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

Guidance document for WHO monographers and reviewers evaluating food additives
(excluding enzyme preparations and flavouring agents)
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List of abbreviations

ADI acceptable daily intake
ARfD acute reference dose
BMDL_x lower 95% confidence limit on the benchmark dose for an x% response
bw body weight
CCFA Codex Committee on Food Additives
CD-ROM compact disc read-only memory
DVD digital video disc
EHC Environmental Health Criteria
FAO Food and Agriculture Organization of the United Nations
GLP good laboratory practice
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
LOEL lowest-observed-effect level
NHANES National Health and Nutrition Examination Survey (USA)
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)
URL uniform resource locator
USA United States of America
USB universal serial bus
WHO World Health Organization
Preface

This guidance document replaces the previous guidance for the safety evaluation of food additives by Joint FAO/WHO Expert Committee on Food Additives (JECFA) monographers and reviewers, issued by WHO in 2000. 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 food additives 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/).

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 food additives 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 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 (“Experts”) 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 food additives 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 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 food additives. 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, 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, 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 compound has been assigned to a monographer and a reviewer, the Secretariat will ensure that the sponsoring company arranges submission of the dossier, which contains the original study reports, relevant papers from the literature and the company overview (summary of the submitted

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1 Previously Temporary Advisers.
2 http://www.who.int/about/declaration-of-interests/en/
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 the establishment of a health-based guidance value.

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 then 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抄ied 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 cc'ed 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 health-based guidance value; if this occurs, the monographer should notify the WHO Joint Secretary.

1.5 Performing literature searches

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 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. Based on the monographer’s experience and on a detailed search of the JECFA database, the monographer should in particular identify previous evaluations of the compound or of its metabolites by JECFA, even if such an assessment was based on a different denomination or chemical name.

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 developmental toxicity studies). 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 study report. If the term is an unfamiliar or unusual one that is not clarified in the study report, then there is the option to ask the sponsor to clarify and/or provide pictures. Standard texts and websites are available that provide descriptions of pathological and developmental toxicity terminology (e.g.

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4 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.

5 http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx
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 end-points (i.e. EHC 240 [IPCS, 2009] 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 data available in the WHO EHC monographs 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).

It is important to note that for food additives, JECFA usually considers only the establishment of a chronic health-based guidance value (i.e. acceptable daily intake [ADI]) or the safety of use for a specified purpose. Acute toxicity is rarely of relevance for food additives; however, should the toxicological database provide an indication of acute toxicity in the range of doses relevant for human exposures, the need to perform an acute risk assessment has to be considered (see also section 4.4.6).

1.7 Preparing the draft monograph before the meeting

The monographer produces a first draft of the monograph, based on the submitted dossier as well as a critical review of the published literature. Each monograph includes a main body of text as well as an Explanation section, a Comments section and an Evaluation section; these three sections will be used as the basis for the meeting report item for the food additive (see Chapter 3). Detailed guidance on preparation of the monograph is provided in Chapter 2. Examples of recent monographs on food additives can be accessed through the WHO JECFA searchable database: http://apps.who.int/food additiv es-contaminants-je cfa-database/search.aspx?fc=35.

In cases where new or additional data are provided to complete an evaluation or to re-evaluate a food additive previously considered by JECFA, an addendum to the original monograph should be prepared with the summaries of the new studies. A short monograph addendum is usually prepared even when the number of studies submitted is low. However, in specific instances, this may be considered unnecessary – for example, where the additional information is restricted to a narrow aspect of the evaluation and does not have any impact on the previously established health-based guidance value. In such cases, only the meeting report item is prepared.

The first draft of the monograph, which is complete except for those sections prepared by other experts (i.e. Chemical and technical considerations and Dietary exposure), is distributed first to the reviewer. Under ideal circumstances, the reviewer should receive the first draft of the monograph three months before the meeting, although it is recognized that this may not occur in practice. The monographer and reviewer are encouraged to work together and discuss critical aspects or studies throughout the preparation of the monograph. It is the responsibility of the reviewer to cross-check critical studies, suggest amendments in both text and tables, and finalize the Comments and Evaluation sections.

The reviewer returns the monograph to the monographer, who incorporates agreed changes into the document and then sends the revised draft monograph to the WHO Joint Secretary. During the preparatory phase, usually 4–6 weeks before the meeting, the WHO Joint Secretary organizes teleconferences for each compound, involving at least the monographer, the reviewer, other JECFA experts, including FAO experts assigned to the same compound, and the WHO Joint Secretary. The purpose of these teleconferences is to clarify issues, coordinate the work between the WHO and FAO experts and identify additional information or clarifications required from the sponsor. A list of any outstanding questions is established for each food additive and sent by the Secretariat to each corresponding sponsor. The monographer is also responsible for making any additional revisions suggested by teleconference participants.

After the final revisions have been made to the draft monograph, the monographer sends a copy of the monograph, without the Evaluation section (containing the proposed health-based guidance value), to the sponsor for an accuracy check of study descriptions, to be completed within two weeks. Any comments received have to be considered by the monographer in discussion with the reviewer.
The final monograph is then submitted to the WHO Joint Secretary, who is responsible for sending the draft monograph to all meeting participants at least 10 days prior to the meeting.

During the preparation of the monograph, the WHO monographer should be in contact with his or her FAO counterpart regarding the status of the preparation of the Chemical and technical considerations section, as well as with the WHO/FAO exposure experts regarding the Dietary exposure section. If those sections have been drafted before the final monograph is submitted to the WHO Joint Secretary, the WHO monographer can insert them into the monograph before the WHO Joint Secretary distributes it to all meeting participants. If they are not ready at that time, then these sections will be inserted into the monograph at the end of the meeting (see section 1.8).

1.8 Preparing the report item and finalizing the monograph at the meeting

The physical meeting is organized jointly by FAO and WHO and generally alternates between Rome and Geneva. During the meeting, the monographers lead the discussions on their particular compounds and prepare the meeting report item for each compound under their responsibility. The report item is prepared from the Explanation, Comments and Evaluation sections of the monograph (see Chapter 3) and is modified during the meeting to incorporate the results of the meeting discussions. In parallel, during the meeting, the monographer updates the draft monograph to ensure that the final version is consistent with the meeting report item, to reflect decisions taken during the meeting (e.g. decisions on the NOAELs) and to include any extra details found to be useful in supporting the conclusions of the Committee.

It is the JECFA Members who have the final responsibility for adopting the report. However, during the meeting, conclusions and decisions are reached by consensus from all participants. Therefore, all monographers (and reviewers) should contribute to discussions on all the compounds and general considerations. This is particularly the case if the monographers have expertise in a specific area of toxicology (e.g. histopathology, genotoxicity, developmental toxicity), such that they can bring additional insights and views to the discussions. It is also important that monographers ask questions when they are unclear about the basis for a decision or if the text relating to a topic is not well presented. However, monographers need to be aware that their report items must be completed prior to the conclusion of the meeting and so must carefully balance the requirement for the timely preparation of drafts of their report items for discussion at the meeting and contributing to discussions on other compounds.

During the meeting, the rapporteur is responsible for ensuring that all necessary revisions resulting from discussions have been made to each draft report item before the item is again discussed by the Committee. The editor is responsible for technical and language editing of each draft report item once the Chair is satisfied that it is in near-final form. The monographer is responsible for responding to any queries raised by the editor during the editing process. After the meeting report item has been edited, subsequent changes, as suggested by meeting participants during discussions, will be tracked onscreen by the editor, until the Chair is satisfied that the meeting report item is in final draft form. At that time, the editor passes the report item on to the FAO rapporteur for FAO review and incorporates any changes suggested by FAO. Additional editing may be performed by the editor after the meeting has concluded (see below).

On the last day of the meeting, all meeting participants (FAO and WHO) review the final version of the meeting report in plenary session and suggest any necessary revisions, which are made onscreen by the editor or by the WHO Joint Secretary, and the JECFA Members formally adopt the report before the meeting is adjourned. The monographer needs to provide an electronic version of the final draft of the monograph to the editor and the WHO Joint Secretary before the end of the meeting on the final day. The WHO monographer will need to insert the final Dietary exposure section from the WHO/FAO exposure experts into the monograph. There is no need for the monographer to update the Explanation (including the Chemical and technical considerations section from FAO), Comments and Evaluation sections of the monograph during the final session, as the editor will insert the final versions of those sections from the meeting report into the monograph during the editing process.

In the weeks following the meeting, a summary report is published and posted on the FAO and WHO websites. It includes the main conclusions and the health-based guidance values (e.g. ADIs) or other safety recommendations for all food additives evaluated at the meeting.
In the months following the meeting, the editor edits the monographs. The monographers are responsible for answering any queries raised during the editing process in a timely fashion (generally within 1–2 months after receiving the monograph back from the editor). The meeting report is not published until the monographs have been edited, so any errors in the meeting report found during the editing process can be corrected before its publication.


The meeting report is intended for non-experts (both policy-makers and risk managers) and contains the description, concise evaluation and interpretation of the key data relevant for the overall assessment of each substance reviewed by JECFA in terms of its toxicological, epidemiological, chemical and analytical aspects, as well as information on the dietary exposure assessment. Reports reflect the agreed view of the Committee as a whole and describe the basis for its conclusions. Any Members who do not agree with the conclusions can express a minority opinion, which should be noted and described in detail in the meeting report, in accordance with WHO rules and procedures for expert committees.

The toxicological monographs are intended for experts and contain detailed descriptions of the full database on biochemical, toxicological and epidemiological data considered in the evaluation, as well as the dietary exposure assessment, in sufficient detail to enable the basis of the conclusions reached by the Committee to be independently verified. The Comments and Evaluation sections of the monographs are in principle identical to the report item (with the inclusion of the Explanation section). In exceptional cases, these sections could contain more detail than in the report.
Chapter 2: Preparing the monograph

2.1 Introduction

The monograph summarizes the data that are used to assess the safety of food additives. As such, it contains the detailed study descriptions and numerical data used to underpin the meeting report item, referred to below as the report item (see Chapter 3). The monograph must therefore contain all the elements identified in the report item, together with sufficient additional details to permit an independent evaluation of the conclusions made.

The guidance provided in this document pertains to all food additives except for enzyme preparations and flavouring agents, which are discussed in separate guidance documents (http://www.who.int/foodsafety/chem/jecfa/guidelines/en/).

A table of contents or template for the monograph (for the JECFA current year) will be provided to monographers when they are assigned to a food additive. An example is included in Annex 1. The layout and sequence of the template should generally be followed, although not all sections will necessarily be included in all monographs, depending on the information available and the type of food additive being evaluated. The template for the current year should always be used, as modifications may have been introduced following the previous meeting.

2.2 General aspects

General aspects to be considered while preparing the monograph are outlined below.

2.2.1 Formatting

- The monograph (or monograph addendum) should be prepared using Microsoft Word or a compatible word processing package. Details of the formatting requirements (e.g. font size, line spacing, line numbering, margins) should be obtained from the monograph template (see Annex 1).
- Details of the formatting requirements for preparing tables are provided in section 2.2.5.

2.2.2 Units of measurement

- Le Système international d’unités (SI units) should be used throughout. This includes the use of milligrams per kilogram of feed (mg/kg feed) instead of parts per million (ppm) for dietary exposure levels and the use of becquerels (Bq) instead of curies (Ci) for radioactivity. One exception is millimetres of mercury (mmHg) for pressure (the equivalent in kilopascals [kPa] should be given in parentheses).
- When expressing dietary exposure levels in milligrams per kilogram, the word “feed” should always be included (i.e. mg/kg feed), to avoid confusion with the actual dose to the animals (in mg/kg bw, where bw is body weight).
- There are no hyphens between numbers and units, but there is a space. For example, 0.5 kg rat (not 0.5-kg rat or 0.5kg rat) is used.
- There should be no words between units and the solidus (/). For example, 3 µg pectin/kg bw is not correct. Instead, the sentence should be rewritten more clearly as, for example, “a pectin dose of 3 µg/kg bw”. It is recognized that there may need to be occasional exceptions to this rule in order to avoid extremely awkward wording.
- Only one solidus should be used. For example, 3 mg/kg bw per day, not 3 mg/kg bw/day, is used.
- Figures with more than four digits use a space (not a comma) to separate groups of three digits on either side of the decimal point (e.g. 12 050; 0.004 56). Note that the WHO rule is that in tables, figures with more than three digits use a space to separate groups of three digits on either side of the decimal point. The WHO rule is to be followed, even though the
guide for the use of SI units (Thompson & Taylor, 2008) states that the practice of inserting spaces in numbers having only four digits on either side of the decimal marker is not usually followed except when uniformity in a table is desired.

