WHO Technical Report Series
947

EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Sixty-eighth report of the
Joint FAO/WHO Expert Committee on
Food Additives

Food and Agriculture Organization of the United Nations

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3.1.9 *Steviol glycosides*

Explanation

Steviol glycosides are natural constituents of the plant *Stevia rebaudiana* Bertoni. Stevioside and rebaudioside A are the component glycosides of principal interest for their sweetening properties.

At its fifty-first meeting, the Committee evaluated toxicological data on stevioside and the aglycone steviol (Annex 1, reference *137*) and specified needs for further information. Based on new data and information, at its sixty-third meeting (Annex 1, reference *173*), the Committee determined that the commercial material should be known as "steviol glycosides" and established tentative specifications for material containing not less than 95% of the total of four specified glycosylated derivatives of steviol (i.e. stevioside, rebaudioside A, rebaudioside C and dulcoside A). Additionally, the sum of stevioside and rebaudioside A content was specified at not less than 70% of the four steviol glycosides. Also at its sixty-third meeting, the Committee reviewed additional biochemical and toxicological data on the major steviol glycosides and on the aglycone steviol. The Committee established a temporary ADI of 0–2 mg/kg bw for steviol glycosides, expressed as steviol, on the basis of the NOEL of 970 mg stevioside/kg bw per day (or 383 mg/kg bw, expressed as steviol) in a 2-year study in rats and a safety factor of 200. The total safety factor incorporated a factor of 2 related to the need for further information, to be provided by 2007, on the pharmacological effects of steviol glycosides in humans. The Committee specified a need for studies involving repeated exposure of normotensive and hypotensive individuals and insulin-dependent and insulin-independent diabetics to dietary and therapeutic doses.

In order to remove the tentative designation from the specifications, the Committee requested further analytical data on the distribution and concentrations of all component steviol glycosides, including those not identified in these tentative specifications; on the method of analysis for the determination of all component steviol glycosides, including those not identified in the tentative specifications; on the nature and concentration of the non-steviol glycoside fractions; on the quantities of residual solvents from purification steps of the manufacturing process; and on the hydrolytic stability of the steviol glycosides in acidic foods and beverages.

At the current meeting, the Committee considered the information that had become available since the sixty-third meeting. This comprised two toxicological submissions, which included a summary of published studies and some unpublished data, additional information identified from the scientific literature and responses intended to resolve the outstanding issues relevant to the specifications. Additionally, the Committee received a request to remove the requirement for a minimum content of the sum of stevioside and rebaudioside A from the specifications. It was noted that such a limit was unnecessary because of the requirement that total steviol glycosides be not less than 95% and because all the steviol glycosides decompose upon ingestion to steviol, on which the temporary ADI was based. The Committee was also informed that results of an ongoing toxicity testing programme, including clinical studies, would be available by August 2007.

Chemical and technical considerations

The Committee received more detail on the process of purification of the additive to support the specified high level of purity.

The Committee examined results of thermal and hydrolytic stability studies for the material under evaluation. Isosteviol, glucose and "oligoglucose" were identified as the only decomposition products of steviol glycosides that had been subjected to various conditions of pH and temperature.

A summary of literature studies that addressed the stabilities of stevioside and rebaudioside A was available to the Committee. Although the summarized studies contained no information on the purities of these two substances, the Committee found the information helpful for the present evaluation because the specified material includes products that may be 95% stevioside or 95% rebaudioside A.

Toxicological data

A number of studies provide further information on the metabolism of steviol glycosides in humans, which will support future risk assessments.

The newly published data mainly involved studies of effects of steviol glycosides in a range of in vitro and animal models related to diabetes. Although these studies provide additional information on the mechanism of action of steviol glycosides, they did not directly address the Committee's stated requirements.

One new study was available relating to genotoxicity. A stevioside product (purity 88.6%) was administered in drinking-water to rats for 45 days (equivalent to about 200 mg/kg bw per day, expressed as steviol). Increased DNA damage (assessed by a comet assay) was observed in nucleated cells of peripheral blood after 5 and 6 weeks compared with concurrent controls. There were no significant effects in blood cells at earlier time points. Increased DNA damage was seen in liver, brain and spleen cells at termination of the study (*21*). The DNA damage in blood cells of control animals was also increased at weeks 5 and 6 compared with earlier time points, and no positive controls were included. Taking into account the lack of genotoxicity of stevioside in studies reviewed previously and that the product tested in this non-standard assay did not meet the proposed specification for steviol glycosides, the Committee considered that the results of this study were not convincing evidence of genotoxicity.

Three new controlled oral studies of effects of steviol glycosides in humans were available.

In an unpublished study submitted to the Committee, 250 mg of a product containing 91.7% total steviol glycosides, including 64.5% stevioside and 18.9% rebaudioside A, were administered to groups of type 1 ($n = 8$) and type 2 diabetics ($n = 15$) and non-diabetics ($n = 15$) 3 times daily for 3 months in a double-blind, placebo-controlled trial. Control groups with the same number of subjects received a placebo. After 3 months, there were no significant changes in systolic or diastolic blood pressure, glycated haemoglobin, blood lipids or renal or hepatic function. No side-effects were reported (*22*). The Committee noted that this product did not meet the proposed specification of "not less than 95% steviol glycosides" and that the study was conducted in a small number of subjects.

A study of antihypertensive effects was conducted in previously untreated mild hypertensive patients with crude stevioside obtained from the leaves of *S. rebaudiana.* Patients with essential hypertension were subjected to a placebo phase for 4 weeks and then received either capsules containing placebo for 24 weeks or crude stevioside at consecutive doses of 3.75 mg/kg bw per day (7 weeks), 7.5 mg/kg bw per day (11 weeks) and 15 mg/kg bw per day (6 weeks). Comparison of patients receiving stevioside with those on placebo showed neither antihypertensive nor adverse effects of stevioside (*23*). The product in this study also did not meet the proposed specification.

According to a study available in abstract form only, a randomized double-blind, placebo-controlled study was conducted in subjects with type 2 diabetes. Fifty-five subjects received 500 mg stevioside (purity unspecified) or placebo (maize starch) 3 times daily for 3 months. Compared with the placebo, stevioside did not reduce the incremental area under the glucose response curve and maintained the insulin response and glycated haemoglobin and fasting blood glucose levels. No difference in lipids or blood pressure was observed (*24*).

In addition, a study of skin prick allergy testing with 10% stevioside conducted in infants (50 per group, aged 4 months to 2 years) indicated a higher prevalence of sensitization to stevioside in infants with allergic diseases compared with healthy infants (*25*).

Evaluation

The Committee considered that the newly available data did not raise additional concerns regarding the safety of steviol glycosides, but that the results of ongoing clinical studies, which more closely address the requirements specified at the sixty-third meeting, would be essential to its evaluation. The Committee therefore agreed to extend the temporary ADI of 0–2 mg/kg bw for steviol glycosides, expressed as steviol, pending submission of the results of the ongoing studies by the end of 2008. No toxicological monograph was prepared.

