Joint FAO/WHO Expert Committee on
Food Additives (JECFA)

Guidance document for WHO monographers and reviewers evaluating flavouring agents

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List of abbreviations

$BMDL_x$	lower 95% confidence limit on the benchmark dose for an x% response
bw	body weight
CD-ROM	compact disc read-only memory
DVD	digital video disc
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FEMA	Flavor and Extracts Manufacturing Association of the USA
GLP	good laboratory practice
IOFI	International Organization of the Flavor Industry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MSDI	maximized survey-derived intake
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OCR	optical character recognition
OECD	Organisation for Economic Co-operation and Development
PDF	portable document format
POD	point of departure
ppm	part per million
QA	quality assurance
SI	Le Système international d'unités (International System of Units)
SPET	single-portion exposure technique
TTC	threshold of toxicological concern
URL	uniform resource locator
USA	United States of America
USB	universal serial bus
WHO	World Health Organization

Preface

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated a large number of flavouring agents grouped according to their chemical structure. Additional flavouring agents in commerce that require evaluation fit into groups that have been evaluated previously. This document provides guidance for preparing meeting report items and, where appropriate, monographs or monograph addenda for those flavouring agents that are additions to already evaluated groups. In this guidance document, reference to JECFA is to JECFA (food additives and contaminants), unless otherwise specified.

This guidance document replaces the previous guidance for the evaluation of flavouring agents by JECFA monographers and reviewers, issued by WHO in 2002. It is intended primarily for WHO Experts (monographers) who prepare monographs for JECFA and for Members (reviewers) who have been assigned to peer review them. The guidance will also be useful to manufacturers who submit dossiers to WHO and other parties interested in understanding the process followed in the evaluation of flavouring agents by JECFA. Detailed scientific guidance on the interpretation of toxicological and epidemiological data may be found in the monograph Environmental Health Criteria 240 (http://www.who.int/foodsafety/publications/chemical-food/en/).

With the aim of harmonizing the work of JECFA with that of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), this guidance document takes into account the document entitled *Guidance document for WHO monographers and reviewers*, prepared by JMPR in 2015 (http://www.who.int/foodsafety/publications/jmpr_guidance_document_1.pdf?ua=1). The authors of the JMPR guidance document as well as the authors of this guidance document for the evaluation of flavouring agents are gratefully acknowledged.

It is envisioned that this guidance document will be modified based upon comments received and experience gained in using it. Comments on this guidance document and suggestions for future editions will be gladly accepted by the WHO Joint Secretary, Joint FAO/WHO Expert Committee on Food Additives, World Health Organization, 1211 Geneva 27, Switzerland, at jecfa@who.int.

Chapter 1: Roles and responsibilities

The roles and responsibilities of the JECFA Secretariat and of both monographers ("Experts"[1]) and reviewers ("Members"), from the time they are assigned to their groups of flavouring agents through to the post-meeting finalization of their monographs or monograph addenda, are outlined below.

1.1 Selection of compounds on the agenda and issuing the call for data

The compounds on the agenda for the next JECFA meeting on food additives, including flavouring agents, are selected on the basis of a priority list established by the Codex Committee on Food Additives, requests by FAO and WHO and their Member States, and recommendations of earlier meetings of JECFA. The WHO and FAO Joint Secretaries post a call for data on the compounds on the agenda 10–12 months in advance of the meeting on the Internet, utilizing as broad a distribution as possible. The deadline for submission of data is ordinarily 6–7 months before the meeting.

1.2 Identification of monographers and reviewers and assignment of groups of flavouring agents and tasks

The WHO Joint Secretary will contact potential monographers and reviewers within the existing roster of experts about their interest and availability to serve as experts for the next meeting of JECFA on food additives, including flavouring agents. Participants are invited as independent experts in their respective areas, and they do not represent any organization or government. Participation is not compensated, although WHO is responsible for return airfare and provides a daily subsistence allowance to cover accommodation, meals and other miscellaneous expenses.

In accordance with WHO rules and procedures for declarations of interest,[2] any potential or perceived interests will be evaluated before any tasks are assigned. In the interest of transparency and to avoid potential conflicts, participants are encouraged to be inclusive in the declaration of interests. It is important to note that the focus should be on a comprehensive declaration of all interests, not just those perceived by the participant as potentially posing conflicts. In accordance with WHO procedures, declarations of interest are not published, but potential conflicts of interest that preclude participation in discussions on particular compounds are noted in the meeting report. The WHO Joint Secretary will take into account whether monographers have been involved with a particular compound, which may be perceived as a conflict or bias. Interests to be considered include the following examples:

- Monographers have worked for or have an interest in the sponsoring company.
- Monographers have performed some of the studies to be evaluated.
- Monographers have recently been closely involved with preparing an evaluation of a compound for a national or supranational body.

The last point is important as, although familiarity with a compound and the supporting data can make preparation of the monograph easier, there might be the perception that the JECFA evaluation is not entirely independent of the previous evaluation.

According to WHO rules and procedures,[3] expert meetings are private in nature, and participation is by invitation only. The data used and discussions held before, during and after the meeting on the subject matter of the meeting are to be held in strict confidence. Discussions held subsequent to the meeting with non-participants should be limited to the public information made available in the monographs and meeting report.

1.3 Dealing with the data submission

After a group of flavouring agents has been assigned to a monographer and a reviewer, the Secretariat will ensure that the sponsoring company arranges submission of the dossier, which

[1] Previously Temporary Advisers.