2.2.3 Presentation of doses

- Parentheses, rather than commas, are used when presenting dose conversions: X and Y mg/kg feed (equal [or equivalent] to x and y mg/kg bw per day for males and a and b mg/kg bw per day for females, respectively).
- “Equal to” is used when the conversions have been calculated using feed or drinking-water consumption and body weight data generated for the animals that have been dosed in a particular study, and “equivalent to” is used when dose conversion factors (i.e. default values) have been used to calculate the doses.
- Where accurate doses cannot be calculated on the basis of measured body weights and feed or drinking-water consumption, approximate doses can be estimated using the dose conversion factors shown in Table 1, adapted from EHC 240 (IPCS, 2009).
- When doses are converted from ppm, mg/kg feed, mg/L drinking-water, mg/animal per day or percentage of the substance in the diet (often given when the lowest dose is 1000 mg/kg feed or more; e.g. 10 000 mg/kg feed = 1%) to mg/kg bw per day, up to two additional significant figures can be used for the converted dose, where necessary, to avoid introducing additional uncertainty in the calculation of the final rounded health-based guidance value.
- As long as the dose conversions have been presented at the beginning of a study description, the original doses (e.g. in mg/kg feed, mg/L drinking-water or percentage in the diet, but not in ppm, which must be changed to mg/kg feed or mg/L drinking-water) can be used throughout the study description until the no-observed-adverse-effect level (NOAEL) is identified at the end of the study description.
- Equivalent doses should be corrected for the purity of the compound, but only when this is less than 90%.
- Doses should be corrected for non-continuous dosing (e.g. 5 days/week dosing).

2.2.4 Presentation of point of departure

- Health-based guidance values (e.g. the ADI) are often established using a point of departure (POD) from a toxicity study in experimental animals. The most frequently used POD is the NOAEL. However, if the data are adequate to permit dose–response modelling, a lower 95% confidence limit on the benchmark dose for an x% response (BMDL<sub>x</sub>) or similar POD can (and should) be used. In such cases, the basis for the derivation of the POD should be provided (for details, see EHC 240 [IPCS, 2009]).
- Past tense should be used when presenting the POD: The NOAEL/BMDL<sub>x</sub> was 10 mg/kg bw per day.
- The POD used in risk assessment by the Committee should be that identified by the monographer/Committee. When this differs from the POD identified by the study authors, the latter should also be reported, with an explanation for the difference.
- When doses have been derived from a dietary or drinking-water concentration using the feed or drinking-water consumption and body weight data from the study, the POD should be expressed as “equal” to x mg/kg bw per day. If predefined dose conversion factors (see Table 1) need to be used, the POD should be expressed as “equivalent” to x mg/kg bw per day.
- The POD, as either “equal to” or “equivalent to” doses, can be (but does not have to be) provided for both males and females in the main text, but only the lower value of the two (usually the value for males) is given in the Comments section. An exception to this rule is where the effect is sex specific, in which case the appropriate POD for the sex in which the effect is observed is provided.
Table 1
Approximate relationship of mg/kg (ppm) in the diet or mg/L (ppm) in drinking-water to mg/kg bw per day

<table>
<thead>
<tr>
<th>Species</th>
<th>Body weight (kg)</th>
<th>Feed consumption (g/day)*</th>
<th>Type of diet</th>
<th>1 mg/kg in feed is equivalent to x mg/kg bw per day</th>
<th>Water consumption (L/day)</th>
<th>1 mg/L in water is equivalent to x mg/kg bw per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>0.02</td>
<td>3</td>
<td>Dry laboratory chow diets</td>
<td>0.150</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>0.03^b</td>
<td>4^b</td>
<td></td>
<td>0.13^b</td>
<td>0.006^b</td>
<td>0.20^b,c</td>
</tr>
<tr>
<td>Rat (young)</td>
<td>0.10</td>
<td>10</td>
<td></td>
<td>0.100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rat (multigeneration studies)</td>
<td>0.10–0.40^d</td>
<td>10–20^d</td>
<td></td>
<td>0.06</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mouse</td>
<td>0.40^b</td>
<td>34^b</td>
<td></td>
<td>0.04^b</td>
<td>0.20^b</td>
<td>0.24^b</td>
</tr>
<tr>
<td>Hamster</td>
<td>2.0</td>
<td>60</td>
<td></td>
<td>0.030</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rabbit</td>
<td>3.8^b</td>
<td>180^b</td>
<td></td>
<td>0.05^b</td>
<td>0.41^b</td>
<td>0.11^b</td>
</tr>
<tr>
<td>Dog</td>
<td>10.0</td>
<td>250</td>
<td></td>
<td>0.025</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>12^b</td>
<td>300^b</td>
<td></td>
<td>0.03^b</td>
<td>0.61^b</td>
<td>0.05^b</td>
</tr>
<tr>
<td>Cat</td>
<td>2</td>
<td>100</td>
<td>Moist, semi-solid diets</td>
<td>0.050</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Monkey (e.g. rhesus, cynomolgus)</td>
<td>5</td>
<td>250</td>
<td></td>
<td>0.050</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rhesus monkey</td>
<td>8.0^b</td>
<td>320^b</td>
<td></td>
<td>0.04^b</td>
<td>0.53^b</td>
<td>0.07^b</td>
</tr>
<tr>
<td>Dog</td>
<td>10</td>
<td>750</td>
<td></td>
<td>0.075</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Human</td>
<td>60</td>
<td>1500</td>
<td></td>
<td>0.025</td>
<td>2</td>
<td>0.033</td>
</tr>
<tr>
<td>Pig or sheep</td>
<td>60</td>
<td>2400</td>
<td>Relatively dry grain forage mixtures</td>
<td>0.040</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pig</td>
<td>80^b</td>
<td>2250^b</td>
<td></td>
<td>0.03^b</td>
<td>5.5^b</td>
<td>0.07^b</td>
</tr>
<tr>
<td>Cow (maintenance)</td>
<td>500</td>
<td>7500</td>
<td></td>
<td>0.015</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cow (fattening)</td>
<td>500</td>
<td>15000</td>
<td></td>
<td>0.030</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Horse</td>
<td>500</td>
<td>10000</td>
<td></td>
<td>0.020</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

bw: body weight; ppm: parts per million

^a Liquids omitted.

^b From Health Canada (1994). Note that the type of diet has not been specified in this reference.

^c EFSA (2012) uses conversion factors of 0.18, 0.15 and 0.09 for mice for subacute, subchronic and chronic studies. The first two types of studies are assumed to start with mice 5–7 weeks of age.

^d Body weight and feed consumption values vary over the stages and generations of the studies. The average values are used in calculating the dose conversion factor.

^e EFSA (2012) uses conversion factors of 0.12, 0.09 and 0.05 for rats for subacute, subchronic and chronic studies. The first two types of studies are assumed to start with rats 5–7 weeks of age.
• The general statement will read as follows: *When the POD is the NOAEL:* The NOAEL was $x$ mg/kg feed (equal to $y$ mg/kg bw per day), based on [effects] observed at $z$ mg/kg feed (equal to $a$ mg/kg bw per day) [where $z$ mg/kg feed is, of course, the lowest-observed-adverse-effect level (LOAEL), but this does not need to be stated explicitly in the text]. *When the POD is the BMDL or similar:* The BMDL$_x$ [or similar] was $y$ mg/kg bw per day, based on [the effects that serve as the basis of the benchmark response $x$].

• When no effects are observed up to the highest dose tested, it is not possible to determine a BMDL. In such cases, the highest dose tested is the NOAEL, which serves as the POD for this study. Consistent language should be used when expressing the NOAEL in such circumstances: The NOAEL was $x$ mg/kg bw per day, the highest dose tested. OR The NOAEL was $x$ mg/kg diet (equal to $y$ mg/kg bw per day), the highest dietary concentration tested.

• When effects are observed at all doses, it is not possible to identify a NOAEL. In such cases, it might be possible to determine a BMDL, or similar POD. Otherwise, the POD for the study is the LOAEL. Consistent language should be used in such circumstances: No NOAEL could be identified, as effects were observed at all doses. The LOAEL was $x$ mg/kg bw per day, the lowest dose tested. OR The LOAEL was $x$ mg/kg diet (equal to $y$ mg/kg bw per day), the lowest dietary concentration tested.

• If an effect has been considered not relevant for determining the POD for a study, a statement should always be made on the reason for this – for example, the effect was considered not to be toxicologically relevant or the effect was considered not to be substance related (with an explanation as to why, if possible), to make the basis for POD determination clear to the reader.

• Determination of overall NOAELs (see section 4.3) is normally reserved for the *Comments* section.

2.2.5 Tables

• It is often preferable to present numerical information in the form of a table rather than in the text (e.g. to illustrate the results of acute toxicity and genotoxicity studies).

• It is the choice of the monographer as to whether data are presented in tables or text, as long as it is possible for readers of the monograph to perform an independent evaluation of the data and reach their own conclusions.

• Pasting tables from PDF documents into the monograph is not recommended and should be done only if there is no realistic alternative (in which case the editor will need to re-enter the tables in Microsoft Word format in order to edit them according to WHO style). If the sponsoring company has not provided tables in Word format, it should be requested to do so by the monographer. Tabs should not be used to create the table columns.

• All tables must be cited in the text, in consecutive numerical order from 1 to $x$.

• Tables should be placed in the text immediately following the paragraph in which they are first cited, or as near to this as is practical. Repeating header rows can be used where the table extends over more than one page.

• The contents of a table should be restricted to the data relevant to decision-making. If a 200-row table contains 16 rows of data that show no changes with dosing, it is difficult to identify the data that are important.

• There should be no blank cells in the table (unless the cells are in a heading row). If a cell does not contain text or figures, then a 0, dash, NA (for not applicable or not available) or ND (for not determined or no data), or something along these lines, is needed, depending on the table, with a clear definition of the terms used included below the table, if necessary.

• Data in tables should be quoted to an appropriate number of significant figures (e.g. quoting organ weights relative to body weight to six significant figures is not appropriate, as it implies spurious accuracy – six significant figures implies that a change of 0.0001% could be determined with confidence and is biologically significant). The appropriate number of
significant figures to be used may vary with the situation but should be sufficient to show differences in outcome while being proportionate to the variance (or standard deviation).

- In some instances, it may be useful to include the standard deviation (or ranges) in addition to mean values.
- An indication of statistical significance should be included wherever appropriate. Boldface type to indicate a statistically significant treatment-related effect can be used, but must be explained in a footnote. Alternatively, superscripts such as * and ** may be used to indicate statistical significance, with definitions included below the table (see next bullet point).
- A listing of all abbreviations used in the table is included below the table, in alphabetical order (e.g. BUN: blood urea nitrogen; Hb: haemoglobin), immediately followed, on the same line, by a description of any \( P \)-values used (e.g. \( *: P < 0.05; **: P < 0.01 \)), together with a description of the statistical test used in parentheses (e.g. Fisher exact test).
- Table notes (given with lowercase superscripted letters: a, b, c...) appear immediately below the listing of abbreviations. Table notes should be inserted manually, not using the Word footnote function. Within the table itself, lettered table notes are to appear sequentially in alphabetical order, reading across and then down the table (i.e. row by row).
- The table source (Source: Smith & Jones (1999)) is given below the abbreviations and any table notes (superscript a, b, c). Note that permissions to reprint (to be requested by the WHO Joint Secretary) are required for any tables (or figures) that are taken directly from published sources. Given this requirement, it is preferable to avoid the direct copying of illustrative material (tables and figures) from published sources wherever possible.
- Additional miscellaneous points relating to table formats follow:
  - Columns of figures are aligned to the decimal point, where possible. Columns of text are aligned at the left-hand side. The alignment of columns of figures and text combined should be decided on a case-by-case basis.
  - Column headings may be set left or centred over the columns as appropriate (usually centred when the columns contain figures and aligned at the left-hand side when the columns contain text). The first column heading is normally aligned at the left-hand side. Column headings should increase in number from the top to the bottom (e.g. one column heading over three subheadings, each of which is itself over two sub-subheadings). All column headings are aligned at the bottom of the header rows.
  - Column headings are in boldface type.
  - Figures with more than three digits on either side of the decimal point should have a space inserted after each group of three digits (e.g. 3 500; 0.002 3). This rule applies to tables only (in the text, figures with more than four digits have a space after each group of three digits). As noted above, this is not an SI requirement, but a WHO one.
  - Each table entry should occupy its own row to ensure that alignment remains correct when the table is edited.
  - It is preferable to have only one or two row heading levels, in which case the first row heading is flush left and the subheading is indented below it.
  - Where several different row heading levels are needed in the first column, the general order of heading is (1) bold, (2) roman and (3) indented roman (where three levels are needed), (1) bold, (2) italics, (3) roman and (4) indented roman (where four levels are needed) and (1) bold, (2) italics, (3) roman, (4) indented roman and (5) roman following a dash (where five levels are needed). The bold heading row may be shaded for emphasis.
- Some examples of table formats are provided in Annex 2. Additional examples may be found in published JECFA monographs (http://www.who.int/foodsafety/publications/jecfa/en/).