The Committee concluded that steviol glycosides are sufficiently thermally and hydrolytically stable for use in foods, including acidic beverages, under normal conditions of processing and storage. The other outstanding issues on method of manufacture and specifications were also adequately resolved.

The existing tentative specifications were revised by requiring an assay of not less than 95% of the total of seven named steviol glycosides, by deleting the assay requirement for the sum of stevioside and rebaudioside A content to be not less than 70%, by adding pH as an identification test, by increasing the limit for loss-on-drying and by establishing a limit for residual solvent. The tentative designation was removed, and the Chemical and Technical Assessment prepared by the Committee at its sixty-third meeting was updated.

Annex 1

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

1. *General principles governing the use of food additives* (First report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 15, 1957; WHO Technical Report Series, No. 129, 1957 (out of print).
2. *Procedures for the testing of intentional food additives to establish their safety for use* (Second report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 17, 1958; WHO Technical Report Series, No. 144, 1958 (out of print).
3. *Specifications for identity and purity of food additives (antimicrobial preservatives and antioxidants)* (Third report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, Vol. I. *Antimicrobial preservatives and antioxidants*, Rome, Food and Agriculture Organization of the United Nations, 1962 (out of print).
4. *Specifications for identity and purity of food additives (food colours)* (Fourth report of the Joint FAO/WHO Expert Committee on Food Additives). These specifications were subsequently revised and published as *Specifications for identity and purity of food additives*, Vol. II. *Food colours*, Rome, Food and Agriculture Organization of the United Nations, 1963 (out of print).
5. *Evaluation of the carcinogenic hazards of food additives* (Fifth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 29, 1961; WHO Technical Report Series, No. 220, 1961 (out of print).
6. *Evaluation of the toxicity of a number of antimicrobials and antioxidants* (Sixth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Report Series, No. 31, 1962; WHO Technical Report Series, No. 228, 1962 (out of print).
7. *Specifications for the identity and purity of food additives and their toxicological evaluation: emulsifiers, stabilizers, bleaching and maturing agents* (Seventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 35, 1964; WHO Technical Report Series, No. 281, 1964 (out of print).
8. *Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants* (Eighth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 38, 1965; WHO Technical Report Series, No. 309, 1965 (out of print).
9. *Specifications for identity and purity and toxicological evaluation of some antimicrobials and antioxidants*. FAO Nutrition Meetings Report Series, No. 38A, 1965; WHO/Food Add/24.65 (out of print).

10. *Specifications for identity and purity and toxicological evaluation of food colours*. FAO Nutrition Meetings Report Series, No. 38B, 1966; WHO/Food Add/66.25.

11. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases* (Ninth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 40, 1966; WHO Technical Report Series, No. 339, 1966 (out of print).

12. *Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour treatment agents, acids, and bases.* FAO Nutrition Meetings Report Series, No. 40A, B, C; WHO/Food Add/67.29.

13. *Specifications for the identity and purity of food additives and their toxicological evaluation: some emulsifiers and stabilizers and certain other substances* (Tenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 43, 1967; WHO Technical Report Series, No. 373, 1967.

14. *Specifications for the identity and purity of food additives and their toxicological evaluation: some flavouring substances and non nu-tritive sweetening agents* (Eleventh report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 44, 1968; WHO Technical Report Series, No. 383, 1968.

15. *Toxicological evaluation of some flavouring substances and non nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44A, 1968; WHO/Food Add/68.33.

16. *Specifications and criteria for identity and purity of some flavouring substances and non-nutritive sweetening agents.* FAO Nutrition Meetings Report Series, No. 44B, 1969; WHO/Food Add/69.31.

17. *Specifications for the identity and purity of food additives and their toxicological evaluation: some antibiotics* (Twelfth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 45, 1969; WHO Technical Report Series, No. 430, 1969.

18. *Specifications for the identity and purity of some antibiotics.* FAO Nutrition Meetings Series, No. 45A, 1969; WHO/Food Add/69.34.

19. *Specifications for the identity and purity of food additives and their toxicological evaluation: some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances* (Thirteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 46, 1970; WHO Technical Report Series, No. 445, 1970.

20. *Toxicological evaluation of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 46A, 1970; WHO/Food Add/70.36.

21. *Specifications for the identity and purity of some food colours, emulsifiers, stabilizers, anticaking agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 46B, 1970; WHO/Food Add/70.37.

22. *Evaluation of food additives: specifications for the identity and purity of food additives and their toxicological evaluation: some extraction solvents and certain other substances; and a review of the technological efficacy of some antimicrobial agents* (Fourteenth report of the Joint FAO/WHO Expert Committee on Food Additives).

FAO Nutrition Meetings Series, No. 48, 1971; WHO Technical Report Series, No. 462, 1971.

23. *Toxicological evaluation of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48A, 1971; WHO/Food Add/70.39.

24. *Specifications for the identity and purity of some extraction solvents and certain other substances.* FAO Nutrition Meetings Report Series, No. 48B, 1971; WHO/Food Add/70.40.

25. *A review of the technological efficacy of some antimicrobial agents.* FAO Nutrition Meetings Report Series, No. 48C, 1971; WHO/Food Add/70.41.

26. *Evaluation of food additives: some enzymes, modified starches, and certain other substances: Toxicological evaluations and specifications and a review of the technological efficacy of some antioxidants* (Fifteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 50, 1972; WHO Technical Report Series, No. 488, 1972.

27. *Toxicological evaluation of some enzymes, modified starches, and certain other substances.* FAO Nutrition Meetings Report Series, No. 50A, 1972; WHO Food Additives Series, No. 1, 1972.

28. *Specifications for the identity and purity of some enzymes and certain other substances.* FAO Nutrition Meetings Report Series, No. 50B, 1972; WHO Food Additives Series, No. 2, 1972.

29. *A review of the technological efficacy of some antioxidants and synergists.* FAO Nutrition Meetings Report Series, No. 50C, 1972; WHO Food Additives Series, No. 3, 1972.

30. *Evaluation of certain food additives and the contaminants mercury, lead, and cadmium* (Sixteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 51, 1972; WHO Technical Report Series, No. 505, 1972, and corrigendum.

31. *Evaluation of mercury, lead, cadmium and the food additives amaranth, diethylpyrocarbamate, and octyl gallate.* FAO Nutrition Meetings Report Series, No. 51A, 1972; WHO Food Additives Series, No. 4, 1972.

32. *Toxicological evaluation of certain food additives with a review of general principles and of specifications* (Seventeenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 53, 1974; WHO Technical Report Series, No. 539, 1974, and corrigendum (out of print).

33. *Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers, and thickening agents.* FAO Nutrition Meetings Report Series, No. 53A, 1974; WHO Food Additives Series, No. 5, 1974.

34. *Specifications for identity and purity of thickening agents, anticaking agents, antimicrobials, antioxidants and emulsifiers.* FAO Food and Nutrition Paper, No. 4, 1978.

