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

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

DRAFT

NOTE: this draft will be tested in preparation of the 83rd JECFA meeting and the final guidance published after the meeting
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February 2016

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Geneva
Table of contents

List of abbreviations ................................................................................................................. v

Preface ......................................................................................................................................... vi

Chapter 1: Roles and responsibilities .......................................................................................... 1
  1.1 Selection of compounds on the agenda and issuing the call for data .................................. 1
  1.2 Identification of monographers and reviewers and assignment of compounds and tasks .. 1
  1.3 Performing a literature search ........................................................................................... 2
  1.4 Dealing with the data submission ...................................................................................... 2
  1.5 Evaluating the data ............................................................................................................ 2
  1.6 Preparing the draft monograph before the meeting ............................................................ 3
  1.7 Preparing the report item and finalizing the monograph at the meeting ......................... 4

Chapter 2: Preparing the monograph ......................................................................................... 6
  2.1 Introduction ....................................................................................................................... 6
  2.2 General aspects ................................................................................................................ 6
    2.2.1 Formatting ................................................................................................................ 6
    2.2.2 Units of measurement ............................................................................................... 6
    2.2.3 Presentation of doses ............................................................................................... 7
    2.2.4 Presentation of point of departure ............................................................................ 7
    2.2.5 Tables ...................................................................................................................... 9
    2.2.6 Historical control data ............................................................................................. 11
    2.2.7 In-text references .................................................................................................... 11
    2.2.8 Miscellaneous ......................................................................................................... 11
  2.3 Detailed content of the monograph ................................................................................... 13
    2.3.1 Explanation .............................................................................................................. 13
    2.3.2 Biological data ........................................................................................................ 14
    2.3.3 Comments ............................................................................................................... 27
    2.3.4 Evaluation .............................................................................................................. 27
    2.3.5 References .............................................................................................................. 28

Chapter 3: Preparing the report item ......................................................................................... 32

Chapter 4: Additional considerations ....................................................................................... 33
  4.1 Dietary exposure estimates in epidemiological studies ..................................................... 33
  4.2 Commentary on the use of NOEL/NOAEL and LOEL/LOAEL ..................................... 34
  4.3 Overall NOAEL ............................................................................................................... 34
  4.4 Modelling of dose–response data ..................................................................................... 34
  4.5 Tolerable intakes for contaminants .................................................................................. 36
  4.6 Expression of the tolerable intake and rounding procedures .......................................... 37
  4.7 Guidance on establishing acute reference doses ............................................................... 37
  4.8 Use of the margin of exposure approach ......................................................................... 37
  4.9 Predicting risks at specified exposure levels ..................................................................... 38

References .................................................................................................................................. 39

Annex 1: Template for monograph ............................................................................................ 41

Annex 2: Examples of table formats ........................................................................................ 44

Annex 3: Template for report item ............................................................................................ 56

Annex 4: Example of report item .............................................................................................. 59
List of abbreviations

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

This guidance document replaces the previous guidance for the risk assessment of contaminants in food by Joint FAO/WHO Expert Committee on Food Additives (JECFA) monographers and reviewers, issued by WHO in 2001. It is intended primarily for WHO 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 parties interested in understanding the process followed by JECFA in the evaluation of contaminants that may be present in food or feed – for example, heavy metals, environmental contaminants, impurities arising in food or feed additives, solvents used in food or feed processing, other substances arising from food or feed processes such as heating, substances migrating from food or feed contact materials, and residues arising from the use of animal feed additives or the non-active components of veterinary drug formulations. Detailed scientific guidance on the interpretation of toxicological and epidemiological data may be found in the monograph Environmental Health Criteria 240 (http://www.who.int/foodsafety/publications/chemical-food/en/).

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

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

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

Separate guidance documents for the evaluation of food additives (excluding enzyme preparations and flavouring agents), enzyme preparations and flavouring agents and for the assessment of dietary exposure to food additives are also available on the WHO website (http://www.who.int/foodsafety/chem/jecfa/guidelines/en/).
Chapter 1: Roles and responsibilities

The roles and responsibilities of the JECFA Secretariat and of both monographers (“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 contaminants are selected on the basis of priority lists established by the Codex Committee on Contaminants in Foods (CCCF), requests by FAO and WHO and their Member States, and recommendations of earlier meetings of JECFA. The WHO and FAO Joint Secretaries post a call for data on the compounds on the agenda 10–12 months in advance of the meeting on the Internet, utilizing as broad a distribution as possible. The deadline for submission of data is ordinarily 6–7 months before the meeting.

1.2 Identification of monographers and reviewers and assignment of compounds and tasks

The WHO Joint Secretary will contact potential monographers and reviewers within the existing roster of experts about their interest and availability to serve as experts for the next meeting of JECFA on contaminants in food and feed. If additional expertise is needed (e.g. in the areas of dose–response modelling, epidemiology, carcinogenicity or genotoxicity), the Secretariat may identify additional experts from the published literature. Usually the Secretariat assigns several experts to one compound (or group of related compounds) who have complementary expertise and are assigned to draft specific sections of the monograph. One of the experts will be assigned to take the overall lead and coordination function for the drafting of the full monograph. For complex evaluations, more than one reviewer may be assigned. In addition to WHO experts, FAO experts will be assigned to the compound who are responsible for the evaluation of analytical methods, including sampling protocols, occurrence data, effects on processing, and prevention and control. Additional experts on exposure assessment will also be assigned to the compound. The entire group of experts assigned to the compound or group of related compounds is sometimes referred to below as the evaluation team.

Participants are invited as independent experts in their respective areas, and they do not represent any organization or government. Participation is not compensated, although WHO is responsible for return airfare and provides a daily subsistence allowance to cover accommodation, meals and other miscellaneous expenses.

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

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

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

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1 Previously Temporary Advisers.
2 http://www.who.int/about/declaration-of-interests/en/
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 Performing a literature search

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.

1.4 Dealing with the data submission

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

1.5 Evaluating the data

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

The JECFA process should not require any significant changes to the monographer’s and reviewer’s usual way of working through the data, provided that each study is described and the relevance (including any potential bias or problems with study design or reporting of results) is documented in a clear and transparent manner. When the monograph is being prepared, all data are evaluated in a thorough and independent manner, taking into account specific guidance prepared for JECFA monographers on the interpretation of toxicological and epidemiological data (i.e. EHC 240 [IPCS, 2009a] and subsequently published guidance). Given the large amount of published literature often available on contaminants in food and feed, the monographers must be sure to allow sufficient time for retrieving, organizing and reviewing references identified during the literature search.

The depth of investigation will clearly vary with the study type, the results and the impact on the overall conclusion. For example, it can be valuable to go down to individual animal-level data for a dog study with a small group size and a marginal response, but this is not normally required for a rodent study with a larger group size and clear effects (e.g. 8/10 animals with grade 3 versus 3/10 controls with grade 1).

If the study authors have discounted particular findings as not being treatment related or adverse, the monographer should pay particular attention to these to see if he or she agrees with the study authors’ conclusions. If the monographer disagrees with the conclusions of the study authors, this should be highlighted in the monograph. The monographer may occasionally wish to contact the study authors for clarification or to request additional information.

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

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

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

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

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

Which type of outcome (health-based guidance value, MOE, quantitative risk assessment) is appropriate and possible for each contaminant or group of contaminants will be decided by the evaluation team on a case-by-case basis.

### 1.6 Preparing the draft monograph before the meeting

The monographers produce a first draft of the monograph, based on a critical review of the published literature, the grey literature and data submitted in response to the call for data. 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 compound (see Chapter 3). Detailed guidance on preparation of the monograph is provided in Chapter 2. Examples of recent monographs on contaminants can be accessed through the WHO JECFA searchable database: http://apps.who.int/food-additives-contaminants-jeefa-database/search.aspx?fc=35.

In cases where new or additional data are provided to complete an evaluation or to re-evaluate a compound previously considered by JECFA or to establish an ARID that was not previously considered, an addendum to the original monograph should be prepared with the summaries of the new studies.

It is critical that the evaluation team (including both WHO and FAO experts) works together and discusses critical aspects or studies throughout the preparation of the monograph. The first draft of the toxicological and epidemiological monograph is distributed first to the reviewer(s). The reviewer(s) should receive the first draft of the monograph two months before the meeting in order to allow sufficient time to perform a thorough review. It is the responsibility of the reviewer(s) to cross-check
critical studies, suggest amendments in both text and tables, and finalize the **Comments** and **Evaluation** sections.

The reviewer(s) return the monograph to the lead 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 – and, as necessary, earlier to clearly define tasks – the WHO Joint Secretary organizes teleconferences for each compound (or group of compounds), involving all WHO experts assigned to the compound, other JECFA experts, in particular FAO experts assigned to the same compound, and the Joint Secretariat. The purpose of these teleconferences is to clarify issues, coordinate the work between the WHO and FAO experts and identify information missing from the literature search. The lead monographer is responsible for making any revisions suggested by teleconference participants.

The final draft is then sent to the WHO Joint Secretary, who is responsible for sending the draft monograph to all meeting participants at the latest 10 days prior to the meeting.

### 1.7 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. The lead monographer is the main individual responsible for revisions and works closely with the other monographers to finalize the monograph.

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 (and reviewers) have expertise in a specific area of toxicology (e.g. histopathology, genotoxicity, developmental toxicity) or epidemiology, 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 the draft before the meeting report 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 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 (by uploading it onto the meeting computer in the “Final monographs” folder) before leaving on the final day of the meeting. There is no need for the monographer to update the **Explanation**, **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 (i.e. tolerable intakes and ARfDs) or other safety recommendations for all contaminants 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 monographs are intended for experts and contain detailed descriptions of the full database on the biochemical, toxicological and epidemiological data considered in the evaluation, the sections prepared by FAO experts (on chemical and technical matters), 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 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 monograph also briefly describes data that were not critical to the evaluation, in order to reflect the full database considered.

A table of contents or template for the monograph (for the JECFA current year) will be provided to monographers when they are assigned a compound. 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 on whether a tolerable intake or ARfD is established, an MOE is derived or a quantitative risk assessment is performed. 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 diet (mg/kg diet) 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 “diet” should always be included (i.e. mg/kg diet), 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 Pb/kg bw is not correct. Instead, the sentence should be rewritten more clearly as, for example, “a lead 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...
2.2.3 Presentation of doses

- Parentheses, rather than commas, are used when presenting dose conversions: $X$ and $Y$ mg/kg diet (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 had 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, 2009a).
- When doses are converted from ppm, mg/kg diet, 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 diet or more; e.g. 10 000 mg/kg diet = 1%) to mg/kg bw per day, up to two additional significant figures can be used for the converted dose, to avoid introducing additional uncertainty in the calculation of the final rounded tolerable intake or ARfD.
- As long as the dose conversions have been presented at the beginning of a study description, the original doses (e.g. in mg/kg diet, mg/L drinking-water or percentage in the diet, but not in ppm, which must be changed to mg/kg diet 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 (i.e. a tolerable intake or an ARfD) are most 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$_{x}$) 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, 2009a]).
- Past tense should be used when presenting the POD: The NOAEL/BMDL$_{x}$ 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 author(s), 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 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 above) have been 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 used 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 equivalent to x mg/kg bw per day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse</strong></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>Dry laboratory chow diets</td>
<td>0.13(^b)</td>
<td>0.006(^b)</td>
<td>0.20(^b)(^c)</td>
</tr>
<tr>
<td><strong>Rat (young)</strong></td>
<td>0.10</td>
<td>10</td>
<td>Dry laboratory chow diets</td>
<td>0.100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rat (multigeneration studies)</strong></td>
<td>0.40(^d)</td>
<td>10–20(^d)</td>
<td>Moist, semi-solid diets</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(average: 0.25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rat (old)</strong></td>
<td>0.40</td>
<td>20</td>
<td>Moist, semi-solid diets</td>
<td>0.050</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0.35(^b)</td>
<td>18(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.05(^b)</td>
<td>0.05(^b)</td>
<td>0.14(^b)(^e)</td>
</tr>
<tr>
<td><strong>Hamster</strong></td>
<td>0.14(^b)</td>
<td>12(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.09(^b)</td>
<td>0.03(^b)</td>
<td>0.21(^b)</td>
</tr>
<tr>
<td><strong>Chick</strong></td>
<td>0.40</td>
<td>50</td>
<td>Moist, semi-solid diets</td>
<td>0.125</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Guinea-pig</strong></td>
<td>0.75</td>
<td>30</td>
<td>Moist, semi-solid diets</td>
<td>0.040</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0.84(^b)</td>
<td>34(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.04(^b)</td>
<td>0.20(^b)</td>
<td>0.24(^b)</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>100</td>
<td>Moist, semi-solid diets</td>
<td>0.025</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rabbit</strong></td>
<td>2.0</td>
<td>60</td>
<td>Moist, semi-solid diets</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3.8(^b)</td>
<td>186(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.05(^b)</td>
<td>0.41(^b)</td>
<td>0.11(^b)</td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td>10.0</td>
<td>250</td>
<td>Moist, semi-solid diets</td>
<td>0.025</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>12(^b)</td>
<td>300(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.03(^b)</td>
<td>0.61(^b)</td>
<td>0.05(^b)</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td>2</td>
<td>100</td>
<td>Moist, semi-solid diets</td>
<td>0.050</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1.5(^b)</td>
<td>168(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.11(^b)</td>
<td>0.15(^b)</td>
<td>0.10(^b)</td>
</tr>
<tr>
<td><strong>Monkey (e.g. rhesus, cynomolgus)</strong></td>
<td>5</td>
<td>250</td>
<td>Moist, semi-solid diets</td>
<td>0.050</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Rhesus monkey</strong></td>
<td>8.0(^b)</td>
<td>320(^b)</td>
<td>Moist, semi-solid diets</td>
<td>0.04(^b)</td>
<td>0.53(^b)</td>
<td>0.07(^b)</td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td>10</td>
<td>750</td>
<td>Moist, semi-solid diets</td>
<td>0.075</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Human</strong></td>
<td>60</td>
<td>1500</td>
<td>Moist, semi-solid diets</td>
<td>0.025</td>
<td>2</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>Pig or sheep</strong></td>
<td>60</td>
<td>2 400</td>
<td>Relatively dry grain forage mixtures</td>
<td>0.040</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pig</strong></td>
<td>80(^b)</td>
<td>2 250(^b)</td>
<td>Relatively dry grain forage mixtures</td>
<td>0.03(^b)</td>
<td>5.5(^b)</td>
<td>0.07(^b)</td>
</tr>
<tr>
<td><strong>Cow (maintenance)</strong></td>
<td>500</td>
<td>7 500</td>
<td>Relatively dry grain forage mixtures</td>
<td>0.015</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cow (fattening)</strong></td>
<td>500</td>
<td>15 000</td>
<td>Relatively dry grain forage mixtures</td>
<td>0.030</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Horse</strong></td>
<td>500</td>
<td>10 000</td>
<td>Relatively dry grain forage mixtures</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 diet (equal to $y$ mg/kg bw per day), based on [effects] observed at $z$ mg/kg diet (equal to $a$ mg/kg bw per day) [where $z$ mg/kg diet 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, [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 is 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) or other PODs is usually 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). 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.

• 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). For tables containing multiple studies using different statistical tests (e.g. epidemiological studies), this information can be included in the body of the table.

- 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 usually 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) taken 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 data provided that there were no changes in interpretative or investigative techniques between the historical control studies and the one on the test compound.

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, 2000c). 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. Overall, the monograph should give a clear description of the full database considered and
provide sufficient details regarding critical data to permit an independent evaluation of the conclusions made.

- 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 a provisional maximum tolerable daily intake (PMTDI) of 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 Associate 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 (tolerable intake, ARfD) are “established” – for example, “the Committee established a PMTDI of 0.1 mg/kg bw”.

- Each study summary should provide a short description of the methodology used in the study. Where studies comply with an Organisation for Economic Co-operation and Development (OECD) test guideline or equivalent national guideline, 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. This is particularly useful when there is a need to establish an ARfD, as such early measurements in repeated-dose studies may provide the critical effect for such a health-based guidance value.

- 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, coenzyme, 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), metanalysis, metabolize, modelled, neurobehavioural, oedema, oesophagus, oxidize, paralyse, pharmacopoeia, postmortem, postnatal, postpartum, pretreatment, programme, re-examine, reopen, side-effect, subgroup, sublethal, sulfur, tumour, webpage, website, worldwide, X-ray.

- Abbreviations are defined 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, in the preparation of the monograph before the meeting, 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 also often useful to include overview tables summarizing the similar toxicological studies and their NOAELs/LOAELs, for discussion purposes only. 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 (e.g. check for findings early on in studies that might be relevant to establishing an ARfD). 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”.

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 contaminant, its origins and its occurrence.