### 2.2.6 Historical control data

- Historical control data should be reported if considered useful and appropriate for interpreting study findings.
• Historical control data are often presented for tumours and developmental effects, but can be used in an attempt to determine whether the observed results for any end-point in test animals fall within the normal biological range.

• Historical control data are most useful when they are from the same strain of animal, come from the same laboratory and are reasonably contemporary to the study with which they are being compared (ideally from two years before the start of the study to two years after the end of the in-life phase). If they do not match these criteria, this should be identified in the text.

• If possible, the historical control data should have been submitted such that the results in each study in the database can be seen separately. As an absolute minimum, the number of studies must be given together with the mean and range (just the upper range is not acceptable, as this could be skewed by one atypical study).

• The monographer should seek confirmation from the sponsor that there were no changes in interpretative or investigative techniques between the historical control studies and the one on the test compound. If the submitted historical control data do not match these criteria, the sponsor should be asked to clearly describe the differences.

2.2.7 In-text references

• References are cited by one (Brown, 1999), two (Brown & Jones, 1999) or three authors (Brown, Smith & Jones, 1999), or first author plus et al. for four or more authors (Brown et al., 2000). Note the use of an ampersand instead of the word “and” and the use of a comma before the year.

• If the same author(s) published more than one reference in the same year, a, b, etc. should be used to differentiate between the references (Jones & Brown, 1999a,b; Smith, 2000b). This rule also applies to et al. references, even if the other authors are not the same in each reference (Brown et al., 1999a,b).

• In the rare case where different authors with the same surname have published a paper in the same year, initials are used to differentiate between the references (Y. Li et al., 2000; R. Li et al., 2000). These references must not be cited as Li et al. (2000a,b).

• References are cited in the text in increasing chronological order (but all references by the same author(s) are given together) and alphabetically when published in the same year (Brown, 1988, 2003; Brown & Smith, 1989; Smith & Brown, 1989, 1991; Brown, Smith & Jones, 1990; Brown et al., 1991; Jones, 1999a,b).

• Reports and monographs from previous JECFA meetings are cited in the text as “(Annex 1, reference xxx)” and are not included in the reference list. Annex 1 refers to the list of previous JECFA publications that is included at the back of both the meeting report and the publication containing all of the monographs from the meeting.

• Personal communications and other unpublished information are cited in the text only, not in the reference list. They should be cited as follows: [name of authority cited], [name of institution], unpublished data or unpublished observations or personal communication, [date]).

• For information on the formatting of references for the reference list at the end of the monograph, see section 2.3.5.

2.2.8 Miscellaneous

• Monographs should be concise documents, with only as much detail as is necessary to be able to understand and reproduce the evaluation; too much detailed description of irrelevant studies and too many non-critical tables should be avoided. Monographers need to make every effort to reduce the length of their monographs without eliminating essential information.

• The physical meeting is referred to as “the meeting” (e.g. the meeting was held in April); the group of meeting participants is referred to as “the Committee” (e.g. the Committee established an ADI of 0–0.3 mg/kg bw).
• “JECFA” is referred to, rather than “the JECFA”. Reference to previous Committees should be made by number (e.g. the thirty-sixth meeting of the Committee) rather than by year, because in many cases reports were not published in the same year as the meeting and in some years more than one meeting was held, which creates confusion.

• It is conventional to list countries alphabetically, and country names must correspond to the most current listing of Member States and Associate Members of WHO, as given in the current version of the WHO style guide or an interim updated list of Member States and Associated Members of WHO.

• Where the POD is a NOAEL, this is “identified”, as it is one of the dose groups used – for example, “0.5 mg/kg bw per day was identified as the NOAEL”. Health-based guidance values (e.g. ADIs) are “established” – for example, “the Committee established an ADI of 0–0.1 mg/kg bw”.

• Each study summary should provide a short description of the methodology used in the study. Most studies will comply with an Organisation for Economic Co-operation and Development (OECD) test guideline or equivalent national guideline, and in such cases there is no need to provide lengthy descriptions of the methodology. Attention should be drawn to any deviations from the test guideline, either omissions or significant additions. If in-life examinations such as ophthalmoscopy and blood sampling are performed at multiple time points, these time points should be identified.

• Studies performed before the implementation of good laboratory practice (GLP) will be considered on a case-by-case basis, with careful consideration of the quality and appropriateness of the study.

• JECFA style is to use free-flowing text rather than large numbers of subheadings for each particular level of investigation.

• Overall conclusions of the Committee regarding, for example, the carcinogenicity and genotoxicity of a compound should generally be reserved for the Comments section. Conclusions of the Committee regarding specific studies (e.g. when the Committee disagrees with the study authors’ conclusions) are given in the body of the monograph.

• WHO house style uses a mix of British and North American spellings. Examples of spellings of some commonly used words in JECFA monographs are as follows: anaesthetize, analyse, antimicrobial, caesarean, centre, coenzymne, colour, cooperate, criticize, decision-making, diarrhoea, end-point, estrogen, et al., etiology, faeces, feed (for animals, not food), fetus, haemoglobin, homepage, hypocalcaemia, in vitro, in vivo, leukocyte, litre (L, not l), meta-analysis, metabolize, modelled, neurobehavioural, oedema, oesophagus, oxidize, paralyse, pharmacopeia, postmortem, postnatal, postpartum, pretreatment, programme, re-examine, reopen, side-effect, subgroup, sublethal, sulfur, tumour, webpage, website, worldwide, X-ray.

• Abbreviations are defined as the first time they are used in the text; thereafter, only the abbreviation is used. A list of abbreviations should be prepared for each monograph. This list will be incorporated by the editor into an overall list of abbreviations for all monographs published after the meeting.

• Monographs will be edited according to the most recent version of the WHO style guide. Monographers can request a copy of the WHO style guide from the WHO Joint Secretary.

2.3 Detailed content of the monograph

The guidance in this section approaches the content of the monograph from the viewpoint of the end result of the meeting – that is, the production of the report item.

As mentioned above, the monograph should contain sufficient information to permit all the details required for the report item to be identified and independently confirmed. If a monographer is in doubt about whether to include extra detail, it should be added to the monograph so that it is available for others to see; it can always be deleted following discussion at the meeting.

Until the final changes are made by the monographer at the end of the meeting, the monograph is a draft document to support the discussion. It is therefore often helpful to include comment boxes or
highlighted text that draws attention to potentially important or contentious aspects of the evaluation, as long as these are subsequently deleted. It is important for the monographer to recognize that the final monograph is the product of the Committee and not of the monographer.

If no studies were available for one of the main headings in the template, this should be noted in the monograph.

For monograph addenda, it may not always be sufficient just to consider new data, especially if there have been changes in evaluation criteria since the last evaluation. An appropriate description of any such studies that were considered in the present evaluation should be included in the monograph addendum. Sometimes, it may be sufficient to copy and paste relevant sections from the previous monograph, in which case they should be so indicated (e.g. indented, italics or smaller font).

Details that should appear in each section of the monograph are described in the following sections. **Note that the section numbering used for the headings (shown in red) is that used in the actual monograph** (see also Annex 1). A table of contents generated from the final headings used in the monograph should be included on the first page of the monograph, below the title, authors and authors’ affiliations. All individuals contributing to the preparation of the draft monograph for the meeting should be listed as authors. As the end product reflects the discussion of the Committee at the meeting, the listing of authors is preceded by the phrase “First draft prepared by”.

Authors may refer to recently published monographs on food additives for examples of formatting and content (e.g. monographs from the seventy-ninth meeting: http://apps.who.int/iris/bitstream/10665/171781/3/9789240693982_eng.pdf?ua=1).

### 2.3.1 Explanation

**1. Explanation**

- This part of the monograph will form the basis for the first few paragraphs of the report item. The editor will insert the final version of the *Explanation* section (following the adoption of the meeting report) into the final draft of the monograph. The monographer can indicate whether any detailed information that was deleted from the *Explanation* section during the preparation of the report item should be retained in the final monograph.

- The first paragraph should provide a brief description of the food additive and its primary uses in food.

- If the Committee has evaluated the food additive previously, previous evaluations should be referenced by number using the standardized reference list of JECFA publications, which may be found in Annex 1 of recent JECFA reports (WHO Technical Report Series) and toxicological evaluations (WHO Food Additives Series). Thus, the report of the seventy-seventh meeting on certain food additives and contaminants would be referenced as (Annex 1, reference 214), and the monographs prepared after the seventy-seventh meeting would be referenced as (Annex 1, reference 215). Reasons for the present re-evaluation should be given and, if a full monograph on a food additive that has been evaluated previously is being prepared, a statement should be made to the effect that the previously published monograph has been expanded and is reproduced in its entirety below.

- If the Committee has not previously evaluated the food additive, the reason for it being placed on the agenda should be given. For example, “[Compound X] has not previously been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The Committee evaluated [compound X] at the present meeting at the request of the [Xth] Session of the Codex Committee on Food Additives (FAO/WHO, 20xx).”

- The final paragraph of the *Explanation* should describe the data that were provided by the sponsor and whether the critical studies were conducted in compliance with GLP, unless otherwise specified. In addition, whether a literature search was conducted, the keywords used and the number of references obtained should be provided.

- The structure of the food additive should normally be included in a full monograph.

- The FAO expert assigned to the food additive prepares one subsection for the *Explanation* section in the monograph: *Chemical and technical considerations.* This
subsection heading should be included in the draft monograph, with “[to be prepared by FAO]” inserted below it (unless the FAO expert is able to provide this section to the WHO monographer before the monograph is distributed to meeting participants). The editor will insert the final FAO subsection into the monograph after the meeting (in other words, the Chemical and technical considerations section in the meeting report is identical to the Chemical and technical considerations section in the monograph).

2.3.2 Biological data

2. Biological data

- This section contains summarized descriptions of studies that are important for assessing the safety of the food additive. Studies that provide the basis for the safety evaluation should be summarized in greater detail than other studies.

- Single paragraphs composed of very brief summaries may be sufficient for reporting the results of studies of limited design or minor relevance for the evaluation.

- Biological data should be grouped under three headings: Biochemical aspects, Toxicological studies and Observations in humans.

- In a full monograph, but not in a monograph addendum, if no data are available under any of these headings or under subheadings under Toxicological studies, except for Special studies, the heading should be included in the monograph together with the statement “No information was available”.

- For food additives, the substance tested should be the (intended) article of commerce. If the article of commerce is not the test substance, its relationship to the test substance must be accurately described.

- Species information is provided in order from smallest to largest species (this differs from many other organizations, where the rat is presented before the mouse). Headings for each species should be included when more than one species is discussed (a) Mice, (b) Rats, (c) Hamsters, (d) Rabbits, (e) Dogs, (f) Pigs, (g) Monkeys), but no species heading is necessary (although it can be inserted if desired) if only one species is discussed. It should be noted that “monkeys” comprise a higher phylogenetic grouping than species, and the individual species (e.g. cynomolgus, rhesus) should be specified.

2.1 Biochemical aspects

- For all food additives, this section describes studies designed to measure the concentration–time profiles of the ingested substance and its metabolites in the various tissues and organs of the body as well as studies of effects on enzymes and other biochemical parameters designed to elucidate the mode of action and toxicodynamics of the food additive.

- The Committee uses the results of these studies in interpreting the toxicological studies, including the elucidation of the mechanism of toxicity, and the results may facilitate the establishment of the health-based guidance value.

- Comparisons of biochemical data between different experimental animal species and humans helps to determine the relevance of the toxicity observed in experimental animals; such comparisons should be summarized at the end of this section.

- The types of biochemical studies that should be summarized under each heading are given below. Human biochemical studies that fall under these categories should be included in this section. Other human studies should be included under Observations in humans.

2.1.1 Absorption, distribution and excretion

- Information in this section should be drawn primarily from studies on experimental animals, such as mice, rats, rabbits and dogs. Information on pharmacokinetics in animals such as pigs, cows, goats, horses and poultry can be included where relevant.
• Information on metabolism following absorption should not be included in this section. Rather, it is included in section 2.1.2 on biotransformation.

• For each study, details on the position and type of radiolabel used, test species, sex and number of animals, dose levels used (in terms of both the drug [mg/kg bw] and radioactivity [MBq/kg bw], as appropriate) and route of exposure should be provided.

• Information in this section includes, where possible:
  o hydrolysis/metabolism of the parent compound and its products in the mammalian gastrointestinal tract (including products of metabolism by the gut microflora) (distinguish between hydrolysis/metabolism before absorption and of biliary excretion products);
  o rate and extent of absorption of the unchanged compound and its hydrolysis products/intestinal metabolites, with time to maximum concentration \( (T_{max}) \) and the concentration achieved \( (C_{max}) \);
  o bioavailability of the parent compound;
  o pattern and rate of distribution of absorbed substances to tissues and organs within the animal;
  o mode, rate and extent of excretion or elimination of the parent compound and/or radiolabel and its identified intestinal metabolites from blood and tissues, with percentage recovery in major excreta (urine, faeces, bile) over a given time interval (e.g. 35% in urine from 0 to 48 hours);
  o pharmacokinetic parameters, such as volume of distribution, terminal elimination half-life from plasma and total body clearance.

