Aspartame as a Case Study in Re-evaluation of Sweetener Safety by the Joint FAO/WHO Expert Committee on Food Additive

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Conflict of Interest Statement

- There exist no real or perceived conflicts of interest
Introduction to JECFA—1

- JECFA is the Joint Expert Committee of the Food and Agriculture Organization (FAO) and World Health Organization (WHO)
  - FAO and WHO are both organizations of the United Nations
- JECFA has been meeting since 1956, initially to evaluate the safety of food additives.
  - Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food
  - Also develops principles for the safety assessment of chemicals in food taking account of recent developments in toxicology and other relevant scientific areas such as epidemiology, biotechnology, exposure assessment, food chemistry including analytical chemistry and assessment of maximum residue limits for veterinary drugs.
Introduction to JECFA—2

- JECFA normally meets twice a year with individual agendas covering either (i) food additives, contaminants and naturally occurring toxicants in food or (ii) residues of veterinary drugs in food.
- The membership of the meetings varies accordingly, with different sets of experts being called on depending on the subject matter.
- JECFA does not formally exist between meetings.
Remit of JECFA

- JECFA is an independent scientific expert committee which performs risk assessments and provides advice to FAO, WHO, and the member countries of both organizations, as well as to the Codex Alimentarius Commission (CAC).
- The requests for scientific advice are for the main part channelled through the subsidiary bodies of the CAC in their work to develop international food standards and guidelines under the Joint FAO/WHO Food Standards Programme.
- The advice to CAC on food additives is normally provided to the Codex Committee on Food Additives (CCFA).
How JECFA Works—the Agenda

- CCFA sets the priority list of food additives for evaluation (or re-evaluation).
- Joint FAO/WHO Secretariat set the agendas, taking into account anticipated time and expertise required for each item.
- Secretariat issues a call for data.
Call for Data—1

96th JECFA June 2023

Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Ninety-sixth meeting

Food Additives

Geneva, 27 June to 6 July 2023

Published 1 July 2022

LIST OF SUBSTANCES SCHEDULED FOR EVALUATION
AND REQUEST FOR DATA

Attached is the list of substances (Annex 1) scheduled for evaluation or re-evaluation at the 96th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). This list has been prepared by the Joint FAO/WHO Secretariat of the Committee and is based on recommendations of the Codex Committee on Food Additives (CCFA), previous Expert Committees, and direct requests from governments, other interested organizations, and producers of substances that have been evaluated previously. The meeting will be held as a physical meeting in Geneva, Switzerland.
1. Food additives for which requests have been received for evaluation or re-evaluation by the 52nd session of the Codex Committee on Food Additives (REP 21/FA - Appendix XI)\(^{(1)}\) and pending re-evaluations

1.1. **Toxicological evaluation, exposure assessment and establishment of specifications of substances used as food additives**

<table>
<thead>
<tr>
<th>Food Additive</th>
<th>Reference (previous evaluations) and background</th>
<th>Information required</th>
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| Aspartame (INS 951) | - Report of the 52nd session of CCFA, REP 21/FA - Appendix XI\(^{(1)}\)  
                      - 82nd report of the Joint FAO/WHO Expert Committee on Food Additives\(^{(2)}\)  
                      - 25th report of the Joint FAO/WHO Expert Committee on Food Additives\(^{(3)}\) | - All data necessary for assessment of safety, dietary intake and specifications, including data used by JECFA at its previous assessment in 1981. |
Expert Rosters

- WHO roster of toxicological and epidemiological experts
- WHO/FAO roster of experts on exposure assessment of chemicals in food
- FAO roster of experts to develop specifications for the identity and purity of food additives
  - Applications are reviewed by a selection panel composed of representatives of FAO and WHO, as well as at least one external expert on the relevant subject.
  - All applicants who fulfill the specified requirements, and agree to sign a standard “Declaration of Interests” and indicate institutional affiliation, are placed on the roster of the appropriate expert body, subject to final approval by the FAO and WHO Directors-General
WHO Committee Members

- WHO Food Safety Advisory Panel exists to select committee members for established expert committees such as the JECFA.
- The WHO secretariat nominates distinguished scientists, including the most experienced experts from the roster, for appointment to the Food Safety Advisory Panel.
- The WHO Director-General makes the final nomination.
Before the Meeting

- For each meeting:
  - Experts from the rosters (monographers) are identified to draft working papers
  - Experts from the WHO Food Safety Advisory Panel identified to be WHO Committee members
  - Experts from the FAO roster identified to be Committee members

- Drafting of working papers before the meeting
  - Monographers review the data submitted by governments, producers of food additives, and other interested organisations
  - Monographers conduct systematic literature searches to identify and evaluate additional relevant data
  - Members of the Committee review the work of the monographers
During and After the Meeting