- If the Committee has evaluated the contaminant previously, the number of the meeting at which the previous evaluation was performed should be indicated (e.g. “The Committee previously evaluated contaminant X at the seventy-seventh meeting”) and 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 contaminant 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 contaminant, the reason for it being placed on the agenda should be given. For example, “[Contaminant X] has not previously been
evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The Committee evaluated [contaminant X] at the present meeting at the request of the [Xth] Session of the Codex Committee on Contaminants in Foods (FAO/WHO, 20xx)."

- The final paragraph of the Explanation describes the available data considered, including the literature search performed: the databases searched, the search terms used and the number of relevant publications retrieved.
- During the meeting, the FAO expert(s) assigned to the contaminant should be given an opportunity to contribute to or modify the Explanation section during the preparation of the (first) draft of the meeting report item (see Chapter 3).

### 2.3.2 Biological data

#### 2. Biological data

- This section contains summarized descriptions of studies that are of importance in the safety evaluation or risk assessment of the contaminant. Studies that elucidate the mode of action, provide the basis for the safety evaluation or are used to estimate toxic or carcinogenic potency in humans 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 four headings: Biochemical aspects, Toxicological studies, Observations in domestic animals/veterinary toxicology 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”.
- 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

- These studies include those designed to identify the pathways of metabolism in experimental animals and humans and to measure the toxicokinetics of the contaminant and its metabolites – i.e. the concentration–time profiles of the contaminant and its metabolites in the various tissues and organs of the body. They also include studies of the effects on enzymes and other biochemical parameters designed to elucidate the mode of action and toxicodynamics of the contaminant as well as the results of any physiologically based pharmacokinetic (PBPK) modelling carried out on the contaminant of interest. Finally, this section can include toxicokinetic studies on food-producing animals, specifically to determine the carry-over or transfer of contaminants in feed into foods for human consumption, such as milk, eggs and meat.
- Comparison of the 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, including studies on biomarkers of exposure, 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 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 any radiolabel used, test species, sex and number of animals, dose levels used (in terms of both the drug \([\text{mg/kg bw}]\) and radioactivity \([\text{MBq/kg bw}]\), as appropriate) and route of exposure should be provided.

- Information in this section includes:
  - 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);
  - rate and extent of absorption of the unchanged compound and its hydrolysis products/intestinal metabolites, with time to maximum concentration \((T_{\text{max}})\) and the concentration achieved \((C_{\text{max}})\);
  - bioavailability of the parent compound;
  - pattern and rate of distribution of absorbed substances to tissues and organs within the animal;
  - 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);
  - 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.

- 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.

- A biotransformation or metabolic scheme showing the main metabolic reactions should be included wherever possible, along with an identification of the species to which it applies.

2.1.3 Effects on enzymes and other biochemical parameters

- This section describes the effects of the absorbed contaminant and/or its metabolites on cellular and tissue enzyme expression, regulation (induction/repression) and post-transcription processing; effects on hormonal regulation and interactions with cellular receptors; and effects on membrane/cytosolic biochemical composition or physicochemical state.

- If there is no relevant information to be included in this section, the heading can be deleted.
2.1.4 Physiologically based pharmacokinetic (PBPK) modelling

- This section describes any PBPK modelling that has been carried out on the contaminant of interest. This information can be useful in predicting absorption, distribution, metabolism and excretion of contaminants, in determining internal concentrations of contaminants and their target sites, and in extrapolating from high doses to doses relevant to human exposure, from one exposure duration to another, from one route of administration to another, from experimental animal studies to humans and from one human subpopulation to another.
- If there is no relevant information to be included in this section, the heading can be deleted.

2.1.5 Transfer from feed to food

- This section is prepared by FAO.
- This section describes the results of studies designed to determine the carry-over or transfer of contaminants in feed for food-producing animals into foods for human consumption, such as milk, eggs and meat.
- Information on the absorption, distribution, metabolism and excretion of contaminants in food-producing animals such as cows, goats, horses and poultry can be included where relevant to human dietary exposure.

2.2 Toxicological studies

- This section contains summarized descriptions of toxicological studies that are important for assessing the safety of the contaminant. These summaries generally comprise the bulk of the monograph.
- Information from five main categories of studies on contaminants 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.
- With respect to the ARfD, it is important to consider data at the earliest measurement period in a study and the results of short-term or acute toxicity studies if appropriate measurements have been performed. It is also important to confirm that the level of investigation in targeted studies, such as the acute neurotoxicity study, is adequate to address the end-points seen in longer-term studies. For example, if the critical finding in a 90-day rat study is haemolysis, but blood samples were not taken in the acute neurotoxicity study, then the acute neurotoxicity study might not be an appropriate basis for establishing an ARfD.
- 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. 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 available. If there is no GLP certification, as is usually the case for studies on contaminants, the monographer needs to evaluate and comment on the apparent quality of the protocol, including reporting and statistical analysis, 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, and the nature of any potentially toxicologically important impurities or co-contaminants where naturally contaminated material is administered;
  - 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 satellite groups are given separately);
  - if the study is a range-finding study with limited investigations or a specific study for mode of action, 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) should 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 diet 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 dose 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 being adverse or relevant to a human risk assessment;
  - any in-life findings early in the study that might be relevant to establishing an 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;
For risk assessment of chemicals in food, studies in which the test substance is administered orally are the most useful. However, in the case of contaminants, many of the available data may be from routes other than the oral route; for resource and animal welfare reasons, it is important to utilize such data where possible. Toxicokinetic data can be used to correct for route-dependent differences in systemic exposure in cases where the available data were taken from non-oral exposure studies.

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:

### 2.2.2 Short-term studies of toxicity

#### (a) Rats

In a comprehensive 90-day study, Sprague-Dawley rats (20 or 30 of each sex per group) were given ammonium perchlorate in the drinking-water at a dose of 0, 0.01, 0.05, 0.2, 1.0 or 10.0 mg/kg bw per day. The animals were approximately 7 weeks of age at the start of treatment. Animals in each group were killed after either 14 or 90 days of treatment; in the 0.05, 1.0 and 10.0 mg/kg bw per day groups, some were killed after a recovery period of 30 days. Analytical chemistry confirmed the absence of nitrate in the drinking-water, the stability of the perchlorate in drinking-water and that the concentrations were within ±10% of the target concentrations. Ten rats of each sex per group were sacrificed at each time point. Body weights, feed consumption and water consumption were measured weekly. Estrous cycles were examined in females by daily vaginal smears taken during the 3 weeks before scheduled sacrifice. Sperm samples were taken from males at termination for measurement of sperm count, motility and morphology. Ophthalmology was conducted just prior to termination. Blood samples were taken at sacrifice for haematology and clinical chemistry, thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4). All animals were subjected to gross necropsy, and a complete set of tissues and organs was preserved for histological examination. In the control and highest-dose groups, all tissues and organs were examined microscopically, including bone marrow samples for micronucleus formation. Liver, kidneys, lungs, thyroid and gross lesions were examined microscopically in the other four dose groups.

There were no effects of treatment on body weight, feed consumption, water consumption, survival, clinical observations, haematology, clinical chemistry, ophthalmology, estrous cycles, sperm parameters or bone marrow micronucleus formation. There were no gross or histopathological changes in any tissues or organs, apart from the thyroid. Absolute and relative thyroid weights were significantly increased in the 10.0 mg/kg bw per day group after 14 or 90 days of treatment in males and after 90 days in females, but did not differ from control values in either sex after the 30-day recovery period. Both sexes in the top-dose group also showed minimal- to mild-grade increases in thyroid follicular cell hypertrophy, microfollicle formation and colloid depletion at both time points, but the changes reached moderate grade in the males only after 14 days of treatment, and there were no differences from controls after the 30-day recovery period. The authors noted that the histopathological changes observed in the thyroid were similar to those reported by others in rats following the feeding of iodine-deficient diets or inhibition of iodine
organification. There were no effects on thyroid weights or histology in any other treatment group. After 14 days of treatment, dose-related increases in TSH concentrations were observed at all dose levels in both males and females; the increases were statistically significant in males from 0.2 mg/kg bw per day and in females from 0.05 mg/kg bw per day. T4 was significantly reduced in males and females at the top dose of 10.0 mg/kg bw per day, and T3 was significantly reduced at all doses in males but not at any dose in females. After 90 days of treatment, TSH was significantly increased from 0.2 mg/kg bw per day in males, but only at 10.0 mg/kg bw per day in females. T3 and T4 were significantly decreased in a dose-related manner at all doses in both sexes. At the end of the 30-day recovery period, at the doses examined (0, 0.5, 1.0 and 10.0 mg/kg bw per day), TSH and T3 were unaffected in males, whereas T4 was significantly reduced at all doses; in the females, TSH was significantly increased at all doses, T4 was reduced, but only at 10.0 mg/kg bw per day, and T3 was unaffected.

The authors concluded that 1.0 mg/kg bw per day represented the overall no-observed-adverse-effect level (NOAEL) for the study; they considered that the effects on TSH and thyroid hormones seen at lower doses were not adverse effects, as they were unaccompanied by any changes in thyroid weight or histology, and the changes seen at 10.0 mg/kg bw per day were reversible (Siglin et al., 2000).

2.2.1 Acute toxicity

- Acute toxicity studies can provide useful information regarding target tissues and species and sex differences.
- For acutely toxic contaminants, acute toxicity data may form the basis of an ARfD or be used to inform relative potencies of a related group of contaminants.
- The results of acute toxicity studies that are expressed in terms of the median lethal dose (LD<sub>50</sub>) should be presented in tabular form, as shown in Annex 2.
- When three or more LD<sub>50</sub> determinations by the oral 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.
- Any other single-dose studies with end-points other than mortality should be described in this section. An example would be studies in which a single dose of nickel (e.g. in drinking-water) administered to nickel-sensitized individuals resulted in an eczematous reaction.

2.2.2 Short-term studies of toxicity

- Toxicological studies in which contaminants 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.

• In some cases, toxicological studies are reported on, for example, fungal biomass or naturally contaminated feed with determined levels of specified contaminant(s). Such studies should be reported separately as special studies (e.g. special studies on fungal biomass or special studies on contaminated corn), as they may be associated with intake of contaminants other than those specified, or other factors, and may not reliably be used for examining dose–response relationships or relative potency evaluations.

• 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 $\alpha_2u$-microglobulin) should be indicated.

• Any early findings of possible relevance to an ARfD, even if at doses above the LOAEL, should be identified, together with the time and the lowest dose at which they were seen. When effects are observed after a few days of dosing, but this was the first time of observation, this should be clearly stated.

2.2.3 Long-term studies of toxicity and carcinogenicity

• Toxicological studies in which contaminants 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 of 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.

• 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), information on the interim kill (e.g. schedule and findings) 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 compound-related increases in 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 contaminant.
- 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 carcinogenicity 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

(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 milligrams per kilogram diet concentrations, the achieved intakes vary greatly with reproductive stage. Achieved intakes are normally determined for various stages of the study (e.g. premating, 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 whether this is related to litter size and whether there are effects on total litter weight.
- If pup mortality is increased in treated groups, it should be determined whether 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 whether 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 determine 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 whether 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 to the safety evaluation of the contaminant, 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 acute and subchronic neurotoxicity studies, studies on effects on organ function (e.g. thyroid toxicity) and studies on effects on particular systems (e.g. the immune system). Special studies on fungal biomass or naturally contaminated feed components should be included in this section. 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 domestic animals/veterinary toxicology

• Observations made in veterinary practice, such as veterinary case-studies of mycotoxicoses, clinical practice or retrospective epidemiological studies of disease of domestic animals attributed to intoxication, may provide useful ancillary information in relation to qualitative interspecies differences in toxic effects and potency.

• Because of the uncontrolled nature of exposure of such studies – the circumstances of exposure are less well defined than in toxicological studies, and the studies may involve exposure to multiple contaminants – they would not usually provide quantitative data suitable for identifying a NOAEL or for a quantitative risk assessment. Such studies should therefore be summarized separately.
• The summary should indicate the species, sex and number of animals involved, the circumstances and duration of consumption of the contaminated feed, and the estimated dose or dietary concentration of the contaminant, where available. Brief details of the observed effects and other details important to the evaluation should also be provided. Similar cases may be summarized as a group.

2.4 Observations in humans

• Observations in humans are the most important information for contaminants and can be particularly useful for defining a POD for the risk assessment, for assessing the relevance of the results of studies in experimental animals and for confirming tolerable intakes or ARIDs or for evaluation of risk.

• All studies dealing with humans (except for those summarized under *Biochemical aspects*) should be included in this section, including studies on biomarkers of exposure, biomarkers of effects, epidemiological surveys, clinical experience, anecdotal observations, health effect studies relating to occupational or accidental exposure, and volunteer studies.

• Epidemiological studies have been of greatest value to JECFA in relation to hazard identification and characterization of food contaminants. Summaries of epidemiological studies are intended to provide an overview of studies relevant to establishing the nature of the effect(s) that may be associated with exposure to the contaminant and the toxic or carcinogenic potency in humans. Studies that are able to provide quantitative relationships between exposure and incidence or severity of effects should be described in greatest detail. The summary should contain the following elements:
  o the nature, purpose or objective of the study;
  o the location, number, sex and age of the population(s) studied;
  o the circumstances of human exposure (e.g. occupational, dietary, acute, sustained or episodic);
  o the magnitude of estimated exposure (expressed on a body weight basis where possible);
  o whether the estimated exposure is supported by biomarkers of exposure;
  o duration of exposure and of observation/health records;
  o parameters examined;
  o possible confounders;
  o effects observed (incidence and severity);
  o study authors’ conclusions and conclusions of the monographer if different from those of the study authors;
  o reference.

• JECFA will use human data in establishing health-based guidance values only if the study is scientifically valid and performed ethically, according to the principles of the Declaration of Helsinki.

3. Analytical methods

• This section is prepared by FAO experts.

• Analytical methods for reliable screening tests and quantitative determinations in the appropriate matrix or matrices, with appropriate performance characteristics, should be described in this section. Conclusions should be provided concerning the limit of detection (LOD) and limit of quantification (LOQ) in relation to any specific requests that may have been made by CCCF.

4. Sampling protocols

• This section is prepared by FAO experts.
• Assessments of various sampling protocols and their influence on the analytical results should be provided in this section.

5. Effects of processing

• This section is prepared by FAO experts.

• Typical ways in which contaminated commodities are processed and information relating to the effects of processing on the level of the contaminant in the product that is consumed (reduction or concentration) should be provided. If the contaminant is degraded during processing, the products of degradation that may be present in food should be described.

6. Prevention and control

• This section is prepared by FAO experts.

• Preharvest and postharvest procedures for preventing or minimizing contamination of food, including good agricultural practices and good manufacturing practices, should be presented in this section. If effective procedures for decontaminating food and/or feed are available, they should be described and evaluated.

7. Levels and patterns of contamination in food [and feed] commodities

• This section is prepared by FAO experts. For more detailed information, the reader should refer to the guidance on data reporting for hazards occurring in food (WHO, 2010).

• Concentrations of the contaminant in various food (or feed) commodities, as provided by countries that submitted national occurrence data or from the GEMS/Food occurrence database, are tabulated in this section. Surveillance data include the commodity (food or feed, where appropriate), year and/or season during which the commodity was studied, the method of sampling, the number of samples, the LOQ and the number of samples that exceeded the LOQ, the mean, maximum and 90th percentile levels, the number of samples that exceeded any hypothetical standards (maximum levels [MLs]) that have been proposed by CCCF and the reference. Distribution curves and data on annual variation in contamination levels should be provided in the monograph.

• Occurrence data may also be obtained from total diet studies, which consist of aggregated samples analysed as consumed. In that case, the number of individual samples combined to obtain the pooled sample should be reported in addition to the other variables listed above.

• Levels and patterns of contamination in feed commodities will normally be included in this section, unless the amount of information is so large that a separate section is needed, in which case it would be inserted below as section 8 (and all subsequent sections would be renumbered).

8. Food consumption and dietary exposure estimates

• This section is prepared by WHO and FAO exposure experts.
Dietary exposure estimates for contaminants are an integral part of the risk assessment and safety evaluation process. Such estimates are based on surveillance data (which are assessed in view of analytical methods used in collecting the data and their performance characteristics, sampling protocols and effects of processing) and on available information on food consumption. Information on biomarkers of exposure (e.g., levels in body fluids) may also be useful for assessing exposure.

This guidance document provides an abbreviated overview of the procedures used for estimating dietary exposure to contaminants. For more information, the reader should refer to Chapter 6 of EHC 240 (IPCS, 2009a).

When the contaminant causes acute toxicological effects, an acute dietary exposure assessment should be conducted.

Information on significant non-dietary exposure to the contaminant should be summarized and quantified to the extent possible.

International data as well as national data submitted by Member States on food consumption and chemical occurrence are available from the Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) (http://www.who.int/foodsafety/areas_work/chemical-risks/gems-food/en/).