• It should be made clear as to whether the findings relate to the radiolabelled material or to the parent compound.

• Differences between sexes, dose sizes and single versus repeated dosing should be noted, together with any other relevant findings.

### 2.1.2 Biotransformation

• Information in this section should be drawn primarily from studies on experimental animals, such as mice, rats, rabbits and dogs. Information on metabolism in animals such as pigs, cows, goats, horses and poultry can be included where relevant.

• Where information on metabolism following absorption has been obtained from studies previously described in section 2.1.1, a brief study description and cross-reference to that section can be made, rather than repeating full study details.

• This section describes the metabolism of the parent compound, if absorbed as such, and of its products if they are not normal dietary or body constituents. Information on the main routes of metabolism, the metabolite profile and the mode, rate and extent of excretion or elimination of identified metabolites is included here.

• If the biotransformation pathway is known, a figure depicting the main metabolic reactions should be included along with an identification of the species to which it applies. Such schemes are usually provided by the sponsor and can be scanned for inclusion in the monograph. If the data sponsor does not provide a metabolic scheme, a scheme should be requested.

### 2.1.3 Effects on enzymes and other biochemical parameters

• This section describes the effects of the absorbed substance and/or its metabolites on cellular and tissue enzyme production and morphology, chemical constitution, enzyme activity or physicochemical state.

• If there is no relevant information to be included in this section, the heading can be deleted.
2.2 Toxicological studies

- This section contains summarized descriptions of toxicological studies that are important for assessing the safety of the food additive. These summaries generally comprise the bulk of the monograph.

- Information from five main categories of studies on food additives should be routinely included: Acute toxicity, Short-term studies of toxicity, Long-term studies of toxicity and carcinogenicity, Genotoxicity and Reproductive and developmental toxicity. Sometimes these routine studies point towards the need to look at particular target organs or tissues or end-points; such studies are classified as Special studies.

- Studies that provide the basis for the evaluation should be summarized in greater detail than other studies. Single paragraphs composed of very brief summaries may be sufficient for reporting the results of studies of limited design or minor relevance for the evaluation.

- The study conclusions should be summarized in this section. If the person who arrived at the conclusion is not identified, it is assumed that it is the author(s) of the study and that the monographer agrees with the conclusions. When the monographer disagrees with the conclusions of the study author(s), he or she should discuss the contentious issues and present his or her own conclusions as a separate paragraph, to flag the issue for discussion by the Committee. In the final monograph, the paragraph concludes with the Committee's conclusion and identification of the NOAEL and the study reference.

- When adjacent paragraphs summarize different studies under the same heading, an extra space should be left between them. However, an extra space should not be left between paragraphs when they both describe the same study.

- The GLP status of the study, along with the relevant authority, should be indicated. If there is no GLP certification, the monographer should at least note whether the study was inspected by a quality assurance (QA) unit, as noted by the presence of a signed QA statement, and make some comment on the apparent quality of the protocol and adequacy of the methods used. In addition, whenever the study author provides information on the test guideline or protocol that was followed, it should be so indicated.

- General study details that should be provided for each toxicological study described in the monograph include the following:
  - purpose or objective of the study;
  - identity, specification and purity of the test material and its batch and/or lot number;
  - species and strain of animal used;
  - the method of dosing (e.g. gavage, capsule, variable dietary concentration);
  - vehicles used for gavage studies (and if there appear to be any findings that change with different vehicles); if the vehicle is not provided, it will be assumed to be water;
  - sex and number of animals in each group (if there are satellite groups, numbers for the main group and satellites are given separately);
  - whether a study is non-guideline or a range-finding study with limited investigations. In such cases, a conclusion on the value of the study in evaluating the toxicological profile of the compound (e.g. provides useful information on repeated-dose effects; end-points studied too limited to provide useful information) can be provided;
  - any additions to the standard test protocol, such as measurement of specified hormone levels or evaluation of toxicokinetics during the dosing period;
  - all the administered dose levels, including 0 for controls; for dietary studies, this should include both mg/kg feed values (even if originally given as parts per million or percentage of contaminant in the diet) and the equal (if measured) or equivalent (if based on default conversion factors) mg/kg bw per day dose for both males and females; for drinking-water studies, this should include both mg/L drinking-water values (even if originally given as parts per million) and the equal (if measured) or equivalent (if based on dose conversion factors) mg/kg bw per day dose for both males and females. If the author of a study presents administration levels in terms of mg/animal per day, these values should be converted to mg/kg bw per day using animal weights if they are included in the report;
  - whether the study used dose patterns that did not involve dosing every day (e.g. 5 days/week rather than 7 days/week). If so, it should be checked whether the stated dose
levels are given only for the days of dosing or averaged over the whole duration of the study. JECFA gives dose levels averaged over the entire study duration;
- whether there were any complications associated with dosing, such as solubility, stability and palatability;
- duration of the study;
- details of any recovery group (e.g. numbers, duration of dosing, interval between last dose and termination, extent of investigation of animals in this group);
- any mortalities seen during the study, both in treated and in control groups, and information on the causes of mortality, if known (e.g. dosing errors in gavage studies, which are not compound related);
- description of compound-related findings, if any, identifying the effect, its severity or magnitude and, for dichotomous data, an indication of the number of animals affected. This information is often presented in tabular form. If no significant effects were seen at a particular dose level, a simple statement to that effect should be made;
- whether there is dose-dependency of the findings and if not, whether there is any explanation for this;
- relevant information on historical control data, if available, where this may help in the interpretation of the findings (e.g. marginal effects at highest dose, incidence in controls is particularly high or low);
- statistical significance of an effect if the effect is biologically or toxicologically relevant;
- any findings that are statistically significant but are discounted as not adverse or not relevant to a human risk assessment;
- any in-life findings early in the study that might be relevant to establishing an acute reference dose (ARfD) (e.g. body weight changes or behavioural effects after one or a few days of dosing);
- anything else of note in the study (e.g. high morbidity in controls);
- the POD, such as the NOAEL (if one was identified), and the critical findings on which the POD was based (e.g. at the LOAEL), given at the end of the study description;
- study authors’ conclusions and conclusions of the monographer, if different;
- the author(s) and date of preparation of the study report, given at the very end of the study description (even if already cited at the beginning of the study description).

Any relevant information that is identified in the peer-reviewed literature that provides insight into the toxicity of the compound additional to that provided by the studies submitted by the sponsor should be summarized under the appropriate heading below. In general, the same format should be followed as for a submitted study, highlighting any important details that are missing (e.g. details of dosing regimen) and also any observations additional to those that might be found in a typical guideline study, which may be of value in evaluating the compound.

As noted above, if studies on more than one animal species are summarized under one heading, then the studies should be grouped in such a way that studies in smaller rodent species are listed first, with larger species and species more closely related to humans last.

The following is an example of a typical summary of a study of toxicity for a food additive:

### 2.2.3 Long-term studies of toxicity and carcinogenicity

**(a) Rats**

Groups of 45 male and 45 female inbred Wistar rats were given diets containing stevioside (purity 85%) at 0, 2000, 6000 or 12 000 mg/kg feed (equivalent to 0, 100, 300 and 600 mg/kg bw per day, respectively) for 2 years. After 6, 12 and 24 months, blood was obtained from the tail vein of five male and five female rats in each dose group for haematological and clinical biochemical tests. One week later, these rats were housed in metabolism cages for urine collection and were then killed for further biochemical, pathological and histopathological examination. All surviving animals were killed at 2 years.

Growth, feed use and consumption, general appearance and mortality were similar in treated and control groups. The mean lifespan of rats given stevioside was not significantly different from that of the controls. No treatment-related changes were observed in haematological, urinary or clinical biochemical values at any stage of the study. The incidence
and severity of non-neoplastic and neoplastic changes were unrelated to the concentration of stevioside in the diet.

The NOAEL was 12,000 mg/kg feed (equivalent to 600 mg/kg bw per day), the highest dietary concentration tested (Xili et al., 1992).

2.2.1 Acute toxicity

- Acute toxicity studies can provide useful information regarding target tissues and species and sex differences.
- The results of acute toxicity studies that are expressed in terms of the median lethal dose (LD\textsubscript{50}) (used for oral, intramuscular, intraperitoneal or dermal administration) and/or median lethal concentration (LC\textsubscript{50}) (used for administration by inhalation) should be presented in tabular form, as illustrated in Annex 2.
- When three or more LD\textsubscript{50} or LC\textsubscript{50} determinations by the same route in the same species are available, the results may be expressed as a range in which the lowest to the highest values are recorded.
- Other acute toxicity data important to the evaluation, such as the nature of toxicity, clinical signs and target tissues, may be presented in summary form as text or in table notes below the table.

2.2.2 Short-term studies of toxicity

- Toxicological studies in which food additives are administered in regularly repeated doses in feed or drinking-water over periods ranging up to, but not including, one year for most small animal species and up to, but not including, two years for dogs and primates should be summarized in this section.
- These studies, when properly performed, provide important information regarding the major toxic effect(s) of the test substance and its dose–response relationships. Short-term studies of toxicity are often performed to help in dose selection for long-term studies of toxicity, and they can give some indication of target tissues and organs. In some cases, short-term studies of toxicity can help clarify lowest-effect dose levels for effects observed in long-term studies of toxicity, and they can provide information that is useful for the interpretation of long-term studies of toxicity and carcinogenicity (e.g. early signs of toxicity in the kidney or liver when tumours appear in these organs after long-term exposure to the test substance).
- It can be useful to comment on findings that were not seen in a study if they were seen in another similar study. For example, if a certain effect was seen in a 28-day rat study, it would be expected that it would also be present in the 90-day study at similar, or lower, dose levels.
- Any findings that were considered not relevant to humans and the reasons why (e.g. kidney findings in male rats only, supported by investigations of α\textsubscript{2u}-microglobulin) should be indicated.

2.2.3 Long-term studies of toxicity and carcinogenicity

- Toxicological studies in which food additives are administered in regularly repeated doses or continuously in feed or drinking-water over the greater part of the normal lifespan of the animal species (i.e. one year or longer for most small animal species, in line with OECD test guidelines, and two years or more for dogs and primates) are summarized in this section. These studies are used for detecting chronic effects that are not observed in shorter-term studies or that show progression with duration of dosing. Long-term studies that are designed to investigate specific effects, such as carcinogenicity, should be included in this section. Often long-term studies, particularly in rats, are designed to assess both chronic toxicity and carcinogenicity.
- Because certain animal strains have high background levels or susceptibilities to developing certain tumour types, it is important to give the strain details (but note that the strain is not given in the meeting report unless the effect is strain specific).
• If the nature of the dose–response relationship is not clear (e.g. response is marginal and is not monotonic) or there is concern about the incidence level in the controls, historical control data should be provided. These should be requested from the sponsor, if necessary.

• It should be indicated whether the survival rate is adequate in the top-dose animals (there should normally be a minimum of 25 animals [50% of a standard group size of 50] in each group surviving to termination). If survival did not meet this level, it should be indicated whether the deaths were mainly towards the last few weeks of the study and whether survival was adequate to enable the various end-points in the study to be assessed.

• It should be noted whether there is any indication of findings occurring earlier in treated animals. This can be important for lesions that have a high background incidence and in interpreting some long-term effects.

• General study details that should be provided for each toxicological study are given above. In addition, the types of observations made (e.g. mortality, feed and water consumption, body weight, haematology, clinical chemistry, urine analysis, ophthalmoscopy examinations, physical/neurological examinations, functional observational batteries, clinical signs, organ weights, gross pathology and histopathology) and any other information about the design of the study considered to be noteworthy should be provided. When histopathological examinations were performed, the tissues that were examined should be indicated, along with the identification of tissues that were of particular interest to the evaluation and whether only certain dose groups were investigated.

• Negative findings should be limited to general statements on survival, growth, organ weights, tumour incidence, organ function tests, and gross and microscopic appearance of tissues. In particular, if there were no increases in compound-related tumour incidences, a clear statement should be made.

2.2.4 Genotoxicity

• Data from an appropriate range of in vitro and in vivo genotoxicity tests can be useful in elucidating the mechanism of toxicity of certain compounds. The results of these studies are also considered when evaluating the results of rodent carcinogenicity bioassays and when determining whether an in vivo carcinogenicity bioassay was necessary to enable adequate assessment of the carcinogenic potential of a compound.

• To present the data in a more understandable form and to conserve space, the results of genotoxicity tests should be tabulated. Annex 2 provides examples of the tabular representation of such data.

• Where the results of a particular genotoxicity study were considered positive or equivocal (e.g. colony counts, size of colony, survival rates or aberrant cell numbers), the study can be described in more detail in textual form or in table notes below the summary table.

