (7-hydroxy-3,7-dimethyloctanal)	611	N	
Hydroxycitronellal dimethyl acetal (8,8-dimethoxy-2,6-dimethyl-2-octanol)	612	N	
Hydroxycitronellal diethyl acetal (8,8-diethoxy-2,6-dimethyloctan-2-ol)	613	N,T	
Diethyl malonate (diethyl propanedioate)	614	N	
Butyl ethyl malonate (butyl ethyl propanedioate)	615	N,T	
Dimethyl succinate (dimethyl butanedioate)	616	N	
Diethyl succinate (diethyl butanedioate)	617	N	
Fumaric acid[c] ((2*E*)2-butenedioic acid)	618	R,T	
(–)-Malic acid ((2*S*)-hydroxybutanedioic acid)	619	R,T	
Diethyl malate (diethyl hydroxybutanedioate)	620	N,T	
Mixture of (+)-, (–)-, (+/–)- and meso-tartaric acid (mixture of (+)-, (–)-, (+/–)- and meso-2,3-dihydroxybutanedioic acid)	621	R	
Diethyl tartrate (diethyl 2,3-dihydroxybutanedioate)	622	N	
Adipic acid (hexanedioic acid)	623	R	
Diethyl sebacate (diethyl decanedioate)	624	N	
Dibutyl sebacate (dibutyl decanedioate)	625	N	
Ethylene brassylate (1,4-dioxacycloheptadecane-5,17-dione)	626	N	
Aconitic acid (1-propene-1,2,3-tricarboxylic acid)	627	N,T	
Ethyl aconitate (mixed esters; ethyl 1-propene-1,2,3-tricarboxylate)	628	N,T	

Flavouring agent[a]	No.	Specifications[b]	Conclusion based on current intake
Aliphatic primary alcohols, aldehydes, carboxylic acids, acetals and esters containing additional oxygenated functional groups (*continued*)			
Structural class I (*continued*)			
Triethyl citrate[c] (triethyl 2-hydroxy-1,2,3-propanetricarboxylate)	629	R,T	No safety concern
Tributyl acetylcitrate (tributyl 2-(acetyloxy)-1,2,3-propanetricarboxylate)	630	N,T	
3-Methyl-2-oxobutanoic acid and its sodium salt	631	N,T	
3-Methyl-2-oxopentanoic acid and its sodium salt	632	N,T	
4-Methyl-2-oxopentanoic acid and its sodium salt	633	N,T	
2-Oxopentanedioic acid	634	N	
3-Hydroxy-2-oxopropionic acid	635	N	

[a] The substance names are given as they appear in the specifications monograph (FAO Food and Nutrition Paper, No. 52, Add. 7, 1999). In cases where substances were evaluated under their trivial name, the systematic name is given in parentheses.
[b] N, new specifications prepared; R, existing specifications revised: T, the existing, new or revised specifications are tentative and further information is required (see Annex 3).
[c] The ADI for this substance was maintained.

Peanut oil and soya bean oil

The Committee reviewed available information on the potential allergenicity of peanut oil and soya bean oil. It concluded that manufacturing processes that would consistently yield safe products have not been defined, since:

- the processes by which the peanut oil and soya bean oil tested clinically in humans were refined were not clearly described;
- comparable data on the protein content of those oils that had been clinically tested were not available; and
- the quality and validation of the analytical procedures used to determine the concentration of residual protein in the oils were not clearly described.

The information that would be required for a full re-evaluation of peanut oil and soya bean oil is described in section 5 of the main report.

Contaminants

Lead

The provisional tolerable weekly intake (PTWI) of 25 µg/kg of body weight was maintained. The Committee considered the results of a quantitative risk assessment and concluded that the concentrations

of lead found currently in food would have negligible effects on the neurobehavioural development of infants and children. The Committee noted, however, that examples of foods with high levels of lead remain in commerce. The simulation model that is presented in the report could be used to evaluate the effects of any proposed regulatory interventions to reduce exposure to lead. A full risk assessment of dietary intake of lead should also take into account other sources of exposure.

Methylmercury

The PTWI of 3.3μg/kg of body weight was maintained. The Committee considered data on intake, quantitative relationships between daily intake of methylmercury and concentrations in blood and hair, and epidemiological studies in progress. The information available was insufficient to evaluate neurodevelopmental effects on the children of mothers who had a low intake of methylmercury. No clear indication of consistent risk was detected in the epidemiological studies. The Committee noted that fish, the major source of methylmercury in the diet, makes an important contribution to nutrition, especially in certain regional and ethnic diets, and recommended that its nutritional benefits be weighed against the possibility of harm when limits on methylmercury concentrations in fish or on fish consumption are being considered.