8.1 Concentrations in food used in the dietary exposure estimates

Describes which occurrence data from Chapter 7 (of national origin or GEMS/Food origin) will be used in the dietary exposure estimates and why these data were selected.

8.2 Food consumption data used in the dietary exposure estimates

Describes which food consumption data (of national origin or from the GEMS/Food consumption cluster diets) will be used in the dietary exposure estimates and why these data were selected.

8.3 Assessments of dietary exposure

8.3.1 National estimates

National assessments of dietary exposure are usually submitted by national authorities and are based on the occurrence of the contaminant in food and estimates of food consumption in the corresponding country. Such data should permit estimation of both mean and “high consumer” dietary exposures. The assessments of dietary exposure should be tabulated to allow a comparison between various national estimates, including the country or region, population groups studied with their estimated levels of exposure to the contaminant, and assumptions (such as the definition of “high consumer”) used. The type of food consumption survey used should be specified either in the text or in the table.

8.3.2 International estimates

International assessments of dietary exposure are performed by the JECFA experts in order to obtain a global perspective and to permit regional comparisons of the potential dietary exposure to the contaminant. Analyses should be performed using the 17 GEMS/Food consumption cluster diets (for more information, the reader should refer to the WHO website) and various assumptions about the concentrations of the contaminant in relevant foods. For

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5 Formerly referred to as “dietary intake”. Reference is made to dietary exposure to a contaminant, rather than intake of a contaminant.
8.4 Potential effect of limits and their enforcement on chronic dietary exposure

- Using the above data, the effects of alternative concentrations of a contaminant in food on chronic dietary exposure to the contaminant can be simulated. Assumed concentrations in food may, for example, be MLs proposed by CCCF, “typical” concentrations of the contaminant in selected foods or realistic “maximum” concentrations in selected foods. Chronic dietary exposure estimates calculated for these alternative scenarios can then be compared with tolerable daily, weekly or monthly intakes for risk assessment purposes.

- Such estimates were performed for fumonisins at the seventy-fourth meeting of JECFA (“Impact assessment of implementation of Codex MLs in maize”), and the monograph may be consulted for examples of the presentation of such data (WHO, 2012).

9. Dose–response analysis and estimation of toxic/carcinogenic risk

- This section, in which the risk is characterized, includes narrative relating to the relevance and significance of the data that were summarized and the experimental/epidemiological basis for the conclusions reached by the monographer.

- When it is concluded that the effect occurs via a mechanism with an apparent threshold, such that a tolerable daily, weekly or monthly intake will be proposed (see section 2.3.4), relevant NOAELs/BMDLs and the basis for them should be included.

- When it is concluded that an apparent non-threshold mechanism of toxicity/carcinogenicity is operative, the relevant potency estimates should be included in this section. Under these conditions, the conclusions of the experimental and epidemiological studies should be outlined and the most significant information provided relating to the identification and characterization of the toxic/carcinogenic hazard, the most relevant experimental species and target tissues, the mode of action, evidence of human toxicity/carcinogenicity and relative potency, and estimates of human exposure.

- A quantitative risk assessment of a contaminant involves consideration of (a) choice of data, (b) measure of exposure, (c) measure of response and (d) choice of mathematical model. These considerations are addressed in this section, and the basis for the selection of data (e.g. only positive epidemiological data versus all epidemiological data; whether exposure estimates used in risk assessment are based on dietary exposure or biomarkers of exposure) should be provided.

- When estimating potency, interspecies differences and the experimental bases for the estimates should be indicated. The section on potencies should list the estimated toxic or carcinogenic potencies in experimental species, and estimates of potency in humans derived from epidemiological data should be included separately. The range of estimates with estimates of central tendency and upper and lower bounds for each species should be indicated graphically if possible, with accompanying narrative as necessary.

- The section on population risks should contain an estimate of the dietary exposure and associated risk (derived where possible from human potency) in various scenarios covering the levels of contamination and dietary patterns in different regions.

- When addressing published estimates of potency and risk assessments, the mathematical models used by the authors of the studies should be made explicit.
2.3.3 Comments

3. 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 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 Biochemical aspects, Toxicological studies, Observations in domestic animals/veterinary toxicology, Observations in humans, Analytical methods, Sampling protocols, Effects of processing, Prevention and control, Levels and patterns of contamination in food [and feed] commodities, Food consumption and dietary exposure estimates and Dose–response analysis and estimation of toxic/carcinogenic risk.

- The first paragraph should contain a general statement as to whether the Committee considered the overall data package sufficient to derive a robust tolerable intake or to perform a quantitative risk assessment or MOE estimation.

- 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.

- A summary table containing all critical studies and their NOAELs/LOAELs should be included.

- Strains of animal species are not given in the Comments section, unless the effect is strain specific.

- The Comments section will comprise the bulk of the meeting report item.

- The Comments section should be fully referenced. The editor will delete all references for the meeting report, except for those for the critical study or studies (see Chapter 3), but all references will be retained for the monograph. The references for the critical studies should be highlighted by the monographer.

- Annex 3 contains a template for the report item (including the summary table), and Annex 4 includes a sample 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 2.3.4).

2.3.4 Evaluation

4. Evaluation

- The form of this section will depend on whether a health-based guidance value (tolerable daily, weekly or monthly intake) is derived, whether a NOAEL/BMDL for carcinogenicity with a genotoxic mode of action is identified or whether a quantitative risk assessment is performed.

- A health-based guidance value may be derived from the NOAEL/BMDL for the most significant toxicological end-point (which may include carcinogenicity by a non-genotoxic mode of action or a non-carcinogenic end-point) from the pivotal study in the most sensitive species by application of an uncertainty factor. The tolerable daily, weekly or monthly intake (provisional maximum tolerable daily intake [PMTDI], provisional tolerable weekly intake [PTWI] or provisional tolerable monthly intake [PTMI])\(^7\) is expressed in terms of the units milligrams per kilogram body weight (mg/kg bw). Unlike acceptable daily intakes (ADIs), tolerable intakes are expressed as a maximum value, not as a range. Guidance on the selection of uncertainty factors is available in EHC 240 (IPCS, 2009a). When sufficient data

\(^7\) The decision as to which health-based guidance value is the most appropriate depends on the half-life of the contaminant in the body. For example, for cadmium, renal dysfunction was identified as the most sensitive toxicological end-point. Because cadmium has a long half-life of 15 years in human kidneys, the Committee decided that a PTMI was the most appropriate health-based guidance value.
are available, JECFA may apply the concept of chemical-specific adjustment factors (CSAFs) when deriving tolerable intakes for contaminants (IPCS, 2005). The tolerable intake is compared with average and high dietary exposures for the general population and any sensitive population subgroups (e.g., children, women of childbearing age), and a conclusion is made as to whether these estimated dietary exposures are of health concern (see section 4.8).

- For compounds that are both genotoxic and carcinogenic, it is not appropriate to derive a health-based guidance value. For these compounds, the NOAEL/BMDL for the induction of tumours is compared with the average and high dietary exposures using the MOE approach, and a conclusion is reached as to whether the resulting MOEs indicate a human health concern (see section 4.8).

- For contaminants with effects observed after a single dose or following exposure for a period of 24 hours or less, an ARfD is derived (see section 4.7) and compared with estimates of acute dietary exposure for average and high consumers in the general population and any sensitive subgroups. The ARfD, if established, is expressed as a single number (x mg/kg bw).

- In some cases, the derivation of a group tolerable intake or group ARfD may be appropriate (see section 4.5).

- When the evaluation takes the form of a quantitative risk assessment, risk is predicted at specified exposure levels. This output can be a prediction, for example, of an excess number of cases of cancer at exposure Y or a decrease of 1 intelligence quotient (IQ) point at exposure Z.

- The effects of applying hypothetical maximum contaminant levels to major contributors to dietary exposure on the percentage rejection rate and residual risk should be estimated to provide guidance to risk managers on the consequences of alternative strategies.

- If CCCF provided very detailed questions to JECFA, these should be addressed in detail.

### 4.1 Recommendations
- JECFA, as part of its evaluation of specific contaminants, often makes requests for additional data, recommendations for subsequent re-evaluation or suggestions for research needed to resolve any outstanding safety issues or to render risk estimates more precise.

### 2.3.5 References

### 5. References
- References should be presented at the end of the monograph 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:**


Agency report


Conference proceedings


Reference in a foreign language (other than French)


Thesis


Secondary reference


Example:


Reference found online

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

Example:

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 contaminant monograph, resolving any contentious issues raised by the lead monographer and reaching agreement on the general approach to be taken in evaluating the contaminant. Once agreement has been reached on a way forward, the monographer, with input from the rest of the evaluation team, 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 lead WHO monographer should request input from his or her FAO counterparts for the contaminant of interest on the **Explanation** section, particularly on aspects concerning its identity and chemistry.

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

- References are cited for all studies in the report item. The editor will retain only the references for the key studies cited in the text or tables and change them to italicized numbers (e.g. (1)) for the meeting report. This facilitates the use of the meeting report item for the final monograph, in which the **Comments** section is fully referenced. The lead monographer should highlight the references for the critical studies in the report item. In the rare event that no monograph or monograph addendum is being prepared, all references in the meeting report item will be retained for the final meeting report.

- Details of the editing process to be followed during the meeting will be explained early in the process.

- After each draft of the report item has been approved by the WHO group and any comments or revisions have been incorporated by the lead monographer and confirmed by the reviewer(s), the WHO rapporteur checks the revisions and, when satisfied, prints the revised draft, usually showing all tracked changes, for the next review by the WHO group.

- When the WHO group is completely satisfied with the report item (referred to as “going to final”), the draft is passed to the editor. The editor edits the draft report item and sends it back to the lead monographer to check all changes made and to answer any questions raised during the editing process.

- Once the editing process has been completed, 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 lead 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. An electronic version of the final monograph needs to be provided to the editor and the WHO Joint Secretary (by uploading the file to the meeting computer in the “Final monographs” folder) before the lead monographer leaves the meeting on the final day.
The EHC monograph entitled *Principles and methods for the risk assessment of chemicals in food* (EHC 240 [IPCS, 2009a]) 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 contaminants.

This chapter includes general considerations relevant to contaminants 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 risk assessments on contaminants.

### 4.1 Dietary exposure estimates in epidemiological studies

The Committee at its seventy-second meeting (FAO/WHO, 2011a) noted that epidemiological studies sometimes rely on responses to a food frequency questionnaire (FFQ) to estimate dietary exposure to a chemical contaminant. An important limitation in the use of FFQ responses for this purpose is the potential for random exposure misclassification (also referred to as non-differential exposure misclassification). This is a non-systematic error, in that dietary exposure to the contaminant will be overestimated for some individuals and underestimated for others, but the direction and magnitude of the error are unrelated to true dietary exposure to the contaminant. Several factors contribute to this error:

- An FFQ designed to assess consumption patterns or to estimate nutrient intake might not be well suited to estimate dietary exposure to a contaminant because of the ways in which foods are grouped into categories or if the FFQ was not designed to capture information about aspects of food preparation that can affect contaminant concentration.
- An FFQ provides data only on the frequency with which a respondent consumes a particular food during a specified interval. If no information on portion size is requested from the respondent, the frequency of consumption needs to be converted to an amount of food consumed by use of standard portion sizes.
- The concentration of a contaminant in samples of a particular food is defined by a distribution rather than by a single value. The larger the variance of this distribution, the greater the error in estimating dietary exposure to a contaminant if a single (e.g. average) concentration is assigned to each food consumed.

Under most circumstances, random exposure misclassification will decrease the statistical power of hypothesis testing and bias effect estimates, such as a relative risk or an odds ratio, towards the null value (i.e. indicating the absence of association). In other words, even if a true association exists between exposure to the contaminant and the risk of an adverse health outcome, the magnitude of the association derived using FFQ responses will tend to underestimate the true magnitude of the association and to estimate it with less precision (i.e. produce a wider confidence interval). This will increase the risk of a Type II error of inference (i.e. a false negative).

As long as mean dietary exposures are estimated correctly (i.e. the errors are not skewed in either direction), exposure misclassification will not greatly influence the dose–response relationship. However, because values in the lowest exposure category (and sometimes also in the highest exposure category) are bounded only in one direction, the most common impact of exposure misclassification is that the dose–response relationship will appear to be flatter than it really is, particularly at the low end of exposure. Background response rates and outcomes for low-dose groups will tend to be overestimated, whereas rates at high doses may be underestimated. If the degree to which exposure misclassification occurs is known, it is possible to represent the potential impact of misclassification on dose–response modelling by conducting a bootstrap analysis in which each individual dose is treated as a source of uncertainty.

When evaluating the results of studies in which FFQ responses provided the basis for estimates of dietary exposure to a contaminant, the extent to which random exposure misclassification might have influenced the conclusions drawn must be considered.
4.2 Commentary on the use of NOEL/NOAEL and LOEL/LOAEL

The sixty-eighth meeting of the Committee (FAO/WHO, 2007b) 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 will be used. This includes assessments where no effects were observed at the highest dose tested. In such cases, the highest dose tested will be taken as the NOEL.

The same approach will be used by the Committee with respect to the terms LOEL and LOAEL. When effects are observed at all doses, the lowest dose will be identified as the LOEL if the effects at the lowest dose are not considered adverse or as the LOAEL if the effects at the lowest dose are considered adverse.

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

4.3 Overall NOAEL

When evaluating experimental animal studies, JECFA generally identifies the lowest NOAEL in the most sensitive species, usually among mice, rats and dogs; 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 and that due consideration is given to the shape of the dose–response curve.

4.4 Modelling of dose–response data

Dose–response modelling is used to define a POD and can be applied in the establishment of tolerable intake values, for quantitative risk assessment or for MOE estimations.

Dose–response modelling can be done on experimental animal data as well as human data, depending on what is identified as the critical studies and provided data are available for dose–response modelling. Detailed descriptions of dose–response assessment, as the core of risk characterization, are given in Chapter 5 of EHC 240 (IPCS, 2009a). A more detailed guidance on dose–response analysis in general can be found in EHC 239 (IPCS, 2009b).

The seventy-second meeting of the Committee (FAO/WHO, 2011a) used dose–response modelling to evaluate exposure-related effects and to derive a POD for the estimation of an MOE or health-based guidance value. The method used was based on that employed at the sixty-fourth meeting of the Committee (FAO/WHO, 2006). At the seventy-second meeting, the Committee proposed and applied the following steps:

- The data are assessed for exposure-related responses.
- The biological relevance to human health of responses found in animal studies is assessed.
- In assessment of the data from epidemiological studies, it may be necessary to make adjustments to the data that involve both the dose (e.g. to take other sources of exposure into account) and the outcome (e.g. conversion of risk per person-year to risk per person over a lifetime).
- A benchmark response (BMR) for the effects to be modelled is selected. The sixty-fourth meeting of the Committee selected a BMR of 10% for carcinogenicity data from 2-year studies in rodents, but other BMRs may be more appropriate for epidemiological studies with large numbers of subjects, for other quantal end-points or for continuous data.
The mathematical models appropriate for the chosen end-points (continuous or quantal data) are selected. The models are fitted to the selected data using suitable software (the United States Environmental Protection Agency’s [USEPA] Benchmark Dose Software [BMDS] and the National Institute for Public Health and the Environment of the Netherlands’ [RIVM] PROAST have been used by the Committee in its evaluations). Results from the models that provide acceptable fits are used for derivation of the POD (e.g. when the BMDS was used for furan, a P-value of >0.1 for the goodness of fit was used to define an acceptable fit). At both the sixty-fourth and the seventy-second meetings, the lowest lower 95% confidence limit on the benchmark dose (BMDL) from the accepted models was used, except when data from a more robust or better designed study measuring the same response resulted in less uncertainty and a slightly higher BMDL.

At the seventy-fourth meeting of the Committee (FAO/WHO, 2011b), further consideration was given to the use of P-values as an exclusion criterion for the selection of BMDL values. The Committee concluded that the P-value can be used to compare models and to exclude models based on how well they fit relative to each other, rather than using a fixed cut-off value. With this approach, the exclusion criterion is relative rather than absolute, and therefore the role of the data set in determining model exclusion is minimized. The BMD analyses conducted for the evaluation of fumonisins at that meeting, in which models with P-values differing by 3-fold or more relative to the highest P-value were excluded, provide an example of the use of P-values as a relative exclusion criterion.

In the report, the BMR(s) and software used are stated, and the effects selected for modelling and the ranges of benchmark doses (BMDs) and BMDLs estimated by the different acceptable fits are tabulated.

In the monograph, the output of the models should be given in tabular and graphical forms. The table of results should show the model, the P-value of the goodness-of-fit test, the BMD and the BMDL. Ideally, the graph should show results for the model resulting in the lowest BMDL, the dose–response data with the fitted curve and the confidence intervals at different dose levels and should indicate the position of the BMD; the graph should also show the curve for the lower bound on the BMD and indicate the position of the BMDL (illustrative examples using BMDS are shown below).