2.2.5 Reproductive and developmental toxicity

• These studies are designed to evaluate effects on the sexuality and fertility of males and females and on the developing organism.

(a) Multigeneration reproductive toxicity

• Multigeneration reproductive toxicity studies provide general information on the effects of the test substance on gonadal function, estrous cycles, mating behaviour, conception, parturition, lactation, and growth and development of the offspring until the age of weaning.

• With dietary exposures at constant milligram per kilogram feed concentrations, the achieved intakes vary greatly with reproductive stage. Achieved intakes are normally determined for various stages of the study (e.g. pre-mating, lactation). When determining NOAELs, JECFA policy is to use the lowest achieved intake of any of the measured stages, unless a critical stage and associated intake can be determined.
Data should be presented for each stage and generation separately (e.g. parental generation for first generation, first mating pups, parental generation for second generation, etc.). Some indication of whether findings were consistent across the generations should be provided subsequently.

It should be indicated whether litters were standardized in size at around day 4.

If pup weights are different in treated groups, it should be determined if this relates to litter size and if there are effects on total litter weight.

If pup mortality is increased in treated groups, it should be determined if there were more pups in the litters to start with (e.g. control litter mean of 10.8 pups with 0.9 dying gives 9.9 alive; test group mean of 12.1 pups with 2.1 dying might be statistically significant, but still gives 10.0 alive, more than in controls).

For developmental end-points (e.g. tooth eruption), it should be determined if there are effects on the time to achievement; the body weight at that time should also be checked.

PODs, usually NOAELs, should be identified for reproductive toxicity (e.g. impairment of fertility, parturition, lactation), parental toxicity (usually systemic toxicity, such as effects on body weight or feed consumption) and offspring toxicity (e.g. effects on pup body weight or pup viability).

(b) Developmental toxicity

Developmental toxicity studies are used for assessing effects on the developing organism, which may include death of the developing organism, structural abnormalities, altered growth or functional deficiencies.

The days of dosing should be indicated (i.e. which days of gestation).

Details of the investigative techniques (e.g. dissection, staining, X-ray) and the proportion of fetuses being examined by each technique should be given.

If a range-finding study has been submitted, it can be described separately if there are important findings. If it adds nothing to the discussions, it can just be mentioned in the introduction to the main study.

The unit for statistical comparison in developmental toxicity studies is the litter, not the individual fetus. Hence, when statistically significant differences are reported in incidences relative to the total number of fetuses per dose group, the monographer should check whether such differences are also apparent when the results are expressed per litter.

If there are developmental anomalies in the main test, it should be determined if they were seen in the range-finding study as well (if submitted). Range-finding studies normally include only limited examinations of maternal toxicity, external malformations and fetal viability.

It should be indicated whether there were any increases in malformations, even at maternally toxic doses.

Any effects that occur within the first day (or first few days, if this was the first time of observation) after dosing should be noted, as they could be used as the basis for establishing an ARfD.

PODs, usually NOAELs, should be identified for maternal toxicity (usually systemic toxicity, such as effects on body weight or feed consumption) and for embryo and fetal toxicity (e.g. effects on fetal weight, fetal mortality, incidence of skeletal and visceral anomalies or variants).

2.2.6 Special studies

Special studies, when relevant and submitted by the sponsor in support of the safety evaluation of the food additive or identified from a literature search, should be reviewed.

It is important for the monographer to be aware that special studies do not typically follow specific well-established protocols, but rather are designed to resolve particular scientific
issues and concerns, and protocols may vary from study to study; hence, no specific guidance is included here.

- General study details reviewed and described by the monographer might include the objective of the special study, number, species and strain of animals, any details specific to the unique special study, the study outcome and its relevance to the end-point being investigated.

- Examples of the types of special studies that might be included are neurotoxicity, cardiotoxicity and immunotoxicity studies (see also Annex 1). Special studies designed to elucidate qualitative interspecies differences in the manifestations of toxicity (e.g. different target organs in different species) should also be included in this section.

- Special studies should be listed alphabetically.

2.3 Observations in humans

- Observations in humans can be particularly useful for establishing health-based guidance values, for assessing the relevance of the results of studies in experimental animals and for confirming health-based guidance values.

- All studies dealing with humans (except for those summarized under Biological aspects) should be included in this section, including epidemiological surveys, clinical experience, anecdotal observations, health effect studies relating to occupational exposure, reports of abuse and volunteer studies measuring intolerance.

- Details such as number of subjects, sex, age and general statements on physical condition should be given if important to the evaluation.

- JECFA will use human data in establishing health-based guidance values if the study is scientifically valid and performed ethically, according to the principles of the Declaration of Helsinki. Documentary evidence of this should be provided by the sponsor, or, where the results are from a published study, a statement to this effect should be included in the paper.

2.3.3 Dietary exposure

3. Dietary exposure

- This section is prepared by exposure experts.

- If it is at all possible, this section should be incorporated by the WHO monographer into the draft monograph before it is distributed to meeting participants.

- At the end of the meeting, before the final monograph is provided to the editor and the WHO Joint Secretary, the WHO monographer should ensure that the final Dietary exposure section has been incorporated into the monograph.

- For more information on what should be included in this section, readers should refer to the separate guidance document on preparing working papers on dietary exposure to (or intake of) food additives (see http://www.who.int/foodsafety/chem/jecfa/guidelines/en/).

2.3.4 Comments

4. Comments

- The objective of the Comments section is to provide a concise summary of the relevant biochemical/toxicological/epidemiological information and its interpretation, while providing sufficient explanation that the bases for the conclusions of the Committee are clear. This section should contain short summaries of the biological findings in the studies of significance for the evaluation. The findings should be listed in the same general order as they are summarized in the main body of the monograph, under the headings Biological aspects, Toxicological studies and Observations in humans.
The section should begin with a statement as to whether the Committee considered the overall data package sufficient to derive a robust health-based guidance value or conclusion as to health concern.

All relevant NOAELs (or other PODs) should be included. Only one value for each NOAEL in units of mg/kg bw per day (usually for the sex with the lower value, unless the effect is sex specific) should be given for each study.

Strains of animal species are not provided in this section unless critical effects are known to be strain specific.

Details such as sex, age and general statements on physical condition should be given if important to the evaluation of observations in humans.

The Comments section will comprise the bulk of the meeting report item (which also includes the Explanation and Evaluation sections) (see Chapter 3).

The Comments section should be fully referenced. This is a change from the usual practice, but it makes the Committee’s conclusions more open, transparent and verifiable and enables the Comments section to be more readily used by other interested groups. The editor will delete these references for the final meeting report, except for those pertaining to the critical study or studies, but they will be retained for the monograph.

Annex 3 contains a template for the report item, and Annex 4 provides an example of a report item. Both should serve as a model for the preparation of the Explanation (see section 2.3.1), Comments and Evaluation sections (see section 2.3.5).

2.3.5 Evaluation

5. Evaluation

A proposal should be provided by the monographer, in agreement with the reviewer, as to whether the Committee should establish a health-based guidance value (usually an ADI) and, if so, on what basis.

The NOAEL from the critical study should be given with the units mg/kg bw per day. Only one value should be reported, which is derived from the sex that gives the lower value based on feed intake (or drinking-water consumption) and body weight data, unless the critical effect is sex specific.

The basis for the uncertainty (or safety) factor applied should be explained. EHC 240 (IPCS, 2009) and previous JECFA meeting reports on food additives should be consulted for guidance on selection of uncertainty factors in establishing ADIs.

The ADI is expressed as a range from 0 to x mg/kg bw, and it should be rounded to one significant figure (see section 4.4.1).

The ARfD, if established, is given as a single number (x mg/kg bw).

An ADI "not specified" may be proposed when the estimated dietary exposure to the food additive is expected to be well below any numerical value that would ordinarily be assigned to it (see section 4.4.2). For example, if the margin of exposure between the NOAEL from the critical study and the dietary exposure estimate is considered adequate (>100), the Committee may establish an ADI “not specified” for a food additive used in the applications specified and in accordance with good manufacturing practice.

It should be noted that for food additives proposed for use in infant formula, lower margins of exposure (<100) could be interpreted as indicating low risk for the health of infants 0–12 weeks of age when uncertainties or conservatisms that may exist in the toxicological point of departure or in the exposure estimates are taken into consideration (see section 4.6).

It should also be noted that where no effects have been observed at the highest dose tested in all available studies, the calculation of a margin of exposure may not be meaningful.
• A group ADI (see section 4.4.4) may also be proposed if several substances that produce similar toxic effects are being considered for use as food additives, in order to limit their overall dietary exposure.

• If a temporary numerical ADI or ADI “not specified” is proposed (see section 4.4.3), information required to resolve the outstanding issues to permit the establishment of an ADI for the substance should be listed, along with a date by which time the results of the indicated studies should be submitted to WHO for evaluation.

• If no ADI can be established because there were critical data gaps or because of appreciable biological uncertainty in the assessment, the information that the Committee would wish to have before reviewing the compound again should be listed.

• Where a numerical ADI is established, high-percentile dietary exposure to the food additive is compared with the upper limit of the ADI range, and the Committee concludes as to whether there is likely to be a health concern.

• The Evaluation section often ends with a statement about the chemical specifications prepared by FAO, which is taken from the meeting report item. (The statement on the preparation of a toxicological monograph that appears in the meeting report item is deleted from the monograph itself.)

2.3.6 References

6. References

• References should be presented at the end of the monograph; the sponsor should be asked to provide the references in the JECFA style.

• Personal communications and other unpublished information are included in the text, not in the reference list (see section 2.2.7).

• In the reference list itself, all authors should be given if there are six or fewer; if there are more than six authors, the first six authors are given, followed by et al.

• Order of references in reference list: single author by increasing year, two authors alphabetically by second author, three authors alphabetically by second or third author, more than three authors by increasing year:
  

• Abbreviated journal names as given by the United States National Library of Medicine (e.g. Am J Toxicol) are used. Note that the abbreviated journal name ends with a period, before the volume number.

• Page ranges use en dashes and are abbreviated (only those digits that change in the higher page number are given): e.g. 310–7; 252–66; 296–305.

• Examples of references in reference list:
Journal reference


Book reference


Unpublished study

There is room for flexibility in the format of unpublished studies. The essential elements of unpublished studies that should be included, where available, are:

- the name of the author(s) who performed the research work, if provided;
- the year in which the experimental work was completed;
- the title of the experimental study (if the title is in a language other than English or French, translation of the title into English is preferred);
- study number, if provided;
- an indication that the study is unpublished;
- the name of the institution at which the experimental study was performed;
- the name of the institution that submitted the report to WHO.

Examples:


EFEMA (2014). Submission of data on citric acid esters of mono- and diglycerides of fatty acids (CITREM) (INS 472c) for proposed use in infant formula and formulas for special medical purposes intended for infants on behalf of EFEMA. Submitted to WHO by the European Food Emulsifiers Manufacturers Association, Brussels, Belgium, 12 February 2014.


**Agency report**


**Conference proceedings**


**Reference in a foreign language (other than French)**


**Secondary reference**


**Examples:**

Reference found online

Give URLs, with access dates, for as many references as possible, particularly WHO products.

Examples:


Databases, electronic publications and website references


Section of a website


Online journals


Chapter 3: Preparing the report item

- During the first few days of the meeting, the Committee will discuss in detail each toxicological monograph, resolving any contentious issues raised by the monographer and reaching agreement on the general approach to be taken in evaluating the food additive. Once agreement has been reached on a way forward, the monographer should prepare the first draft of the meeting report item.

- The monographer prepares the report item during the meeting by following the template shown in Annex 3 (the current template will be made available on the computers in the meeting room). This involves extracting the Explanation, Comments and Evaluation sections from the monograph into the meeting report template and modifying them as suggested during initial discussions of the Committee.

- During the preparation of the first draft of the meeting report item, the WHO monographer should include headings for the sections being prepared by the FAO and exposure experts assigned to the food additive. These include Chemical and technical considerations after the Explanation section and Assessment of dietary exposure after the Observations in humans section. These sections will be inserted by the editor after the meeting if they have not already been inserted by the monographer or by FAO during its review of the WHO meeting report item.

- The Evaluation section may include a statement prepared by FAO concerning the chemical specifications and the preparation of a Chemical and Technical Assessment for the food additive. This statement is usually added by FAO during its review of the WHO meeting report item.

- The Evaluation section in the report ends with a statement that a monograph or monograph addendum has been prepared. (This statement is deleted from the monograph.)

- References should be cited for all of the studies in the report item. The editor will retain only the references for the key study or studies and will change them to italicized numbers (e.g. (1)) for the final meeting report, unless no monograph or monograph addendum is being prepared, in which case all references in the report item will be retained for the final meeting report. All of the references will be retained in the Explanation, Comments and Evaluation sections that are inserted into the final monograph by the editor after the meeting.

