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-nutritive 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 anti-oxidants, 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 Additive 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.
129. **Toxicological evaluation of certain veterinary drug residues in food**. WHO Food Additives Series, No. 39, 1997.
130. **Residues of some veterinary drugs in animals and foods**. FAO Food and Nutrition Paper, No. 41/10, 1998.
131. **Evaluation of certain food additives and contaminants** (Forty-ninth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 884, 1999.
132. **Safety evaluation of certain food additives and contaminants**. WHO Food Additives Series, No. 40, 1998.
133. **Compendium of food additive specifications: addendum 5**. FAO Food and Nutrition Paper, No. 52, Add. 5, 1997.
134. **Evaluation of certain veterinary drug residues in food** (Fiftieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 888, 1999.
135. **Toxicological evaluation of certain veterinary drug residues in food**. WHO Food Additives Series, No. 41, 1998.
136. **Residues of some veterinary drugs in animals and foods**. FAO Food and Nutrition Paper, No. 41/11, 1999.
137. **Evaluation of certain food additives** (Fifty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 891, 2000.

138. **Safety evaluation of certain food additives.** WHO Food Additives Series, No. 42, 1999.
139. **Compendium of food additive specifications: addendum 6.** FAO Food and Nutrition Paper, No. 52, Add. 6, 1998.
140. **Evaluation of certain veterinary drug residues in food** (Fifty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 893, 2000.
141. **Toxicological evaluation of certain veterinary drug residues in food.** WHO Food Additives Series, No. 43, 2000.
142. **Residues of some veterinary drugs in animals and foods.** FAO Food and Nutrition Paper, No. 41/12, 2000.
143. **Evaluation of certain food additives and contaminants** (Fifty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 896, 2000.
144. **Safety evaluation of certain food additives and contaminants.** WHO Food Additives Series, No. 44, 2000.
145. **Compendium of food additive specifications: addendum 7.** FAO Food and Nutrition Paper, No. 52, Add. 7, 1999.
146. **Evaluation of certain veterinary drug residues in food** (Fifty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 900, 2001.
147. **Toxicological evaluation of certain veterinary drug residues in food.** WHO Food Additives Series, No. 45, 2000.
148. **Residues of some veterinary drugs in animals and foods.** FAO Food and Nutrition Paper, No. 41/13, 2000.
149. **Evaluation of certain food additives and contaminants** (Fifty-fifth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 901, 2001.
150. **Safety evaluation of certain food additives and contaminants.** WHO Food Additives Series, No. 46, 2001.
151. **Compendium of food additive specifications: addendum 8.** FAO Food and Nutrition Paper, No. 52, Add. 8, 2000.
152. **Evaluation of certain mycotoxins in food** (Fifty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series No. 906, 2002.
153. **Safety evaluation of certain mycotoxins in food.** WHO Food Additives Series, No. 47/FAO Food and Nutrition Paper 74, 2001.
154. **Evaluation of certain food additives and contaminants** (Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 909, 2002.
155. **Safety evaluation of certain food additives and contaminants.** WHO Food Additives Series, No. 48, 2002.
156. **Compendium of food additive specifications: addendum 9.** FAO Food and Nutrition Paper, No. 52, Add. 9, 2001.
157. **Evaluation of certain veterinary drug residues in food** (Fifty-eighth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 911, 2002.
158. **Toxicological evaluation of certain veterinary drug residues in food.** WHO Food Additives Series, No. 49, 2002.
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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.
163. **Evaluation of certain veterinary drug residues in food** (Sixtieth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 918, 2003.
164. **Toxicological evaluation of certain veterinary drug residues in food**. WHO Food Additives Series, No. 51, 2003.
165. **Residues of some veterinary drugs in animals and foods**. FAO Food and Nutrition Paper, No. 41/15, 2003.
166. **Evaluation of certain food additives and contaminants** (Sixty-first report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 922, 2004.
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.
169. **Evaluation of certain veterinary drug residues in food** (Sixty-second report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 925, 2004.
170. **Residues of some veterinary drugs in animals and foods**. FAO Food and Nutrition Paper, No. 41/16, 2004.
171. **Toxicological evaluation of certain veterinary drug residues in food**. WHO Food Additives Series, No. 53, 2005.
172. **Compendium of food additive specifications: addendum 12**. FAO Food and Nutrition Paper, No. 52, Add. 12, 2004.
173. **Evaluation of certain food additives** (Sixty-third report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 928, 2005.
174. **Evaluation of certain food contaminants** (Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives). WHO Technical Report Series, No. 930, 2005 (in preparation).
175. **Safety evaluation of certain contaminants in food**. WHO Food Additives Series, No. 55/FAO Food and Nutrition Paper, No. 82, 2006.