The Committee recognized that use of the lowest BMDL from the accepted models could result in a POD from a model with a less robust fit being used in preference to the BMDL from a model that showed a better fit and higher BMDL in the presence of a comparable BMD. Any selection as POD needs to be clearly explained and documented.

As the use of dose–response modelling is a developing field, this section will be updated more regularly taking new developments and JECFA decisions into account.

**Example of data tabulation for the monograph**

The example chosen for illustrative purposes (Table 2) is the modelling output for hepatocellular adenoma and carcinoma for female mice treated with furan.

### Table 2
Example of modelling output for hepatocellular adenoma and carcinoma for female mice treated with furan

<table>
<thead>
<tr>
<th></th>
<th>Gamma</th>
<th>Logistic</th>
<th>Log-logistic</th>
<th>Log-probit</th>
<th>Multi-stage</th>
<th>Multistage-cancer</th>
<th>Probit</th>
<th>Weibull</th>
<th>Quantal-linear</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIC</strong></td>
<td>235.3</td>
<td>233.9</td>
<td>235.3</td>
<td>235.2</td>
<td>235.5</td>
<td>233.6</td>
<td>234.2</td>
<td>235.5</td>
<td>241.6</td>
</tr>
<tr>
<td><strong>Chi-square</strong></td>
<td>0.36</td>
<td>0.88</td>
<td>0.33</td>
<td>0.27</td>
<td>0.53</td>
<td>0.66</td>
<td>1.17</td>
<td>0.50</td>
<td>8.01</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.95</td>
<td>0.93</td>
<td>0.96</td>
<td>0.97</td>
<td>0.91</td>
<td>0.96</td>
<td>0.88</td>
<td>0.92</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td>2.76</td>
<td>2.03</td>
<td>2.78</td>
<td>2.86</td>
<td>2.66</td>
<td>2.34</td>
<td>1.87</td>
<td>2.62</td>
<td>0.96</td>
</tr>
</tbody>
</table>
The models were fitted using the BMDS program and a BMR of 10%; the values are in the units of milligrams per kilogram of body weight per day. The multistage model gave the lowest BMDL of the models with acceptable fits and is used for graphical presentation, as shown in Fig. 1.

Fig. 1
BMD and BMDL from the multistage model (example for quantal data)

The lower line is the fit of the model to the experimental data. The vertical bars are the confidence intervals around the experimental data. The upper line is the upper bound for the response from which the lower confidence bound of the BMD (BMDL) can be defined.

4.5 Tolerable intakes for contaminants

For food contaminants that are generally unavoidable, JECFA has used the term “tolerable” for health-based guidance values, as it signifies permissibility for the intake of (or dietary exposure to) contaminants associated with the consumption of otherwise wholesome and nutritious food. Unlike the acceptable daily intake (ADI), which is expressed as a range from 0 to an upper bound, tolerable intakes are given as a single value only. Principles in deriving tolerable intake levels are the same as for ADIs: either the NOAEL or BMDL can be used as the POD to set health-based guidance values for contaminants. Guidance values may be expressed as a provisional maximum tolerable daily intake (PMTDI), provisional tolerable weekly intake (PTWI) or provisional tolerable monthly intake (PTMI). The tolerable intake is generally referred to as “provisional” as there is often a paucity of data on the consequences of human exposure at low levels, and new data may result in a change to the tolerable level.

PMTDIs are established for food contaminants that are known not to accumulate in the body. The value assigned to a PMTDI represents permissible human exposure as a result of the background occurrence of the contaminant in food and also in drinking-water.
For contaminants that may accumulate within the body over a period of time, JECFA has used the PTWI and PTMI. On any particular day, consumption of food containing above-average levels of the contaminant may exceed the proportionate share of its weekly or monthly tolerable intake. JECFA's assessment takes into account such daily variations, its real concern being prolonged exposure to the contaminant, because of its ability to accumulate within the body over a period of time.

JECFA has also used group tolerable intakes for closely related contaminants that occur as mixtures. An approach that takes account of dose additivity is the toxic equivalency factor (TEF) approach, which scales the exposure for each component of a mixture relative to the potency of an index chemical (e.g. for dioxins and dioxin-like chemicals).

4.6 Expression of the tolerable intake and rounding procedures

The tolerable intake is derived from the POD (e.g. NOAEL, BMDL10) from the appropriate toxicological studies, using an uncertainty factor. Given that there are assumptions and uncertainties in deriving the tolerable intake, 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 tolerable intake to only one significant figure to avoid any inference of inappropriate precision. If a tolerable intake is calculated from a POD that has more than one significant figure, the tolerable intake would therefore be rounded to one significant figure, consistent with accepted rounding procedures.

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.

JECFA has confirmed that the rounding practices used in expressing the tolerable intake are scientifically and mathematically sound.

4.7 Guidance on establishing acute reference doses

The ARfD of a chemical is an estimate of the amount of the substance in food and/or drinking-water, normally expressed on a body weight basis, that can be ingested in a period of 24 hours or less, without appreciable risk to the health of the consumer, on the basis of all the known facts at the time of the evaluation.

JECFA has established ARfDs for a number of contaminants. For example, JECFA derived an ARfD for cyanogenic glycosides, expressed as cyanide equivalents, based on increased skeletal defects in developing hamster fetuses following acute exposure of maternal animals, at the seventy-fourth meeting (FAO/WHO, 2011b). JECFA has also established group ARfDs where appropriate, such as for deoxynivalenol and its acetylated derivatives, based on emesis in pigs, at the seventh-second meeting (FAO/WHO, 2011a).

Specific detailed guidance on the derivation of ARfDs for pesticides can be found in FAO/WHO (2004), Solecki et al. (2005), OECD (2010) and WHO (2015); these publications serve as guidance for the derivation of ARfDs for contaminants as well.

4.8 Use of the margin of exposure approach

The MOE is derived by taking the ratio of the POD for the most relevant, sensitive end-point to estimates of exposure for high and average consumers. For contaminants, JECFA will generally report an MOE in two situations: (1) when the nature of the end-point is such that derivation of a health-based guidance value is not appropriate and (2) when there are deficiencies in the database such that it is not possible to derive a health-based guidance value with confidence.

The most common example of the first situation is for compounds that JECFA considers to be both genotoxic and carcinogenic, for which JECFA typically considers it inappropriate to establish a health-based guidance value (i.e. tolerable intake or ARfD in the case of contaminants). At its sixty-fourth meeting (FAO/WHO, 2006), JECFA calculated the MOEs for a number of genotoxic and carcinogenic food contaminants using BMDL values derived by fitting a range of models to the available experimental dose–response data. Annex 3 of the report of that meeting provides useful background information on the use of the BMD approach for risk assessment purposes.
For compounds that are genotoxic and carcinogenic, it is generally not considered possible to determine a threshold of effect, and the use of the NOAEL is not appropriate. For such compounds, where a BMDL cannot be determined, the $T_{25}$ (the chronic daily dose in mg/kg bw that will give 25% of the animals tumours at a specific tissue site, after correction for spontaneous incidence, within the standard lifespan of that species) may provide an alternative POD. However, the suitability of the $T_{25}$ for a given data set needs to be considered on a case-by-case basis.

In general, the interpretation of an MOE is based on considerations similar to those used in the derivation of a health-based guidance value. Hence, when based on data from experimental animals, as a default, an MOE of at least 100 (10-fold for each of interspecies and intraspecies variability) would be considered as indication for low health concern for effects with an apparent threshold. For compounds with carcinogenic and genotoxic properties, JECFA has indicated a low health concern for compounds with an MOE above 10 000. In interpreting the MOE, consideration needs to be given to all relevant factors, including the conservatism of assumptions, the completeness of the database (have all potentially relevant end-points been assessed?), whether the response might reasonably be considered to exhibit an apparent threshold and whether residues arise through permitted use, inadvertently or unavoidably. These need to be clearly described in the report.

Examples of the use of the MOE approach by JECFA for contaminants, other than for end-points for genotoxic carcinogens, include the evaluation of the neurotoxic and reproductive effects of acrylamide, for which a health-based guidance value could not be proposed because of its additional genotoxic and carcinogenic properties (FAO/WHO, 2006); the characterization of risks associated with polybrominated diphenyl ethers, for which the available data were insufficient to establish a health-based guidance value (FAO/WHO, 2006); and the evaluation of furans, for which the MOEs between the POD for induction of hepatocellular adenomas and carcinomas in female mice and average and high dietary exposures indicated a human health concern for a carcinogenic compound that might act via a DNA-reactive genotoxic metabolite (FAO/WHO, 2011a).

It is important to note that an MOE is not an absolute value but rather a relative comparison, intended to provide some indication to risk managers as to the level of concern and help in assessing the need for and urgency of further action. For substances that are both genotoxic and carcinogenic, this approach provides advice to inform risk managers of how close human exposures are to those anticipated to produce a measurable effect in laboratory animals or humans. In addition, MOEs for different substances can be compared to assist risk managers in prioritizing risk management actions.

MOEs should be rounded to at most two significant figures to avoid spurious precision.

### 4.9 Predicting risks at specified exposure levels

Another type of risk characterization output from dose–response modelling is the prediction of risks at specified exposure levels. This output can take the generic form of predicting “X number of health-impacted individuals at exposure Y”. An example of such estimates is the case of aflatoxins, where JECFA predicted the additional cancer risk at different levels of exposure (FAO/WHO, 1999, 2007). Such quantitative risk estimates have also been performed for lead (FAO/WHO, 2000).

Other assessments have evaluated the impact of reduced exposure (e.g. through application of different hypothetical maximum limits; see “8.4 Potential effect of limits and their enforcement on chronic dietary exposure” under section 2.3.2 of this document) on health risk. Such assessment have been performed for cadmium (FAO/WHO, 2006), methylmercury (FAO/WHO, 2007a), aflatoxins in tree nuts and dried figs (FAO/WHO, 2007b) and fumonisins in maize (FAO/WHO, 2011b).

In the optimal case, such estimates are supported by parallel assessments that describe the uncertainty in such estimates by providing additional information on the range of estimates, rather than a single value. The risk manager can then make statements such as “Up to X number of individuals may be adversely affected by exposure Y”. Assumptions inherent in such estimates can influence risk management decisions. These include choice of models, choice of end-points and limitations in initial data sets that were extrapolated. In this context, it may be desirable to create a statistical model that estimates the range of effects expected for a population. The availability of such estimates can provide additional information for risk managers to conduct cost–benefit analyses, risk–benefit assessments and evaluations of public health interventions.


Annex 1: Template for monograph

A sample table of contents for the contaminant monographs 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 each subsequent paragraph 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.

The most recent version of the template will be provided to all monographers when the compound assignments are made.

Contaminant name (addendum, if applicable)

First draft prepared by
Author 1, Author 2 … and Author x

1 Affiliation of author 1
2 Affiliation of author 2
…
x 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)

1. Explanation ........................................................................................................ x
2. Biological data ................................................................................................... x
   2.1 Biochemical aspects ...................................................................................... x
      2.1.1 Absorption, distribution and excretion ................................................ x
          (a) Absorption ......................................................................................... x
          (b) Distribution ....................................................................................... x
          (c) Excretion ........................................................................................... x
      2.1.2 Biotransformation ............................................................................... x
      2.1.3 Effects on enzymes and other biochemical parameters .................... x
      2.1.4 Physiologically based pharmacokinetic (PBPK) modelling ............. x
      2.1.5 Transfer from feed to food (FAO) ..................................................... x
   2.2 Toxicological studies .................................................................................... x
      2.2.1 Acute toxicity ........................................................................................ x
      2.2.2 Short-term studies of toxicity ............................................................... x
          (a) Mice .................................................................................................... x
          (b) Rats ................................................................................................... x
          (c) Hamsters .......................................................................................... x
          (d) Rabbits ............................................................................................. x
          (e) Dogs .................................................................................................. x
          (f) Pigs .................................................................................................... x
          (g) Horses ............................................................................................... x
          (h) Monkeys ........................................................................................... x
      2.2.3 Long-term studies of toxicity and carcinogenicity .............................. x
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) Breakdown products [e.g. of “detoxification” processes] .......... x
   (b) Covalent binding to nucleic acids and/or proteins .............. x
   (c) Hormonal activity/effects ....................................... x
   (d) Immunotoxicity .................................................. x
   (e) Metabolites ....................................................... x
   (f) Neurotoxicity ..................................................... x
   (g) Pancreatic function/glucose tolerance .......................... x
   (h) Related contaminants [where relevant] ........................ x
   (i) Thyroid function ................................................ x
2.3 Observations in domestic animals/veterinary toxicology ........... x
2.4 Observations in humans .............................................. x
   2.4.1 Biomarkers of exposure ...................................... x
   2.4.2 Biomarkers of effects ....................................... x
   2.4.3 Clinical observations ........................................ x
   2.4.4 Epidemiological studies .................................... x
3. Analytical methods (FAO) .............................................. x
   3.1 Chemistry .......................................................... x
   3.2 Description of analytical methods ................................ x
      3.2.1 Introduction ................................................ x
      3.2.2 Screening tests ............................................. x
      3.2.3 Quantitative methods ...................................... x
4. Sampling protocols (FAO) .............................................. x
5. Effects of processing (FAO) .......................................... x
6. Prevention and control (FAO) ......................................... x
   6.1 Preharvest control ................................................. x
   6.2 Postharvest control .............................................. x
   6.3 Decontamination ................................................ x
7. Levels and patterns of contamination in food [and feed] commodities (FAO) .... x
   7.1 Surveillance data .................................................... x
   7.2 Distribution curves .............................................. x
   7.3 Data on annual variation in contaminant levels ................ x
8. Food consumption and dietary exposure estimates (WHO & FAO) ........ x
   8.1 Concentrations in food used in the dietary exposure estimates ... x
   8.2 Food consumption data used in the dietary exposure estimates ... x
   8.3 Assessments of dietary exposure ................................ x
      8.3.1 National estimates ........................................ x
         (a) Country A ..................................................... x
         (b) Country B .................................................... x
         (c) Country C [etc.; countries are listed in alphabetical order] x
      8.3.2 International estimates .................................... x
8.4 Potential effect of limits and their enforcement on chronic dietary exposure. x
   9.1 Identification of key data for risk assessment ................... x
      9.1.1 Pivotal data from biochemical and toxicological studies ........ x
      9.1.2 Pivotal data from human clinical/epidemiological studies ...... x
      9.1.3 Biomarker studies ........................................... x
   9.2 General modelling considerations ................................ x
9.2.1 Selection of data ................................................................. x
9.2.2 Measure of exposure ......................................................... x
9.2.3 Measure of response ......................................................... x
9.2.4 Selection of mathematical model ....................................... x
9.3 Potency estimates .................................................................. x
  9.3.1 Potency estimates in humans based on epidemiological data .... x
  9.3.2 Potency estimates in humans based on biomarkers ............... x
  9.3.3 Potency estimates in test species [and basis of extrapolation to humans where relevant, e.g. comparative biochemical indices] ........ x
10. Comments [note: includes references] ........................................ x
  10.1 Biochemical aspects .......................................................... x
  10.2 Toxicological studies ......................................................... x
  10.3 Observations in domestic animals/veterinary toxicology .......... x
  10.4 Observations in humans .................................................... x
  10.5 Analytical methods ........................................................... x
  10.6 Sampling protocols ............................................................ x
  10.7 Effects of processing ........................................................ x
  10.8 Prevention and control ....................................................... x
  10.9 Levels and patterns of contamination in food [and feed] commodities .... x
  10.10 Food consumption and dietary exposure estimates ............... x
  10.11 Dose–response analysis and estimation of toxic/carcinogenic risk ... x
11. Evaluation ............................................................................. x
  11.1 Recommendations .......................................................... x
12. References ............................................................................. x
### Table 1
Comparison of molar percentages of dose excreted in urine of rodents and humans after oral administration of acrylamide

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose (mg/kg bw)</th>
<th>% of dose excreted in urine</th>
<th>GAMA/AAMA as % of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>50°</td>
<td>21.0 ± 1.10</td>
<td>0.81 ± 0.60</td>
</tr>
<tr>
<td></td>
<td>0.1°</td>
<td>6.0– 0.7</td>
<td>5.9– 1.8</td>
</tr>
<tr>
<td></td>
<td>0.6– 0.7</td>
<td>5– 9</td>
<td>16– 18</td>
</tr>
<tr>
<td></td>
<td>0.1°</td>
<td>2</td>
<td>12± 0.60</td>
</tr>
<tr>
<td></td>
<td>0.02°</td>
<td>29.7 ± 5.13</td>
<td>2.8 ± 0.60</td>
</tr>
<tr>
<td></td>
<td>0.1°</td>
<td>34.9 ± 7.40</td>
<td>2.8 ± 0.60</td>
</tr>
<tr>
<td>Rat</td>
<td>50°</td>
<td>34.0 ± 1.80</td>
<td>0.35 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>50°</td>
<td>38</td>
<td>0.28 ± 0.50</td>
</tr>
<tr>
<td></td>
<td>3°</td>
<td>29.0 ± 4.50</td>
<td>0.72 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>0.1°</td>
<td>32</td>
<td>0.93 ± 0.60</td>
</tr>
<tr>
<td></td>
<td>0.02°</td>
<td>29.7 ± 5.13</td>
<td>0.86 ± 0.50</td>
</tr>
<tr>
<td></td>
<td>0.1°</td>
<td>34.9 ± 7.40</td>
<td>0.77 ± 0.40</td>
</tr>
<tr>
<td>Human</td>
<td>3°</td>
<td>22.0 ± 4.50</td>
<td>3.30 ± 1.10</td>
</tr>
<tr>
<td></td>
<td>0.013°</td>
<td>45.1 ± 5.30</td>
<td>0.06 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>0.5°</td>
<td>31.2 ± 6.55</td>
<td>0.82 ± 0.16</td>
</tr>
<tr>
<td></td>
<td>1.34</td>
<td>6.55 ± 0.20</td>
<td>45.6 ± 8.50</td>
</tr>
<tr>
<td></td>
<td>1°</td>
<td>34.4 ± 5.21</td>
<td>0.82 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>1.65</td>
<td>5.21 ± 0.33</td>
<td>49.9 ± 6.30</td>
</tr>
<tr>
<td></td>
<td>3°</td>
<td>27.8 ± 7.99</td>
<td>0.70 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>0.49</td>
<td>7.99 ± 0.21</td>
<td>39.9 ± 9.90</td>
</tr>
<tr>
<td></td>
<td>0.000 5°</td>
<td>41.4 ± 3.47</td>
<td>0.09 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>0.02°</td>
<td>37.4 ± 2.92</td>
<td>0.09 ± 0.24</td>
</tr>
<tr>
<td></td>
<td>0.0124°</td>
<td>4.4 ± 9.4</td>
<td>0.12 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>0.014°</td>
<td>2.9 ± 1.5</td>
<td>0.024 ± 71°</td>
</tr>
</tbody>
</table>


*All information given is referenced to collection periods of 24 hours after administration.*
Total amount excreted within 24 hours after exposure calculated as percentage of dose.