- After the (usually) first draft of the report item has been approved by the Committee and any suggested revisions have been incorporated by the monographer, the WHO rapporteur checks the revisions and, when satisfied, passes the file to the editor. The editor edits the draft report item and sends it back to the monographer to check all changes made and to answer any questions raised during the editing process.

- During subsequent discussions on the report item, the editor is responsible for making all necessary revisions onscreen, until the Committee is completely satisfied with the report item (referred to as “going to final”). At this point, the editor passes the final report item to FAO (usually the FAO rapporteur) for its review and incorporates any changes resulting from that review.

- It is the monographer’s responsibility to keep track of any changes made to the report item that will require corresponding changes to the monograph. By the end of the meeting, all such changes to the monograph need to have been made so that the two are consistent. The editor can provide the monographer with the final edited version of the meeting report item at the end of the meeting to facilitate this task. An electronic version of the final monograph needs to be provided to the editor and WHO Joint Secretary (by uploading it to the meeting computer in the “Final monographs” folder) before the monographer leaves the meeting on the final day.
Chapter 4: Additional considerations

The EHC monograph entitled *Principles and methods for the risk assessment of chemicals in food* (EHC 240 [IPCS, 2009]) should be referred to for detailed information on hazard identification and characterization, dose–response assessment, derivation of a health-based guidance value, dietary exposure assessment and risk characterization for food additives.

This chapter includes general considerations relevant to food additives that were discussed at meetings of the Committee subsequent to publication of the above monograph. It also highlights some relevant definitions and other information from that monograph that are critical in performing safety assessments of food additives.

4.1 Re-evaluation of food additives by JECFA

Since its establishment, JECFA has evaluated more than 600 food additives (excluding flavouring agents), and approximately 30% of JECFA evaluations are more than 30 years old. JECFA has repeatedly noted the importance of reviewing substances previously evaluated when new data on those substances become available and in light of further developments in science and risk assessment methodologies.

The Committee has developed criteria that will trigger a review of substances, which were published in EHC 240 (IPCS, 2009). Periodic review of past decisions on safety may be made necessary by one or more of the following developments:

- a new manufacturing process for the food additive;
- a new specification;
- new data on the biological properties of the compound;
- new data concerning the nature and/or the biological properties of the impurities present in a food additive;
- advances in scientific knowledge relevant to the nature or mode of action of food additives;
- changes in consumption patterns or level of use of a food additive; and
- improved requirements for safety evaluation, made possible by new scientific knowledge and the quality and quantity of safety data considered necessary in the case of food additives.

4.2 Commentary on the use of NOEL/NOAEL and LOEL/LOAEL

The sixty-eighth meeting of the Committee (FAO/WHO, 2007) reconsidered the use of the terms no-observed-effect level (NOEL), no-observed-adverse-effect level (NOAEL) and the related terms lowest-observed-effect level (LOEL) and lowest-observed-adverse-effect level (LOAEL) in evaluations of the safety of food additives and contaminants. The Committee decided to use the term NOAEL when the relevant effect at the next higher dose is considered adverse. If such an effect is not considered adverse, then the term NOEL would be used. This included assessments where no effects were observed at the highest dose tested, in which case the highest dose tested would be taken as the NOEL. The same approach would be used by the Committee with respect to the terms LOEL and LOAEL. When effects were observed at all doses, the lowest dose would be identified as the LOEL if the effects at the lowest dose were not considered adverse or as the LOAEL if the effects at the lowest dose were considered adverse.

The Committee emphasized that this decision does not entail any change in its evaluation practice and has no impact on any of the previous evaluations made by this Committee.

4.3 Overall NOAEL

JECFA generally uses the lowest NOAEL in the most sensitive species, usually among mice, rats and dogs, to establish the ADI; however, there might be situations where there is more than one study in which the same end-points have been addressed. In such situations, the dose spacing may be different, resulting in different NOAELs and LOAELs. In such circumstances, it might be appropriate to consider the studies together. When they are comparable, including consideration of study design, duration, end-points addressed, and species and strain of animal, an “overall NOAEL” is identified,
which is the highest NOAEL in the available studies, provided that there is a reasonable margin (≥ 2) over the lowest LOAEL (which becomes to the "overall LOAEL") and that due consideration is given to the shape of the dose–response curve.

JECFA has applied this approach in the evaluation of, for example, phytosterols, phytostanols and their esters (FAO/WHO, 2009).

4.4 Health-based guidance values for food additives

4.4.1 Acceptable daily intake (ADI)

JECFA generally sets the ADI on the basis of the lowest relevant NOAEL or other POD in the most sensitive species and application of an uncertainty (safety) factor to account for the inherent uncertainties in extrapolating toxicity data from experimental animal studies to potential effects in humans as well as variation within the human species. The ADI is usually expressed in the units of milligrams or micrograms per kilogram of body weight, as a range from 0 to an upper limit.

Given that there are assumptions and uncertainties in deriving the ADI, such as the use of uncertainty factors, the use of a range of doses in toxicological studies and normal biological variation, it is more meaningful to express the ADI to only one significant figure to avoid any inference of inappropriate precision. If an ADI is calculated from a POD that has more than one significant figure, the ADI would therefore be rounded to one significant figure, consistent with accepted rounding procedures. JECFA has confirmed that the rounding practices used in expressing the ADI are scientifically and mathematically sound.

4.4.2 ADI “not specified”

There are occasions when JECFA considers the setting of an ADI in numerical terms not to be appropriate. This situation arises when the estimated dietary exposure to the food additive is expected to be well below any numerical value that would ordinarily be assigned to it. Under such circumstances, JECFA uses the term ADI “not specified”. The Committee defines this term to mean that, on the basis of available data (chemical, biochemical, toxicological and other), the total daily exposure to the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice – that is, it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance.

4.4.3 Temporary ADI and ADI “not specified”

JECFA has encountered several situations in which either the body of available data on a new food additive had some limitations or the safety of a food additive for which the Committee had previously assigned an ADI was brought into question by new data. When the Committee feels confident that the use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but is not confident that its use is safe over a lifetime, it often establishes a “temporary” ADI, pending the submission of appropriate data to resolve the safety issue on a timetable established by JECFA. When establishing a temporary (numerical) ADI, the Committee always uses a higher than usual uncertainty (safety) factor, usually increasing it by a factor of 2. The additional biochemical or toxicological data required for the establishment of an ADI are clearly stated, and a review of these new data is conducted before expiry of the provisional period. In many cases, long-term studies are requested, but timetables are not met, which means that JECFA has had to extend temporary ADIs for further periods of time. In instances where data have not been forthcoming, JECFA has withdrawn temporary ADIs as a safety precaution. When establishing a temporary ADI “not specified”, the additional data (e.g. a non-proprietary analytical method) required for the

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6 The general rounding rule for mid-way values (x.5) is to round up, in line with common convention (e.g. Standards Australia International, 2003). Examples for rounding to one significant figure are as follows: 1.25 becomes 1, 0.73 becomes 0.7 and 1.5 becomes 2.
establishment of an ADI “not specified” are clearly stated as well as the time by which the data must be submitted.

4.4.4 Group ADIs

If several substances that produce similar toxic effects are to be considered for use as food additives, it may be appropriate in establishing an ADI to consider the group of substances in order to limit their overall dietary exposure. For this procedure to be feasible, the substances should have a similar mode of action and a similar range of toxic potency. Flexibility should be used in determining which NOAEL is to be used in calculating the ADI. In some cases, the average NOAEL for all the substances in the group may be used for calculating the group ADI. A more conservative approach is to base the group ADI on the substance with the lowest NOAEL. The relative quality and length of studies on the various substances should be considered when setting the group ADI. When the NOAEL for one of the substances is out of line with the others in the group, it should be treated separately.

When JECFA is considering a substance for which toxicological information is limited but that substance is a member of a series of substances that are very closely related chemically (e.g. fatty acids), it may be possible for JECFA to base its evaluation on the group ADI established for the series of substances. This procedure can be followed only if a great deal of toxicological information is available on at least one member of the series and if the known toxic properties of the various substances fall along a well-defined continuum. Interpolation, but not extrapolation, can be performed. The use of this procedure by JECFA represents one of the few situations in which the Committee has used structure-activity relationships in its safety assessments.

In some instances, group ADIs can be established primarily on the basis of metabolic information. For example, the safety of esters used as food flavouring agents could be assessed on the basis of toxicological information on their constituent acids and alcohols, provided that it is shown that they are quantitatively hydrolysed in the gut.

The calculation of a group ADI is also appropriate for substances that cause additive physiological or toxic effects, even if they are not closely related chemically. For example, it may be appropriate to establish a group ADI for additives such as bulk sweeteners that are poorly absorbed and cause a laxative effect.

4.4.5 Substances that are genotoxic and carcinogenic

Substances that are both genotoxic and carcinogenic would generally not be considered acceptable for use as food additives, and JECFA does not establish health-based guidance values for such substances.

4.4.6 Acute reference dose (ARfD)

For most food additives, no acute toxicity occurs at the doses relevant for human exposure. Therefore, no acute reference doses (ARfDs) are established, and no acute dietary exposure assessments are needed. Occasionally, acute intolerance reactions may be relevant, such as laxation from polyol sweeteners. For some chemicals, allergic reactions may also sometimes be of concern, but there are currently no accepted procedures for establishing safe exposure levels for allergic reactions to use in evaluating the significance of acute exposures. Research is under way to allow the identification of thresholds for allergenicity of a variety of food allergens.

4.5 Extension of an existing ADI to substances obtained from different sources and/or by different manufacturing processes

A recurring question facing the Committee is whether an ADI allocated to an additive obtained from a specific source material and/or by a specific manufacturing process can be applied to encompass similar additives obtained by other means or from other sources. The Committee at the sixty-eighth meeting (FAO/WHO, 2007) therefore considered the possibility of elaborating principles or guidelines for evaluations in this area.

At previous meetings, the Committee had evaluated several food additives containing the same chemical entity as the functional component in relation to its food additive use but obtained from
different source materials and/or different manufacturing processes. One such example is colours containing β-carotene, which may be obtained by extraction from vegetables, algae or a genetically modified microorganism or produced by chemical synthesis.

Depending on the substance in question and information received, the Committee has reached various conclusions in its evaluations.

A guiding principle in the safety evaluation of food additives has been that the material tested toxicologically is representative of the material of commerce. To this end, specifications have been established primarily to reflect substances that have been toxicologically tested and secondarily to cover as far as possible products commercially available in the market. When additives containing the same chemical entity or entities as the functional component are produced from different sources or by different methods of manufacture, possibly leading to substantial differences in composition, it has been found necessary to prepare more than one specifications monograph, as was the case for the above-mentioned β-carotene-containing additives.

In order to answer the question of whether it is possible to apply an existing ADI to an additive from a new source or novel method of manufacture (the “new product”), the Committee considered that it is necessary to compare the source, method of manufacture and composition of the new product with those of the product that was tested toxicologically and for which the ADI was originally allocated (the “old product”).

In addition to the source, the composition of a product is commonly related to the manufacturing process. Typical methods of manufacture are chemical synthesis, extraction from natural source materials and production by a microorganism (with or without genetic modification). All of these may result in different residues and impurities that have to be taken into account.

The content of the functional component(s) is often low in products obtained by extraction of natural source materials, whereas the content is normally high in products obtained by chemical synthesis. It is evident that a product with a low content of the functional component contains significant amounts of other substances (e.g. components resulting from the source material or from an organism used in its production).

The Committee recommended that the following stepwise procedure be adopted to determine whether a new product might be included in a previously allocated ADI:

1. Information on manufacture and composition of both the new and the old products should be collated and compared, and any major differences or significant lack of information identified.
2. Data from the first step might be used to determine whether
   a) the new product is sufficiently similar to the old product to be included in the ADI,
   b) it is impossible to include the new product in the ADI because of substantial compositional differences between the two products, or
   c) it may be possible to include the new product in the ADI provided that additional information is received by the Committee.

In all cases, both the nature and amount of any new by-products/solvent residues or other contaminants need to be considered. If the content of the functional component(s) of the additive is high and any new contaminants would be present in only minute amounts, consideration of exposure to the additive and consequential exposure to the minor contaminant may indicate whether the presence is of safety concern.

3. The specifications should include information on source, manufacture and composition in order to reflect materials covered by the evaluation. In particular, where indicated for toxicological reasons, criteria/limits for specific components should be included in the specifications.

