



Food and Agriculture
Organization of the
United Nations



World Health
Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninety-second meeting (Safety evaluation of certain food additives)
Virtual meeting, 7–18 June 2021

SUMMARY AND CONCLUSIONS

Issued on 9 July 2021

(Section on evaluation of benzoic acid, its salts and derivatives updated in August 2021)

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held on a virtual online platform on 7–18 June 2021. The purpose of the meeting was to evaluate the safety of certain food additives and flavourings. The present meeting was the 92nd in a series of similar meetings. The tasks before the Committee were (a) to further elaborate principles governing the evaluation of food additives, (b) to undertake safety evaluations of certain food additives, (c) to review and prepare specifications for certain food additives and (d) to establish specifications for certain flavouring agents.

Owing to travel restrictions and lockdowns due to the response to the COVID-19 pandemic in many countries, it was not possible to convene a physical meeting and it was instead decided to hold it online by video-conferencing. In view of the time differences in the countries of the invited experts, the only possible time for a video-conference was restricted to a 4-h time slot (12:00–16:00 CET) each day. This allowed only 40% of the usual daily length (8–10 h) of a typical JECFA meeting.

Dr R. Cantrill served as Chairperson, and Dr D. Benford as Vice-Chairperson.

Mr Kim Petersen, World Health Organization (WHO), and Dr Markus Lipp, Food and Agriculture Organization of the United Nations (FAO), served as joint secretaries.

The Committee evaluated the safety of six food additives and revised the specifications for one group of food additives.

The report of the meeting will be published in the WHO Technical Report Series. The report will summarize the main conclusions of the Committee in terms of acceptable daily intakes and other toxicological, dietary exposure and safety recommendations. Information on deliberations and conclusions with regard to the specifications for the identity and purity of certain food additives examined by the Committee and on specifications for the flavouring agents will also be included.

The participants are listed in Annex 1. Information of a general nature that the Committee wishes to disseminate quickly is provided in Annex 2. Future work and recommendations arising from the summary report of the ninety-second meeting of JECFA are summarized in Annex 3. Annex 4 details the selection of compounds and observations by experts with regard to the feasibility of holding the expert meetings online rather than in-person.

Toxicological monographs summarizing the data that were considered by the Committee in establishing ADIs will be published in WHO Food Additives Series No. 83. New and revised specifications for the identity and purity of the compounds will be published in FAO JECFA Monographs 27.

More information on the work of JECFA is available at:

<http://www.fao.org/food-safety/scientific-advice/jecfa/en/> and

<https://www.who.int/foodsafety/en/>

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Toxicological and dietary exposure information and information on specifications

Food additives evaluated toxicologically and assessed for dietary exposure

Food additive	Specifications	Acceptable daily intakes (ADIs) and other conclusions on toxicology and dietary exposure
Benzoic acid, its salts and derivatives	N	<p>The Committee evaluated a new extended one-generation reproductive toxicity study on benzoic acid. This study showed no treatment-related adverse effects, indicating a NOAEL of 1000 mg/kg bw per day, the highest dose tested.</p> <p>Applying a chemical specific adjustment factor of 2 for interspecies toxicokinetics variation instead of the default factor of 4.0, the Committee established a group ADI of 0–20 mg/kg bw, which applies to benzoic acid, the benzoate salts (calcium, potassium and sodium), benzaldehyde, benzyl acetate, benzyl alcohol and benzyl benzoate, expressed as benzoic acid equivalents. The Committee withdrew the previous group ADI of 0–5 mg/kg bw. The Committee noted that the high dietary exposure estimate, expressed as benzoic acid, of 7.1 mg/kg bw per day for children aged 3–9 years does not exceed the group ADI of 0–20 mg/kg bw.</p>
Collagenase from <i>Streptomyces violaceoruber</i> expressed in <i>S. violaceoruber</i>	N	<p>Negative results were observed in genotoxicity studies with a powdered enzyme concentrate. The Committee identified a NOAEL of 940 mg TOS/kg bw per day (rounded from 939.6), the highest dose tested in a 13-week study of oral toxicity in rats. The Committee identified a NOAEL of 940 mg TOS/kg bw per day, the highest dose tested in a 13-week study of oral toxicity in rats. Comparison of this NOAEL with the estimated dietary exposure of 0.43 mg TOS/kg bw per day gave a margin of exposure (MOE) of > 2100.</p> <p>In view of this MOE and the lack of concern about genotoxicity, the Committee established an ADI “not specified”¹ for collagenase from <i>S. violaceoruber</i>, when used in the applications specified and in accordance with good manufacturing practice.</p>
β -Glucanase from <i>Streptomyces violaceoruber</i> expressed in <i>S. violaceoruber</i>	N	<p>The Committee noted negative results in studies of genotoxicity and in studies of oral toxicity in rats. The Committee identified a NOAEL of 950 mg TOS/kg bw per day (rounded by the Committee from 953.3), the highest dose tested. Comparison of this NOAEL with the estimated dietary exposure of 0.15 mg TOS/kg bw per day gave an MOE > 6300.</p> <p>On the basis of this MOE and the lack of concern about genotoxicity, the Committee established an ADI “not specified”¹ for β-glucanase from <i>S. violaceoruber</i>, for the proposed uses and in accordance with good manufacturing practice.</p>

¹ The reader is referred to the Technical Report of the 87th JECFA meeting for clarification of the term “ADI not specified”.

