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

World Health Organization
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Joint FAO/WHO Expert Committee on Food Additives

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Members

Dr J. Alexander, Professor and Director, Department of Food Toxicology, Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway

Dr Junshi Chen, Chinese Centers for Disease Control and Prevention, Institute of Nutrition and Food Safety, Beijing, China

Dr S.M. Dagher. Professor, American University of Beirut, Beirut, Lebanon

Dr D.G. Hattan, Senior Toxicologist, Office of Food Additives Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, Maryland, USA

Dr Y. Kawamura, Section Chief, Division of Food Additives, National Institute of Health Sciences, Tokyo, Japan (*FAO Consultant*)

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

Dr P.M. Kuznesof, Senior Chemist, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, Maryland, USA (*Joint Rapporteur*)

Dr J.C. Larsen, Head, Division of Gene Technology and Biochemistry, Institute of Food Safety and Nutrition, Danish Veterinary and Food Administration, Ministry of Food, Agriculture and Fisheries, Søborg, Denmark (*Chairman*)

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 (*Vice-Chairman*)

Dr G. Pascal, Scientific Director for Human Nutrition and Food Safety, National Institute for Agricultural Research, Paris, France (*Joint Rapporteur*)

Dr M.V. Rao, Head of Chemistry Unit, Food and Environment Laboratory, Dubai Municipality, Dubai, United Arab Emirates

Ms E. Vavasour, Food Directorate, Health Canada, Ottawa, Ontario, Canada

Professor R. Walker, Emeritus Professor of Food Science, School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey, England

Mrs H. Wallin, Senior Food Control Officer, National Food Agency, Helsinki, Finland

Dr D.B. Whitehouse, Consultant, Food Regulatory Affairs, Bowdon, Cheshire, England

Secretariat

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Dr C.E. Fisher, Hatfield, Herts, England (*FAO Consultant*)

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Mr E.F.F. Hecker, Chairman of the Codex Committee on Food Additives and Contaminants, Deputy Director of the Department of Food and Veterinary Affairs, Ministry of Agriculture, Nature Management and Fisheries, The Hague, Netherlands

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

Dr T. Inoue, Director, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr Taiyi Jin, Department of Occupational Health and Toxicology, Public Health School, Fudan University, Shanghai, China (*WHO Temporary Adviser*)

Dr C.A. Lawrie, Food Standards Agency, London, England (*FAO Consultant*)

Ms C. LeClercq, National Research Institute for Food and Nutrition Research, Rome, Italy (*FAO Consultant*)

Mr M. Luetzow, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, Rome, Italy (*Joint Secretary*)

Professor J.R. Lupton, Regents Professor and University Faculty Fellow, Faculty of Nutrition, Texas A&M University, College Station, Texas, USA (*WHO Temporary Adviser*)

Dr A. Mattia, Division of Petition Review, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, Maryland, USA (*WHO Temporary Adviser*)

Dr G. Moy, Food Safety Programme, World Health Organization, Geneva, Switzerland

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

Dr A. Nishikawa, Section Chief, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan (*WHO Temporary Adviser*)

Dr S.W. Page, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

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

Dr S. Resnik, Department of Industry, Faculty of Exact and Natural Sciences, University of Buenos Aires, Buenos Aires, Argentina (*FAO Consultant*)

Dr O. Sabzevari, Associate Professor in Molecular Toxicology and Drug Metabolism, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran (*WHO Temporary Adviser*)

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

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

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

Specifications are issued separately by FAO under the title:

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

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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

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

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

Dr C. Tohyama, Director, Environmental Health Sciences Division, National Institute for Environmental Studies, Tsukuba, Japan (*WHO Temporary Adviser*)

Dr P.J.P. Verger, Scientific Directorate on Human Nutrition and Food Safety, National Institute for Agricultural Research, Paris, France (*FAO Consultant*)

Professor G. Williams, Professor of Pathology, Director, Environmental Pathology and Toxicology, New York Medical College, Valhalla, New York, USA (*WHO Temporary Adviser*)

Contents

1. Introduction

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

2. General considerations

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

The tasks before the Committee were:

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

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

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

2.1 Modification of the agenda

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

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

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

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

2.2 Principles governing the toxicological evaluation of compounds on the agenda

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

2.2.1 *Safety evaluation of flavouring agents*

Flavouring agents with other functional uses

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

Flavouring agents that undergo chemical change in food

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

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

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

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

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

- chemical characterization (including contaminants and natural constituents) and development of specifications for food additives, pesticides and veterinary drugs;
- maximum residue levels for pesticides and veterinary drugs;
- exposure assessment (including short- and long-term intake, deterministic and probabilistic approaches and cumulative and aggregate exposure);
- toxicological test procedures and evaluation (including general issues and specific toxicological end-points);
- human data (clinical studies, epidemiological studies including biomarkers, potentially susceptible populations, allergenicity, intolerance and interactions with the diet);
- evaluations (including such issues as thresholds of toxicological concern, potency estimates, margins of safety, benchmark doses, acute reference doses, special considerations for contaminants, uncertainty and variability, scientific criteria for re-evaluation);
- principles related to specific substances (e.g. flavouring agents and substances consumed in large amounts); and
- a glossary (nomenclature and terminology).

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

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

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

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

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

2.3.1 *Specifications of identity and purity of food additives*

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

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

In considering this issue, the Committee recommended that:

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

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

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

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

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

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

2.5 Risk analysis principles and exposure assessment

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

2.6 Risk analysis terms related to food safety

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

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

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

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

2.7 Consideration of guidelines

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

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

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

2.8 Specifications for flavouring agents

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

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

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

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

3. Specific food additives (other than flavouring agents)

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

3.1 Safety evaluations

3.1.1 *Alitame*

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

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

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

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

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

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

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