35. *Evaluation of certain food additives* (Eighteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 54, 1974; WHO Technical Report Series, No. 557, 1974, and corrigendum.

36. *Toxicological evaluation of some food colours, enzymes, flavour enhancers, thickening agents, and certain other food additives.* FAO Nutrition Meetings Report Series, No. 54A, 1975; WHO Food Additives Series, No. 6, 1975.

37. *Specifications for the identity and purity of some food colours, enhancers, thickening agents, and certain food additives.* FAO Nutrition Meetings Report Series, No. 54B, 1975; WHO Food Additives Series, No. 7, 1975.

38. *Evaluation of certain food additives: some food colours, thickening agents, smoke condensates, and certain other substances* (Nineteenth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Nutrition Meetings Series, No. 55, 1975; WHO Technical Report Series, No. 576, 1975.

39. *Toxicological evaluation of some food colours, thickening agents, and certain other substances.* FAO Nutrition Meetings Report Series, No. 55A, 1975; WHO Food Additives Series, No. 8, 1975.

40. *Specifications for the identity and purity of certain food additives.* FAO Nutrition Meetings Report Series, No. 55B, 1976; WHO Food Additives Series, No. 9, 1976.

41. *Evaluation of certain food additives* (Twentieth report of the Joint FAO/WHO Expert Committee on Food Additives). FAO Food and Nutrition Meetings Series, No. 1, 1976; WHO Technical Report Series, No. 599, 1976.

42. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 10, 1976.

43. *Specifications for the identity and purity of some food additives.* FAO Food and Nutrition Series, No. 1B, 1977; WHO Food Additives Series, No. 11, 1977.

44. *Evaluation of certain food additives* (Twenty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 617, 1978.

45. *Summary of toxicological data of certain food additives.* WHO Food Additives Series, No. 12, 1977.

46. *Specifications for identity and purity of some food additives, including antioxidant, food colours, thickeners, and others.* FAO Nutrition Meetings Report Series, No. 57, 1977.

47. *Evaluation of certain food additives and contaminants* (Twenty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 631, 1978.

48. *Summary of toxicological data of certain food additives and contaminants.* WHO Food Additives Series, No. 13, 1978.

49. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 7, 1978.

50. *Evaluation of certain food additives* (Twenty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 648, 1980, and corrigenda.

51. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 14, 1980.

52. *Specifications for identity and purity of food colours, flavouring agents, and other food additives.* FAO Food and Nutrition Paper, No. 12, 1979.

53. *Evaluation of certain food additives* (Twenty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 653, 1980.

54. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 15, 1980.

55. *Specifications for identity and purity of food additives (sweetening agents, emulsifying agents, and other food additives).* FAO Food and Nutrition Paper, No. 17, 1980.

56. *Evaluation of certain food additives* (Twenty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 669, 1981.

57. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 16, 1981.

58. *Specifications for identity and purity of food additives (carrier solvents, emulsifiers and stabilizers, enzyme preparations, flavouring agents, food colours, sweetening agents, and other food additives).* FAO Food and Nutrition Paper, No. 19, 1981.

59. *Evaluation of certain food additives and contaminants* (Twenty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 683, 1982.

60. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 17, 1982.

61. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 25, 1982.

62. *Evaluation of certain food additives and contaminants* (Twenty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 696, 1983, and corrigenda.

63. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 18, 1983.

64. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 28, 1983.

65. *Guide to specifications—General notices, general methods, identification tests, test solutions, and other reference materials.* FAO Food and Nutrition Paper, No. 5, Rev. 1, 1983.

66. *Evaluation of certain food additives and contaminants* (Twenty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 710, 1984, and corrigendum.

67. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 19, 1984.

68. *Specifications for the identity and purity of food colours.* FAO Food and Nutrition Paper, No. 31/1, 1984.

69. *Specifications for the identity and purity of food additives.* FAO Food and Nutrition Paper, No. 31/2, 1984.

70. *Evaluation of certain food additives and contaminants* (Twenty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 733, 1986, and corrigendum.

71. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 34, 1986.

72. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 20. Cambridge University Press, 1987.

73. *Evaluation of certain food additives and contaminants* (Thirtieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 751, 1987.

74. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 21. Cambridge University Press, 1987.

75. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 37, 1986.

76. *Principles for the safety assessment of food additives and contaminants in food.* WHO Environmental Health Criteria, No. 70. Geneva, World Health Organization, 1987 (out of print). The full text is available electronically at www.who.int/pcs.

77. *Evaluation of certain food additives and contaminants* (Thirty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 759, 1987, and corrigendum.

78. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 22. Cambridge University Press, 1988.

79. *Specifications for the identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 38, 1988.

80. *Evaluation of certain veterinary drug residues in food* (Thirty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 763, 1988.

81. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 23. Cambridge University Press, 1988.

82. *Residues of some veterinary drugs in animals and foods*. FAO Food and Nutrition Paper, No. 41, 1988.

83. *Evaluation of certain food additives and contaminants* (Thirty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 776, 1989.

84. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 24. Cambridge University Press, 1989.

85. *Evaluation of certain veterinary drug residues in food* (Thirty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 788, 1989.

86. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 25, 1990.

87. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/2, 1990.

88. *Evaluation of certain food additives and contaminants* (Thirty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 789, 1990, and corrigenda.

89. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 26, 1990.

90. *Specifications for identity and purity of certain food additives.* FAO Food and Nutrition Paper, No. 49, 1990.

91. *Evaluation of certain veterinary drug residues in food* (Thirty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 799, 1990.

92. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 27, 1991.

93. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/3, 1991.

94. *Evaluation of certain food additives and contaminants* (Thirty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 806, 1991, and corrigenda.

95. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 28, 1991.

96. *Compendium of food additive specifications (Joint FAO/WHO Expert Committee on Food Additives (JECFA)). Combined specifications from 1st through the 37th meetings, 1956–1990*. Rome, Food and Agricultural Organization of the United Nations, 1992 (2 volumes).

97. *Evaluation of certain veterinary drug residues in food* (Thirty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 815, 1991.

98. *Toxicological evaluation of certain veterinary residues in food.* WHO Food Additives Series, No. 29, 1991.

99. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/4, 1991.

100. *Guide to specifications—General notices, general analytical techniques, identification tests, test solutions, and other reference materials.* FAO Food and Nutrition Paper, No. 5, Ref. 2, 1991.

101. *Evaluation of certain food additives and naturally occurring toxicants* (Thirty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 828, 1992.

102. *Toxicological evaluation of certain food additives and naturally occurring toxicants.* WHO Food Additives Series, No. 30, 1993.

103. *Compendium of food additive specifications: addendum 1.* FAO Food and Nutrition Paper, No. 52, 1992.

104. *Evaluation of certain veterinary drug residues in food* (Fortieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 832, 1993.

105. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 31, 1993.

106. *Residues of some veterinary drugs in animals and food.* FAO Food and Nutrition Paper, No. 41/5, 1993.

107. *Evaluation of certain food additives and contaminants* (Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 837, 1993.

108. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 32, 1993.