Phospholipase A2 from <i>Streptomyces violaceoruber</i> expressed in <i>S. violaceoruber</i>	R	<p>Negative results were obtained in genotoxicity tests. In a 13-week study of oral toxicity in rats, small effects were seen at low incidence at the high dose of 956 mg TOS/kg bw per day, which might have been related to treatment. The Committee therefore identified a NOAEL of 190 mg TOS/kg per day (rounded by the Committee from 191 mg TOS/kg bw per day). A comparison of the estimated dietary exposure of 0.25 mg TOS/kg bw per day with the NOAEL of 190 mg TOS/kg bw per day from the oral toxicity study gives a MOE of 760.</p> <p>On this basis and in the absence of concern about genotoxicity, the Committee established an ADI “not specified”¹ for the phospholipase A2 enzyme preparation from <i>S. violaceoruber</i> when used in the applications specified and in accordance with good manufacturing practice.</p>
Riboflavin from <i>Ashbya gossypii</i>	N	<p>The Committee noted that riboflavin from <i>A. gossypii</i> has low acute toxicity and does not raise concern for genotoxicity. The NOAEL from a 90-day oral toxicity study in rats was 3000 mg/kg bw per day, the highest dose tested. Comparison of this NOAEL with the estimated dietary exposure of 3.6 mg/kg bw per day, based on maximum reported use levels, resulted in an MOE > 800.</p> <p>The Committee established a group ADI “not specified”¹ for riboflavin, riboflavin- 5'-phosphate, riboflavin from <i>B. subtilis</i> and riboflavin from <i>A. gossypii</i>, expressed as riboflavin. The Committee withdrew the previous group ADI of 0–0.5 mg/kg bw.</p>
Ribonuclease P from <i>Penicillium citrinum</i>	N	<p>The Committee identified a NOAEL of 980 mg TOS/kg bw per day (the highest dose tested) in a 13-week study in which rats were treated with ribonuclease P concentrate from <i>P. citrinum</i> AE-RP by gavage. A comparison of the estimated dietary exposure of 1.3 mg TOS/kg bw per day with the NOAEL of 980 mg TOS/kg bw per day gives an MOE > 750.</p> <p>On the basis of this MOE and the lack of concern for genotoxicity, the Committee established an ADI “not specified”¹ for the ribonuclease P enzyme preparation from <i>P. citrinum</i> AE-RP, used in the applications specified and in accordance with good manufacturing practice.</p>

N: new specifications, R: revised specifications

Food additives considered for specifications only

Food additive	Specifications
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Modified starches	R
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R: revised specifications

Annex 1. List of participants

Members

Dr S. Barlow, Brighton, East Sussex, United Kingdom
Dr J. Bend, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada
Dr D. Benford (Co-Chairperson), Cheddington, United Kingdom
Dr P.E. Boon, Department for Food Safety, Centre for Nutrition, Prevention and Health, National Institute for Public Health and the Environment, Bilthoven, Netherlands
Dr R. Cantrill (Co-Chairperson), Bedford, Nova Scotia, Canada
Dr E. Dessipri, General Chemical State Laboratory, Athens, Greece
Dr M. DiNovi, Food and Drug Administration, College Park (MD), United States of America
Ms T. Hambridge, Food Standards Australia New Zealand, Kingston, Australian Capital Territory, Australia
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Ms K. Laurvick, Food Standards, United States Pharmacopeia, Rockville (MD), United States of America (Co-rapporteur)
Dr U. Mueller, Australian Pesticide and Veterinary Medicines Authority, Armidale, New South Wales, Australia (Co-rapporteur)
Dr J. Schlatter, Zürich, Switzerland
Dr J. Smith, Executive Director Bio|Food|Tech, Charlottetown, Prince Edward Island, Canada
Dr J.R. Srinivasan, Food and Drug Administration, College Park (MD), United States of America
Dr N. Sugimoto, Section 2, Division of Food Additives, National Institute of Health Sciences, Tokyo, Japan