Sumner, MacNeela & Fennell (1992). Gavage male rats; gavage male mice.

Doerge et al. (2007). Gavage male mice; gavage male rats.

Sumner et al. (2003). Gavage male rats.

Fennell et al. (2005). Gavage male rats; oral administration, 24 male volunteers.


GAMA not measured, so ratio not quantified.

Boettcher et al. (2006). Oral administration, male volunteer (n = 1). Excretion within 22 hours following exposure.

Fennell et al. (2006). Oral administration, male volunteers; same samples, but more sensitive assay than for Fennell et al. (2005).

Kopp & Dekant (2009). Oral administration, male and female volunteers (three of each sex). Excretion within 22 hours following exposure.

Fuhr et al. (2006). Oral administration (potato crisps; USA = chips), male and female volunteers (three of each sex). Excretion over 72 hours.

Doroshenko et al. (2009). Oral administration (potato crisps), male and female volunteers (eight of each sex; mean body weight assumed to be 70 kg). Excretion over 72 hours.

After 72 hours.

### Table 2

**Acute toxicity of sodium chlorite**

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex</th>
<th>Route</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg bw)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Male</td>
<td>Oral</td>
<td>158</td>
<td>Seta et al. (1991)</td>
</tr>
<tr>
<td>Rat</td>
<td>Female</td>
<td>Oral</td>
<td>177</td>
<td>Seta et al. (1991)</td>
</tr>
<tr>
<td>Rat</td>
<td>NS</td>
<td>Oral</td>
<td>350 (251–449)</td>
<td>Pisko et al. (1980)</td>
</tr>
<tr>
<td>Rat</td>
<td>NS</td>
<td>Oral</td>
<td>165</td>
<td>Perry et al. (1994)</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>NS</td>
<td>Oral</td>
<td>300</td>
<td>Pisko et al. (1980)</td>
</tr>
<tr>
<td>Quail</td>
<td>NS</td>
<td>Oral</td>
<td>496</td>
<td>WHO (2003)</td>
</tr>
</tbody>
</table>

bw: body weight; LD<sub>50</sub>: median lethal dose; NS: not stated

<sup>a</sup> Unclear if doses expressed as sodium chlorite or chlorite. Mean provided; numbers in parentheses are ranges.

### Table 3

**Oral LD<sub>50</sub> values for mercury compounds**

<table>
<thead>
<tr>
<th>Mercury compound</th>
<th>Species</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg bw)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercury(I) chloride (Hg&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>Rat</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>180</td>
</tr>
<tr>
<td>Mercury(II) chloride (HgCl&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>Rat</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Human (LD&lt;sub&gt;lo&lt;/sub&gt;)</td>
<td>10–42</td>
</tr>
<tr>
<td>Mercury(II) cyanide (Hg(CN)&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>Rat</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>33</td>
</tr>
<tr>
<td>Mercury(I) sulfate (Hg&lt;sub&gt;2&lt;/sub&gt;SO&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>Rat</td>
<td>205</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>152</td>
</tr>
<tr>
<td>Mercury(II) sulfate (HgSO&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>Rat</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>25</td>
</tr>
</tbody>
</table>

bw: body weight; LD<sub>50</sub>: median lethal dose; LD<sub>lo</sub>: lowest reported lethal dose

Source: Adapted from Von Burg (1995)
Table 4
Key neoplastic and non-neoplastic thyroid lesions in the 2-year carcinogenicity study of sodium chlorate in F344/N rats

<table>
<thead>
<tr>
<th>Concentration of sodium chlorate in drinking-water (mg/L)</th>
<th>Approximate dose of sodium chlorate (mg/kg bw per day)</th>
<th>Survival</th>
<th>Incidence of thyroid gland follicular cell hypertrophy</th>
<th>Incidence of follicular cell adenoma and carcinoma (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>36/50</td>
<td>4/47</td>
<td>1/47</td>
</tr>
<tr>
<td>125</td>
<td>5</td>
<td>27/50</td>
<td>13/44</td>
<td>0/44</td>
</tr>
<tr>
<td>1 000</td>
<td>35</td>
<td>31/50</td>
<td>33/43</td>
<td>0/42</td>
</tr>
<tr>
<td>2 000</td>
<td>75</td>
<td>40/47</td>
<td>40/47</td>
<td>6/47</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>37/50</td>
<td>3/47</td>
<td>1/47</td>
</tr>
<tr>
<td>125</td>
<td>5</td>
<td>36/50</td>
<td>7/47</td>
<td>0/47</td>
</tr>
<tr>
<td>1 000</td>
<td>45</td>
<td>33/50</td>
<td>27/43</td>
<td>1/43</td>
</tr>
<tr>
<td>2 000</td>
<td>95</td>
<td>41/50</td>
<td>42/46</td>
<td>4/46</td>
</tr>
</tbody>
</table>

Source: NTP (2005)

Table 5
Incidence of neoplasms in acrylamide-treated male and female B6C3F1 mice

<table>
<thead>
<tr>
<th>Sex</th>
<th>Neoplastic or non-neoplastic finding</th>
<th>Poly-3 survival-adjusted incidence (%)</th>
<th>0 mmol/L a</th>
<th>0.0875 mmol/L a</th>
<th>0.175 mmol/L a</th>
<th>0.35 mmol/L a</th>
<th>0.70 mmol/L a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Harderian gland adenoma</td>
<td>4.8**</td>
<td>59.7**</td>
<td>78.8**</td>
<td>87.5**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Harderian gland adenoma or carcinoma</td>
<td>4.8**</td>
<td>59.7**</td>
<td>81.0**</td>
<td>87.5**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Lung alveolar/bronchiolar adenoma</td>
<td>11.9*</td>
<td>29.8**</td>
<td>23.5</td>
<td>47.0**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Lung alveolar/bronchiolar adenoma or carcinoma</td>
<td>14.3*</td>
<td>32.1**</td>
<td>23.5</td>
<td>49.5**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Forestomach squamous cell papilloma</td>
<td>0.0*</td>
<td>4.6</td>
<td>13.5</td>
<td>15.3**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Harderian gland adenoma</td>
<td>0.0*</td>
<td>4.5</td>
<td>4.6</td>
<td>15.7**</td>
<td>20.4**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Lung alveolar/bronchiolar adenoma</td>
<td>2.2*</td>
<td>8.9</td>
<td>13.7</td>
<td>29.2**</td>
<td>52.1**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Lung alveolar/bronchiolar adenoma or carcinoma</td>
<td>4.5*</td>
<td>8.9</td>
<td>13.7</td>
<td>29.2**</td>
<td>54.8**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Mammary gland adenocarcinoma</td>
<td>0.0*</td>
<td>8.9</td>
<td>13.8**</td>
<td>5.2</td>
<td>33.4**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Mammary gland adenoacanthoma</td>
<td>0.0*</td>
<td>2.3</td>
<td>2.3</td>
<td>5.3</td>
<td>10.8**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Mammary gland adenocarcinoma or adenoacanthoma</td>
<td>0.0*</td>
<td>8.9</td>
<td>13.8**</td>
<td>5.2</td>
<td>35.4**</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Ovarian benign granulosa cell tumour</td>
<td>0.0*</td>
<td>2.4</td>
<td>0.0</td>
<td>2.7</td>
<td>15.2**</td>
<td></td>
</tr>
</tbody>
</table>

*: Significant (P < 0.05) trend; **: significantly different (P < 0.05) from the control group (0 mmol/L)
Equivalent to 0, 1.05, 2.23, 4.16 and 9.11 mg/kg bw per day in males and 1.11, 2.25, 4.71 and 9.97 mg/kg bw per day in females.

Table 6
Summary of special studies on metabolites

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Purity</th>
<th>Effect</th>
<th>LOAEL (mg/kg bw per day)</th>
<th>NOAEL (mg/kg bw per day)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice, outbred albino [Crl:CDl (ICR) BR], males, weanling</td>
<td>Gavage</td>
<td>Purified 3-Ac-DON (purity not reported)</td>
<td>Clinical signs of toxicity, necrotic lesions in duodenal crypts, thymus and spleen, reduced mitotic activity</td>
<td>5 mg/kg bw per day</td>
<td>–</td>
<td>Schiefer et al. (1985)</td>
</tr>
<tr>
<td>Mice CD1 Swiss, male, 18–20 g</td>
<td>Diet</td>
<td>Purified 3-Ac-DON (purity not reported)</td>
<td>Increased T cell–dependent antibody response</td>
<td>10 mg/kg diet, equivalent to 1.5 mg/kg bw per day</td>
<td>5 mg/kg diet, equivalent to 0.75 mg/kg bw per day</td>
<td>Tomar, Blakley &amp; Decoteau (1987)</td>
</tr>
</tbody>
</table>

3-Ac-DON: 3-acetyl-deoxynivalenol; bw: body weight; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level

Table 7
BMD$_{10}$ and BMDL$_{10}$ calculations for thyroid gland follicular cell hypertrophy in male F344/N rats administered sodium chlorate in drinking-water for 2 years

<table>
<thead>
<tr>
<th>Model</th>
<th>Log (likelihood)</th>
<th>$P$-value</th>
<th>AIC</th>
<th>Chi-square</th>
<th>$P$-value</th>
<th>Accept</th>
<th>BMD$_{10}$ (mg/kg bw per day)</th>
<th>BMDL$_{10}$ (mg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>−83.49</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gamma multistage</td>
<td>−85.46</td>
<td>0.14</td>
<td>174.9</td>
<td>4.13</td>
<td>0.13</td>
<td>??</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>−83.61</td>
<td>0.65</td>
<td>173.2</td>
<td>0.24</td>
<td>0.65</td>
<td>Yes</td>
<td>1.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Multistage</td>
<td>−85.46</td>
<td>0.14</td>
<td>174.9</td>
<td>4.13</td>
<td>0.13</td>
<td>??</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Log-probit</td>
<td>−86.20</td>
<td>0.07</td>
<td>176.4</td>
<td>5.74</td>
<td>0.06</td>
<td>??</td>
<td>5.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Quantal-linear</td>
<td>−85.46</td>
<td>0.14</td>
<td>174.9</td>
<td>4.13</td>
<td>0.13</td>
<td>??</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Weibull</td>
<td>−85.46</td>
<td>0.13</td>
<td>174.9</td>
<td>4.13</td>
<td>0.13</td>
<td>??</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Reduced model</td>
<td>−127.46</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AIC: Akaike information criterion; BMD$_{10}$: benchmark dose for a 10% response; BMDL$_{10}$: lower 95% confidence limit on the benchmark dose for a 10% response
Table 8
Outcome of dose–response models on emesis in pigs

<table>
<thead>
<tr>
<th>Model</th>
<th>npar</th>
<th>Log-likelihood</th>
<th>Accepted</th>
<th>BMD₁₀ (mg/kg bw per day)</th>
<th>BMDL₁₀ (mg/kg bw per day)</th>
<th>BMDU₁₀ (mg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>1</td>
<td>-43.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>22</td>
<td>-16.27</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-stage</td>
<td>2</td>
<td>-24.78</td>
<td>Yes</td>
<td>0.34</td>
<td>0.22</td>
<td>0.55</td>
</tr>
<tr>
<td>Two-stage</td>
<td>3</td>
<td>-24.54&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>0.49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log-logistic</td>
<td>3</td>
<td>-24.33</td>
<td>Yes</td>
<td>0.63</td>
<td>0.21</td>
<td>1.12</td>
</tr>
<tr>
<td>Weibull</td>
<td>3</td>
<td>-24.43</td>
<td>Yes</td>
<td>0.57</td>
<td>0.21</td>
<td>1.06</td>
</tr>
<tr>
<td>Log-probit</td>
<td>3</td>
<td>-24.21</td>
<td>Yes</td>
<td>0.61</td>
<td>0.21</td>
<td>1.09</td>
</tr>
<tr>
<td>Gamma</td>
<td>3</td>
<td>-24.36</td>
<td>Yes</td>
<td>0.62</td>
<td>0.21</td>
<td>1.10</td>
</tr>
<tr>
<td>Logistic</td>
<td>2</td>
<td>-26.14</td>
<td>Yes</td>
<td>0.99</td>
<td>0.74</td>
<td>1.29</td>
</tr>
<tr>
<td>Probit</td>
<td>2</td>
<td>-25.75</td>
<td>Yes</td>
<td>0.93</td>
<td>0.69</td>
<td>1.22</td>
</tr>
</tbody>
</table>

BMD₁₀: benchmark dose for a 10% response; BMDL₁₀: lower 95% confidence limit on the benchmark dose for a 10% response; BMDU₁₀: upper 95% confidence limit on the benchmark dose for a 10% response; bw: body weight; npar: number of parameters in dose–response model

<sup>a</sup> No constraint; <sup>b</sup> P-value goodness-of-fit test: 0.05.

Not accepted for not being significantly better than the one-stage model.

Table 9
BMD₀.₅ for lung cancer from arsenic exposure based on Chen et al. (2010b)

<table>
<thead>
<tr>
<th>Model name</th>
<th>P-value</th>
<th>BMD₀.₅ (µg/person per day)</th>
<th>BMDL₀.₅ (µg/person per day)</th>
<th>BMD₀.₅ (µg/kg bw per day)</th>
<th>BMDL₀.₅ (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>0.79</td>
<td>402</td>
<td>167</td>
<td>7.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Logistic</td>
<td>0.92</td>
<td>351</td>
<td>273</td>
<td>6.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>0.79</td>
<td>400</td>
<td>165</td>
<td>7.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Log-probit (constrained)</td>
<td>0.67</td>
<td>728</td>
<td>597</td>
<td>13.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Log-probit (unconstrained)</td>
<td>0.80</td>
<td>435</td>
<td>0.4</td>
<td>7.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Multistage</td>
<td>0.78</td>
<td>357</td>
<td>167</td>
<td>6.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Multistage cancer</td>
<td>0.89</td>
<td>250</td>
<td>165</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Probit</td>
<td>0.92</td>
<td>336</td>
<td>257</td>
<td>6.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Weibull</td>
<td>0.79</td>
<td>399</td>
<td>167</td>
<td>7.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Quantal-linear</td>
<td>0.89</td>
<td>250</td>
<td>165</td>
<td>4.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

BMD₀.₅: benchmark dose for a 0.5% response; BMDL₀.₅: lower 95% confidence limit on the benchmark dose for a 0.5% response; bw: body weight
Notes: x-axis: exposure in µg/person per day; y-axis: cohort incidence. The lower line is the fit of the model to the data. The vertical bars are the confidence intervals around the data. The upper line is the upper bound for the response from which the lower confidence bound of the BMD (BMDL) can be defined.