- Proceedings are confidential pending publication
  - Committee, including monographers, review the draft working papers
  - Draft reports are produced, discussed, and revised in Committee
  - Final report is adopted on the final day of the meeting
  - Draft working papers are revised to ensure consistency with the adopted report and become the agreed monographs

- Publications
  - Summary report about 2 weeks after the meeting
  - Reports—Technical Report Series
  - Toxicological and dietary exposure monographs—Food Additive Series
  - FAO Chemical and Technical Assessments (CTA) and Compendium of Food Additive Specifications
The Ninety-sixth meeting of the Joint FAO/WHO Executive Committee on Food Additives was held in Geneva from 27 June to 6 July 2023. The purpose of the meeting was to evaluate the safety of certain food additives and flavourings. The present meeting was the Ninety-sixth in a series of similar meetings. The tasks before the Committee were to (a) further elaborate principles governing the evaluation of food additives; (b) undertake safety evaluations of certain food additives; (c) review and prepare specifications for certain food additives; and (d) establish specifications for certain flavouring agents.
## 96th JECFA Meeting June/July 2023—Members

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<tr>
<th>WHO</th>
<th>FAO</th>
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<tr>
<td>A Agudo</td>
<td>R Cantrell (vice-chair)</td>
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<td>S Barlow</td>
<td>M DiNovi</td>
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<td>D Benford (chair)</td>
<td>D Folmer (joint rapporteur)</td>
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96th JECFA Meeting June/July 2023—Experts

WHO
R Dalefield
S Kabadi
L le Hégarat
D Lovell
D Pallapies
S Stice
X-F Yang

FAO
M B de Abreu Gloria
M J Frutos Fernández
T Hambridge
K Papadopoulou
J Srivinisan
A Tada
96th JECFA Meeting June/July 2023—Secretariat

WHO

L Benbrahim-Tallaa (IARC)
N Y Ho
F Madia (IARC)
J Montez
K Peterson
M Sanaa

FAO

M Lipp
A Vlachou
Aspartame

Aspartic acid

Phenylalanine
Aspartame Uses

- Flavour enhancer and sweetener.
- Said to be approximately 200 times sweeter than sucrose.
- Used in a range of food categories at maximum permitted levels (MPLs) between 300 and 10,000 mg/kg and at Good Manufacturing Practice (GMP) for table-top sweeteners.
- It is permitted for use both on its own in food products, and in combination with other sweeteners.
Previous JECFA Evaluations

- At the 25th meeting, the Committee established an Acceptable Daily Intake (ADI) of 0–40 mg/kg bw for aspartame.
- An ADI is an “estimate of the amount of a chemical in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk to the consumer.”
- The ADI was calculated based on the no-observed-adverse-effect level (NOAEL) of 4000 mg/kg bw per day, the highest dose tested in a 104-week study in rats exposed to aspartame in the diet, with application of a 100-fold uncertainty factor.
- Dietary exposure was not assessed by JECFA at that time.
The 2023 Evaluation—Toxicokinetics

- Fully hydrolysed in the GI tract of humans and rodents to phenylalanine, aspartic acid and methanol.
  - There is no systemic exposure to aspartame after dietary exposure.
- Phenylalanine, aspartic acid and methanol are also released from commonly consumed foods by enzymic hydrolysis.
  - After presystemic exposure to aspartame these substances enter the systemic circulation at lower levels than derived from consumption of common foods.
- Studies in human volunteers at doses up to the ADI have shown no increased in the plasma concentrations of the metabolites.
The Committee reviewed a large number of studies of genotoxicity, *in vitro* and *in vivo* and did not find convincing evidence.

- Concluded that there was no concern for genotoxicity of oral exposure to aspartame.

Reviewed 12 oral carcinogenicity studies of aspartame in rodents, all with limitations.

- The study closest to meeting current testing guidelines was negative (Ishii et al., 1981).

Studies of possible mechanisms of carcinogenicity, such as oxidative stress, were not supported by findings in other studies of aspartame.
Conclusions on Carcinogenicity in Animals

“Based on the negative results of the Ishii et al. study, no concern of genotoxicity, and a lack of a plausible mechanism by which oral exposure to aspartame could induce cancer, the Committee concluded that there was no concern for carcinogenicity in animals from oral exposure to aspartame.”
Reproductive and Developmental Toxicity

- No effects were observed in one- or two-generation reproductive and developmental toxicity studies in rats up to the highest dose tested, of 4000 mg/kg bw per day.
- No effects were observed in a developmental toxicity study in mice up to the highest dose tested, of 5700 mg/kg bw per day.

