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

Guidance document for WHO monographers and reviewers evaluating contaminants in food and feed

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List of abbreviations

ADI	acceptable daily intake
ARfD	acute reference dose
BMD	benchmark dose
BMDL	lower 95% confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BMDS	Benchmark Dose Software (USEPA)
BMR	benchmark response
bw	body weight
CCCF	Codex Committee on Contaminants in Foods
C_{max}	maximum concentration
CSAF	chemical-specific adjustment factor
EHC	Environmental Health Criteria
FAO	Food and Agriculture Organization of the United Nations
FFQ	food frequency questionnaire
GEMS/Food	Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme
GLP	good laboratory practice
IQ	intelligence quotient
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOEL	lowest-observed-effect level
LOQ	limit of quantification
ML	maximum level
MOE	margin of exposure
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
PMTDI	provisional maximum tolerable daily intake
POD	point of departure
ppm	part per million
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
QA	quality assurance
RIVM	National Institute for Public Health and the Environment (the Netherlands)
SI	Le Système international d'unités (International System of Units)
T_{25}	chronic daily dose that will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard lifespan of that species
TDI	tolerable daily intake
TEF	toxic equivalency factor
T_{max}	time to maximum concentration
URL	uniform resource locator
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

Preface

This guidance document replaces the previous guidance for the risk assessment of contaminants in food by Joint FAO/WHO Expert Committee on Food Additives (JECFA) monographers and reviewers, issued by WHO in 2001. It is intended primarily for WHO Temporary Advisers (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 parties interested in understanding the process followed by JECFA in the evaluation of contaminants that may be present in food or feed – for example, heavy metals, environmental contaminants, impurities arising in food or feed additives, solvents used in food or feed processing, other substances arising from food or feed processes such as heating, substances migrating from food or feed contact materials, and residues arising from the use of animal feed additives or the non-active components of veterinary drug formulations. 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/).

In this guidance document, reference to JECFA is to JECFA (food additives and contaminants).

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 contaminants in food and feed 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.

Separate guidance documents for the evaluation of food additives (excluding enzyme preparations and flavouring agents), enzyme preparations and flavouring agents and for the assessment of dietary exposure to food additives are also available on the WHO website (http://www.who.int/foodsafety/chem/jecfa/guidelines/en/).

Chapter 1: Roles and responsibilities

The roles and responsibilities of the JECFA Secretariat and of both monographers ("Temporary Advisers") and reviewers ("Members"), from the time they are assigned to their compounds through to the post-meeting finalization of their monographs, 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 contaminants are selected on the basis of priority lists established by the Codex Committee on Contaminants in Foods (CCCF), 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 compounds 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 contaminants in food and feed. If additional expertise is needed (e.g. in the areas of dose–response modelling, epidemiology, carcinogenicity or genotoxicity), the Secretariat may identify additional experts from the published literature. Usually the Secretariat assigns several experts to one compound (or group of related compounds) who have complementary expertise and are assigned to draft specific sections of the monograph. One of the experts will be assigned to take the overall lead and coordination function for the drafting of the full monograph. For complex evaluations, more than one reviewer may be assigned. In addition to WHO experts, FAO experts will be assigned to the compound who are responsible for the evaluation of analytical methods, sampling protocols, effects on processing, and prevention and control, as well as occurrence data in food and feed. Additional experts on dietary exposure assessment will also be assigned to the compound. The entire group of experts assigned to the compound or group of related compounds is sometimes referred to below as the evaluation team.

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,[1] 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 their 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 performed some of the studies to be evaluated.
- Monographers have recently been involved closely with preparing an evaluation of a compound for a national or another supranational body.

The latter 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.

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

According to WHO rules and procedures,[2] 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 Performing a literature search[3]

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.

Previous evaluations by national or international organizations, if relatively recent and comprehensive, may in some cases serve as the starting point for the JECFA evaluation, as agreed between the JECFA Secretariat and the lead monographer and reviewer; in such cases, the monographer will search the public literature for references published after the cut-off date for the previous evaluation. It will not usually be necessary for the monographer to retrieve original publications cited in the previous evaluation, except for critical studies.