Table 10
Results of assays for genotoxicity with sodium chlorite and related compounds

<table>
<thead>
<tr>
<th>Test system</th>
<th>Test object</th>
<th>Concentration and test substance</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reverse mutation</td>
<td><em>Salmonella typhimurium</em> TA92, TA94, TA98, TA100, TA1535, TA1537</td>
<td>0.3 mg sodium chlorite/plate (purity 88.8%)</td>
<td>Positive +S9</td>
<td>Ishidate et al. (1984)</td>
</tr>
<tr>
<td>Reverse mutation</td>
<td><em>S. typhimurium</em> TA94, TA97, TA98, TA100, TA102, TA1537</td>
<td>0, 0.001, 0.005, 0.01, 0.05 and 0.1 mg sodium chlorite/plate</td>
<td>Negative</td>
<td>Fujita &amp; Sasaki (1987)</td>
</tr>
<tr>
<td>Reverse mutation</td>
<td><em>S. typhimurium</em> TA98, TA100</td>
<td>10, 20 and 30 mg chlorine dioxide/L added to fish samples</td>
<td>Negative</td>
<td>Kim et al. (1999)</td>
</tr>
<tr>
<td>Reverse mutation</td>
<td><em>S. typhimurium</em> TA97, TA98, TA100, TA104, TA1535</td>
<td>Sodium chlorate, concentration not specified</td>
<td>Negative ±S9</td>
<td>NTP (2005)</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Chinese hamster fibroblast cells</td>
<td>0.02 mg sodium chlorite/mL</td>
<td>Positive</td>
<td>Ishidate et al. (1984)</td>
</tr>
<tr>
<td>Mutation</td>
<td><em>Chlamydomonas reinhardtii</em></td>
<td>100 mmol potassium chlorate/L</td>
<td>Positive</td>
<td>Prieto &amp; Fernandez (1993)</td>
</tr>
<tr>
<td>Mutation</td>
<td><em>Rhodobacter capsulatus</em></td>
<td>100 mmol potassium chlorate/L</td>
<td>Positive</td>
<td>Prieto &amp; Fernandez (1993)</td>
</tr>
<tr>
<td>Mutation</td>
<td><em>S. typhimurium</em></td>
<td>0, 5, 10, 50 and 100 mmol potassium chlorate/L</td>
<td>Negative</td>
<td>Prieto &amp; Fernandez (1993)</td>
</tr>
<tr>
<td>Test system</td>
<td>Test object</td>
<td>Concentration and test substance</td>
<td>Results</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------</td>
<td>----------------------------------</td>
<td>---------</td>
<td>-------------------</td>
</tr>
<tr>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse bone marrow</td>
<td>1 dose of 7.5, 15, 30 or 60 mg sodium chlorite/kg bw intraperitoneally</td>
<td>Positive(^d)</td>
<td>Hayashi et al. (1988)</td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse bone marrow</td>
<td>4 doses in 24 h, 15 mg sodium chlorite/kg bw intraperitoneally</td>
<td>Negative(^e)</td>
<td>Hayashi et al. (1988)</td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse bone marrow</td>
<td>1 dose of 37.5, 75, 150 or 300 mg sodium chlorite/kg bw by gavage</td>
<td>Negative(^d)</td>
<td>Hayashi et al. (1988)</td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse bone marrow</td>
<td>0.2, 0.5 and 1 mg of sodium chlorate or sodium chlorite/day for 5 days (equivalent to 10, 25 and 50 mg sodium chlorite/kg bw per day) by gavage</td>
<td>Positive(^f)</td>
<td>Meier et al. (1985)</td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse bone marrow</td>
<td>0.2, 0.5 and 1 mg of sodium chlorate or sodium chlorite/day for 5 days (equivalent to 10, 25 and 50 mg sodium chlorite/kg bw per day) by gavage</td>
<td>Negative(^g)</td>
<td>Meier et al. (1985)</td>
</tr>
<tr>
<td>Micronucleus formation</td>
<td>Mouse peripheral blood</td>
<td>Up to 350–365 mg sodium chlorate/kg bw per day in drinking-water for 3 weeks</td>
<td>Negative(^i)</td>
<td>NTP (2005)</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Mouse bone marrow</td>
<td>0.2, 0.5 and 1 mg of sodium chlorate or sodium chlorite/day once or for 5 days (equivalent to 10, 25 and 50 mg sodium chlorite/kg bw per day) by gavage</td>
<td>Negative(^g)</td>
<td>Meier et al. (1985)</td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Mouse bone marrow</td>
<td>0.2, 0.5 and 1 mg of sodium chlorate or sodium chlorite/day once or for 5 days (equivalent to 10, 25 and 50 mg sodium chlorite/kg bw per day) by gavage</td>
<td>Negative(^g)</td>
<td>Meier et al. (1985)</td>
</tr>
<tr>
<td>Sperm head abnormalities</td>
<td>Mouse sperm</td>
<td>1 dose of 0.2, 0.5 or 1 mg of sodium chlorate or sodium chlorite (equivalent to 10, 25 and 50 mg sodium chlorite/kg bw per day) by gavage</td>
<td>Negative(^h)</td>
<td>Meier et al. (1985)</td>
</tr>
</tbody>
</table>

bw: body weight; S9: 9000 × g supernatant fraction from rat liver homogenate

\(^a\) In the presence and absence of Kanechlor KC-400-induced rat liver microsomes.

\(^b\) Chlorine dioxide added to seafood samples at a ratio of 2:1. Chlorite was quantified in samples, and levels did not exceed the detection limit of 0.05 mg/L.

\(^c\) Twenty-four-hour and 48-hour sampling times.

\(^d\) Killed at 18 hours.

\(^e\) Killed 24 hours after final dose.
f Killed 6 hours after final dose.
g Killed at 6 hours after final dose or 6, 24 and 48 hours after single dose.
h Killed 1, 3 and 5 weeks after final dose.

Table 11
Results of assays for the genotoxicity of DON

<table>
<thead>
<tr>
<th>End-point</th>
<th>Test object</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDS</td>
<td>Male SD rat primary hepatocytes</td>
<td>0, 0.003, 0.03, 0.3 µg/mL</td>
<td>Positive</td>
<td>Guo &amp; Xu (1997)*</td>
</tr>
<tr>
<td>RDS</td>
<td>Male SD rat primary hepatocytes</td>
<td>0, 0.01, 0.1, 1 µg/mL (incubation time 3 h)</td>
<td>Positive</td>
<td>Li &amp; Guo (2000)*</td>
</tr>
<tr>
<td>Comet assay (DNA breaks)</td>
<td>Male SD rat primary hepatocytes</td>
<td>0, 0.01, 0.1, 1 µg/mL (incubation time 2 h)</td>
<td>Positive</td>
<td>Li &amp; Guo (2001)*</td>
</tr>
<tr>
<td>Comet assay (DNA breaks)</td>
<td>Vero cells</td>
<td>0, 1, 5, 10 µmol (incubation time 4 and 16 h)</td>
<td>Positive</td>
<td>Li &amp; Sun (2004)*</td>
</tr>
<tr>
<td>Comet assay (DNA breaks)</td>
<td>Vero cells</td>
<td>0, 10 µmol (incubation time 4 and 16 h, reincubate for 15, 30, 60 and 120 min)</td>
<td>Positive</td>
<td>Li &amp; Sun (2004)*</td>
</tr>
<tr>
<td>Comet assay (DNA breaks)</td>
<td>Human Caco-2 cells</td>
<td>0.01–0.5 µmol/L (incubation time 24 and 72 h)</td>
<td>Positive</td>
<td>Bony et al. (2006)*</td>
</tr>
<tr>
<td>Cell transformation (tumour initiation and promotion)</td>
<td>BALB/c3T3 cells</td>
<td>0.01–0.2 µg/mL</td>
<td>Negative</td>
<td>Sakai et al. (2007)</td>
</tr>
<tr>
<td>In vivo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comet assay (DNA breaks)</td>
<td>Chicken spleen leukocytes</td>
<td>10 mg/kg bw per day by gavage for 17 weeks in diet</td>
<td>Positive</td>
<td>Frankic et al. (2006)</td>
</tr>
</tbody>
</table>

bw: body weight; DNA: deoxyribonucleic acid; DON: deoxynivalenol; RDS: replicative DNA synthesis; SD: Sprague-Dawley; UDS: unscheduled DNA synthesis

*a An asterisk (*) indicates that the original study was not available; the data were reported in the review by Ma & Guo (2008).

Table 12
Results of assays for the genotoxicity of fumonisin B₁

<table>
<thead>
<tr>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse mutation</td>
<td><em>Salmonella typhimurium</em></td>
<td>FB₁: 25–200 µg/mL (±)</td>
<td>Negative</td>
<td>Ehrlich et al.</td>
</tr>
</tbody>
</table>
### End-point

<table>
<thead>
<tr>
<th>End-point</th>
<th>Test system</th>
<th>Concentration</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OH-dG and DNA</td>
<td>TA98, TA100, TA102, TA1535 and TA1537</td>
<td>HepG2-derived enzyme [S9 mix]</td>
<td></td>
<td>(2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C6 cells: 3–36 µmol/L FB&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Positive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Mobio et al. (2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEF cells: 3–18 µmol/L FB&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronucleus</td>
<td>Human-derived hepatoma (HepG2) cells</td>
<td>25–200 µg/mL</td>
<td>Positive&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ehrlich et al. (2002)</td>
</tr>
</tbody>
</table>

### In vivo

**DNA damage in the kidney (comet assay)**
- Male Wistar rats
- Intrapitoneal FB<sub>1</sub> doses (500 µg/kg bw per day for 7 days)
  - Positive<sup>5</sup> Domijan et al. (2007a)

**DNA damage in the liver (comet assay)**
- Male Wistar rats
- Single oral (gavage) FB<sub>1</sub> doses (5, 50 and 500 µg/kg bw)
  - Positive<sup>d</sup> Domijan et al. (2008)

### 8-OH-dG: 8-hydroxy-2′-deoxyguanosine; bw: body weight; DNA: deoxyribonucleic acid; S9: 9000 × g supenant fraction from rat liver homogenate

<sup>a</sup> Increased 8-OH-dG formation and DNA fragmentation were found, which are likely to be the result of increased formation of reactive oxygen species. The results suggest a possible loss of protective mechanisms (such as p53-dependent apoptosis and cell cycle arrest) in FB<sub>1</sub>-damaged MEF cells and confirm that cells lacking mechanisms governed by the p53 gene would be more susceptible to neoplastic cascade or mutation following DNA lesions induced indirectly by this mycotoxin.

<sup>b</sup> The results may indicate that FB<sub>1</sub> is clastogenic in human-derived cells, although a non-genotoxic effect (aneuploidy) cannot be excluded.

<sup>c</sup> Increased DNA damage was observed in the kidney, as demonstrated by the comet assay. The ratio of sphinganine to sphingosine was also significantly increased. The DNA effects preceded effects on catalase activity and the concentration of protein carbonyls and malondialdehyde. The study authors concluded that disturbed sphingolipid metabolism induced by FB<sub>1</sub> may play a role in the observed DNA damage.

<sup>d</sup> Increased DNA damage was observed in the liver, as demonstrated by the comet assay. Apoptosis in rat liver appeared 24 hours after a single oral FB<sub>1</sub> dose of 5 µg/kg bw. Its appearance was time and dose dependent. As apoptosis appeared before DNA damage, the study authors concluded that FB<sub>1</sub>-induced apoptosis is not primarily caused by DNA damage. Mitotic figures seen at low doses of FB<sub>1</sub> support the conclusion that regenerative processes are involved in FB<sub>1</sub> carcinogenesis, as they increase DNA replication. This conclusion supports the mechanism of carcinogenesis summarized in the previous evaluation by the Committee (Annex 1, reference 153) and the IARC (2002) evaluation.

### Table 13

**BMD<sub>10</sub> and BMDL<sub>10</sub> for renal cytotoxicity in male rats, based on NTP (2001)**

<table>
<thead>
<tr>
<th>Model name</th>
<th>P-value</th>
<th>BMD&lt;sub&gt;10&lt;/sub&gt; (µg/kg bw per day)</th>
<th>BMDL&lt;sub&gt;10&lt;/sub&gt; (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>1.00</td>
<td>431</td>
<td>295</td>
</tr>
<tr>
<td>Logistic</td>
<td>1.00</td>
<td>602</td>
<td>356</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>1.00</td>
<td>565</td>
<td>306</td>
</tr>
<tr>
<td>Log-probit</td>
<td>1.00</td>
<td>487</td>
<td>286</td>
</tr>
<tr>
<td>Multistage</td>
<td>0.26</td>
<td>222</td>
<td>180</td>
</tr>
<tr>
<td>Multistage cancer</td>
<td>0.00</td>
<td>78</td>
<td>61</td>
</tr>
<tr>
<td>Probit</td>
<td>1.00</td>
<td>541</td>
<td>328</td>
</tr>
<tr>
<td>Weibull</td>
<td>1.00</td>
<td>496</td>
<td>313</td>
</tr>
<tr>
<td>Quantal-linear</td>
<td>0.00</td>
<td>78</td>
<td>61</td>
</tr>
</tbody>
</table>

*BMD<sub>10</sub>: benchmark dose for a 10% response; BMDL<sub>10</sub>: lower 95% confidence limit on the benchmark dose for a 10% response; bw: body weight*
### Table 14
**Blood lead levels associated with a change decrease of 1 IQ point in children**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>2.6</td>
<td>5.6 (4.1) (^b)</td>
<td>5.1 (2.8–25)</td>
</tr>
<tr>
<td>Hockey stick</td>
<td>7.6</td>
<td>—</td>
<td>5.1 (2.8–25)</td>
</tr>
<tr>
<td>Mass action</td>
<td>—</td>
<td>—</td>
<td>1.4 (0.1–9)</td>
</tr>
<tr>
<td>Hill</td>
<td>6.9</td>
<td>—</td>
<td>8.5 (0.7–27)</td>
</tr>
<tr>
<td>Bilinear10</td>
<td>—</td>
<td>1.8 (1.2)</td>
<td>2.3 (0.9–19)</td>
</tr>
<tr>
<td>Bilinear</td>
<td>—</td>
<td>—</td>
<td>2.1 (0.8–17)</td>
</tr>
</tbody>
</table>

BMD: benchmark dose; BMDL: lower 95% confidence limit on the benchmark dose; CI: confidence interval; IQ: intelligence quotient
\(^a\) Annex 1, reference 144.
\(^b\) From Budtz-Jørgensen (2010).

### Table 15
**Dose–response modelling of skeletal defects from Frakes, Sharma & Willhite (1985)**

<table>
<thead>
<tr>
<th>Model</th>
<th>P-value</th>
<th>AIC</th>
<th>BMD(_{10})</th>
<th>BMDL(_{10})</th>
<th>BMD(_{05})</th>
<th>BMDL(_{05})</th>
<th>BMD(_{01})</th>
<th>BMDL(_{01})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma(^a)</td>
<td>0.303</td>
<td>172.02</td>
<td>110.12</td>
<td>97.46</td>
<td>94.26</td>
<td>75.79</td>
<td>69.00</td>
<td>42.93</td>
</tr>
<tr>
<td>Logistic</td>
<td>0.231 3</td>
<td>172.378</td>
<td>107.06</td>
<td>95.53</td>
<td>83.42</td>
<td>68.17</td>
<td>38.03</td>
<td>22.37</td>
</tr>
<tr>
<td>Log-logistic(^b)</td>
<td>0.272 6</td>
<td>172.398</td>
<td>110.421</td>
<td>96.96</td>
<td>93.61</td>
<td>74.14</td>
<td>64.99</td>
<td>39.23</td>
</tr>
<tr>
<td>Log-probit(^b)</td>
<td>0.338 8</td>
<td>171.703</td>
<td>109.473</td>
<td>97.05</td>
<td>94.14</td>
<td>76.82</td>
<td>70.93</td>
<td>47.74</td>
</tr>
<tr>
<td>Multistage 2(^c)</td>
<td>0.187 7</td>
<td>174.548</td>
<td>99.93</td>
<td>85.26</td>
<td>69.72</td>
<td>53.12</td>
<td>30.86</td>
<td>13.74</td>
</tr>
<tr>
<td>Multistage 3(^c)</td>
<td>0.388 4</td>
<td>171.657</td>
<td>105.87</td>
<td>94.22</td>
<td>83.29</td>
<td>67.46</td>
<td>48.37</td>
<td>19.96</td>
</tr>
<tr>
<td>Probit</td>
<td>0.149 6</td>
<td>173.192</td>
<td>103.61</td>
<td>91.21</td>
<td>78.11</td>
<td>63.0</td>
<td>34.59</td>
<td>19.69</td>
</tr>
<tr>
<td>Weibull(^a)</td>
<td>0.252 7</td>
<td>172.617</td>
<td>110.86</td>
<td>97.01</td>
<td>93.39</td>
<td>73.16</td>
<td>63.33</td>
<td>36.99</td>
</tr>
</tbody>
</table>

AIC: Akaike information criterion; BMD: benchmark dose; BMDL: lower 95% confidence limit on the benchmark dose; bw: body weight
\(^a\) Power parameter ≥1.
\(^b\) Slope ≥1.
\(^c\) Beta ≥1.