Secretariat

Dr F. Aguilar Morales, Agency for Food, Environmental and Occupational Health and Safety, Paris, France (WHO temporary adviser)
Ms E. Heseltine, Saint Léon-sur-Vézère, France (WHO technical editor)
Ms N. Y. Ho, Department of Nutrition and Food Safety, World Health Organization, Geneva, Switzerland (WHO Joint Secretary)
Dr M. Lipp, Food Systems and Food Safety Division, Food and Agriculture Organization of the United Nations, Rome, Italy (FAO Joint Secretary)
Dr O.E. Orisakwe, University of Port Harcourt, Port Harcourt, Nigeria (WHO temporary adviser)
Mr K. Petersen, Department of Nutrition and Food Safety, World Health Organization, Geneva, Switzerland (WHO Joint Secretary)
Dr J. Rotstein, Pre-market Toxicology Assessment Section, Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Food Directorate, Health Products and Food Branch, Health Canada, Ottawa, Ontario, Canada (WHO temporary adviser)
Dr S.G. Walch, Executive Director, Chemisches und Veterinäruntersuchungsamt, Karlsruhe, Germany (FAO expert)
Dr X. Yang, School of Public Health, Southern Medical University, China (WHO temporary adviser)
Dr H.J. Yoon, Korea Food and Drug Administration, Seoul, Republic of Korea (WHO temporary adviser)

Annex 2. Corrigenda

The following requests for corrections, reported to the JECFA Secretariat, were evaluated by the 92nd JECFA meeting and found to be necessary. These corrections will be made, however, only in the electronic versions and in the online database of specifications.

Food additive	Original text	Revised text	Additional information
Riboflavin INS 101(i)	$\% \text{ Riboflavin} = \frac{A \times 5000}{328 \times W} \times 1.367$	$\% \text{ Riboflavin} = \frac{A \times 5000}{328 \times W}$	Correction to calculation in the method of assay; removal of a wrongly assigned factor
Riboflavin from <i>Bacillus subtilis</i> INS 101(iii)	$\% \text{ Riboflavin} = \frac{A \times 5000}{328 \times W} \times 1.367$	$\% \text{ Riboflavin} = \frac{A \times 5000}{328 \times W}$	Correction to calculation in the method of assay; removal of a wrongly assigned factor
Riboflavin 5'-phosphate sodium INS 101(ii)	CAS number 130-40-5	CAS number 130-40-5 (anhydrous) CAS number 6184-17-4 (dihydrate)	Current specifications provide the formula for the dihydrate but no applicable CAS number
Potassium polyaspartate	Missing "Method of assay"	Add "Method of assay" under "Purity tests" after the test entitled "Molecular weight and molecular weight distribution". Delete the bold text "Potassium polyaspartate", which appears in the test for "Molecular weight and molecular weight distribution", and replace with "Principle" (as the method of assay).	Correct errors in format of specifications monograph
Vol. 4 procedure			
Unulfonated primary aromatic amines	See printed version of Vol. 4	See revised text below; modified text is in bold.	Correction to the range of the standard curve

Revised text:

Procedure

Preparation of standard aniline solution

Weigh **100 mg** of redistilled aniline into a small beaker, and transfer to a 100-mL volumetric flask, rinsing the beaker several times with water. Add 30 mL of 3 N hydrochloric acid, and dilute to the mark with water at room temperature. Dilute 10.0 mL of this solution to 100 mL with water, and mix well. **Dilute 20.0 mL of this solution to 100 mL with water, and mix well (1 mL of this standard solution is equivalent to 20 µg of aniline).** Measure the following volumes of the standard aniline solution into a series of 100-mL volumetric flasks: 5 mL, 10 mL, 15 mL, 20 mL and 25 mL. Dilute to 100 mL with 1 N hydrochloric acid, and mix well (**100 mL of the resulting working standard solutions contains 100, 200, 300, 400 and 500 µg of aniline, respectively).** Prepare all standard solutions freshly.

Construction of standard curve

Pipette 10 mL of each **working standard** solution into clean, dry test tubes; cool them for 10 min by immersion in a beaker of ice water. To each tube, add 1 mL of the potassium bromide solution and 0.05 mL of

the sodium nitrite solution. Mix, and allow the tubes to stand for 10 min in the ice-water bath while the aniline is diazotized. Into each of five 25-mL volumetric flasks, measure 1 mL of the R salt solution and 10 mL of the sodium carbonate solution. Pour each diazotized aniline solution into a separate flask containing R salt solution and sodium carbonate solution; rinse each test tube with a few drops of water. Dilute to the mark with water, stopper the flasks, mix the contents well, and allow them to stand for 15 min in the dark. Measure the absorbance of each coupled solution at 510 nm in 40-mm cells. As a reference solution, use a mixture of 10.0 mL of 1 N hydrochloric acid, 10.0 mL of the sodium carbonate solution and 2.0 mL of the R salt solution, diluted to 25.0 mL with water. **Construct a standard curve of the absorbance versus the weight (g) of aniline in each 100 mL of working standard solution.**