1.4 Dealing with the data submission

After a compound has been assigned to the lead monographer and a reviewer, the Secretariat will ensure that the evaluation team receives any data submitted, usually by national authorities, in response to the JECFA call for data. The evaluation team should review the data submission in detail and identify any need for further clarification.

1.5 Evaluating the data

The basic principles on how to evaluate toxicological and epidemiological data are outlined in Environmental Health Criteria (EHC) 240 (IPCS, 2009a). A JECFA monographer will already be an experienced assessor of toxicological, epidemiological or other relevant data and will have his or her own ways of working through the toxicological and epidemiological database on a compound, including published peer-reviewed studies, the grey literature and data submitted during the call for data. The WHO Joint Secretary will also inform the monographers of any previous evaluations of the compound or of its metabolites by JECFA.

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. 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, 2009a] and subsequently published guidance). Given the large amount of published literature often available on contaminants in food and feed, the monographers must be sure to allow sufficient time for retrieving, organizing and reviewing references identified during the literature search.

When a JECFA evaluation uses a previously published evaluation by a national or international organization as a starting point, the monographer will review the sections and if in agreement will accept the conclusions of the previous evaluation and summarize them briefly in the appropriate sections of the monograph. Where the critical study is taken from the previous evaluation, the monographer will obtain and review the original publication to ensure that he or she is in agreement with the previous evaluation's findings.

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

[3] The JECFA Secretariat is currently investigating the applicability of systematic review methodology to the work of JECFA, with the ultimate aim of developing a workable approach that is manageable and follows the basic principles on transparency, minimizing risk of bias and reproducibility.

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).

If the study 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 authors' conclusions. If the monographer disagrees with the conclusions of the study authors, this should be highlighted in the monograph. The monographer may occasionally wish to contact the study authors for clarification or to request additional information.

In presenting findings where descriptive terms are used, it is important to use the precise terms as given in the published study (e.g. in the histopathology tables or descriptions of anomalies in developmental toxicity studies). It is, however, acceptable to provide another term (e.g. more recent histopathological terminology) in parentheses. If for any reason a revised term is used, there should be some commentary about this, as it can produce confusion for someone comparing reviews with the published study. If the term is an unfamiliar or unusual one that is not clarified in the published report, then there is the option to ask the study author(s) to clarify and/or provide pictures. Standard texts and websites are available that provide descriptions of pathological and developmental toxicity terminology (e.g. http://www.devtox.org; http://www.goreni.org; see also the guidance below under specific systems and effects).

Where JECFA has its own criteria for the interpretation of toxicological or epidemiological end-points (i.e. EHC 240 [IPCS, 2009a] and subsequently published guidance), these should always be used in the preparation of monographs in preference to those from national or other supranational bodies. Where JECFA does not have its own criteria, then general guidance on the evaluation and interpretation of toxicological and epidemiological data available in the WHO EHC monographs (http://www.inchem.org/pages/ehc.html) and elsewhere may be used. It is expected that standard approaches will be applied (e.g. statistical significance, clear dose–response relationship, change outside the normal biological range). If a conclusion in a monograph is based on a non-standard approach (e.g. the use of a specific cut-off), then the basis for this approach should be provided (or a publicly available supporting guidance document should be cited).

The risk assessment of a contaminant or group of contaminants can result in one of several possible outcomes. The first is the establishment of chronic (tolerable intake; see section 4.5) and/or acute (acute reference dose [ARfD]; see section 4.7) health-based guidance values. Where these are established, chronic dietary exposure estimates are used for comparison with tolerable intakes in a risk assessment process, and acute dietary exposure estimates, which should cover a time period of food consumption over a single meal or 24 hours, are used for comparison with ARfD values.

A second possible outcome is the derivation of a relative level of concern – the margin of exposure (MOE). Where a contaminant is found to be a genotoxic carcinogen, for which JECFA considers it inappropriate to establish a health-based guidance value, JECFA will usually calculate a margin of exposure (MOE) between the critical point of departure and the dietary exposure for a high or average consumer to provide guidance for risk managers.

A third outcome is the performance of a quantitative assessment of the risk (e.g. additional cancer risk)