### Table 16
**Dose–response modelling of relative kidney weights in male and female F344 rats gavaged with mercury(II) chloride for 6 months\(^a\)**

<table>
<thead>
<tr>
<th>Model</th>
<th>P-value</th>
<th>AIC</th>
<th>BMD(_{1SD})</th>
<th>BMDL(_{1SD})</th>
<th>BMD(_{10})</th>
<th>BMDL(_{10})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential 4(^b)</td>
<td>0.118 9</td>
<td>−93.481</td>
<td>0.136</td>
<td>0.072</td>
<td>0.220</td>
<td>0.112</td>
</tr>
<tr>
<td>Exponential 4(^c)</td>
<td>0.123</td>
<td>−265.555</td>
<td>0.119</td>
<td>0.063</td>
<td>0.221</td>
<td>0.115</td>
</tr>
<tr>
<td>Exponential 5(^b)</td>
<td>0.127</td>
<td>−93.208</td>
<td>0.275</td>
<td>0.094</td>
<td>0.308</td>
<td>0.148</td>
</tr>
<tr>
<td>Exponential 5(^c)</td>
<td>0.131</td>
<td>−265.271</td>
<td>0.267</td>
<td>0.082</td>
<td>0.307</td>
<td>0.152</td>
</tr>
</tbody>
</table>

\(^a\) Reference 144.
### Table 17

**Ranges of BMD$_{10}$ and BMDL$_{10}$ values for dietary exposure to purified fumonisin B$_1$**

<table>
<thead>
<tr>
<th>End-point and study</th>
<th>BMD$_{10}$ (µg/kg bw per day)</th>
<th>BMDL$_{10}$ (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat renal toxicity (NTP, 2001)</td>
<td>431–602</td>
<td>286–356</td>
</tr>
<tr>
<td>Rat renal cell tumours (NTP, 2001)</td>
<td>1 603–2 118</td>
<td>1 108–1 692</td>
</tr>
<tr>
<td>Mouse hepatocyte apoptosis (Howard et al., 2002)</td>
<td>2 053–8 443</td>
<td>944–2 064</td>
</tr>
<tr>
<td>Mouse hepatocyte hypertrophy (Howard et al., 2002)</td>
<td>1 109–10 260</td>
<td>673–3 939</td>
</tr>
<tr>
<td>Mouse megalocytic hepatocytes (Bondy et al., 2010)</td>
<td>284–1 675</td>
<td>165–1 178</td>
</tr>
<tr>
<td>Mouse hepatocyte apoptosis (Bondy et al., 2010)</td>
<td>969–3 342</td>
<td>463–1 216</td>
</tr>
</tbody>
</table>

BMD$_{10}$: benchmark dose for a 10% response; BMDL$_{10}$: lower 95% confidence limit on the benchmark dose for a 10% response; bw: body weight

### Table 18

**Summary information on epidemiological studies associating fumonisin exposure with health effects – oesophageal cancer, human immunodeficiency virus, stunting and neural tube defects**

<table>
<thead>
<tr>
<th>Geographic region/country</th>
<th>Reference</th>
<th>Age-standardized incidence (cases per 100 000)</th>
<th>Mycotoxin contamination or biomarker levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China, Huaiian, Fusui and Huantai counties</td>
<td>Sun et al. (2007)</td>
<td>Huaiian &gt;800; Huantai &lt;100</td>
<td>Huaian: Fusui 1.27 (0.1–14.9) mg/kg; Huaiian 2.84 (0.1–25.5) mg/kg; Huantai 0.65 (0.1–5.7) mg/kg</td>
</tr>
<tr>
<td>China, Huaiian, Fusui and Huantai counties</td>
<td>Sun et al. (2011)</td>
<td>Huaiian: high risk, oesophageal cancer; Fusui: high risk, liver cancer; Huantai: low risk, oesophageal and liver cancer</td>
<td>Huaiian maize: AFB$_1$ 13.5 mg/kg, FB$_1$ 2.6 mg/kg; Fusui maize: AFB$_1$ 2.3 mg/kg, FB$_1$ 0.4 mg/kg, plant oil 52.3 mg/kg; Huantai maize: AFB$_1$ 1.3 mg/kg, FB$_1$ 0.3 mg/kg</td>
</tr>
<tr>
<td>Geographic region/country</td>
<td>Reference</td>
<td>Age-standardized incidence (cases per 100,000)</td>
<td>Mycotoxin contamination or biomarker levels</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>South Africa, Bizana and Centane</td>
<td>Shephard et al. (2007)</td>
<td>N/A</td>
<td>FB$_1$: 281 ± 262 (38–1066) ng/mL; total fumonisins: 369 ± 345 (43–1329) ng/mL</td>
</tr>
<tr>
<td>Islamic Republic of Iran, Mazandaran and Isfahan provinces</td>
<td>Shephard et al. (2002a)</td>
<td>N/A</td>
<td>FB$_1$: Mazandaran 3.18 (0.68–7.66) mg/kg; Isfahan 0.22 (&lt;0.01–0.88) mg/kg</td>
</tr>
<tr>
<td>China, Linxian County, Henan Province</td>
<td>Abnet et al. (2001)</td>
<td>150 men, 125 women</td>
<td>No significant associations were found between cancer incidence and the geometric means of any of these potential biomarkers: sphingosine in nmol/L (60.7 [SD 22.2] in cases, 63.3 [SD 26.0] in controls), sphinganine in nmol/L (48.2 [SD 44.3] in cases, 54.6 [SD 52.5] in controls) and the ratio of sphinganine to sphingosine (0.79 [SD 0.75] in cases, 0.86 [SD 0.90] in controls</td>
</tr>
<tr>
<td>HIV</td>
<td>Williams et al. (2010)</td>
<td>435</td>
<td>N/A</td>
</tr>
<tr>
<td>Stunting</td>
<td>Kimanya et al. (2010)</td>
<td>Children under age of 5:</td>
<td>Total fumonisins: 0.158 (0.021–3.201) mg/kg; FB$_1$: 0.106 (0.021–2.375) mg/kg; FB$_2$: 0.067 (0.020–1.076) mg/kg; FB$_3$: 0.060 (0.018–0.604) mg/kg</td>
</tr>
<tr>
<td>United Republic of Tanzania</td>
<td>Stunting: 38%; Underweight: 22%; Wasting: 3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>Missmer et al. (2006)</td>
<td>270</td>
<td>Total fumonisins: 234 (0–1690) ng/g</td>
</tr>
<tr>
<td>Texas, USA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HIV: human immunodeficiency virus; N/A: not available; SD: standard deviation
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 paragraph below heading is flush left, first line of all subsequent paragraphs is indented 0.5 inch, no spacing between paragraphs, paragraphs are fully justified.

The most recent version of the template will be available on the computers in the meeting room.

WHO template

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

**x.x Contaminant name**

*Explanation*

(general introduction to the compound; if it has been evaluated before, including short description of the conclusions, and why it is on the agenda; also short introduction to chemical nature of compound and reasons for its occurrence in food)

*Biochemical aspects*

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

*Toxicological studies*

(short summary of the key toxicological/epidemiological data relevant for the evaluation, including summary table of critical studies and NOAELs/LOAELs)

*Studies relevant to risk assessment [example only; species and headings will vary]*

<table>
<thead>
<tr>
<th>Species / study type (route of administration)</th>
<th>Doses (mg/kg bw per day)</th>
<th>Critical end-point</th>
<th>NOAEL (mg/kg bw per day)</th>
<th>LOAEL (mg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse Eighteen-month study of toxicity and carcinogenicity (diet)</td>
<td>0, x, y, z</td>
<td>Finding</td>
<td>x&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>Rat Two-year study of toxicity and carcinogenicity (diet)</td>
<td>0, x, y, z</td>
<td>Finding</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Multigeneration reproductive</td>
<td>0, x, y, z</td>
<td><strong>Parental toxicity:</strong> x&lt;sup&gt;+&lt;/sup&gt;</td>
<td>y</td>
<td></td>
</tr>
<tr>
<td>Species / study type (route of administration)</td>
<td>Doses (mg/kg bw per day)</td>
<td>Critical end-point</td>
<td>NOAEL (mg/kg bw per day)</td>
<td>LOAEL (mg/kg bw per day)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>toxicity study (diet)</td>
<td></td>
<td>Finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reproductive toxicity: Finding</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offspring toxicity: Finding</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Developmental toxicity study (gavage)</td>
<td>0, x, y, z</td>
<td>Maternal toxicity: Finding</td>
<td>–</td>
<td>x^b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryo and fetal toxicity: Finding</td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Rabbit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental toxicity study (gavage)</td>
<td>0, x, y, z</td>
<td>Maternal toxicity: Finding</td>
<td>–</td>
<td>x^b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryo and fetal toxicity: Finding</td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thirteen-week and 1-year toxicity studies (diet)</td>
<td>0, x, y, z</td>
<td>Finding</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemiological study</td>
<td>0, x, y, z</td>
<td>Finding</td>
<td>y</td>
<td>z</td>
</tr>
</tbody>
</table>

* Pivotal study value (reference)

a Highest dose tested.
b Lowest dose tested.
c Two or more studies combined.

**Observations in domestic animals/veterinary toxicology**

(brief summary of veterinary case-studies, clinical practice, retrospective epidemiological studies of disease in domestic animals)

**Observations in humans**

(brief summary of most relevant human data, including biomarkers of exposure and effect, clinical studies, epidemiological studies)

**Analytical methods (FAO)**

(brief description of analytical methods, advantages, limitations, limits of detection and quantification)

**Sampling protocols (if applicable) (FAO)**
Effects of processing (if applicable) (FAO)
(brief description of processing conditions and known effects)

Prevention and control (if applicable) (FAO)

Levels and patterns of contamination in food commodities (FAO)
(brief description of data, if possible summaries as tables and graphs)

Food consumption and dietary exposure assessment (WHO/FAO)
(short summary of food consumption data and national and international dietary exposure assessments; if health-based guidance value – tolerable intake or ARfD – is established, the estimated dietary exposure – chronic or acute dietary exposure, respectively – is compared with these values in the Evaluation section)

Dose–response analysis
(brief description of and justification for data set selected, dose–response models applied, BMD and BMDL results)

Evaluation
(gives the Committee’s conclusion – establishment of a health-based guidance value (e.g. PMTDI, PTWI, PTMI, ARfD), derivation of margin of exposure and any other safety recommendations – and recommendations for research needed, etc.; short sentence to indicate whether monograph or monograph addendum has been prepared)
The excerpt below includes only the toxicological portions of the report item on arsenic. The full meeting report item can be found in the meeting report of the seventy-second meeting of the Committee (http://apps.who.int/iris/bitstream/10665/44514/1/WHO_TRS_959_eng.pdf). Note that this meeting report item was published before the requirement for a summary table was implemented.

3.2 Arsenic

Explanation

Arsenic is a metalloid that occurs in different inorganic and organic forms, which are found in the environment both from natural occurrence and from anthropogenic activity. Arsenic was previously evaluated by the Committee at its tenth, twenty-seventh and thirty-third meetings (Annex 1, references 13, 63 and 84). At its twenty-seventh meeting (1983), it was concluded that “on the basis of the data available the Committee could arrive at only an estimate of 0.002 mg/kg b.w. as a provisional maximum tolerable daily intake for ingested inorganic arsenic; no figure could be arrived at for organic arsenicals in food” (Annex 1, reference 63). This was based on the observation that arsenicism can be associated with water supplies containing an upper arsenic concentration of 1 mg/L or greater and that a concentration of 0.1 mg/L may give rise to presumptive signs of toxicity. Assuming a daily water consumption of 1.5 L, the Committee concluded that inorganic arsenic intakes of 1.5 mg/day were likely to result in chronic arsenic toxicity and that daily intakes of 0.15 mg may also be toxic in the long term to some individuals. The Committee noted that the International Programme on Chemical Safety (IPCS) had estimated that an arsenic concentration of 0.2 mg/L in drinking-water would lead to a 5% lifetime risk of skin cancer, but that skin cancer did not occur in the absence of other toxic effects due to arsenic. The Committee also noted a need for information on:

- arsenic accumulation in humans exposed to various forms of arsenic in the diet and drinking-water;
- the identification, absorption, elimination and toxicity of arsenic compounds in food, with particular reference to arsenic in fish;
- the contribution of arsenic in fish to human body burden of arsenic;
- epidemiological studies on populations exposed to elevated intakes of arsenic of known speciation.

At its thirty-third meeting (1988), the Committee considered information relevant to assessing the significance of organoarsenicals in fish. The previous evaluation was confirmed by assigning a provisional tolerable weekly intake (PTWI) of 0.015 mg/kg bw for inorganic arsenic, “with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow” (Annex 1, reference 84). The Committee noted that the organic forms of arsenic present in seafood needed different consideration from the inorganic arsenic in water. It concluded that there had been no reports of ill-effects among populations consuming large quantities of fish that result in organoarsenic intakes of about 0.05 mg/kg bw per day, but further investigation would be desirable to assess the implications for human health of exposure to naturally occurring organoarsenic compounds in marine products.

Inorganic arsenic has also been evaluated on a number of occasions by the International Agency for Research on Cancer (IARC). In 1973, IARC concluded that there was a causal relationship between skin cancer and exposure to inorganic arsenic in drugs, in
drinking-water with a high arsenic content or in the occupational environment and that the risk of lung cancer was clearly increased in certain smelter workers who inhaled high levels of arsenic trioxide. However, the causative role of arsenic was uncertain, as the influence of other constituents of the working atmosphere could not be determined. In 1980, IARC concluded that there was sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans (Group 1). In 2004, IARC concluded that there was sufficient evidence in humans that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin, whereas the evidence for carcinogenicity in experimental animals was limited. In 2009, IARC again concluded that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin and that the evidence was “limited” for cancers of the kidney, liver and prostate.

At its present meeting, the Committee was asked to consider all information related to the toxicology and epidemiology, exposure assessment, including biomarker studies, analytical methodology, speciation and occurrence in food and drinking-water, in order to re-evaluate and review the PTWI for inorganic arsenic. The literature relating to arsenic is extensive, and the present Committee used three recent reviews – by the United States Agency for Toxic Substances and Disease Registry, the European Food Safety Authority (EFSA) and IARC – as the starting point for its evaluation and also took into account newer studies that were considered to be informative for the evaluation. The arsenic-containing compounds found in water, foods and biological samples are shown in Table 4.

<table>
<thead>
<tr>
<th>Name</th>
<th>Synonyms and abbreviations</th>
<th>CAS No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenate</td>
<td>As\textsuperscript{V}</td>
<td>–</td>
</tr>
<tr>
<td>Arsenite</td>
<td>As\textsuperscript{III}</td>
<td>–</td>
</tr>
<tr>
<td>Methylarsonic acid</td>
<td>Monomethylarsonic acid, methylarsonate, MMA\textsuperscript{V}</td>
<td>124-58-3</td>
</tr>
<tr>
<td>Dimethylarsinic acid</td>
<td>Dimethylarsinite, cacodylic acid, DMA\textsuperscript{V}</td>
<td>75-60-5</td>
</tr>
<tr>
<td>Methylarsonous acid</td>
<td>Monomethylarsonous acid, MMA\textsuperscript{III}</td>
<td>–</td>
</tr>
<tr>
<td>Dimethylarsinous acid</td>
<td>DMA\textsuperscript{III}</td>
<td>–</td>
</tr>
<tr>
<td>Arsenobetaine</td>
<td>AB</td>
<td>64436-13-1</td>
</tr>
<tr>
<td>Arsenocholine</td>
<td>AC</td>
<td>39895-81-3</td>
</tr>
<tr>
<td>Trimethyl arsine oxide</td>
<td>TMAO</td>
<td>4964-14-1</td>
</tr>
<tr>
<td>Tetramethylersonium ion</td>
<td>TMA\textsuperscript{+}</td>
<td>27742-38-7</td>
</tr>
<tr>
<td>Dimethylarsionylethanol</td>
<td>DMAE</td>
<td>–</td>
</tr>
<tr>
<td>Trimethylarsoniopropionate</td>
<td>TMAP</td>
<td>–</td>
</tr>
<tr>
<td>Dimethylarsionylribosides</td>
<td>Oxo-arsenosugars</td>
<td>–</td>
</tr>
<tr>
<td>Dimethylmonotheiosinic acid</td>
<td>DMHTA\textsuperscript{V}</td>
<td>–</td>
</tr>
<tr>
<td>Dimethylthioarsinic acid</td>
<td>DMDTA\textsuperscript{V}</td>
<td>–</td>
</tr>
</tbody>
</table>

CAS: Chemical Abstracts Service

Note: Except for biochemical and toxicological studies of specific arsenic compounds, the valency of MMA and DMA is usually not specified. The analysis of MMA\textsuperscript{III} and DMA\textsuperscript{III} has become possible only recently. In this report, the terms MMA and DMA are used as cited in the original papers. Where MMA and DMA are measured in foods, they have been measured as the pentavalent form. Where biological samples have been analysed, it is assumed that MMA and DMA refer to total [MMA\textsuperscript{III} + MMM\textsuperscript{V}] and total [DMA\textsuperscript{III} + DMM\textsuperscript{V}], respectively.
Absorption, distribution, metabolism and excretion

Absorption of arsenic depends on the chemical species and its solubility as well as the matrix in which it is present. Soluble arsenicals in water are highly bioavailable. Inorganic arsenic is rapidly cleared from blood both in humans and in most experimental animal species that have been tested; an exception is rats, in which arsenic binds to erythrocytes, delaying clearance. Inorganic arsenic is metabolized primarily by stepwise reduction of pentavalent arsenic (arsenate) to trivalent arsenic (arsenite) followed by oxidative addition of methyl groups, although alternative pathways have also been proposed that include methylated arsenical glutathione metabolites. Most ingested arsenic species are excreted via the kidney within a few days. Ingested inorganic arsenic is excreted as inorganic arsenate and arsenite and as the pentavalent methylated metabolites MMA\textsuperscript{V} and DMA\textsuperscript{V}, with lesser amounts of the trivalent methylated metabolites MMA\textsuperscript{III}, DMA\textsuperscript{III} and thioarsenical metabolites. Whereas it has previously been assumed that methylation of inorganic arsenic was a detoxification route, it is not entirely clear whether or not this is correct, because, based on limited in vitro and in vivo data, MMA\textsuperscript{III} and DMA\textsuperscript{III} appear to be more toxic than inorganic arsenic and have high affinity for thiols and cellular proteins.