109. *Compendium of food additive specifications: addendum 2.* FAO Food and Nutrition Paper, No. 52, Add. 2, 1993.

110. *Evaluation of certain veterinary drug residues in food* (Forty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 851, 1995.

111. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 33, 1994.

112. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/6, 1994.

113. *Evaluation of certain veterinary drug residues in food* (Forty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 855, 1995, and corrigendum.

114. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 34, 1995.

115. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/7, 1995.

116. *Evaluation of certain food additives and contaminants* (Forty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 859, 1995.

117. *Toxicological evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 35, 1996.

118. *Compendium of food additive specifications: addendum 3.* FAO Food and Nutrition Paper, No. 52, Add. 3, 1995.

119. *Evaluation of certain veterinary drug residues in food* (Forty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 864, 1996.

120. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 36, 1996.

121. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/8, 1996.

122. *Evaluation of certain food additives and contaminants* (Forty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 868, 1997.

123. *Toxicological evaluation of certain food additives.* WHO Food Additives Series, No. 37, 1996.

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

125. *Evaluation of certain veterinary drug residues in food* (Forty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 876, 1998.

126. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 38, 1996.

127. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/9, 1997.

128. *Evaluation of certain veterinary drug residues in food* (Forty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 879, 1998.

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159. *Residues of some veterinary drugs in animals and foods.* FAO Food and Nutrition Paper, No. 41/14, 2002.

160. *Evaluation of certain food additives and contaminants* (Fifty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 913, 2002.

161. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 50, 2003.

162. *Compendium of food additive specifications: addendum 10*. FAO Food and Nutrition Paper, No. 52, Add. 10, 2002.

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167. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 52, 2004.

168. *Compendium of food additive specifications: addendum 11.* FAO Food and Nutrition Paper, No. 52, Add. 11, 2003.

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172. *Compendium of food additive specifications: addendum 12.* FAO Food and Nutrition Paper, No. 52, Add. 12, 2004.

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179. *Safety evaluation of certain food additives.* WHO Food Additives Series, No. 56, 2006.

180. *Combined compendium of food additive specifications.* FAO JECFA Monographs 1, 2005.

181. *Evaluation of certain veterinary drug residues in food* (Sixty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 939, 2006.

182. *Residue evaluation of certain veterinary drugs.* FAO JECFA Monographs 2, 2006.

183. *Toxicological evaluation of certain veterinary drug residues in food.* WHO Food Additives Series, No. 57, 2006.

184. *Evaluation of certain food additives and contaminants* (Sixty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 940, 2007.

185. *Compendium of food additive specifications.* FAO JECFA Monographs 3, 2006.

186. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 58 (in preparation).

187. *Evaluation of certain food additives and contaminants* (Sixty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 947, 2007.

188. *Safety evaluation of certain food additives and contaminants.* WHO Food Additives Series, No. 59 (in preparation).

189. *Compendium of food additive specifications.* FAO JECFA Monographs 4 (in preparation).

Annex 2

Acceptable daily intakes, other toxicological information and information on specifications

Food additives and ingredients evaluated toxicologically or assessed for dietary exposure

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Acidified sodium chlorite (ASC)		The available toxicological data were sufficient to assess the safety of ASC by setting ADIs for chlorite and chlorate. Chlorite: ADI of 0–0.03 mg/kg bw Chlorate: ADI of 0–0.01 mg/kg bw New specifications were prepared for sodium chlorite and one of the acids used in the preparation of ASC, sodium hydrogen sulfate.
Asparaginase from *Aspergillus oryzae* expressed in *Aspergillus oryzae*	N	ADI "not specified"[b] when used in the applications specified and in accordance with good manufacturing practice.
Carrageenan and processed *Eucheuma* seaweed	R R	The group ADI "not specified"[b] for the sum of carrageenan and processed *Eucheuma* seaweed was maintained for food additive uses in foods other than infant formula. The Committee was of the view that based on the information available, it is inadvisable to use carrageenan or processed *Eucheuma* seaweed in infant formulas.
Cyclotetraglucose and cyclotetraglucose syrup (listed on draft agenda as cyclotetraose)	N N,T	A temporary ADI "not specified"[b] was allocated for cyclotetraglucose and cyclotetraglucose syrup pending submission of data on the identity of the bacterial strain used to produce the 6-GT/IMT enzyme preparation and evidence of its lack of pathogenicity and toxigenicity. The specifications for cyclotetraglucose syrup were made tentative pending information on the total saccharide content and test methods and the unidentified fraction.

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Isoamylase from *Pseudomonas amyloderamosa*	N	ADI "not specified"[b] when used in the applications specified and in accordance with good manufacturing practice.
Magnesium sulfate	R	ADI "not specified"[b]
Phospholipase A1 from *Fusarium venenatum* produced by *Aspergillus oryzae*	S	ADI "not specified"[b] when used in the applications specified and in accordance with good manufacturing practice.
Sodium iron(III) ethylenediaminetetraacetic acid (EDTA)	S	Sodium iron EDTA is suitable for use as a source of iron for food fortification to fulfil nutritional iron requirements, provided that the total intake of iron from all food sources including contaminants does not exceed the PMTDI of 0.8 mg/kg bw. Total intake of EDTA should not exceed acceptable levels, also taking into account the intake of EDTA from the food additive use of other EDTA compounds. An ADI of 0–2.5 mg/kg bw was previously established for the calcium disodium and disodium salts of EDTA, equivalent to up to 1.9 mg EDTA/kg bw.
Steviol glycosides	R	The temporary ADI of 0–2 mg/kg bw for steviol glycosides, expressed as steviol, was extended until 2008, pending submission of the results of the ongoing studies. The Committee considered that the newly available data did not raise additional concerns regarding the safety of steviol glycosides, but that the results of ongoing clinical studies, which more closely address the requirements specified at the sixty-third meeting, would be essential to its evaluation. The specifications were revised and the tentative assignation was removed. The method of assay includes a minimum requirement of 95% of the total of seven steviol glycosides.

[a] N: new specifications prepared; R: existing specifications revised; S: existing specifications maintained; T: tentative specifications.

[b] ADI "not specified" is used to refer to a food substance of very low toxicity that, 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 effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI expressed in numerical form is not deemed necessary. An additive 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.

Food additives, including flavouring agents, considered for specifications only

Food additive	Specifications[a]
Anisyl acetone	W
Furfural	W
Ethyl maltol	R
Maltol	R
Nisin preparation	R
Pectins	R
Polyvinyl alcohol	R
Sucrose esters of fatty acids	R
Zeaxanthin-rich extract from *Tagetes erecta*	W

Flavouring agent	JECFA No.	Specifications[a]
3-Acetyl-2,5-dimethylfuran	1506	R
Ethyl maltol	1481	R
Maltol	1480	R
Maltyl isobutyrate	1482	R
3-Methyl-2-oxobutanoic acid	631	R
3-Methyl-2-oxopentanoic acid	632	R
4-Methyl-2-oxopentanoic acid	633	R
Sodium 3-methyl-2-oxobutanoate	631.1	R
Sodium 3-methyl-2-oxopentanoate	632.1	R
Sodium 4-methyl-2-oxopentanoate	633.1	R
Sodium 2-oxo-3-phenylpropionate	1479	R
2,4,5-Trimethyl-delta-oxazolin	1559	R

[a] R: existing specifications revised; W: existing specifications withdrawn.