The information that would be required for a full re-evaluation of methylmercury is described in Annex 3.

Zearalenone

A provisional maximum tolerable daily intake (PMTDI) of 0.5μg/kg of body weight was established.

Food additives considered for specifications

Food additive	Specifications[a]
α-Acetolactate decarboxylase from *Bacillus brevis* expressed in *B. subtilis*	R
Adipic acid	R
α-Amylase from *B. megaterium* expressed in *B. subtilis*	R
α-Amylase from *B. stearothermophilus* expressed in *B. subtilis*	R
Argon	N
Calcium hydrogen sulfite	W
Carob bean gum	R
Carotenes, algae	S
Carotenes, vegetable	S
Chymosin A from *Escherichia coli* K-12 containing the prochymosin A gene	R

Food additive	Specifications[a]
Chymosin B from *Aspergillus niger* var. *awamori* containing the prochymosin B gene	R
Chymosin B from *Kluyveromyces lactis* containing the prochymosin B gene	R
Citric acid	R
Ferrous gluconate	R
Ferrous sulfate	R
Ferrous sulfate, dried	N
Fumaric acid	R
Guar gum	R
Helium	N
Magnesium gluconate	R
DL-Malic acid	R
Maltogenic amylase from *B. stearothermophilus* expressed in *B. subtilis*	R
Nitrogen	R
Oxygen	N
Potassium metabisulfite	R
Potassium sulfite	R
Riboflavin from *B. subtilis*	R
Sodium hydrogen sulfite	R
Sodium metabisulfite	R
Sodium sulfite	R
Sodium thiosulfate	R
Sucrose esters of fatty acids	R
DL-Tartaric acid	R
L(+)-Tartaric acid	R
Thaumatin	R
Xanthan gum	R

[a] N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or not required; W, existing specifications withdrawn.

Food additives considered for evaluation of national intake assessments

Substance	Conclusions
Annatto extracts (bixin)	Intake estimates based on levels proposed in the draft General Standard for Food Additives[a] and the range of foods in which use is allowed integrated with national food consumption data exceeded the ADI of 0–0.065 mg/kg of body weight, expressed as bixin. Intake assessments based on national permitted levels would not exceed the ADI for most population groups. Data from Brazil, however, provided evidence that 28% of the population consume annatto seeds directly as a condiment and have chronic intakes of the order of 150% of the ADI.

Substance	Conclusions
Annatto extracts (bixin) (*continued*)	The Committee recommended that populations that have a high intake of annatto extracts continue to be monitored. The Committee also recommended that annatto extracts be re-evaluated in 2001, to ensure that all the relevant data on annatto extracts have been reviewed.
Canthaxanthin	Intake estimates based on levels proposed in the draft General Standard for Food Additives[a] and the range of foods in which use is allowed integrated with national food consumption data exceeded the ADI of 0–0.03 mg/kg of body weight. Indirect exposure through the use of canthaxanthin as a colourant in animal feeds is the major source of canthaxanthin in food. The Committee concluded that long-term intake of canthaxanthin is unlikely to exceed the ADI.
Erythrosine	The intake of erythrosine could exceed the ADI of 0–0.1 mg/kg of body weight if the maximum limits proposed in the draft General Standard for Food Additives[a] are widely adopted at the national level. Non-food sources of erythrosine, such as pharmaceutical products, should be included in intake assessments, as they may make a significant contribution to total intake if consumed over a long period. The Committee concluded that long-term intake of erythrosine is unlikely to exceed the ADI, as erythrosine would be used in only a limited number of foods.
Iron oxides	Iron oxides are permitted for use in foods in the draft General Standard for Food Additives[a] under conditions of good manufacturing practice. On the basis of national standards, the Committee concluded that it is unlikely that intake of iron oxides would exceed the ADI of 0–0.5 mg/kg of body weight.

[a] Intake estimates based on food additive levels in the draft General Standard for Food Additives (GSFA) being developed by the Codex Committee on Food Additives and Contaminants integrated with national food consumption data will be gross overestimates of actual intakes in any one country because the levels proposed in the draft GSFA are generally compiled by adopting the highest level of use of any one food category submitted by Member States or nongovernmental organizations. The range of food uses specified in the draft GSFA is also usually much wider than in national standards.

Annex 3
Further information required

Thickening agent

Curdlan

The following information is required for evaluation in 2001:

- information on the use of curdlan, including the maximum and typical levels expected to occur in the food categories proposed in the draft General Standard for Food Additives being developed by the Codex Committee on Food Additives and Contaminants;
- data on the consumption of foodstuffs that might contain curdlan in different regions of the world, to permit assessment of the intake.