ANNEX 2

ABBREVIATIONS USED IN THE MONOGRAPHS

3-APA	3-aminopropionamide
8-OH-dG	8-hydroxy-2'-deoxyguanosine
AA	acrylamide
ABS	acrylonitrile–butadiene–styrene
ADI	acceptable daily intake
AED	atomic emission detection
Ah	aryl hydrocarbon
AhR	aryl hydrocarbon receptor
ALARA	as low as reasonably achievable
ALT	alanine transferase
AR	androgen receptor
ARA	arachidonic acid
ARfD	acute reference dose
ATDS	Australian Total Diet Survey
AUC	area under the curve
BCG	Bacillus Calmette-Guérin
BDE	brominated diphenyl ether
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
BMR	benchmark response
Br-GC-MS	bromination–gas chromatography–mass spectrometry
BROD	benzyloxyresorufin *O*-deethylase
bw	body weight
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
cGMP	cyclic guanosine monophosphate
CI	confidence interval
CIAA	Confederation of Food and Drink Industries of the European Union
COX	prostaglandin H synthase
CRM	certified reference material
CV	coefficient of variation
CYP	cytochrome P450
Cys	cysteine
dA	deoxyadenosine
dC	deoxycytidine
DDT	dichlorodiphenyltrichloroethane
dG	deoxyguanosine
DHT	dihydrotestosterone
DNA	deoxyribonucleic acid
EA	early antigen

EC_{50}	median effective concentration
ECD	electron capture detection
ECNI	electron capture negative ionization
ED_{50}	median effective dose
EI	electron impact
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency (USA)
ER	estrogen receptor
EROD	7-ethoxyresorufin *O*-deethylase
ESI	electrospray ionization
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FCA	Freund's complete adjuvant
FD	fluorescence detection
FID	flame ionization detection
FOB	functional observational (test) battery
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GA	glycidamide
GC	gas chromatography
GD	gestation day
GEMS/Food	Global Environment Monitoring System Food Contamination Monitoring and Assessment Programme
GM-CSF	granulocyte-macrophage colony stimulating factor
GSD	geometric standard deviation
GST	glutathione-*S*-transferase
GSTM1	glutathione-*S*-transferase M1
GSTT1	glutathione-*S*-transferase T1
hAR	human androgen receptor
HPLC	high-performance liquid chromatography
HRGC	high-resolution gas chromatography
HRMS	high-resolution mass spectrometry
IARC	International Agency for Research on Cancer
IC_{50}	median inhibitory concentration
IEF	induction equivalency factor
Ig	immunoglobulin
IGF	insulin-like growth factor
i.m.	intramuscular
i.p.	intraperitoneal
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IU	international units
IUPAC	International Union for Pure and Applied Chemistry
JECFA	Joint FAO/WHO Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
K_i	inhibition constant
K_m	Michaelis-Menten constant

K_{ow}	octanol–water partition coefficient
LC	liquid chromatography
LD	lactational day
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOEL	lowest-observed-effect level
LOQ	limit of quantification
LOR	limit of reporting
LRMS	low-resolution mass spectrometry
LTP	long-term potentiation
MAE	microwave-assisted extraction
MAP	mitogen-activated protein
MEK	mitogen-activated protein kinase
MeO	methoxy
ML	maximum level
MOE	margin of exposure
MPO	medial preoptic area
mRNA	messenger ribonucleic acid
MROD	7-methoxyresorufin *O*-deethylase
MS	mass spectrometry
m/z	mass to charge ratio
N1-GA-dA	N1-(2-carboxy-2-hydroxyethyl)-2'-deoxyadenosine
N3-GA-Ade	N3-(2-carbamoyl-2-hydroxyethyl)adenine
N^6-GA-dA	N^6-(2-carboxy-2-hydroxyethyl)-2'-deoxyadenosine
N7-GA-Gua	N7-(2-carbamoyl-2-hydroxyethyl)guanine
NA	not available; not analysed
NADH	nicotinamide adenine dinucleotide, reduced form
NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
NAT	*N*-acetyltransferase
NCV	nerve conduction velocity
ND	not detected
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health (USA)
NK	natural killer
NMA	*N*-methylolacrylamide
NMDA	*N*-methyl-D-aspartate
nNOS	neural nitric oxide synthase
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NPD	nitrogen–phosphorus detection
NQ	not quantified
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
OH	hydroxy
OR	odds ratio