4.6 The use of the margin of exposure (MOE) for the evaluation of additives used in infant formulas

The ADI concept does not apply to infants up to the age of 12 weeks because they might be at risk at lower levels of exposure compared with older age groups. This is due to special considerations, such as their immature metabolic capacities, the greater permeability of the immature gut, and their rapid growth and development. Therefore, risk characterization for very young infants has to be considered on a case-by-case basis.
Toxicological testing strategies for additives to be used in infant formulas require approaches that differ from those generally adopted for food additives. For example, evaluation of food additives to be used in infant formulas requires consideration of safety studies involving exposure of very young animals. The reproductive and developmental toxicity studies commonly available for evaluations of chemicals in food address the possible impact on neonatal animals arising through in utero and lactational exposure. However, they frequently do not incorporate direct oral administration to neonatal animals, and such studies are required for the evaluation of food additives in infant formula. If the additive is proposed for use in infant formula at relatively high levels (e.g. 0.1% or greater), then conducting toxicological studies in neonatal animals at doses two or more orders of magnitude greater than the anticipated human exposure, which is the approach commonly taken for food additives, may not be feasible.

The Committee at its seventy-ninth meeting (FAO/WHO, 2014) noted that for several food additives that are proposed for use in infant formulas, the margins of exposure (MOEs) between the NOAEL and the estimated daily exposures to the food additives were in the range of 0.8–12 for infants. Interpretation of the MOE needs to take into account uncertainties or conservatisms that may exist in the toxicological point of departure or in the exposure estimates.

Considerations related to the toxicological point of departure to be taken into account in interpreting the MOE include:

- absorption, distribution, metabolism and excretion – for example, whether or not the additive is absorbed, comparison of potential for metabolic activation and detoxication in the neonatal organism compared with the adult;
- the overall toxicological profile of the substance, including identification of critical effects;
- the potential effects of exposure during life stages in experimental animals of relevance to human infants;
- the relevance for the human infant of the neonatal animal models used in toxicological testing;
- whether adverse effects have been identified in the toxicological studies in neonatal animals, or if the NOAELs are the highest doses tested;
- the design and outcome of any clinical studies conducted with infants (e.g. total number and age of infants tested, growth, tolerance, types of adverse reaction examined); and
- reports of adverse reactions in post-marketing surveillance, where the infant formula is already in use in some countries.

Factors related to the dietary exposure assessments that should be taken into account for the interpretation of an MOE include the following assumptions and considerations:

- Formula is the only source of nutrition for the first 12 weeks of life.
- The additive will be used at the maximum proposed level.
- An energy density of 67 kcal/100 mL (280 kJ/100 mL) is used to convert energy to the volume of formula ingested daily.
- High infant formula consumption is derived from 95th percentile energy intakes.
- Variability of exposure among infants is small.
- Duration of exposure is for a limited time, and exposure decreases on a body weight basis during the exposure period.

The Committee concluded that when the above issues have been taken into account, an MOE in the region of 1–10 could be interpreted as indicating low risk for the health of infants aged 0–12 weeks consuming the food additive in infant formula (FAO/WHO, 2014).


Annex 1: Template for monograph

A sample table of contents for the toxicological and dietary exposure monographs for food additives is given below. Not all headings will be applicable in all cases; “No information was available” can be inserted under main headings (usually up to third level), or minor headings that are not applicable can be deleted.

It should be noted that the design of the monographs was changed in 2015, which has resulted in several formatting changes. Text is 12 pt Times New Roman, headings are 14/12/10/9 pt Arial, paper size A4, 1 inch margins, single spaced, first line of first paragraph under each heading is flush left, first line of all subsequent paragraphs is indented 0.5 inch, no spacing between paragraphs, paragraphs are fully justified, extra line space is added between different study descriptions, line numbering is required for the draft monograph.

Food additive name (addendum, if applicable)

First draft prepared by
Author 1,¹ Author 2² … and Author x³

¹ Affiliation of author 1
² Affiliation of author 2
³ …

³ Affiliation of author x

(include names and affiliations of all experts who contributed to the draft, including WHO and FAO authors and reviewers; main WHO author is given first, followed by rest of contributors in alphabetical order)

<p>| | |</p>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
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</tr>
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<td>2.1.1(b)</td>
<td>Distribution ........................................................................</td>
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<tr>
<td>2.1.1(c)</td>
<td>Excretion .............................................................................</td>
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<tr>
<td>2.1.2</td>
<td>Biotransformation ..................................................................</td>
</tr>
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<td>2.1.3</td>
<td>Effects on enzymes and other biochemical parameters .............</td>
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<td>Mice .....................................................................................</td>
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<tr>
<td>2.2.2(b)</td>
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<td>Hamsters ................................................................................</td>
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<td>2.2.2(e)</td>
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<tr>
<td>2.2.2(f)</td>
<td>Pigs ......................................................................................</td>
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<td>Monkeys ................................................................................</td>
</tr>
<tr>
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<td>Long-term studies of toxicity and carcinogenicity .................</td>
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<td>Mice .....................................................................................</td>
</tr>
<tr>
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<td>Rats ......................................................................................</td>
</tr>
<tr>
<td>2.2.3(c)</td>
<td>etc. .......................................................................................</td>
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2.2.4 Genotoxicity ................................................................. x
2.2.5 Reproductive and developmental toxicity ................................ x
   (a) Multigeneration reproductive toxicity..................................... x
   (b) Developmental toxicity......................................................... x
2.2.6 Special studies (below are examples only; note alphabetical order)... x
   (a) Allergenicity ......................................................................... x
   (b) Cardiovascular effects.............................................................. x
   (c) Immune responses ................................................................. x
   (d) Macromolecular binding ......................................................... x
   (e) Metabolites ........................................................................... x
   (f) Neurotoxicity ........................................................................ x
   (g) No-hormonal-effect levels....................................................... x
   (h) Ocular toxicity ....................................................................... x
   (i) Photoisomerization products .................................................. x
   (j) Thyroid function .................................................................... x
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4. Comments (note: includes reference citations) ..................................... x
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   4.2 Toxicological studies ............................................................... x
   4.3 Observations in humans............................................................ x
   4.4 Assessment of dietary exposure ................................................ x
5. Evaluation ...................................................................................... x
   5.1 Recommendations .................................................................... x
6. References ..................................................................................... x
### Table 1
Pharmacokinetic parameters following a single oral (gavage) dose of ethyl lauroyl arginate (propylene glycol/water formulation) administered to male rats

<table>
<thead>
<tr>
<th>Dose level (mg/kg bw)</th>
<th>$C_{\text{max}}$ (ng/mL) / $T_{\text{max}}$ (h)</th>
<th>AUC (ng·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethyl lauroyl arginate</td>
<td>$N^\alpha$-Lauroyl-$L$-arginine</td>
</tr>
<tr>
<td>40</td>
<td>2.02 ± 1.28 / 0.5</td>
<td>24.2 ± 31.9 / 1</td>
</tr>
<tr>
<td>120</td>
<td>1.23 ± 0.29 / 1</td>
<td>23.2 ± 2.5 / 0.75</td>
</tr>
<tr>
<td>320</td>
<td>2.6 ± 1.81 / 3</td>
<td>96.9 ± 79.7 / 1.5</td>
</tr>
</tbody>
</table>

AUC: area under the plasma concentration–time curve; bw: body weight; $C_{\text{max}}$: maximum concentration in plasma; $T_{\text{max}}$: time taken to reach $C_{\text{max}}$.

*a Could not be calculated owing to the small number of quantifiable samples.

### Table 2
Mean cumulative excretion of radioactive material following administration of single oral doses of $^{13}$C-labelled PVA-PEG graft copolymer to male and female rats

<table>
<thead>
<tr>
<th>Dose (mg/kg bw)</th>
<th>Faeces</th>
<th>Urine</th>
<th>Bile</th>
<th>Exhaled air</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>100.05</td>
<td>103.45</td>
<td>0.50</td>
<td>0.45</td>
</tr>
<tr>
<td>1 000</td>
<td>100.76</td>
<td>105.27</td>
<td>0.27</td>
<td>0.22</td>
</tr>
<tr>
<td>168 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>100.14</td>
<td>103.63</td>
<td>0.53</td>
<td>0.47</td>
</tr>
<tr>
<td>1 000</td>
<td>101.30</td>
<td>105.35</td>
<td>0.31</td>
<td>0.23</td>
</tr>
</tbody>
</table>

bw: body weight; ND: not determined

### Table 3
Acute toxicity of steviol glycosides and related substances

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Test substance</th>
<th>Route</th>
<th>LD$_{50}$ (mg/kg bw)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Male and female</td>
<td>93–95% stevioside</td>
<td>Gavage</td>
<td>&gt;15 000</td>
<td>Akashi &amp; Yokoyama (1975)</td>
</tr>
<tr>
<td>Mouse</td>
<td>Male</td>
<td>Isosteviol (purity not supplied)</td>
<td>Oral</td>
<td>&gt;500</td>
<td>Bazotte et al. (1986)</td>
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<tr>
<td>Mouse</td>
<td>Male</td>
<td>Isosteviol (purity not supplied)</td>
<td>Intraperitoneal</td>
<td>229.81</td>
<td>Bazotte et al. (1986)</td>
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<tr>
<td>Mouse</td>
<td>Male</td>
<td>Isosteviol (purity not supplied)</td>
<td>Intravenous</td>
<td>89.79</td>
<td>Bazotte et al. (1986)</td>
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<tr>
<td>Rat</td>
<td>Male</td>
<td>Isosteviol (purity not supplied)</td>
<td>Oral</td>
<td>&gt;500</td>
<td>Bazotte et al. (1986)</td>
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Table 4
Body weight change and feed efficiency in a 3-week dietary toxicity study of OSA-modified starch in farm piglets

<table>
<thead>
<tr>
<th>OSA dose (mg/kg bw per day)</th>
<th>Mean body weight, day 1 (kg)</th>
<th>Mean body weight, day 21 (kg)</th>
<th>Total body weight change (kg)</th>
<th>Total feed consumption (kg)</th>
<th>Feed efficiency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>2.08</td>
<td>5.43</td>
<td>3.35</td>
<td>30.7</td>
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<td>1 000</td>
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<td>29.6</td>
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<td>4.52</td>
<td>2.47</td>
<td>23.1</td>
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<td>Females</td>
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<td>0</td>
<td>1.97</td>
<td>4.95</td>
<td>2.98</td>
<td>27.0</td>
<td>0.110</td>
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<td>4.92</td>
<td>3.00</td>
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<td>1.92</td>
<td>5.00</td>
<td>3.08</td>
<td>27.2</td>
<td>0.113</td>
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</tbody>
</table>

bw: body weight; OSA: octenyl succinic acid

* Feed efficiency = body weight change/feed consumption.

Source: Adapted from MPI Research (2012)

Table 5
Mean terminal body weight and relevant relative organ weights in F1 rats (10 of each sex per group) after receiving pAOS via the diet for 13 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative organ weight (g/kg bw)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>Terminal body weight (g)</td>
<td>336 ± 20</td>
</tr>
<tr>
<td>Kidneys</td>
<td>5.37 ± 0.34</td>
</tr>
<tr>
<td>Caecum full</td>
<td>11.0 ± 3.1</td>
</tr>
<tr>
<td>Caecum empty</td>
<td>2.4 ± 0.3</td>
</tr>
</tbody>
</table>
### Relative organ weight (g/kg bw)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Reference control (10% sc-FOS)</th>
<th>Test groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5% pAOS</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Terminal body weight (g)</em></td>
<td>200 ± 11</td>
<td>193 ± 9</td>
<td>198 ± 10</td>
</tr>
<tr>
<td>Kidneys</td>
<td>5.98 ± 0.37</td>
<td>5.80 ± 0.30</td>
<td>6.11 ± 0.46</td>
</tr>
<tr>
<td>Caecum full</td>
<td>13.6 ± 3.9</td>
<td>19.4 ± 2.5*</td>
<td>15.2 ± 2.5*</td>
</tr>
<tr>
<td>Caecum empty</td>
<td>3.2 ± 0.3</td>
<td>4.2 ± 0.2*</td>
<td>3.4 ± 0.4*</td>
</tr>
</tbody>
</table>

bw: body weight; pAOS: pectin acidic oligosaccharides; sc-FOS: short-chain fructo-oligosaccharides

*: P < 0.05, significantly different from controls; #: P < 0.05, significantly different from reference controls

*a Values are presented as means ± standard deviation.

