

Report on meetings of expert committees and study groups^{1,2}

Report by the Director-General

EVALUATION OF CERTAIN CONTAMINANTS IN FOOD

Ninety-third report of the Joint FAO/WHO Expert Committee on Food Additives, virtual meeting,³ 24, 25, 29, 30 March and 1 April 2022⁴

Main recommendations

1. The report contains the Joint FAO/WHO Expert Committee on Food Additives' evaluations of technical, toxicological and epidemiological data, including the occurrence of and dietary exposure to food contaminants, specifically the trichothecenes T-2, HT-2 and 4,15-diacetoxyscirpenol (DAS) from all food sources. The exposure assessment and chemical characterization had already been carried out at the ninetieth meeting of the Committee. Therefore, the purpose of the ninety-third meeting was to review the toxicological data on the trichothecenes T-2, HT-2 and 4,15-diacetoxyscirpenol (DAS) and evaluate their safety and re-evaluate their combined dietary exposure.
2. The Committee established a group acute reference dose and a group tolerable daily intake for the three trichothecenes. The Committee estimated that chronic dietary exposure to trichothecenes for some population groups might exceed the health-based guidance value and that this might indicate a human health concern.
3. The assessments, recommendations and comments by the Committee will be discussed by the Codex Committee on Contaminants in Food in order to generate recommendations to national authorities to identify and recommend appropriate risk management and risk-mitigation measures to reduce human exposure, where necessary.

¹ The Regulations for Expert Advisory Panels and Committees provide that the Director-General shall submit to the Executive Board a report on meetings of expert committees containing observations on the implications of the expert committee reports and recommendations on the follow-up action to be taken.

² Information on expert advisory panels and committees and their membership is provided in document EB152/53 Add.1.

³ Coordinated from WHO headquarters, Geneva.

⁴ WHO Technical Report Series, No. 1040 (in press).

4. WHO will publish detailed monographs in the WHO Food Additives Series with the toxicological and other related information upon which the safety assessments of the compounds were based.¹ FAO publishes summaries of the identity and purity of previous cargoes and contaminants.

Significance for public health policies

5. The Committee identifies and, where possible, quantifies the public health significance of exposure to chemicals in food – in these cases, contaminants in food – through scientific risk assessment based on international consensus. When a health concern is identified, clear recommendations are issued for action by national governments or through the relevant organs of the Joint FAO/WHO Food Standards Programme.

6. The Committee's recommendations are used by the Codex Alimentarius Commission in the development of international food safety standards and other guidance and recommendations. Such standards are science based and are established only for substances that have been evaluated by the Committee. This ensures that food commodities that are traded internationally meet strict safety standards to protect the health of the consumer and ensure fair practices in food trade.

7. The advice provided by the Committee is also considered by Member States directly when national or regional food safety standards are being established.

8. The Committee's work, in its complexity and in reaching an international scientific consensus on the evaluation of these compounds, is unique in its importance for and impact on global public health decisions related to food safety.

Implications for the Organization's programmes

9. The evaluation of chemicals in food by the Committee is an ongoing activity. Five meetings of the Committee on food additives were held in the biennium 2021–2022.² Two of the meetings focused on evaluating the safety of food additives, two on contaminants in food and one on residues of veterinary drugs.

10. WHO is a partner in the Joint FAO/WHO Food Standards Programme, whose principal organ is the Codex Alimentarius Commission. In its capacity to assure the sound scientific basis for international standards and recommendations on food additives, contaminants in food and veterinary drug residues in food, the work of the Committee is crucial to the work of the Codex Alimentarius Commission.

11. The Committee's evaluations are also used by Heads of WHO offices in countries, territories and areas and by regional offices when advice is provided to Member States on food safety issues.

¹ Safety evaluation of certain contaminants in food. WHO Food Additives Series, No. 84. Toxicological monographs of the ninety-third meeting (in preparation).

² For more information, see [https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-\(jecfa\)](https://www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)) (accessed 19 October 2022).