Major organic arsenicals present in fish when ingested undergo very little biotransformation and are excreted almost entirely unchanged. However, some organoarsenicals, such as arsenolipids present in cod liver and arsenosugars in mussels and algae, can be metabolized to DMA\textsuperscript{V} when ingested.

Toxicological data

Arsenic toxicity depends on the chemical form and its solubility and varies among animal species and with route of administration. Generally, trivalent arsenic is more toxic than the pentavalent forms. Oral administration of inorganic arsenicals to laboratory animals has a number of effects, including effects on the cardiovascular, respiratory, gastrointestinal, haematological, immune, reproductive and nervous systems. MMA\textsuperscript{V} administration to experimental animals has been shown to have effects on the gastrointestinal tract, kidney, thyroid and reproductive system, with the effect seen at the lowest doses being diarrhoea. DMA\textsuperscript{V} has effects on the urinary bladder, kidneys, thyroid and fetal development.

Studies in experimental animals conducted according to standard protocols have generally not shown increased tumour incidences following chronic oral exposure to inorganic arsenic. However, evidence of tumour promotion and co-carcinogenicity has been reported. In addition, studies involving administration of arsenite to pregnant mice in their drinking-water have shown evidence of transplacental carcinogenesis.

MMA\textsuperscript{V} has not shown evidence of carcinogenicity in 2-year cancer bioassays with doses equivalent to up to 100 mg/kg bw per day. DMA\textsuperscript{V} (administered in drinking-water at $\geq 50$ mg/L) was carcinogenic in the urinary bladder of rats, but not mice. DMA\textsuperscript{V} is not genotoxic, and its carcinogenic mode of action is considered to involve cytotoxicity to the bladder epithelium and sustained increased cell proliferation; the rat is considered to be particularly sensitive to DMA\textsuperscript{V} because of slower elimination and possibly a greater potential for metabolism to DMA\textsuperscript{III} compared with other species. The NOAEL was equivalent to 0.73 mg/kg bw per day.

In its most recent evaluation, IARC concluded that there is sufficient evidence for carcinogenicity of inorganic arsenic compounds in experimental animals and sufficient evidence for carcinogenicity of DMA\textsuperscript{V} in experimental animals. Evidence from a wide range of studies has led to the conclusion that arsenic compounds do not react directly with DNA. There are a number of proposed mechanisms of carcinogenicity of inorganic arsenic, including oxidative damage, epigenetic effects and interference with DNA damage repair.
Because of a general lack of data on both exposure and toxicity of organic arsenicals, the Committee further considered only inorganic arsenic for this report.

Taking into account the lack of a good animal model for carcinogenicity of inorganic arsenic compounds and the large number of data available from epidemiological studies, the Committee did not consider the data from experimental animals appropriate for the dose–response analysis.

**Observations in humans**

The main adverse effects reported to be associated with long-term ingestion of inorganic arsenic by humans are cancer, skin lesions, developmental effects, cardiovascular disease, neurotoxicity and diabetes.

The classification of arsenic as a carcinogen was originally based on evidence of skin cancers. Studies in Taiwan, China, and other regions where high exposures to arsenic in drinking-water occurred have confirmed the relationship. Significant associations between exposure to high levels of ingested arsenic in drinking-water and bladder cancer have been observed in ecological studies from Chile, Argentina and Taiwan, China, and cohort studies in Taiwan, China. Some of the studies showed an association only in smokers. In studies from Chile, Argentina and Taiwan, China, exposure to arsenic at high concentrations in drinking-water has been shown to be associated with lung cancer. Again, when smokers and non-smokers were compared, the associations were stronger in the smokers. Nutritional status of exposed populations has been observed to influence cancer risk. Thus, compromised nutrition (e.g. low protein intake) is likely to be associated with significantly higher risk. The evidence for an association with cancers at other sites, including prostate, liver and kidney, is less conclusive.

Epidemiological studies in different regions of the world have consistently demonstrated a strong association between long-term inorganic arsenic ingestion and skin lesions, typically in the form of hyperkeratosis, hyperpigmentation or hypopigmentation. Observations of skin lesions following low chronic exposure have suggested that these characteristic dermal changes are sensitive indications of the toxic effects of inorganic arsenic. Available epidemiological studies indicate a positive relationship between high concentrations of inorganic arsenic in drinking-water and sensitive end-points for peripheral and central neurotoxicity. There is some evidence that exposure of children to inorganic arsenic in areas with elevated arsenic concentrations (>50 µg/L) in drinking-water produces effects on cognitive performance, but so far this is not conclusive.

The cardiovascular outcomes that have been associated with chronic exposure to arsenic through drinking-water include blackfoot disease (BFD), increased mortality or prevalence of coronary heart disease, peripheral arterial disease, myocardial infarction and stroke, and other cardiovascular end-points, such as increased blood pressure and prolonged QT interval of the electrocardiogram. The association between BFD and inorganic arsenic exposure has been confirmed by many studies, but BFD has been reported primarily in an area along the south-western coast of Taiwan, China, where arsenic contamination in well water is very high (170–880 µg/L). Except for BFD, the reported associations between inorganic arsenic exposure and cardiovascular disease prevalence/mortality and other cardiovascular end-points currently do not provide sufficient evidence of causality and are not considered pivotal for the assessment.

Studies conducted in Bangladesh and Taiwan, China, indicated an extra risk of diabetes among high-exposure populations. In addition, recent findings suggest that in utero arsenic exposure impaired child thymic development and that enhanced morbidity and
immunosuppression might occur. However, as a result of limitations in the studies, the relationship between arsenic exposure and these outcomes remains uncertain.

The Committee concluded that the greatest strength of evidence for a causal association between inorganic arsenic and adverse effects in humans is for cancers of the skin, urinary bladder and lung and skin lesions (hyperkeratosis, hyperpigmentation and hypopigmentation) observed in studies in which levels of arsenic in drinking-water were relatively high (e.g. ≥100 µg/L). For this evaluation, studies were preferred that included documentation of exposure from drinking-water both at higher concentrations (e.g. ≥300 µg/L) and also at relatively lower concentrations (e.g. <100 µg/L). This was in order to assess effects across a broad gradient of exposure and to avoid extrapolation below the observed range in the dose–response modelling. For skin cancer, three of the four most recent studies of low-level exposure utilized toenail arsenic as a biomarker of exposure; however, the relationship between toenail arsenic and total dietary exposure to inorganic arsenic remains uncertain. Further, as arsenic-related skin lesions may be a possible precursor to skin cancer and have been reported at lower concentrations of arsenic in drinking-water compared with skin cancer, the Committee considered the data for skin lesions to be a more sensitive adverse effect than skin cancer. Thus, pivotal data were identified from epidemiological studies reporting a positive association with arsenic exposure and these effects (i.e. cancers of the lung and urinary tract and skin lesions).

**Analytical methods (FAO)**

**Effects of processing (FAO)**

**Prevention and control (FAO)**

**Levels and patterns of contamination in food commodities (FAO)**

**Food consumption and dietary exposure assessment (WHO/FAO)**

**Dose–response analysis**

The following studies were selected for dose–response modelling of the respective end-points. For lung cancer, data were from a recent prospective study in north-eastern Taiwan, China, of 6888 residents for whom arsenic concentrations in drinking-water had been ascertained, with an average 11.5 years of follow-up. Residents ≥40 years of age at study initiation with 178 incident lung cancer cases identified (4) were used for modelling. An earlier case–control study of lung cancer was not preferred for modelling due to potential selection bias in hospital-based controls. For urinary tract cancer, data from the same prospective study in north-eastern Taiwan, China, with 45 incident cases of urinary tract cancer (5) were used for dose–response modelling. Three arsenic-related skin lesion case–control studies were considered: two conducted in Bangladesh and one conducted in Inner Mongolia, China. Substantial differences exist among the studies in factors such as case definition, exposure assessment methods and assessment of possible confounders, including smoking and sun exposure. Considering these differences, these studies were not used for the evaluation.

The exposure metric in these studies was concentration of arsenic in drinking-water; total dietary exposure to inorganic arsenic from food and water was not assessed. In order to
provide an opinion on the risks to health related to the presence of inorganic arsenic in foodstuffs, it was necessary to convert from the arsenic concentrations in drinking-water to total dietary exposure to inorganic arsenic. This conversion required assumptions about the arsenic exposure from food before cooking and the volumes of drinking-water consumed directly and in cooking for the populations in which the respective health end-points were studied. Because of the uncertainty about actual exposure, the Committee used average estimates of exposure from food and volumes of water consumed to extrapolate from concentrations in drinking-water to total dietary exposure to inorganic arsenic from food and water. A range of low to high values for exposure from food and volume of water consumed was identified to be used in a sensitivity analysis, taking into account the dietary habits and levels of arsenic in food in the relevant region (north-eastern Taiwan, China). The identified ranges were 50–200 µg/day from food excluding water and volumes of 2–4 L of water consumed directly and used in cooking per day. The average estimates were 75 µg/day from food and 3 L of water per day. From the available data, an average body weight of 55 kg was assumed for this population.

In order to utilize the adjustment made for other variables (e.g. smoking) in the original analyses in the studies in north-eastern Taiwan, China, of cancers of the lung (4) and urinary tract (5), adjusted cases were calculated based on the relative risks. This two-step process involved calculating case frequency by multiplying the rate in the referent group by the relative risk and then estimating the number of adjusted cases by multiplying the number of subjects by the case frequency. The resulting adjustment was small relative to the reported number of cases.

In the dose–response analysis using the USEPA BMD software (BMDS version 2.1.1), the nine different dichotomous models were fitted to the adjusted data. Those resulting in acceptable fits based on statistical considerations were selected to derive BMD and BMDL values for a BMR at the low end of the observed range of the data (Table 8). All nine models resulted in an acceptable fit for the lung and urinary tract data. In modelling the epidemiological data, the BMD and BMDL estimated by the log-probit model differed from those of other models, with higher values when the model was constrained within the BMDS and very much lower values when unconstrained. In consequence, the Committee decided that the outputs of the log-probit model should be excluded from the assessment.

**Table 8**

Ranges of BMD and BMDL values for lung and urinary cancer associated with dietary exposure to inorganic arsenic, based on average estimates of exposure

<table>
<thead>
<tr>
<th></th>
<th>BMD&lt;sub&gt;0.5&lt;/sub&gt; (µg/kg bw per day)</th>
<th>BMDL&lt;sub&gt;0.5&lt;/sub&gt; (µg/kg bw per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer (4)</td>
<td>4.5–7.3</td>
<td>3.0–5.0</td>
</tr>
<tr>
<td>Urinary tract cancer (5)</td>
<td>7.9–13.9</td>
<td>5.2–11.4</td>
</tr>
</tbody>
</table>

BMD<sub>0.5</sub>: benchmark dose for 0.5% increased incidence of cancer over background in north-eastern Taiwan, China, with average 11.5 years of follow-up; BMDL<sub>0.5</sub>: 95% confidence limit for the benchmark dose for 0.5% increased incidence of cancer over background; bw: body weight

The lowest calculated BMDL was 3.0 µg/kg bw per day for a 0.5% increased incidence of lung cancer above background over the average 11.5 years of follow-up, based on average estimates of the exposure. A sensitivity analysis to investigate the impact of uncertainty in the exposure estimate in this study indicated that this BMDL<sub>0.5</sub> could be in the range of 2.0–7.0 µg/kg bw per day, with the assumption made with respect to volume of drinking-water consumed and used in cooking having a greater impact than the assumption regarding inorganic arsenic in food.
**Evaluation**

From epidemiological studies measuring arsenic levels in drinking-water, inorganic arsenic has been identified as a human carcinogen. It is present naturally in food and water because of geochemical conditions, and consequently exposure varies significantly in different regions and even within regions, primarily through the presence or absence of arsenic in groundwater sources for drinking-water.

The approach to quantitative assessment of cancer risk from inorganic arsenic is limited, inter alia, by the lack of information on total exposure in the available epidemiological studies. The inorganic arsenic BMDL for a 0.5% increased incidence of lung cancer was determined by using a range of assumptions to estimate exposure from drinking-water and food with differing concentrations of inorganic arsenic. The BMDL\(_{0.5}\) was computed to be 3.0 µg/kg bw per day (2.0–7.0 µg/kg bw per day based on the range of estimated total dietary exposure). The uncertainties in this BMDL\(_{0.5}\) relate to the assumptions regarding total exposure and to extrapolation of the BMDL\(_{0.5}\) to other populations due to the influence of nutritional status, such as low protein intake, and other lifestyle factors on the effects observed in the studied population. The Committee noted that the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) is in the region of the BMDL\(_{0.5}\) and therefore was no longer appropriate, and the Committee withdrew the previous PTWI.

The Committee noted that more accurate information on the inorganic arsenic content of foods as they are consumed is needed to improve assessments of dietary exposures to inorganic arsenic species. Analytical constraints to achieving this goal include the lack of validated methods for selective determination of inorganic arsenic species in food matrices and the lack of certified reference materials for inorganic arsenic in foods. The proportion of inorganic arsenic in some foods was found to vary widely, indicating that dietary exposures to inorganic arsenic should be based on actual data rather than using generalized conversion factors from total arsenic measurements.

Reported mean dietary exposure to inorganic arsenic in the USA and various European and Asian countries ranged from 0.1 to 3.0 µg/kg bw per day. Drinking-water was a major contributor to total inorganic arsenic dietary exposures and, depending on the concentration, can also be an important source of arsenic in food through food preparation and possibly irrigation of crops, particularly rice. The proportion of total exposure to inorganic arsenic arising from food relative to the proportion from water increases as the concentration of inorganic arsenic in the water decreases. At the lower end of the exposure range, food can also be a major contributor to total inorganic arsenic exposure.

For certain regions of the world where concentrations of inorganic arsenic in drinking-water exceed 50–100 µg/L, some epidemiological studies provide evidence of adverse effects. There are other areas where arsenic concentrations in water are elevated (e.g., above the WHO guideline value of 10 µg/L) but are less than 50 µg/L. In these circumstances, there is a possibility that adverse effects could occur as a result of exposure to inorganic arsenic from water and food, but these would be at a low incidence that would be difficult to detect in epidemiological studies.

A detailed addendum to the monograph was prepared.

**Recommendations**

There is a need for validated methods for selective extraction and determination of inorganic arsenic in food matrices and for certified reference materials for inorganic arsenic.

There is a need for improved data on occurrence of different species of arsenic in, and their bioavailability from, different foods as consumed in order to improve the estimates of
dietary and systemic exposure. Further information on the toxicity of arsenic species found in food is also required.

The Committee recommended that future epidemiological studies of the health impacts of arsenic should incorporate appropriate measures of total exposure to inorganic arsenic, including from food and from water used in cooking and processing of food.

Further, it is recommended that epidemiological studies not only focus on relative risks, but also analyse and report the data such that they are suitable for estimating exposure levels associated with additional (lifetime) risks, so as to make their results usable for quantitative risk assessment.