**Source:** Garthoff et al. (2010)

### Foamy histiocytosis and Tubular vacuolation

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence</th>
<th>Mean severity</th>
<th>Incidence</th>
<th>Mean severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>0/20</td>
<td>–</td>
<td>0/20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0/20</td>
<td>–</td>
<td>0/20</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>4/20</td>
<td>1.0</td>
<td>0/20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>3/20</td>
<td>1.0</td>
<td>0/20</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>17/20</td>
<td>1.3</td>
<td>0/20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>8/20</td>
<td>1.3</td>
<td>5/20</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>20/20</td>
<td>2.3</td>
<td>3/20</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>19/20</td>
<td>2.1</td>
<td>13/20</td>
</tr>
<tr>
<td>Recovery group 1</td>
<td>Male</td>
<td>0/10</td>
<td>–</td>
<td>0/10</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0/10</td>
<td>–</td>
<td>0/10</td>
</tr>
<tr>
<td>Recovery group 4</td>
<td>Male</td>
<td>10/10</td>
<td>2.1</td>
<td>4/10</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10/10</td>
<td>1.8</td>
<td>5/10</td>
</tr>
</tbody>
</table>

**Source:** Brown et al. (1998)
**Table 7**
Genotoxicity of PVA-PEG graft copolymer in vitro and in vivo

<table>
<thead>
<tr>
<th>End-point</th>
<th>Test system</th>
<th>Route of administration</th>
<th>Concentration</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse mutation</td>
<td><em>Salmonella typhimurium</em> TA98, TA100, TA1535 and TA1537 and <em>Escherichia coli</em> WP2uvrA</td>
<td>–</td>
<td>20–5 000 µg/plate, ±S9</td>
<td>Negative&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Engelhardt &amp; Hoffmann (2000)</td>
</tr>
<tr>
<td>Gene mutation</td>
<td>Mouse lymphoma L5178Y TK&lt;sup&gt;−&lt;/sup&gt; cells</td>
<td>–</td>
<td>First experiment: 312.5–5 000 µg/mL, ±S9 Second experiment: 79–5 000 µg/mL, –S9 312.5–5 000 µg/mL, +S9</td>
<td>Negative&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Engelhardt &amp; Hildebrand (2000a)</td>
</tr>
<tr>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronucleus induction</td>
<td>Mouse; male</td>
<td>Intraperitoneal</td>
<td>500, 1 000 and 2 000 mg/kg bw</td>
<td>Negative&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Engelhardt &amp; Hildebrand (2000b)</td>
</tr>
</tbody>
</table>

bw: body weight; PVA-PEG: polyvinyl alcohol – polyethylene glycol; S9: 9000 × g supernatant fraction from rat liver homogenate

<sup>a</sup> Two independent experiments were performed. The first experiment was performed using the plate incorporation method, and the second experiment was performed using the preincubation method. A slight decrease in the number of revertants and a slight reduction in bacterial growth were occasionally observed from 2500 µg/mL onwards.

<sup>b</sup> Two independent experiments were performed. Cells were exposed for 4 hours in the absence and presence of S9 (except in the second experiment, in which cells were exposed for 24 hours in the absence of S9), followed by an expression phase of 30–48 hours and a selection period of approximately 10 days. After an exposure period of 24 hours, relative total growth was decreased at 2500 µg/mL (~55%) and 5000 µg/mL (~37%).

<sup>c</sup> Two doses were administered intraperitoneally at 0 and 24 hours. Examinations were 24 hours after the last dosing (i.e. at 48 hours). No increases in group mean micronuclei were observed. The Committee noted that intraperitoneal administration is not a relevant route for human exposure to PVA-PEG graft copolymer.
Annex 3: Template for report item

A sample template for the meeting report item is given below.

It should be noted that the design of the meeting report changed in 2015, resulting in several formatting changes. Text is Times New Roman 12 pt, headings are Arial 11 pt, paper size A4, 1 inch margins, 1.5 line spacing, first line of first paragraph below each heading is flush left, first line of all subsequent paragraphs is indented 0.5 inch, no spacing between paragraphs, paragraphs are fully justified.

WHO template

Report topic: 
Author(s): 
Date: 
Version:

3.1.x Food additive name

Explanation

(general introduction to the compound; whether it has been evaluated before, including short description of the conclusions of previous evaluations, and why it is on the agenda; also short introduction to chemical nature of compound and primary uses in food)

Chemical and technical considerations (FAO)

Biochemical aspects (WHO)

(brief description of key information on absorption, distribution, metabolism and excretion)

Toxicological studies

(short summary of the key toxicological data relevant for the evaluation)

Observations in humans

(brief summary of the most relevant human data)

Assessment of dietary exposure (exposure experts)
**Dose–response analysis**

(where appropriate, brief description of and justification for data set selected, dose–response models applied, benchmark dose results)

**Evaluation**

(gives the Committee’s conclusion re derivation of health-based guideline value or margin of exposure between dietary exposure and critical effect level)

**Recommendations**

(gives recommendations for research needed, information required to complete evaluation, etc.)

(report item ends with a short sentence to indicate whether a monograph or monograph addendum has been prepared *(WHO)* and a short sentence to indicate whether new specifications and a Chemical and Technical Assessment were prepared *(FAO)*)
3.1.2 Magnesium dihydrogen diphosphate

Explanation

At the present meeting, the Committee evaluated magnesium dihydrogen diphosphate for use as an acidifier, stabilizer and raising agent. It is proposed for use as an alternative to sodium-based acidifiers and raising agents, primarily in self-raising flour, noodles (oriental style), batters and processed cereals.

Magnesium dihydrogen diphosphate has not been evaluated previously by the Committee. Phosphates, diphosphates and polyphosphates were evaluated by the Committee at its sixth, seventh, eighth, ninth, thirteenth, fourteenth, seventeenth, twenty-sixth and fifty-seventh meetings (Annex 1, references 6–8, 11, 19, 22, 32, 59 and 154). A maximum tolerable daily intake (MTDI) of 70 mg/kg of body weight (bw) was established at the twenty-sixth meeting on the basis of the lowest dietary concentration of phosphorus (1% in the diet) that caused nephrocalcinosis in rats. It was considered inappropriate to establish an acceptable daily intake (ADI), because phosphorus (primarily as phosphate) is an essential nutrient and an unavoidable constituent of food. The MTDI is expressed as phosphorus and applies to the sum of phosphates naturally present in food and the phosphates derived from use of these food additives. At its seventy-first meeting, the Committee evaluated ferrous ammonium phosphate and concluded that consideration of the toxicity of phosphate did not indicate a need to revise the Committee’s previous evaluation of this ion (Annex 1, reference 191).

The MTDI was considered to cover a number of phosphate salts, according to the principle established by the Committee at its ninth, twenty-third and twenty-ninth meetings (Annex 1, references 11, 50 and 70) that the ADI (or MTDI) established for ionizable salts should be based on previously accepted recommendations for the constituent cations and anions. Magnesium-based salts previously discussed by the Committee and covered by the MTDI for phosphates included magnesium phosphate (monobasic, dibasic and tribasic) and monomagnesium phosphate. However, certain specific phosphate salts were not included, because specifications were lacking and because information was not available to indicate whether they were being used as food-grade materials.

The Committee has previously evaluated other magnesium salts, allocating ADIs “not limited”7 or “not specified” to magnesium carbonate, magnesium hydroxide, magnesium chloride, magnesium DL-lactate, magnesium hydrogen carbonate, magnesium gluconate, magnesium di-L-glutamate and magnesium sulfate (Annex 1, references 11, 50, 70, 77, 137 and 187). At its twenty-ninth meeting (Annex 1, reference 70), the Committee highlighted that the use of magnesium salts as food additives was acceptable, provided that the following were taken into consideration:

- The minimum laxative effective dose is approximately 1000 mg of magnesium moiety from a magnesium salt (observed only when the magnesium salt is administered as a single dose).
- Infants are particularly sensitive to the sedative effects of magnesium salts.
- Individuals with chronic renal impairment retain 15–30% of administered magnesium.

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7 At its eighteenth meeting (Annex 1, reference 35), the Committee replaced the term ADI “not limited” with ADI “not specified”.

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At its present meeting, the Committee was asked to conduct a safety assessment and set specifications for magnesium dihydrogen diphosphate by the Forty-third Session of the Codex Committee on Food Additives (3). The Committee received a submission that included tests for acute toxicity, skin and eye irritation and genotoxicity of magnesium dihydrogen diphosphate and considered other information available in the literature of relevance to the magnesium and phosphate ions.

**Chemical and technical considerations**

Magnesium dihydrogen diphosphate (chemical formula: MgH$_2$P$_2$O$_7$; Chemical Abstracts Service registry number: 20768-12-1) is the acidic magnesium salt of diphosphoric acid. It is manufactured by adding an aqueous dispersion of magnesium hydroxide slowly to phosphoric acid until a magnesium to phosphorus ratio of about 1:2 is reached. The temperature is held under 60 °C during the reaction. About 0.1% hydrogen peroxide is added to the reaction mixture, and the slurry is then dried and milled.

**Toxicological data**

Magnesium dihydrogen diphosphate ionizes into its component ions: magnesium, hydrogen and diphosphate. Therefore, the safety assessment should be based on previously accepted recommendations for the constituent cations and anions. Magnesium and phosphorus (primarily as phosphate) are essential minerals that are naturally present in the human body and in food.

The Committee received data showing that magnesium dihydrogen diphosphate does not exert acute toxicity, skin or eye irritation or genotoxicity.

At previous meetings, the Committee noted that toxicity can arise from an imbalance of calcium, magnesium and phosphate. Excessive dietary phosphorus causes hypocalcaemia, which can result in bone loss and calcification of soft tissues. The MTDI of 70 mg/kg bw was derived from studies demonstrating nephrocalcinosis in rats at dietary concentrations of 1% phosphorus. Nephrocalcinosis has been defined as calcified deposits, mainly in the form of calcium phosphate, in tubules located predominantly at the corticomedullary junction of the kidney. The exact approach taken in deriving the MTDI from this end-point is unclear. In addition, the Committee noted that there is evidence that rats are particularly sensitive to mineralization in the kidneys resulting from an imbalance of calcium and phosphate in the diet. Therefore, the relevance of mineralization in the rat kidney for safety assessment is unclear. The available toxicological information on phosphate salts did not indicate that the MTDI is insufficiently health protective.

**Assessment of dietary exposure**

For the evaluation of magnesium dihydrogen diphosphate as a new food additive intended to be used as an alternative to sodium-based acidifiers and raising agents, the Committee evaluated an anticipated dietary exposure based on individual food consumption data from the European Union with the maximum proposed use levels of magnesium dihydrogen diphosphate (0.1% up to 0.7% by weight in solid food, as phosphorus) in the Codex General Standard for Food Additives (GSFA) food categories such as flours, pasta, noodles and similar products, puffed products, bread and rolls and fine bakery wares.

Based on this conservative scenario, assuming that 100% of food products would be manufactured and consumed at the maximum proposed use levels, the Committee concluded that anticipated average dietary exposures to magnesium dihydrogen diphosphate would be up to approximately 20 mg of phosphorus per kilogram of body weight per day for an adult and up to 70 mg of phosphorus per kilogram of body weight per day for a child. The 95th
percentiles of exposure are estimated to be up to 40 mg of phosphorus per kilogram of body weight per day for an adult and up to 115 mg of phosphorus per kilogram of body weight per day for a child. The main food groups contributing to these overall dietary exposures within all population groups were bread and rolls (7–86%), fine bakery wares (6–58%) and flours and starches (5–98%).

The dietary exposure to magnesium estimated from the anticipated use of magnesium dihydrogen diphosphate would be 39% of the estimated exposure to phosphorus, based on the contribution to molecular weight. This corresponds to an average dietary exposure of up to approximately 8 mg of magnesium per kilogram of body weight per day for an adult and up to 27 mg of magnesium per kilogram of body weight per day for a child. The 95th percentiles of exposure are estimated to be up to 16 mg of magnesium per kilogram of body weight per day for an adult and up to 45 mg of magnesium per kilogram of body weight per day for a child.

Evaluation

Although an ADI “not specified” has been established for a number of magnesium salts used as food additives, the estimated chronic dietary exposures to magnesium (960 mg/day for a 60 kg adult at the 95th percentile) from the proposed uses of magnesium dihydrogen diphosphate are up to twice the background exposures from food previously noted by the Committee (180–480 mg/day) and in the region of the minimum laxative effective dose of approximately 1000 mg of magnesium when taken as a single dose. The estimates of dietary exposure to phosphorus from the proposed uses of magnesium dihydrogen diphosphate are in the region of, or slightly exceed, the MTDI of 70 mg/kg bw for phosphate salts, expressed as phosphorus, from this source alone. Thus, the MTDI is further exceeded when other sources of phosphate in the diet are taken into account. The Committee therefore concluded that the proposed use levels and food categories result in an estimated dietary exposure to magnesium dihydrogen diphosphate that is a potential concern.

The Committee emphasized that in evaluating individual phosphate-containing food additives, there is a need for assessment of total dietary exposure to phosphorus.

Recommendations

The Committee noted that an ADI “not specified” has been allocated individually to a number of magnesium-containing food additives and recommended that total dietary exposure to magnesium from food additives and other sources in the diet should be assessed.

The information submitted to the Committee and in the scientific literature did not indicate that the MTDI of 70 mg/kg bw for phosphate salts, expressed as phosphorus, is insufficiently health protective. On the contrary, because the basis for its derivation might not be relevant to humans, it could be overly conservative. Therefore, there is a need to review the toxicological basis of the MTDI for phosphate salts expressed as phosphorus.

A toxicological monograph was prepared.

New specifications and a Chemical and Technical Assessment for magnesium dihydrogen diphosphate were prepared.