BIOLOGICAL STANDARDIZATION

Seventy-fifth report of the Expert Committee on Biological Standardization, virtual meeting,¹ 4–8 April 2022²

12. The Expert Committee on Biological Standardization reviews developments in the field of biological products used in human medicine. Such products include vaccines, biotherapeutics, blood products, cell and gene therapy products, and in vitro diagnostics. The Committee coordinates activities leading to the adoption of WHO recommendations, guidelines and other guidance documents (written standards) that help to ensure the quality, safety and efficacy of such products, and to the establishment of WHO international reference standards (measurement standards).

13. The adoption and publication of WHO written standards and the establishment and use of WHO measurement standards designating the activity of biological products used for the diagnosis, prevention or treatment of disease allow for the comparison of nonclinical and clinical data worldwide. Ensuring the comparable quality, safety and efficacy of biological products is a vital step in facilitating their equitable global availability and thus contributes towards the attainment of the key strategic WHO goal of universal health coverage.

14. During its seventy-fifth meeting, the Committee made recommendations on a wide range of recent WHO activities, including a number of ongoing biological standardization activities relating to the coronavirus disease (COVID-19) pandemic.

Main recommendations

15. Following detailed discussion and review, the Committee recommended the adoption of three WHO written standards:

- (a) WHO manual for the preparation of reference materials for use as secondary standards in antibody testing;
- (b) Guidelines on evaluation of biosimilars; and
- (c) Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use.

16. Following careful consideration of the reports of international collaborative laboratory studies, the Committee also recommended the establishment of five new WHO measurement standards. In addition, the Committee endorsed three proposals to develop new or replacement WHO measurement standards.

17. The Committee noted that standardization issues relating to the ongoing COVID-19 pandemic continued to form a major part of its agenda and highlighted that the above-mentioned WHO manual for the preparation of reference materials for use as secondary standards in antibody testing and the Guidelines for the production and quality control of monoclonal antibodies and related products

¹ Coordinated from WHO headquarters, Geneva.

² WHO Technical Report Series, No. 1043, 2022.

intended for medicinal use would be directly relevant to the continuing development and assessment of COVID-19 therapeutics and vaccines.

18. Following discussion of the challenges encountered and lessons learned in the development of WHO measurement standards during the COVID-19 pandemic, the Committee recommended that communications in this area should be improved and made less hierarchical to ensure that all stakeholders receive critical information in a timely manner, including information on urgently established WHO measurement standards. In addition, supportive instructional materials should be produced for end users to ensure the appropriate and most efficient use of WHO measurement standards that may be in short supply during an emergency. Furthermore, given the need to improve the sourcing of candidate reference materials during a public health emergency, the Committee also expressed its support for the WHO BioHub System and other repository initiatives now in development.

19. Recognizing the significant contribution of WHO in driving changes in the use of animals for product testing, the Committee applauded the progress made by a three-year project that had been endorsed by the Committee in 2019. This project had been initiated to review the animal testing requirements and methods described in WHO guidelines and other WHO written standards. To avoid any perception of bias arising from WHO reviewing its own documents, the review was being conducted by the independent National Centre for the Replacement, Refinement & Reduction of Animals in Research (NC3Rs) in the United Kingdom of Great Britain and Northern Ireland. Project objectives included identifying any available 3Rs approaches not currently considered in WHO documents, exploring potential barriers to the adoption of 3Rs principles by regulators and manufacturers, and identifying future WHO strategies in this area.

20. The Committee also expressed its support for the initial project recommendations, which included using language that emphasized the scientific benefits of adhering to the 3Rs principles and ensuring consistency in the recommendations provided across different WHO documents on the best methods to use during product quality control and lot release testing. The Committee agreed that following its review in 2023 of the final report on the first phase of the project, consideration should be given to drafting a WHO position paper and guidance on the incorporation of 3Rs principles and practices into lot release testing, and to the potential development of WHO guidance specifically on endotoxin and pyrogen testing.

21. The Committee reviewed current WHO priorities for the development of new and revised WHO written standards for biological products and indicated its overall support for the approach proposed. Several potentially outdated disease-specific WHO written standards (for example, on vaccines against poliomyelitis, yellow fever, rotavirus, malaria, dengue and measles/mumps/rubella) had been highlighted for revision to reflect new manufacturing technologies and quality control methods, and to improve consistency with other WHO written standards. Furthermore, depending on the outcome of ongoing vaccine developments in the respective fields, a number of new WHO guidelines may be required (for example, on vaccines against tuberculosis, shigellosis and Group B streptococcus).