Food contaminants evaluated toxicologically or assessed for dietary exposure

Food contaminant	Tolerable intakes and other toxicological recommendations
Aflatoxins (AFL) (Intake assessment from almonds, Brazil nuts, hazelnuts, pistachios and dried figs, impact of various MLs)	The Committee decided to base the assessment of the impact of different MLs for AFL exposure on data provided by producing countries, noting that these better represent the materials in commerce and result in a robust estimate of AFL dietary exposure from the tree nuts. Consumption of almonds, Brazil nuts, hazelnuts, pistachios and dried figs contributes greater than 5% of the total AFL dietary exposure in only 5 of the 13 GEMS/Food Consumption Cluster Diets (clusters B, C, D, E and M). If fully enforced, an ML at 20 µg/kg in almonds, Brazil nuts, hazelnuts, pistachios and dried figs would have an impact on the relative contribution to dietary AFL exposure only in these clusters, including high-level consumers of tree nuts. This

Food contaminant	Tolerable intakes and other toxicological recommendations
	contribution is due solely to the elevated AFL level in pistachios. For tree nuts other than pistachios, the presence of an ML has no effect on dietary AFL exposure. Moreover, the Committee concluded that enforcing an ML of 15, 10, 8 or 4 µg/kg would have little further impact on the overall dietary exposure to AFL in all five of the highest exposed population groups compared with setting an ML of 20 µg/kg. Regarding dried figs, the Committee concluded that whatever the hypothetical ML scenario applied (no ML, 4, 8, 10, 15 or 20 µg/kg), there would be no impact on the overall dietary exposure to AFL. The Committee noted that the reduction of dietary AFL exposure is an important public health goal, particularly in populations that consume high levels of any potentially AFL-contaminated food.
Ochratoxin A	The previous PTWI of 100 ng/kg bw was retained. The new data, including data on mode of action of ochratoxin A in the kidney, do not indicate any reason to modify the previous risk assessment approach taken by JECFA. The current estimate of overall dietary exposure to ochratoxin A from cereals, based mainly on European data, is about 8–17 ng/kg bw per week, based on processed cereals, compared with 25 ng/kg bw per week in the previous evaluation, based on raw cereals. The current estimates are well below the PTWI. Contamination levels in the majority of raw cereal samples were below 5 µg/kg. Owing to the very small number of samples contaminated above the highest proposed limit of 20 µg/kg, such an ML would have very limited impact compared with no ML. The Committee concluded that the use of an ML of 5 or 20 µg/kg would be unlikely to have an impact on dietary exposure to ochratoxin A. The Committee was unable to reach a conclusion regarding the situation in developing countries, owing to the lack of adequate data to consider.

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

A. Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Ethyl-2-methyl-3,4-pentadienoate	353	S	No safety concern
Methyl 4-pentenoate	1616	N	No safety concern
2-Methylbut-2-en-1-ol	1617	N	No safety concern
Ethyl 4-pentenoate	1618	N	No safety concern
4-Pentenal	1619	N	No safety concern
3-Isopropenylpentanedioic acid	1620	N	No safety concern
trans-3-Hexenol	1621	N	No safety concern
trans-4-Hexenal	1622	N	No safety concern
5-Hexenol	1623	N	No safety concern

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Methyl (*Z*)-3-hexenoate	1624	N	No safety concern
cis-4-Octenol	1625	N	No safety concern
Ethyl (*Z*)-3-hexenoate	1626	N	No safety concern
3-Octenoic acid	1627	N	No safety concern
(*Z*)-3-Octenyl propionate	1628	N	No safety concern
trans-4-Octenoic acid	1629	N	No safety concern
Methyl (*Z*)-5-octenoate	1630	N	No safety concern
cis-5-Octenoic acid	1631	N	No safety concern
Ethyl 3-octenoate	1632	N	No safety concern
cis-4-Decenol	1633	N	No safety concern
Isobutyl 10-undecenoate	1634	N	No safety concern
11-Dodecenoic acid	1635	N	No safety concern
(*Z*)-4-Dodecenal	1636	N	No safety concern
cis-9-Octadecenol	1637	N	No safety concern
cis-9-Octadecenyl acetate	1638	N	No safety concern
Methyl 10-undecenoate	1639	N	No safety concern
(*Z*)-8-Tetradecenal	1640	N	No safety concern
9-Octadecenal	1641	N	No safety concern
(*E*)-4-Nonenal	1642	N	No safety concern

[a] N: new specifications prepared; S: existing specifications maintained.

B. Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
2,3,4-Trimethyl-3-pentanol	1643	N	No safety concern
(±)-2,4,8-Trimethyl-7-nonen-2-ol	1644	N	No safety concern
(*E*)- and (*Z*)-2,4,8-Trimethyl-3,7-nonadien-2-ol	1645	N	No safety concern
Nerolidol	1646	N	No safety concern
1-Phenyl-3-methyl-3-pentanol	1649	N	No safety concern
p-α,α-Trimethylbenzyl alcohol	1650	N	No safety concern
(±)-Ethyl 2-hydroxy-2-methylbutyrate	1651	N	No safety concern
(±)-Ethyl 2-hydroxy-3-methylvalerate	1652	N	No safety concern
α,α-Dimethylphenethyl alcohol	1653	N	No safety concern
α,α-Dimethylphenethyl formate	1654	N	No safety concern
α,α-Dimethylphenethyl acetate	1655	N	No safety concern
α,α-Dimethylphenethyl butyrate	1656	N	No safety concern
α,α-Dimethylbenzyl isobutyrate	1657	N	No safety concern
Structural class II			
6-Acetoxydihydrotheaspirane	1647	N	No safety concern
6-Hydroxydihydrotheaspirane	1648	N	No safety concern

[a] N: new specifications prepared.