The Committee therefore concluded that aspartame was not a reproductive or developmental toxicant in animals.
Human Observations—Cancer

- Statistically significant increases were reported for some cancers, such as hepatocellular, breast, and haematological (non-Hodgkin lymphoma and multiple myeloma) cancers in some cohort studies conducted with aspartame or beverages containing aspartame as an intense sweetener.
- A consistent association between aspartame consumption and a specific cancer type was not observed.
- All studies have limitations with respect to their assessment of exposure and, in many studies, particularly with respect to aspartame versus intense sweeteners in general.
- Reverse causality, chance, bias, and confounding by consumption of other dietary components, socioeconomic or lifestyle factors cannot be ruled out.
Conclusions on Associations with Cancer in Humans

“Overall, the Committee concluded that the evidence of an association between aspartame consumption and cancer in humans is not convincing.”
Effects of aspartame consumption on type 2 diabetes (T2D) and other non-cancer health end-points in humans showed inconsistent results.

- E.g., in T2D studies randomised controlled trials (RCTs) showed negative associations between aspartame consumption and glycaemic responses, whereas in epidemiological studies aspartame consumption was associated with a greater T2D risk.
- The Committee noted that the results of the epidemiological studies may be biased by how T2D cases were identified (either specific medications and self-reported physician diagnosis).

The Committee concluded that “the evidence of an association between aspartame consumption and the evaluated non-cancer health end-points is not convincing.”
Overall Conclusions on Hazard

- “There was no convincing evidence from experimental animal or human data that aspartame has adverse effects after ingestion.”
- “This conclusion is underpinned by the information that aspartame is fully hydrolysed in the GI tract into metabolites that are identical to those absorbed after consumption of common foods, and that no aspartame enters the systemic circulation.”
- “Overall, the data evaluated at the present meeting indicated no reason to change the previously established ADI of 0–40 mg/kg bw for aspartame. The Committee therefore reaffirmed the ADI of 0–40 mg/kg bw for aspartame at the present meeting.”
Comparison of Estimated Exposure to the ADI

- Estimates of mean dietary exposure to aspartame were up to 10 mg/kg bw per day for children and 5 mg/kg bw per day for adults.
- Estimates of high dietary exposures to aspartame were up to 20 mg/kg bw per day for children and 12 mg/kg bw per day for adults.
- Because these dietary exposure estimates do not exceed the ADI, the Committee concluded that dietary exposure to aspartame does not pose a health concern.
IARC classifications
- Group 1—carcinogenic to humans
- Group 2a—probably carcinogenic to humans
- Group 2b—possibly carcinogenic to humans
- Group 3—not classifiable as to its carcinogenicity to humans

Strands of evidence
- Carcinogenicity in humans
- Carcinogenicity in experimental animals
- Mechanistic information, e.g., absorption, distribution, metabolism and excretion (ADME) and ten key characteristics of carcinogens (KCC)
The 2023 IARC Evaluation of Aspartame—Cancer

● Evidence in humans
  - “Limited” evidence of hepatocellular carcinoma in 3 studies comprising 4 prospective cohorts
  - Association of artificially sweetened beverage consumption with liver cancer
  - Chance, bias or confounding could not be ruled out
  - “inadequate” evidence for other cancer types

● Evidence in experimental animals
  - Limitations in all studies because of questions about adequacy of design, conduct, interpretation and reporting
  - IARC concluded “limited evidence” (majority view)
IARC KCC (from Smith et al., 2016)

1. Is electrophilic or can be metabolically activated
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply
The 2023 IARC Evaluation of Aspartame—KKC

KKC 2. Genotoxicity
- Some positive findings, but limitations in design, data analysis and interpretation

KKC 5. Oxidative stress
- Induction of some biomarkers in several tissues including liver

KKC 6. Chronic inflammation
- Suggestions in some studies

KKC 10. Alters cell proliferation, cell death or nutrient supply
- Some studies suggested angiogenesis was increased

● Overall conclusion—“limited” evidence for the KKC
IARC Conclusion on Aspartame

- “Possibly carcinogenic to humans” (Group 2B)
  - Limited evidence in humans
  - Limited evidence in experimental animals
  - Limited mechanistic evidence
References Cited in the Presentation

- Summary and conclusions of the 96th meeting of JECFA
  - https://www.who.int/publications/m/item/ninety-sixth-meeting-joint-fao-who-expert-committee-on-food-additives-(jecfa)

- Toxicity of aspartame and its diketopiperazine for Wistar rats by dietary administration for 104 weeks

- Carcinogenicity of aspartame, methyleugenol, and isoeugenol
  - Riboli et al. The Lancet Oncology (2023), 24: 848-850

- Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis
  - Smith et al. Environmental Health Perspectives (2016), 124: 713-721
Acknowledgements

- Members and secretariat at the 96th meeting of JECFA