22. The Committee also indicated its support for the potential revision of a number of more general WHO documents, including the Recommendations for the preparation, characterization and establishment of international and other biological reference standards. This foundational document was scheduled for review during 2022 to 2023 with a view to developing two separate documents that provide guidance to custodian laboratories and to end users of WHO measurement standards. With regard to other general guidance documents, the Committee noted that the adoption of the revised Guidelines on evaluation of biosimilars at the seventy-fifth meeting would be complemented by the development of biosimilar product-specific case studies. In the light of this package of revised

WHO guidance, the Committee advised that the 2018 document entitled WHO Questions and Answers: similar biotherapeutic products should now be withdrawn from the WHO website.

Significance for public health policies

23. As with all WHO written standards, the three adopted at the seventy-fifth meeting are scientific and advisory in nature and are intended to provide accurate, up-to-date guidance to national regulatory authorities and to manufacturers of biological products. If so desired, such guidance, suitably modified where required, may be adopted as definitive national requirements by countries.

24. Following feedback received by WHO and subsequent unprecedented levels of demand for the First WHO International Standard for anti-SARS-CoV-2 immunoglobulin, a clear need had previously been identified for WHO guidance on secondary standards used in antibody testing. By providing clear guidance on the preparation, characterization, calibration, storage and distribution of such standards, the above-mentioned WHO manual will help to ensure both the appropriate use and conservation of crucially important WHO international antibody standards, including through the preparation and calibration of national biological standards.

25. Guided by resolution WHA67.21 (2014) on access to biotherapeutic products, and following technological advances in the production and characterization of such products, the revised Guidelines on evaluation of biosimilars allows for greater regulatory flexibility and reduced regulatory burden, while at the same time continuing to ensure product quality, safety and efficacy. The provision of its globally acceptable principles will help to harmonize global regulatory requirements thus accelerating the approval and wider availability of these vitally needed products.

26. The adoption of the Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use will help to address the current lack of global regulatory harmonization and limited regulatory experience of such products in low- and middle-income countries. Therapeutic monoclonal antibody products have become increasingly important over the past 25 years as the predominant treatment for a wide variety of diseases and it is envisaged that facilitating their wider availability in countries will bring about significant public health benefits.

27. The timely availability of WHO measurement standards is crucial for countries and manufacturers in harnessing the benefits of scientific advances in the production and evaluation of biological products. The five WHO measurement standards recommended by the Committee at its seventy-fifth meeting for establishment, along with the proposed development of three new or replacement WHO measurement standards, represent the continuation of this core WHO activity.

Implications for the Organization's programmes

28. The Committee's review of and agreement with the proposed WHO priorities for the development of new and revised WHO written standards for biological products is an important step in ensuring that WHO written standards remain relevant and up to date.

29. The development, establishment and promotion of globally relevant biological measurement standards remains a core normative WHO activity and the decision of the Committee to recommend establishment of the five new WHO measurement standards directly supports the continuation of this core activity. In addition, the endorsement by the Committee of the proposed development of the three new or replacement WHO measurement standards will ensure that such standards continue to

become available in a timely manner to support the work of WHO programmes in addressing both the existing and the emerging global health priorities of the Organization.

30. The decisions and recommendations of the Committee have direct implications for the regulation and quality control of biological products and are thus relevant to regulators in all countries and to the numerous programmes and initiatives within WHO and other international organizations that rely on the availability of vaccines, biotherapeutics, blood products, cell and gene therapy products, in vitro diagnostics and other biological products.

SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Fifty-sixth report of the Expert Committee on Specifications for Pharmaceutical Preparations, virtual meeting,¹ 25 April–2 May 2022²

31. The Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General in the area of quality assurance of medicines. It oversees the maintenance of *The International Pharmacopoeia* and provides guidance for use by relevant WHO programmes and regulatory authorities in Member States, to ensure that medicines meet unified standards of quality, safety and efficacy.