PAH	polycyclic aromatic hydrocarbon
PBB	polybrominated biphenyl
PBDD	polybrominated dibenzo-*p*-dioxin
PBDE	polybrominated diphenyl ether
PBDF	polybrominated dibenzofuran
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDE	polychlorinated diphenyl ether
PCDF	polychlorinated dibenzofuran
PCE	polychromatic erythrocyte
PCNA	proliferating cell nuclear antigen
PFC	plaque-forming cell
PKC	protein kinase C
PLA_2	phospolipase A_2
PMTDI	provisional maximum tolerable daily intake
PND	postnatal day
ppm	part per million
ppt	part per trillion
PR	progesterone receptor
PROD	7-pentoxyresorufin *O*-depentylase
PTWI	provisional tolerable weekly intake
$PTWI_d$	daily equivalent of the provisional tolerable weekly intake
QA	quality assurance
QC	quality control
QSAR	quantitative structure–activity relationship
RIVM	National Institute of Public Health and the Environment (Netherlands)
RIVO	Netherlands Institute of Fisheries Research
RNA	ribonucleic acid
RR	relative risk
SAR	Special Administrative Region
s.c.	subcutaneous
SCOOP	Scientific Cooperation on Food
SD	standard deviation
SFE	supercritical fluid extraction
SIM	selected ion monitoring
SMR	standardized mortality ratio
SPE	solid-phase extraction
SRM	selective-reaction monitoring
T3	triiodothyronine
T4	thyroxine
TBG	thyroxine binding globulin
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TD_{50}	chronic dose that results in one half of animals developing tumours
TDS	Total Diet Study
TEF	toxic equivalency factor

TGF	transforming growth factor
TLC	thin-layer chromatography
TPA	tetradecanoyl-phorbol acetate
TSH	thyroid stimulating hormone
TT3	total triiodothyronine
TT4	total thyroxine
TTC	threshold of toxicological concern
TTR	transthyretin
UDPGT	uridine diphosphate glucuronosyltransferase
USA	United States of America
US EPA	United States Environmental Protection Agency
UV	ultraviolet
Val	valine
V_d	volume of distribution
V_{max}	maximum rate of metabolism
VMH	ventromedial hypothalamic nucleus
v/v	volume by volume
WHO	World Health Organization
w/w	weight by weight

ANNEX 3

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES

Rome, 8–17 February 2005

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ANNEX 4

THE FORMULATION OF ADVICE ON COMPOUNDS THAT ARE BOTH GENOTOXIC AND CARCINOGENIC[1]

The Committee has established procedures for determining health-based guidance values, such as the acceptable daily intake (ADI) or provisional tolerable weekly intake (PTWI), for chemicals that produce adverse effects that are thought to show a threshold in their dose–response relationships. Compounds that are both genotoxic and carcinogenic may show non-linear dose–response relationships, but the no-observed-effect level (NOEL) in a study of carcinogenicity represents the limit of detection in that bioassay, rather than an estimate of a possible threshold. Therefore, the Committee does not establish health-based guidance values for compounds that are genotoxic and carcinogenic using the NOEL and safety (uncertainty) factors. In the absence of evidence on the influence of non-linearity on the incidence of cancer at low levels of exposure, the advice given previously by the Committee for compounds that are both genotoxic and carcinogenic has been that intakes should be reduced to as low as reasonably achievable (ALARA). Such advice is of limited value, because it does not take into account either human exposure or carcinogenic potency and has not allowed risk managers to prioritize different contaminants or to target risk management actions. In addition, ever-increasing analytical sensitivity means that the number of chemicals with both genotoxic and carcinogenic potential detected in food will increase.