[2] http://www.who.int/about/declaration-of-interests/en/

[3] http://apps.who.int/gb/bd/PDF/bd48/basic-documents-48th-edition-en.pdf#page=127

contains the original study reports, relevant papers from the literature and the company overview (summary of the submitted data). As a good practice, the sponsoring company is asked to alert the monographer, the reviewer and the WHO Joint Secretary when the data have been sent. Normally, the data are submitted as searchable PDF files on a suitably indexed CD-ROM, DVD or USB stick. A table of contents using fully descriptive file names needs to be submitted with each electronic submission; for example, a title of "xyz 33564-05" is not going to help the monographer locate a 90-day dog study by Jones et al. (2001). Sponsoring companies should submit editable PDFs whenever possible; when documents are scanned, these should be converted using OCR to editable format, if at all possible. This facilitates the accurate transfer of information to the monograph. Companies should be aware that, owing to the workload of experts reviewing the dossiers, delay of a submission may cause the compound to be removed from the JECFA agenda.

When the data are received, it is important for the monographer to confirm receipt to the sponsor and the WHO Joint Secretary. If the data submission has not arrived in a reasonable length of time, the monographer should contact the sponsor and the WHO Joint Secretary, as it is not unknown for items to go missing in transit. On opening the package, it is recommended that the monographer perform some basic checks on the quality and usability of the documentation:

- For electronic submissions
  - Do the document files open properly?
  - Are a table of contents and an appropriate index provided?
  - Are the files searchable?
  - Are the pages legible, especially older study reports that have been scanned?
  - Are the titles of the files helpful?
- Check the company overview
  - Is it in the JECFA style and in a suitable format (PDF and/or Microsoft Word) to permit the use of text or tables for the monograph?
  - Does it contain a reference list in the JECFA style (see section 2.3.5)?

If the monographer identifies any issues with the data submission where it is believed that the sponsor could provide an improved submission, then the monographer should inform the WHO Joint Secretary, who will contact the sponsor with a detailed request for what is needed. It is in the sponsor's interest to provide a usable submission. If the monographer cannot read data in a key study report, this might prevent a conclusion regarding safety from being reached.

Unpublished confidential studies that are submitted will be safeguarded and will be used only for evaluation purposes by JECFA. Summaries of the confidential studies will be published by FAO and WHO after the meetings in the form of specifications and toxicological monographs.

Submitted confidential data can be either returned to submitters at their expense or destroyed after the evaluations have been completed. Key material can be stored by WHO for up to five years and will then be destroyed.

1.4 Handling contacts with the sponsor

To ensure transparency, it is important that all contacts between the monographer and the sponsor are documented and copied to the WHO Joint Secretary. With respect to contact with the sponsor:

- It is preferable to use email rather than telephone. Emails need to be copied to the WHO Joint Secretary.
- If the sponsor telephones to discuss an issue, the monographer should consider whether the discussions can be performed by email. If the monographer chooses to proceed with the call, the monographer should notify the WHO Joint Secretary about the contact, with a brief outline of the details. If a teleconference is requested or considered useful, the monographer should involve the WHO Joint Secretary, who will set up the call.
- The sponsor should assist the monographer by providing information required to perform a thorough and independent evaluation. The monographer may send questions to the sponsor, copied to the WHO Joint Secretary, well in advance of the meeting as well as, on occasion, during the meeting itself.

- The sponsor must not contact a monographer with repeated requests for progress updates or for information that is not appropriate to be shared, such as the conclusion regarding safety; if this occurs, the monographer should notify the WHO Joint Secretary.

1.5 Performing literature searches[4]

In addition to the unpublished study reports and other material submitted by the sponsor, a search of the public literature is required to ensure that all available information is being considered in the evaluation. The monographer is requested to perform a detailed search of the public literature. The literature search should be documented in detail, listing the exact search terms used, the databases that were searched, the number of references retrieved and the number of relevant references selected, as well as the criteria (both inclusion and exclusion) for the selection of relevant references. The WHO JECFA Secretariat can assist in developing search strategies and in retrieving the full text of relevant publications.

1.6 Evaluating the data

The basic principles on how to evaluate toxicological and epidemiological data are outlined in Environmental Health Criteria (EHC) 240 (IPCS, 2009). A JECFA monographer will already be an experienced assessor of toxicological and epidemiological data and will have his or her own ways of working through the toxicological and epidemiological database on a compound, including submitted data and publicly available information. The JECFA process should not require any significant changes to the monographer's and reviewer's usual way of working through the data, provided that each study is described and the relevance (including any potential bias or problems with study design or reporting of results) is documented in a clear and transparent manner. One important difference for monographers from a regulatory agency background is that "stop the clock" and demand for new studies are not foreseen; even when major deficiencies are identified, a monograph summarizing available data and clearly identifying the deficiencies may need to be prepared. When the monograph is being prepared, all data are evaluated in a thorough and independent manner, taking into account specific guidance prepared for JECFA monographers on the interpretation of toxicological and epidemiological data (i.e. EHC 240 [IPCS, 2009] and subsequently published guidance).

The depth of investigation will clearly vary with the study type, the results and the impact on the overall conclusion. For example, it can be valuable to go down to individual animal-level data for a dog study with a small group size and a marginal response, but this is not normally required for a rodent study with a larger group size and clear effects (e.g. 8/10 animals with grade 3 versus 3/10 controls with grade 1). In general, the monographer should always check at least the results in the main study report, and not just the sponsor's or study report authors' summary. If the study report authors have discounted particular findings as not being treatment related or adverse, the monographer should pay particular attention to these to see if he or she agrees with the study report authors' conclusions. If the monographer disagrees with the conclusions of the study report authors, this should be highlighted in the monograph.

In presenting findings where descriptive terms are used, it is important to use the precise terms as given in the study report (e.g. in the histopathology tables or descriptions of anomalies in