Miscellaneous substance

Sodium sulfate

Information on the functional effect and actual uses of sodium sulfate in food is required for evaluation in 2001.

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

Information on those flavouring agents for which the specifications are designated as "tentative" is required for evaluation in 2000.

Contaminant

Methylmercury

The results of the 96-month evaluation of the cohort of children in the Seychelles exposed pre- and postnatally to methylmercury in fish, and other relevant data that have become available, are required for evaluation in 2002.

Annex 4
Report of an ad hoc Panel on Food Allergens

An ad hoc Panel on Food Allergens met in Geneva, Switzerland, from 18 to 19 February 1999 to provide advice to the Joint FAO/WHO Expert Committee on Food Additives about criteria for labelling. The following scientists participated:

Members

Dr J. Greig, Joint Food Safety and Standards Group, Department of Health, London, England

Dr M. Lovik, Department of Environmental Medicine, National Institute of Public Health, Oslo, Norway

Dr C. Madsen, Institute of Food Safety and Toxicology, Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark

Professor S.L. Taylor, Department of Food Science and Toxicology, University of Nebraska, Lincoln, NE, USA

Secretariat

Dr J.L. Herrman, International Programme on Chemical Safety, WHO, Geneva, Switzerland

Dr E. Smith, International Programme on Chemical Safety, WHO, Geneva, Switzerland

Introduction

Allergens in food have been considered by the Codex Committee on Food Labelling on a number of occasions since 1993, when a working paper on the consideration of potential allergens in foods was prepared by Norway, in cooperation with Finland, Iceland and Sweden (*1*).

An FAO Technical Consultation on Food Allergies was held in Rome from 13 to 14 November 1995, which was asked inter alia to "provide guidance on the development of science-based criteria to determine which foods or food products should be placed on a list of those foods or food products whose presence should always be declared in the list of ingredients on a food label, because of their allergenic properties". The Consultation confirmed that the listing of foods and ingredients known to cause allergies and intolerance that had been developed by the Codex Committee on Food Labelling was appropriate, with some modifications (*2*).

The revised list of those foods and ingredients known to cause food allergies and intolerance and whose presence should always be declared was identified as the following:

- cereals containing gluten (i.e. wheat, rye, barley, oats, spelt or their hybridized strains) and their products;

- crustacea and their products;
- eggs and egg products;
- fish and fish products;
- peanuts, soya beans and their products;
- milk and milk products (including lactose);
- tree nuts and nut products; and
- sulfite at concentrations ≥10mg/kg.

After debate in the Codex Committee on Food Labelling, this list was forwarded at step 8 for adoption by the Codex Alimentarius Commission. During the debate, further questions arose which required advice from the Joint FAO/WHO Expert Committee on Food Additives, the Committee that provides scientific recommendations to the Codex Alimentarius Commission relating to food additives and ingredients in food.

The Panel was convened to consider the issues forwarded by the Codex Committee and to provide guidance on them to the Expert Committee. The issues included:

- identifying criteria for adding foodstuffs to the list of common allergenic foods forwarded by the Codex Committee on Food Labelling, if found to be necessary;
- developing criteria for identifying products of foodstuffs on the list of the Codex Committee for which labelling of the food source is unnecessary; and
- considering ways in which FAO and WHO could provide continuous guidance in this area to the Expert Committee.

The literature on food allergies

The Panel noted that the scientific literature contains numerous recent authoritative reviews on food allergy, its manifestations and its causes. It considered that a selection of articles (*1–6*), complemented by this report, would provide the information that the Expert Committee required.

Terminology

The Panel noted some inconsistency in the use of certain terms in various documents. It therefore agreed on the following definitions of terms. The Panel recognized that individual heightened responses to foods and food ingredients can occur through a variety of mechanisms. "Food allergies" involve abnormal responses of the immune system to food components, which are usually naturally-occurring proteins. They can be classified as either immunoglobulin E (IgE)-mediated reactions (e.g. allergies to peanuts or eggs) or cell-mediated

reactions (e.g. coeliac disease). "Food intolerance" is an abnormal response to food components that occurs through a non-immunological mechanism. Food intolerance may include metabolic food disorders, anaphylactoid reactions and idiosyncratic illnesses. "Metabolic food disorders" are enzymatic deficiencies such as lactose intolerance. "Anaphylactoid reactions" involve the release of histamine and other mediators from mast cells without the intervention of IgE. Although anaphylactoid reactions to specific drugs have been well documented, the involvement of this mechanism in adverse food reactions remains unproven. "Idiosyncratic reactions" are those that occur through unknown mechanisms in susceptible individuals. Although the cause-and-effect relationship between the ingestion of a specific food and the onset of symptoms of idiosyncratic illnesses is a subject of some debate, sulfite-induced asthma is an example of an idiosyncratic illness in which the cause-and-effect relationship is unequivocally established but the mechanism of the reaction remains unknown. Food additive intolerances are usually considered as idiosyncratic illnesses.