The Committee at its present meeting considered a number of compounds for which genotoxicity and carcinogenicity are important issues. The Committee was aware of a number of recent developments relevant to the risk assessment of such compounds, including:

— a WHO workshop that developed a strategy for dose–response assessment and the formulation of advice (*1*);

— discussions within the European Food Safety Authority about a margin of exposure (MOE) that would indicate the level of priority for risk management action (*2*); and

— Australian recommendations for genotoxic and carcinogenic soil contaminants regarding a guideline dose that would be protective of human health based on a modified benchmark dose and the application of uncertainty factors to allow for interspecies differences, intraspecies variability, quality of the database and the seriousness of the carcinogenic response (*3*).

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[1] Taken from section 2.1 of the Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, reference 174).

The Committee discussed approaches to the formulation of advice on contaminants that are both genotoxic[1] and carcinogenic, which would inform risk managers about the possible magnitude of health concerns at different levels of intake in humans.

Hazard identification would normally be based on data from studies on genotoxicity and from cancer bioassays. Some chemicals increase the incidence of cancer in experimental animals by non-genotoxic mechanisms, and establishing a health-based guidance value, such as a PTWI, would be appropriate. The present guidance relates to chemicals that are both genotoxic and carcinogenic.

Hazard characterization (dose–response assessment) would be based on the available dose–response data for cancer, which would mostly be derived from studies in rodents given daily doses many orders of magnitude greater than the estimated intakes in humans. Dose–response data from studies of epidemiology may also be used for hazard characterization and would avoid interspecies comparisons and extrapolation over many orders of magnitude. The recent WHO workshop recommended the use of the benchmark dose lower confidence limit (BMDL) as a starting point for hazard characterization based on data from a bioassay for cancer in animals when the data are suitable for dose–response modelling. The BMDL is the lower one-sided confidence limit of the benchmark dose (BMD) for a predetermined level of response, called the benchmark response (BMR), such as a 5% or 10% incidence. The BMD in most cases shows less variation than the BMDL for different mathematical models and may be more suitable for ranking different compounds in terms of their potency, while the BMDL may be more appropriate for risk characterization purposes because it reflects the quality of the data. The derivation and interpretation of a BMDL require considerable statistical and biological expertise.

A number of aspects of the database need to be considered in dose–response modelling, including data selection, model selection, statistical linkage, parameter estimation, implementation and evaluation (*1*). The dose metric used for modelling could be a biomarker, providing that it was critically related to the process by which cancer arises and had been validated in relation to the external dose or intake. For carcinogenesis, selection of the dose–response data for modelling will need to consider both site-specific incidences of tumours, especially for the site showing the greatest sensitivity, and combined data (e.g. numbers of tumour-bearing animals) for compounds that do not show clear organ specificity. Analyses based on the numbers of tumour-bearing animals may also be

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[1] The present guidance does not address the situation where a compound shows genotoxicity, or has structural alerts for genotoxicity, but where a bioassay for cancer has not been performed. The Committee is aware of developments, such as the threshold of toxicological concern (TTC) for compounds with structural alerts for genotoxicity, that may allow the formulation of limited advice to risk managers, and would welcome a critical evaluation of such approaches.

appropriate under other circumstances, for example in the assessment of complex mixtures of compounds that are both genotoxic and carcinogenic. Dose–response characterization should aim to define the BMDL for the carcinogenic response(s) of relevance to human health, at the lowest level of response (the BMR) that reliably defines the lower end of the observed experimental dose–response relationship. A BMR of a 10% incidence is likely to be the most appropriate for modelling of data from bioassays for cancer, because the values for different mathematical models show wider divergence at incidences below 10%. The consistent use of the same benchmark response, i.e. 10%, will facilitate comparisons of the risks associated with different compounds that are both genotoxic and carcinogenic. Non-cancer effects produced by compounds that are both genotoxic and carcinogenic may be analysed using the same approach, and comparison of the derived BMDL values and their associated slopes can help to identify the adverse effect that is critical to risk assessment of the compound.

The intake (exposure) assessment for a compound that is both genotoxic and carcinogenic is no different from that for other types of contaminants.