C. Simple aliphatic and aromatic sulfides and thiols

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Simple sulfides			
Structural class I			
2-Methyl-1-methylthio-2-butene	1683	N	No safety concern
2,4,6-Trithiaheptane	1684	N	No safety concern
2,5-Dithiahexane	1707	N	No safety concern
Acyclic sulfides with oxidized and thiol side-chains			
Structural class I			
Methionyl butyrate	1668	N	No safety concern
Methylthiomethylmercaptan	1675	N	No safety concern
(±)-Isobutyl 3-methylthiobutyrate	1677	N	No safety concern
3-(Methylthio)-2-butanone	1688	N	No safety concern
4-(Methylthio)-2-pentanone	1689	N	No safety concern
Methyl 3-(methylthio)butanoate	1690	N	No safety concern
Methyl (methylthio)acetate	1691	N	No safety concern
(±)-3-(Methylthio)heptanal	1692	N	No safety concern
(±)-3-(Ethylthio)butanol	1703	N	No safety concern
S-Allyl-L-cysteine	1710	N	No safety concern
Heterocyclic sulfides			
Structural class I			
(±)-2,8-Epithio-*cis*-*p*-menthane	1685	N	No safety concern
Simple thiols			
Structural class I			
Ethanethiol	1659	N	No safety concern
1-Pentanethiol	1662	N	No safety concern
Heptane-1-thiol	1663	N	No safety concern
2-Heptanethiol	1664	N	No safety concern
Structural class II			
(±)-1-Phenylethylmercaptan	1665	N	No safety concern
Thiols with oxidized side-chains			
Structural class I			
Propyl 2-mercaptopropionate	1667	N	No safety concern
(±)-4-Mercapto-4-methyl-2-pentanol	1669	N	No safety concern
4-Mercapto-2-pentanone	1670	N	No safety concern
(*S*)-1-Methoxy-3-heptanethiol	1671	N	No safety concern
Methyl 3-mercaptobutanoate	1674	N	No safety concern
Hexyl 3-mercaptobutanoate	1704	N	No safety concern
(±)-3-Mercapto-1-butyl acetate	1705	N	No safety concern
3-Mercapto-3-methyl-1-butyl acetate	1706	N	No safety concern
3-Mercaptoheptyl acetate	1708	N	No safety concern
Structural class II			
cis- and *trans*-Mercapto-*p*-menthan-3-one	1673	N	No safety concern
Structural class III			
2-Mercaptoanisole	1666	N	No safety concern
Diisopentyl thiomalate	1672	N	No safety concern

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Dithiols			
Structural class I			
Ethane-1,1-dithiol	1660	N	No safety concern
Dimercaptomethane	1661	N	No safety concern
bis(1-Mercaptopropyl)sulfide	1709	N	No safety concern
Simple disulfides			
Structural class I			
Ethyl methyl disulfide	1693	N	No safety concern
Ethyl propyl disulfide	1694	N	No safety concern
Methyl isopentyl disulfide	1696	N	No safety concern
Amyl methyl disulfide	1697	N	No safety concern
Butyl ethyl disulfide	1698	N	No safety concern
Diethyl disulfide	1699	N	No safety concern
Structural class II			
Allyl propyl disulfide	1700	N	No safety concern
Trisulfides			
Structural class I			
Ethyl propyl trisulfide	1695	N	No safety concern
Diethyl trisulfide	1701	N	No safety concern
Heterocyclic disulfides			
Structural class II			
3,5-Diethyl-1,2,4-trithiolane	1686	N	No safety concern
Mixture of 3,6-diethyl-1,2,4,5-tetrathiane (approx. 55%) and 3,5-diethyl-1,2,4-trithiolane (approx. 45%)	1687	N	No safety concern
Thioesters and acids			
Structural class I			
Thioacetic acid	1676	N	No safety concern
(*S*)-Methyl propanethioate	1678	N	No safety concern
(*S*)-Isopropyl 3-methylbut-2-enethioate	1679	N	No safety concern
Structural class II			
Allyl thiohexanoate	1681	N	No safety concern
Structural class III			
(*S*)-Ethyl 2-acetylaminoethanethioate	1680	N	No safety concern
Propyl propane thiosulfonate	1702	N	No safety concern

[a] N: new specifications prepared.

D. Aliphatic acyclic diols, triols and related substances

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
Dihydroxyacetone dimer	1716	N	No safety concern
1-Hydroxy-2-butanone	1717	N	No safety concern
Ethyl 3-acetoxy-2-methylbutyrate	1718	N	No safety concern
Methyl 5-acetoxyhexanoate	1719	N	No safety concern
Structural class III			
2,4-Dimethyl-1,3-dioxolane	1711	N	No safety concern
2-Hexyl-4,5-dimethyl-1,3-dioxolane	1712	N	No safety concern
cis- and *trans*-Ethyl 2,4-dimethyl-1,3-dioxolane-2-acetate	1715	N	No safety concern

[a] N: new specifications prepared.

E. Aliphatic acetals

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
(±)-1-Acetoxy-1-ethoxyethane	1726	N	No safety concern
Acetaldehyde hexyl isoamyl acetal	1727	N	No safety concern
1,1-Dimethoxy-*trans*-2-hexene	1728	N	No safety concern
Acetaldehyde diisoamyl acetal	1729	N	No safety concern
Isovaleraldehyde diethyl acetal	1730	N	No safety concern
Valeraldehyde dibutyl acetal	1731	N	No safety concern
Hexanal hexyl isoamyl acetal	1735	N	No safety concern
Hexanal dihexyl acetal	1738	N	No safety concern
Nonanal dimethyl acetal	1742	N	No safety concern
Dodecanal dimethyl acetal	1746	N	No safety concern
Acetaldehyde di-*cis*-3-hexenyl acetal	1747	N	No safety concern
Structural class III			
Isovaleraldehyde propyleneglycol acetal	1732	N	No safety concern
Isovaleraldehyde glyceryl acetal	1733	N	No safety concern
Valeraldehyde propyleneglycol acetal	1734	N	No safety concern
Hexanal octane-1,3-diol acetal	1736	N	No safety concern
Hexanal butane-2,3-diol acetal	1737	N	No safety concern
Heptanal propyleneglycol acetal	1739	N	No safety concern
2,6-Dimethyl-5-heptenal propyleneglycol acetal	1740	N	No safety concern
Octanal propyleneglycol acetal	1741	N	No safety concern
Nonanal propyleneglycol acetal	1743	N	No safety concern
Decanal propyleneglycol acetal	1744	N	No safety concern

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Undecanal propyleneglycol acetal	1745	N	No safety concern
Isobutanal propyleneglycol acetal	1748	N	No safety concern
Acetaldehyde 1,3-octanediol acetal	1749	N	No safety concern

[a] N: new specifications prepared.

F. Sulfur-containing heterocyclic compounds

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class II			
1-(3-Hydroxy-5-methyl-2-thienyl)ethanone	1750	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl formate	1751	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl propionate	1752	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl butanoate	1753	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl isobutyrate	1754	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl hexanoate	1755	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl octanoate	1756	N	No safety concern
2-(4-Methyl-5-thiazolyl)ethyl decanoate	1757	N	No safety concern
2,5-Dimethylthiazole	1758	N	No safety concern
2-Acetyl-2-thiazoline	1759	N	No safety concern
2-Propionyl-2-thiazoline	1760	N	No safety concern
2-Hexylthiophene	1764	N	No safety concern
5-Acetyl-2,3-dihydro-1,4-thiazine	1766	N	No safety concern
Structural class III			
cis- and *trans*-5-Ethyl-4-methyl-2-(2-methylpropyl) thiazoline	1761	N	No safety concern
cis- and *trans*-5-Ethyl-4-methyl-2-(1-methylpropyl) thiazoline	1762	N	No safety concern
Pyrrolidino-[1,2e]-4H-2,4-dimethyl-1,3,5-dithiazine	1763	N	No safety concern
3-(Methylthio)-methylthiophene	1765	N	No safety concern

[a] N: new specifications prepared.