The Panel further recognized that certain types of food intoxication such as with histamine-containing toxins (e.g. scombrotoxins) involve allergy-like reactions, but in contrast to the situation with food allergies and intolerance, all consumers are susceptible.

Criteria for the addition of foodstuffs to the list of the Codex Committee on Food Labelling

In determining whether a foodstuff should be added to the list of common allergenic foods drawn up by the Codex Committee on Food Labelling, the Panel recommended that all of the following criteria be met:

(i) The existence of a credible cause-and-effect relationship, based on a positive reaction to a double-blind placebo-controlled food challenge or unequivocal reports of a reaction with the typical features of a severe allergic or intolerance reaction.

(ii) The existence of reports of systemic reactions after exposure to the foodstuff, the reactions including atopic dermatitis, urticaria, angio-oedema, laryngeal oedema, asthma, rhinitis, abdominal pain, diarrhoea, vomiting, anaphylactic shock and chronic severe malabsorption syndrome.

(iii) Data on the prevalence of food allergies in children and adults, supported by appropriate clinical studies (i.e. double-blind placebo-controlled food challenges) in the general population of several countries. However, the Panel noted that such information is available only for infants, from certain countries and for certain foodstuffs. The Panel therefore agreed that any available

data, such as the comparative prevalence of a specific food allergy in groups of patients in several countries, could be used as an alternative, preferably backed up by the results of a double-blind placebo-controlled food challenge.

The list adopted by the Codex Committee on Food Labelling includes not only allergenic foods but also products of such foods. Because allergens are naturally-occurring proteins, the Panel considered whether the definition is too broad in that it may include products that are not allergenic because they do not contain sufficient protein to elicit an allergic reaction. The available data do not, however, permit definition of the amount of allergenic protein necessary to elicit an allergic reaction.

The Panel therefore recommended that products of the allergenic foods on the list of the Codex Committee on Food Labelling should always be labelled as such, unless they are on the list of products that are excluded from the requirement for labelling of the food source.

The criteria for inclusion of a product on the latter list are:

(i) evidence that a clinical study with a double-blind placebo-controlled food challenge has confirmed that the specific product does not elicit allergic reactions in a group of patients with clinical allergy to the parent foodstuff;
(ii) submission of specifications for the product and its manufacturing process which demonstrate that the process yields a consistently safe product; and
(iii) for products implicated in coeliac disease:

   (a) products of rye, barley and oats would not be required to meet the criteria set out in (i) and (ii) above because IgE-mediated allergic reactions to these cereal grains are uncommon;
   (b) products of wheat, spelt and their hybridized strains would be required to meet the criteria set out in (i) and (ii) above; and
   (c) products of wheat, rye, barley, oats and spelt and their hybridized strains would be required to adhere to existing specifications for gluten-free products.

To the knowledge of the Panel, only two products may currently fulfil these criteria: highly refined peanut oil and soya bean oil. The Panel recommended that these two products be reviewed at the next meeting of the Joint FAO/WHO Expert Committee on Food Additives to consider food additives and contaminants.

The Panel recognized that application of all the criteria set out above would rely heavily on expert advice. It considered that such advice would best be provided by a body which, because of geographical variation in food allergy and in diets, should be constituted so as to have representation from a variety of disciplines and global regions.

References

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2. *Report of the Technical Consultation on Food Allergies, Rome, Italy, 13–14 November 1995.* Rome, Food and Agriculture Organization of the United Nations, 1995 (unpublished document).
3. Løvik M et al., eds. Chemical exposure and food allergy/intolerance. Proceedings of an IPCS/NIPH scientific symposium on chemical exposure and food allergy/intolerance. *Environmental Toxicology and Pharmacology*, 1997, 4:1–186.
4. Metcalfe DD, Sampson HA, Simon RA, eds. *Food allergy: adverse reactions to foods and food additives*, 2nd ed. Cambridge, MA, Blackwell Science, 1997.
5. Bousquet J et al. Scientific criteria and the selection of allergenic foods for product labelling. *Allergy*, 1998, 53 (Suppl. 47):3–21.
6. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. *Peanut allergy*. London, Department of Health, 1998.