Risk characterization involves comparison of the estimated exposure with the identified BMDL. In principle, this can take different forms:

- *Calculation of the margin of exposure* (MOE, the ratio of the BMDL to the estimated intake in humans). The MOE can be used to prioritize different contaminants, providing that a consistent approach has been adopted. The acceptability of an MOE depends on its magnitude and is ultimately a risk management decision (*1*). To aid that decision, the risk assessor should provide information on the nature and magnitude of uncertainties in both the toxicological and exposure data. Although the risk assessor should not provide an assessment of the acceptability of the MOE, guidance should be given on its adequacy taking into account the inherent uncertainties and variability.
- *Dose–response analysis outside the observed dose range.* Quantitative dose–response analysis could be used to calculate the incidence of cancer that is theoretically associated with the estimated exposure for humans, or the exposure associated with a predetermined incidence (e.g. 1 in 1 million). In order to provide realistic estimates of the possible carcinogenic effect at the estimated exposure for humans, mathematical modelling would need to take into account the shape of the dose–response relationship for the high doses used in the bioassay for cancer and for the much lower intakes by humans. Such information cannot be derived from the available data on cancer incidence from studies in animals. In the future, it may be possible to incorporate data on dose–response or concentration–response relationships for the critical biological activities involved in the generation of cancer (e.g. metabolic bioactivation and detoxication processes, DNA binding, DNA repair, rates of cell proliferation and apoptosis) into a biologically based dose–response model for cancer that would also incorporate data on species differences in these processes. However, such data are not currently

available. At present, any estimate of the possible incidence of cancer in experimental animals at intakes equal to those for humans has to be based on empirical mathematical equations that may not reflect the complexity of the underlying biology. A number of mathematical equations have been proposed for extrapolation to low doses. The resulting risk estimates are dependent on the mathematical model used; the divergence increases as the dose decreases, and the output by different equations can differ by orders of magnitude at very low incidences.

- *Linear extrapolation from a point of departure.* Because the estimated risks at low doses are model-dependent, linear extrapolation from the BMDL, which is conservative and simple to apply, has been used as a matter of policy by some agencies in order to calculate levels of exposure associated with different theoretical incidences of cancer. The incidence used is regarded as an upper-bound estimate for lifetime risk of cancer, and the actual risk may lie anywhere between zero and the calculated upper-bound estimate. Calculation of the intake associated with an incidence of 1 in 1 million from the BMDL for a 10% incidence using linear extrapolation is simply equivalent to dividing the BMDL by 100 000, and this approach is therefore no more informative than calculation of an MOE.

Of the three options given above, the MOE and linear extrapolation from a point of departure are the most pragmatic and usable at the present time. Linear extrapolation from a point of departure offers no advantages over an MOE, and the results are open to misinterpretation because the numerical estimates may be regarded as quantification of the actual risk.

The Committee at its present meeting decided that advice on compounds that are both genotoxic and carcinogenic should be based on estimated MOEs. The strengths and weaknesses inherent in the data used to calculate the MOE should be given as part of the advice to risk managers, together with advice on its interpretation.

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2. *EFSA Scientific Committee Draft Opinion on a harmonised approach for risk assessment of compounds which are both genotoxic and carcinogenic.* Brussels, European Food Safety Authority, 2005 (Request No. EFSA-Q-2004-20 ; http://www.efsa.eu.int/science/sc_commitee/sc_consultations/882/sc_consultation_genocar_draft_opinion_en1.pdf).

3. *Toxicity assessment for carcinogenic soil contaminants.* Commonwealth of Australia, Canberra, National Health and Medical Research Council, 1999.

ANNEX 5

APPROACH TO DOSE–RESPONSE MODELLING[1]

At the present meeting, cancer dose–response data were analysed by dose–response modelling, in accordance with the International Programme on Chemical Safety (IPCS) document *Principles for modelling dose–response for the risk assessment of chemicals* (*1*). The statistical methods of dose–response modelling as applied at this meeting are briefly described below.