Preparation and evaluation of a test solution

Weigh, to the nearest 0.01 g, about 2.0 g of the colouring matter sample (W) into a separatory funnel containing 100 mL of water, rinse the sides of the funnel with a further 50 mL of water, swirling to dissolve the sample, and add 5 mL of 1 N sodium hydroxide. Extract with two 50-mL portions of toluene, and wash the combined toluene extracts with 10-mL portions of 0.1 N sodium hydroxide to remove traces of colour. Extract the washed toluene with three 10-mL portions of 3 N hydrochloric acid, and dilute the combined extract to 100 mL with water. Mix well. Call this "solution T". **Pipette** 10.0 mL of solution T into a clean, dry test tube, cool for 10 min by immersion in a beaker of iced water, add 1 mL of the potassium bromide solution, and proceed as described above for preparation of the **standard curve**, starting with addition of 0.05 mL of the sodium nitrite solution. Measure the absorbance of the coupled test solution at 510 nm in a 40-mm cell. Use a reference solution prepared from 10.0 mL of solution T, 10 mL of the sodium carbonate solution and 2.0 mL of the R salt solution diluted to 25.0 mL with water. From the **standard curve**, read the weight of aniline (WA) corresponding to the observed absorbance of the test solution.

Calculation: % unsulfonated primary aromatic amine (as aniline) = $100 \times WA/W$

Annex 3. Recommendations and future work

Riboflavin from *A. gossypii*

In view of information received at the current meeting which implies that riboflavin is no longer produced synthetically for use as a food additive, the Committee recommends that the CCFA reconsider the requirement for specifications for synthetically produced riboflavin.

Future work

Regarding the previously established specifications for riboflavin and riboflavin from *B. subtilis*, the Committee proposes to:

- rename “riboflavin” as “riboflavin, synthetic”;
- replace the existing method for determination of lumiflavin in both specifications to avoid use of chloroform; and
- delete the functional use of “nutrient supplement” from the specifications monograph on riboflavin from *B. subtilis*, as the Codex food additive definition does not include nutrients.

Ribonuclease P from *Penicillium citrinum*

Ribonuclease P can also be produced by *P. citrinum* RP-4, but insufficient information was available on the enzyme concentrate produced from this strain. To evaluate the safety of ribonuclease P from *P. citrinum* RP-4, toxicological studies with well-characterized enzyme concentrate are required.

Annex 4. Procedural matters

Owing to travel restrictions and lockdowns due to the response to the COVID-19 pandemic in many countries, it was not possible to convene a physical meeting and it was instead decided to hold it online by video-conferencing. In view of the time differences in the countries of the invited experts, the only possible time for a video-conference was restricted to a 4-h time slot (12:00–16:00 CET) each day. This allowed only 40% of the usual daily length (8–10 h) of a typical JECFA meeting. Although the experts participated fully, they noted that online meetings do not permit the necessary in-depth, robust scientific discussions that are characteristic of JECFA meetings and are therefore not a suitable substitute for face-to-face meetings. In particular, the experts felt that the online format did not foster the atmosphere of trust, inclusiveness and openness that has marked all physical JECFA meetings. The experts considered that the success of the ninety-second meeting was due mainly to the cohesion among them stemming from the trust built on the relationships they had formed during previous face-to-face meetings. The experts also decried the significant difficulty of holding any informal meetings outside the scheduled meeting times because of the widely differing time zones. Perhaps the greatest loss due to the virtual meeting format rather than in-person meetings is in efficiency in solving issues that arise shortly before or during the meeting that require immediate input from individuals or small groups of both FAO and WHO representatives. Indeed, this deficiency means that fewer food additives can be evaluated within a two-week meeting.

The experts emphasized further that an invitation to a physical JECFA meeting at FAO or WHO headquarters gives rise to more significant recognition by the expert's employer of the weight, reach, responsibility and workload required for full participation in a JECFA meeting. The same degree of acknowledgement is not granted by employers for online meetings, as the experts remain available locally. This lack of recognition of the workload and significance of participation in a JECFA meeting led to an increase in other demands on the experts, resulting in more distractions and more frequent scheduling conflicts. The experts concluded that, cumulatively, such factors would be counterproductive for participation in future JECFA meetings if FAO and WHO maintained the online-only format.

In recognition of the difficulties and the tremendous efforts made, the Joint FAO/WHO Secretariat expressed its deep gratitude to all the experts for their commitment and flexibility, not least as the scheduled meeting times were exceedingly inconvenient for many.

The meeting report was adopted on 18 June 2021.