Main recommendations

32. Regarding quality control and testing of medicines, the Committee adopted 18 new and revised specifications and general texts for inclusion in *The International Pharmacopoeia* and 11 International Chemical Reference Substances established by a custodian centre. The Committee advised continuing the External Quality Assurance Assessment Scheme for quality control laboratories, including continuing the post-assessment assistance programme. Regarding manufacturing, the Committee adopted the following guidelines and guidance texts:

- (a) WHO good manufacturing practices for sterile pharmaceutical products;
- (b) WHO guidelines on technology transfer in pharmaceutical manufacturing;
- (c) WHO good manufacturing practices for medicinal gases;
- (d) WHO good practices for research and development facilities of pharmaceutical products;
and
- (e) WHO good manufacturing practices for investigational products.

In addition, the IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products, developed in collaboration with IAEA, was adopted.

33. To facilitate the distribution and supply of medical products during emergencies, the Committee amended the guidance on Points to consider for setting the remaining shelf-life of medical products upon

¹ Coordinated from WHO headquarters, Geneva

² WHO Technical Report Series, No. 1044 (in preparation).

delivery, with the inclusion of guidance on emergency health kits. Regarding reproductive health, the Committee adopted two guidelines developed in collaboration with UNFPA:

- (a) WHO/UNFPA guidance on natural rubber male latex condom stability studies; and
- (b) WHO/UNFPA technical specifications for TCU380A intrauterine device.

34. To facilitate the development of affordable generic medicines of good quality, the Committee updated the WHO Biowaiver List: proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. The Biowaiver List now includes eight new essential medicines, bringing the total to 34 since the WHO Biowaiver Project started in 2018.

Significance for public health policies

35. The Committee provides a wide spectrum of written and physical standards to enable medicines to be tested for their quality during their life cycle, from development to distribution to patients. It also recommends regulatory guidelines of importance to multisource medicines designed to be used globally, be it in hot and humid climates, small or large countries, well or less developed settings. The outcome is intended to protect patients and facilitate access to good-quality medicines. Much of the Committee's work is aimed at increasing convergence in quality assurance and regulatory guidance, facilitating efficient synergies among and within the respective authorities and pharmacopoeias, and reducing duplication of effort and thus costs. The quality standards and guidelines are designed to serve all Member States, especially their national and regional regulatory authorities, entities of the United Nations system, and regional and interregional harmonization efforts, and underpin important public health initiatives, including the prequalification and procurement of good-quality medicines through major international bodies, such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations, such as UNICEF.

Implications for the Organization's programmes

36. The outcome and recommendations of this Committee have broad inter- and intracluster relationships, links with regional offices, country offices and partnerships, as well as other WHO expert committees. The Committee especially serves the WHO Secretariat teams dealing with prequalification of medicines and regulatory systems strengthening through the availability of WHO's international guidelines, standards and specifications. In return, practical feedback is provided to the Committee through its direct link to those who implement the more than 100 current guidelines, 200 standards and 700 specifications. This Committee provides norms and standards to determine the quality of medicines globally and thus assists WHO in fulfilling its normative role, which includes supporting the global response to the COVID-19 pandemic.

EVALUATION OF CERTAIN VETERINARY DRUG RESIDUES IN FOOD

Ninety-fourth report of the Joint FAO/WHO Expert Committee on Food Additives, virtual meeting,¹ 16–27 May 2022²

Main recommendations

37. The report contains the Joint FAO/WHO Expert Committee on Food Additives' evaluations of technical, toxicological, epidemiological, occurrence and dietary exposure data for three veterinary drug residues: imidacloprid (a parasiticide), ivermectin (a broad-spectrum antiparasitic agent) and nicarbazin (a coccidiostat). In addition, the Committee further evaluated selamectin (a broad-spectrum parasiticide), for which additional data had been received to refine the evaluation carried out at the eighty-eighth meeting of the Committee.

38. The report also presents general considerations and guidance as well as updated methodological approaches for assessing veterinary drug residues in food.

39. The assessments, recommendations and comments provided by the Committee will be discussed by the Codex Committee on Residues of Veterinary Drugs in Food and will result in the identification of appropriate risk management and risk-mitigation measures to reduce human exposure where necessary and in recommendations to national authorities for the safe use of these veterinary drugs in food-producing animals.