G. Aliphatic and aromatic amines and amides

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
4-Aminobutyric acid	1771	N	No safety concern
N-Gluconyl ethanolamine	1772	N	No safety concern
N-Gluconyl ethanolamine phosphate	1773	N	No safety concern
N-Lactoyl ethanolamine	1774	N	No safety concern
N-Lactoyl ethanolamine phosphate	1775	N	No safety concern
Structural class III			
N-(Heptan-4-yl)benzo[d][1,3]dioxole-5-carboxamide	1767	N	No safety concern
*N*1-(2,4-Dimethoxybenzyl)-*N*2-(2-(pyridin-2-yl)ethyl)oxalamide	1768	N	No safety concern
*N*1-(2-Methoxy-4-methylbenzyl)-*N*2-(2-(5-methylpyridin-2-yl)ethyl)oxalamide	1769	N	No safety concern
*N*1-(2-Methoxy-4-methylbenzyl)-*N*2-(2-(pyridin-2-yl)ethyl)oxalamide	1770	N	No safety concern
N-[(Ethoxycarbonyl)methyl]-*p*-menthane-3-carboxamide	1776	N	No safety concern
N-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dimethoxycinnamic acid amide	1777	N	No safety concern
N-3,7-Dimethyl-2,6-octadienyl cyclopropylcarboxamide	1779	N	No safety concern

[a] N: new specifications prepared.

H. Aliphatic alicyclic linear α,β-unsaturated di- and trienals and related alcohols, acids and esters

Flavouring agent	JECFA No.	Specifications[a]	Conclusions based on current estimated intake
Structural class I			
2,4-Hexadienyl acetate	1780	N	No safety concern
2,4-Hexadienyl propionate	1781	N	No safety concern
2,4-Hexadienyl isobutyrate	1782	N	No safety concern
2,4-Hexadienyl butyrate	1783	N	No safety concern
2,4-Heptadien-1-ol	1784	N	No safety concern
Nona-2,4,6-trienal	1785	N	No safety concern
2,4,7-Decatrienal	1786	N	No safety concern

[a] N: new specifications prepared.

Annex 3

Further information required or desired

Cyclotetraglucose and cyclotetraglucose syrup

Data are required on the identity of the bacterial strain used to produce the 6-GT/IMT enzyme preparation and evidence of its lack of pathogenicity and toxigenicity. For cyclotetraglucose syrup, information is needed on total saccharide content and test methods and the unidentified saccharide fraction.

Estragole

The evaluation of estragole was deferred to a future meeting, pending submission of data requested for the assessment of safety and specifications for use as a flavouring agent.

Steviol glycosides

The results of the ongoing toxicological and clinical studies, in particular studies addressing pharmacological effects, should be submitted by the end of 2008.

Annex 4

Summary of the safety evaluation of secondary components for flavouring agents with minimum assay values of less than 95%

JECFA No.	Flavouring agent	Minimum assay value (%)	Secondary components	Comments on secondary components
Linear and branched-chain aliphatic, unsaturated, unconjugated alcohols, aldehydes, acids and related esters				
1622	*trans*-4-Hexenal	76	16–20% *cis*-4-hexenal, 2–4% *cis*-3-hexen-1-ol, 1–2% hexanal	*cis*-4-Hexenal (No. 319) was evaluated by the Committee in 1998. It was concluded that *cis*-4-hexenal was not a safety concern at current levels of intake. *cis*-3-Hexen-1-ol (No. 315) was evaluated by the Committee in 1998. It was concluded that *cis*-3-hexen-1-ol was not a safety concern at current levels of intake. In a 98-day rat drinking-water study, *cis*-3-hexen-1-ol exhibited a NOEL of 120–180 mg/kg bw per day (Gaunt et al., 1969). Hexanal (No. 92) was evaluated by the Committee in 1997. It was concluded that hexanal was not a safety concern at current levels of intake.
1636	(*Z*)-4-Dodecenal	94	3–4% dodecanal	Dodecanal is expected to share the same metabolic fate as (*Z*)-4-dodecenal and the other saturated and unsaturated aliphatic alcohols, aldehydes, carboxylic acids and related esters in this group (Dawson et al., 1964; Gaillard & Derache, 1965).
1637	*cis*-9-Octadecenol	85	8–9% hexadecanol, 5–6% octadecanol	Hexadecanol and octadecanol are expected to share the same metabolic fate as *cis*-9-octadecenol and the other saturated and unsaturated aliphatic alcohols, aldehydes, carboxylic acids and related esters in this group (Dawson et al., 1964; Gaillard & Derache, 1965).

1638	*cis*-9-Octadecenyl acetate	92	2–3% hexadecyl acetate, 2–3% octadecyl acetate	Hexadecyl acetate and octadecyl acetate are anticipated to share the same metabolic fate as *cis*-9-octadecenyl acetate and the other alcohols, aldehydes, carboxylic acids and related esters in this group (Gangolli & Shilling, 1968; Longland et al., 1977; Drake et al., 1978; Heymann, 1980; Graffner-Nordberg et al., 1998; Hosokawa et al., 2001).
1641	9-Octadecenal	94	3–5% octadecenal	Octadecenal is anticipated to share the same metabolic fate as 9-octadecenal and the other alcohols, aldehydes, carboxylic acids and related esters in this group (Dawson et al., 1964; Gaillard & Derache, 1965).
1642	(*E*)-4-Nonenal	93	1–2% 2-nonen-4-ol, 5–6% 2*E*,4*E*-nonadienal	2-Nonen-4-ol and 2*E*,4*E*-nonadienal are anticipated to share the same metabolic fate as (*E*)-4-nonenal and the other alcohols, aldehydes, carboxylic acids and related esters in this group (Dawson et al., 1964; Gaillard & Derache, 1965).
Aliphatic acyclic and alicyclic terpenoid tertiary alcohols and structurally related substances				
1650	*p*-α,α-trimethylbenzyl alcohol	90	9–11% *p*-isopropenyltoluene	*p*-Isopropenyltoluene (No. 1333, *p*,α-dimethylstyrene) was evaluated by the Committee in 2004. It was concluded that *p*,α-dimethylstyrene was not a safety concern at current levels of intake. In a 90-day rat study, *p*,α-dimethylstyrene exhibited NOELs of 0.63 and 0.62 mg/kg bw per day for males and females, respectively (Posternak et al., 1969).
1654	α,α-Dimethylphenethyl formate	93	5–7% α,α-dimethylphenethyl alcohol	α,α-Dimethylphenethyl alcohol is anticipated to share the same metabolic fate as the other tertiary terpenoid alcohols in this group (Williams, 1959; Parke et al., 1974; Horning et al., 1976; Ventura et al., 1985).