For each tumour end-point considered relevant, the quantal dose–response models given in Table 1 were fitted to the dose–incidence data:

Table 1. Dose–response models used

Model	Model equation	Constraints
One-stage	$R = a + (1-a)(1-\exp(-x/b))$	$0 \le a \le 1$,
Two-stage	$R = a + (1-a)(1-\exp(-(x/b)-c(x/b)^2))$	$0 \le a \le 1$
Log-logistic	$R = a+(1-a)/(1+\exp(c \log10(b/x)))$	$0 \le a \le 1$, $c \ge \ln(10)$
Log-probit	$R = a+(1-a)\,\Phi(c \log10(x/b))$	$0 \le a \le 1$
Weibull	$R = a + (1-a)(1-\exp(-(x/b)^c))$	$0 \le a \le 1$, $c > 1$
Proast M2	$y = \exp(bx)$, *th1*	
Proast M3	$y = \exp(b\,x^d)$, *th1*	$d \ge 1$
Proast M4	$y = c - (c-1)\exp(-bx)$, *th1*	

Φ denotes the (cumulative) standard normal distribution function.

The first five of these models directly relate the incidence (R, expressed as a fraction) to the dose (x). In these models, the parameter a (also expressed as a fraction) reflects the incidence in the controls, the parameter b denotes the slope and parameter c can be considered as a shape parameter. The last three models (Proast M2–M4) are a specific family of models that assume an underlying continuous response (indicated by y), which is translated into a binary response

[1] Taken from Annex 3 of the Sixty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives (see Annex 1, reference 174).

(incidence) by incorporating a cut-off point (*th1*) in the normal distribution around *y*, below which an animal does not respond, and above which it does respond.

Some of the models are nested members of a larger family of models. Two models are nested when the one model can be seen as an extension of the other (simpler) model by incorporating one or more parameters. For instance, the two-stage model is an extension of the one-stage model by including parameter *c*. Also, the Proast models are a nested family of models (*2*). Nested models can be formally compared with each other as follows. Inclusion of an extra model parameter should result in a higher log-likelihood value, and if this increase is >1.92, inclusion of the parameter has resulted in a significantly better fit (log-likelihood ratio test). If the increase is <1.92, the fit is not significantly better, and the parameter is omitted.

When dose–response data are available from more than one study, or for both sexes, these models are fitted simultaneously to both such subgroups. This was done either by assuming all parameters in the model being the same for all subgroups or by assuming only the background response parameter (*a*) being different, or only the slope (*b*). When all parameters are assumed to be the same, a single curve results, otherwise different curves for the subgroups will result. A model in which a parameter is assumed to be different represents a model that is nested to the same model with the parameter assumed the same for the subgroups. Hence, the log-likelihood ratio test can be used for testing if an additional background or slope parameter results in a significantly better fit.

Selection of models

In general, those models that do not result in a significantly worse fit than the saturated model (one parameter per data point) are considered to be acceptable. For instance, when the saturated model has eight parameters (i.e. eight observed incidences available), a fitted dose–response model with three parameters should result in a log-likelihood that is no more than 5.54 lower than the log-likelihood associated with the saturated model. Table 2 summarizes the critical differences in log-likelihood values for various numbers of degrees of freedom (= difference in number of parameters between the models to be compared).

For those models that were considered acceptable according to the criteria mentioned, the benchmark dose (BMD) values as well as the benchmark dose lower confidence limit (BMDL) values were calculated. All BMD and BMDL values were calculated for a 10% extra risk, defined as:

$$extra\ risk = \frac{R(BMD) - R(0)}{1 - R(0)}$$

This represents the additional-response fraction divided by the tumour-free fraction in the controls.

Table 2. Critical differences in log-likelihood values making an increase by a number of parameters (= number of degrees of freedom) to result in a significantly better fit

Number of degrees of freedom	Critical difference in log-likelihood ($\alpha = 0.05$)
1	1.92
2	3.00
3	3.91
4	4.74
5	5.54
6	6.30
7	7.03
8	7.75

The BMD and BMDL values were estimated by the bootstrap method, usually performing 500 bootstrap runs. These values therefore contain some random error, but usually no more than about 10% for the BMDL.

The calculations were performed using the dose–response software package PROAST, version V07 (developed at the National Institute of Public Health and the Environment [RIVM], Bilthoven, The Netherlands), which is freely available.

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14/10 Training in mycotoxin analysis, 1990 (E S)

14/11 Management of food control programmes, 1991 (E)

14/12 Quality assurance in the food control microbiological laboratory, 1992 (E F S)

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