40. In addition, WHO will publish detailed monographs in the WHO Food Additives Series of the toxicological, epidemiological and other related information upon which the health risk assessments of the compounds were based.³

Significance for public health policies⁴

41. The Committee identifies and, where possible, quantifies the public health significance of exposure to chemicals in food – in these cases, residues of veterinary drugs – through scientific risk assessment based on international consensus. When a health concern is identified, clear recommendations are issued for action by national governments or through the Joint FAO/WHO Food Standards Programme (the Codex Alimentarius Commission and its subsidiary bodies).

42. All Member States face the problem of assessing the potential health risks of chemicals in food; however, only a few scientific national and regional institutions systematically assess all relevant toxicological, epidemiological and other related data. It is therefore important that the reports of the Committee provide Member States with valid information on both the general aspects of risk assessment and the specific evaluations of the veterinary drugs mentioned above.

¹ Coordinated from WHO headquarters, Geneva.

² WHO Technical Report Series, No. 1041, 2022.

³ Toxicological evaluation of certain veterinary drug residues in food. WHO Food Additives Series, No. 85. Toxicological monographs of the ninety-fourth meeting (in preparation).

⁴ Further details of the significance for public health policies and the implications for the Organization's programmes are given in paragraphs 6–11 above, in the section on the ninety-third report of the Joint FAO/WHO Expert Committee on Food Additives.

EVALUATION OF CERTAIN FOOD ADDITIVES IN FOOD

Ninety-fifth report of the Joint FAO/WHO Expert Committee on Food Additives, virtual meeting,¹ 6–17 June 2022^{2,3}

Main recommendations⁴

43. The report contains the Joint FAO/WHO Expert Committee on Food Additives' evaluations of technical, toxicological and epidemiological data, occurrence and dietary exposure data for nine food additives:

- (a) α -amylase (JECFA95-1) from *Geobacillus stearothermophilus* expressed in *Bacillus licheniformis*;
- (b) α -amylase (JECFA95-2) from *Geobacillus stearothermophilus* expressed in *Bacillus licheniformis*;
- (c) α -amylase (JECFA95-3) from *Rhizomucor pusillus* expressed in *Aspergillus niger*;
- (d) amyloglucosidase (JECFA95-4) from *Rasamsonia emersonii* expressed in *Aspergillus niger*;
- (e) asparaginase (JECFA95-5) from *Pyrococcus furiosus* expressed in *Bacillus subtilis*;
- (f) β -amylase (JECFA95-6) from *Bacillus flexus* expressed in *Bacillus licheniformis*;
- (g) lipase (JECFA95-7) from *Thermomyces lanuginosus* and *Fusarium oxysporum* expressed in *Aspergillus oryzae*;
- (h) phospholipase A2 (JECFA95-8) from porcine pancreas expressed in *Aspergillus niger*; and
- (i) xylanase (JECFA95-9) from *Bacillus licheniformis* expressed in *Bacillus licheniformis*.

In addition, two flavouring agents were also evaluated.

44. Specifications for the food additive spirulina extract were revised.

45. The assessments, recommendations and comments by the Committee will be discussed by the Codex Committee on Food Additives in order to generate recommendations to national authorities on the safe use of these food additives and to identify and recommend appropriate risk-management and risk-mitigation measures to reduce human exposure, where necessary.

¹ Coordinated from FAO headquarters, Rome.

² WHO Technical Report Series, No. 1042 (in press).

³ With an additional day on 22 June 2022 for adoption of the report.

⁴ Note that the significance for public health policies and implications for the Organization's programmes are the same as those for the ninety-third report of the Joint FAO/WHO Expert Committee on Food Additives, outlined in paragraphs 5–11 above.

46. WHO will publish detailed monographs in the WHO Food Additives Series with the toxicological and other related information upon which the safety assessments of the compounds were based.¹ FAO publishes summaries of the identity and purity of food additives.

ACTION BY THE EXECUTIVE BOARD

47. The Board is invited to note the report.

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¹ Safety evaluation of certain food additives. WHO Food Additives Series, No. 86. Toxicological monographs of the ninety-fifth meeting (in preparation).