Simple aliphatic and aromatic sulfides and thiols				
1660	Ethane-1,1-dithiol	1	Owing to malodorous nature, available only as a 1% solution in ethanol	Ethanol (No. 41) was evaluated by the Committee in 1996. It was concluded that ethanol was not a safety concern at current levels of intake.
1670	4-Mercapto-2-pentanone	1	Owing to malodorous nature, available only as a 1% solution in acetoin	Acetoin (No. 405) was evaluated by the Committee in 1998. It was concluded that acetoin was not a safety concern at current levels of intake.
1672	Diisopentyl thiomalate	94	2–3% diisopentyl thiotartronate	Diisopentyl thiotartronate is anticipated to undergo simultaneous metabolism of sulfur and oxygenated functional groups (Gachon et al., 1988; Karim et al., 1988; Feng & Solsten, 1991; Wilson et al., 1991; Black et al., 1993). Sulfoxide formation is usually the predominant metabolic detoxication pathway.
1673	*cis*- and *trans*-Mercapto-*p*-menthan-3-one	89	8–9% piperitone, 1–2% α-terpineol	Piperitone (No. 435) was evaluated by the Committee in 1998. It was concluded that piperitone was not a safety concern at current levels of intake. α-Terpineol (No. 366) was evaluated by the Committee in 1998. It was concluded that α-terpineol was not a safety concern at current levels of intake.
1684	2,4,6-Trithiaheptane	10	Owing to malodorous nature, available only as a 10% solution in triacetin	Triacetin (No. 920) was evaluated by the Committee in 2002. It was concluded that triacetin was not a safety concern at current levels of intake.
1685	(±)-2,8-Epithio-*cis*-*p*-menthane	93	5–6% d-limonene	d-Limonene (No. 1324) was evaluated by the Committee in 2004. It was concluded that d-limonene was not a safety concern at current levels of intake.
1687	Mixture of 3,6-diethyl-1,2,4,5-tetrathiane and 3,5-diethyl-1,2,4-trithiolane	1	Owing to malodorous nature, available only as a 1% solution in vegetable oil	Vegetable oil is a common component of traditional foods.

1692	(±)-3-(Methylthio)heptanal	92	5–7% 2-(*E*)-heptenal	2-(*E*)-Heptenal (No. 1360, *trans*-2-heptenal) was evaluated by the Committee in 2004. It was concluded that 2-(*E*)-heptenal was not a safety concern at current levels of intake.
1693	Ethyl methyl disulfide	80	8–10% dimethyl disulfide, 7–8% diethyl disulfide	Dimethyl disulfide (No. 564) was evaluated by the Committee in 1999. It was concluded that dimethyl disulfide was not a safety concern at current levels of intake. Diethyl disulfide (No. 1699) was evaluated by the Committee at the present meeting. It was concluded that diethyl disulfide was not a safety concern at current levels of intake. Diethyl disulfide is anticipated to undergo reduction to ethylthiol with subsequent methylation. Ethyl methyl sulfide is oxidized and eliminated in the urine (Snow, 1957).
1695	Ethyl propyl trisulfide	50	20–30% diethyl trisulfide, 20–30% dipropyl trisulfide	Diethyl trisulfide (No. 1701) was evaluated by the Committee at the present meeting. It was concluded that diethyl trisulfide was not a safety concern at current levels of intake. Diethyl trisulfide is predicted to be converted rapidly to the corresponding disulfide with subsequent reduction to thiol (Moutiez et al., 1994), which is then metabolized via the various pathways for simple thiols. Dipropyl trisulfide (No. 585) was evaluated by the Committee in 1999. It was concluded that dipropyl trisulfide was not a safety concern at current levels of intake.
1696	Methyl isopentyl disulfide	92	3–5% crotonic acid	Crotonic acid (No. 1371, (*E*)-2-butenoic acid) was evaluated by the Committee in 2004. It was concluded that (*E*)-2-butenoic acid was not a safety concern at current levels of intake.

1698	Butyl ethyl disulfide	90	2–3% diethyl disulfide, 5–6% dibutyl disulfide	Diethyl disulfide (No. 1699) was evaluated by the Committee at the present meeting. It was concluded that diethyl disulfide was not a safety concern at current levels of intake. Diethyl disulfide is anticipated to undergo reduction to ethylthiol with subsequent methylation. Ethyl methyl sulfide is oxidized and eliminated in the urine (Snow, 1957). Dibutyl disulfide is anticipated to undergo reduction to the corresponding thiol, which will be methylated. Butyl methyl sulfide will be oxidized and eliminated in the urine (Snow, 1957).
1700	Allyl propyl disulfide	93	1–2% allyl propyl sulfide, 1–2% dipropyl sulfide	Allyl propyl sulfide and dipropyl sulfide are anticipated to undergo rapid oxidation to form the corresponding sulfoxides and potentially sulfones, which are eliminated in the urine (Damani, 1987).
1709	bis-(1-Mercaptopropyl)sulfide	56	36% 3,5-diethyl-1,2, 4-trithiolane, approximately 5% dipropyl trisulfide	3,5-Diethyl-1,2,4-trithiolane (No. 1686) was evaluated by the Committee at the present meeting. It was concluded that 3,5-diethyl-1,2,4-trithiolane was not a safety concern at current levels of intake. 3,5-Diethyl-1,2,4-trithiolane is anticipated to undergo oxidation and subsequent elimination in the urine or reduction to the free dithiol (Nelson & Cox, 2000). Dipropyl trisulfide (No. 585) was evaluated by the Committee in 1999. It was concluded that dipropyl trisulfide was not a safety concern at current levels of intake.
1717	1-Hydroxy-2-butanone	90	5–10% acetoin	Acetoin (No. 405) was evaluated by the Committee in 1998. It was concluded that acetoin was not a safety concern at current levels of intake.

Aliphatic and aromatic amines and amides				
1774	*N*-Lactoyl ethanolamine	90	6–8% 2-aminoethanol lactate	2-Aminoethanol lactate is anticipated to undergo hydrolysis to form ethanolamine and lactic acid (Schmid et al., 1985). Lactic acid (No. 930) was evaluated by the Committee in 2001. It was concluded that lactic acid was of no safety concern at current levels of intake. 2-Aminoethanol is anticipated to undergo conjugation with glucuronic acid via the alcohol moiety, or, as a primary aliphatic amine with an accessible α-substituted carbon atom, it may be *N*-oxidized to nitroso groups and subsequently oximes by cytochrome P450 enzymes (Uehleke, 1973).
1775	*N*-Lactoyl ethanolamine phosphate	90	6–10% ammonium formate	Ammonium formate is anticipated to hydrolyse to form ammonia and formic acid. Formic acid (No. 79) was evaluated by the Committee in 1997. It was concluded that formic acid was not a safety concern at current levels of intake. Ammonia found in the intestinal lumen by either ingestion or endogenous production is rapidly absorbed into the portal vein and converted to urea by the liver via the Krebs-Henseleit urea cycle (Furst et al., 1969; Pitts, 1971; Mathews & van Holde, 1990; Nelson & Cox, 2000).

References for Annex 4

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