

**GUIDELINES FOR THE PREPARATION OF  
CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENTS  
(CICADs)**

**May 2002**

**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY**

**CONTENTS**

**INTRODUCTION**.....1

**Criteria of priority for a CICAD** .....1

**CICAD PROCEDURE**.....1

**PREPARATION OF A CICAD**.....3

**CONTENTS AND LAYOUT OF A CICAD**.....4

**ANNEX 1 - FORMATTING OF DRAFT CICADS** .....17

**ANNEX 2 - AUTHORS' RESPONSES TO PEER REVIEW COMMENTS** .....18

**ANNEX 3 - ROLES AND RESPONSIBILITIES OF AUTHORS, PEER REVIEWERS, FINAL REVIEW BOARD CHAIRPERSON AND MEMBERS, AND IPCS SECRETARIAT**.....20

**ANNEX 4 USE OF NON-PUBLIC INFORMATION IN THE CICADS**.....25

**ANNEX 5. CICAD PREPARATION FLOW-CHART** .....26

## INTRODUCTION

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise though informative documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

## CRITERIA OF PRIORITY FOR A CICAD

The principal criteria of priority in the selection of chemicals for the CICADs series are that

- there is the probability of exposure, and/or
- significant toxicity/ecotoxicity

Thus it is typical of a priority chemical that it is of transboundary concern; it is of concern to a range of countries (developed, developing and those with economies in transition) for possible risk management; there is significant international trade; the use is dispersive; oftentimes, also the production volume is high.

A CICAD is normally only produced when the available information allows a meaningful hazard characterization, as well as a sample risk characterization. A prerequisite of the production of a CICAD is the availability of a recent high-quality national/ regional risk assessment document = source document.

In the selection of a chemical for a CICAD, special emphasis is on avoiding duplication of effort by WHO and other international organizations.

## CICAD PROCEDURE

The flow chart [ANNEX 5] illustrates the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

A standard outline has been developed in order to encourage consistency in form. Guidance to authors with respect to the preparation, layout and formatting of draft CICADs is provided below and in ANNEX 1. For further information, an annotated CICAD is also presented at this web site.

The first stage of the process involves preparation of a first draft of the CICAD which is based on an existing national, regional, or international review, or on a review in preparation (where the source document does not contain the sections on environmental fate/effects, these are produced *de novo* for the CICAD). Authors of the first draft are usually, but not necessarily, from the institution that developed or is developing the original review.

The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs, and if necessary the author is request to revise the draft. The Criteria for first stage acceptance review for CICADs is a follows:

- Adequacy of coverage - Spot check for inclusion of appropriate references.
- Format - Is the document in the correct format?
- Level of detail - Are the critical studies described in sufficient detail to support the conclusions drawn? Are non-critical studies described in too much detail?
- Are defensible draft Hazard Evaluation, Dose-Response Analysis, and Sample risk Characterization included? If not, can additional expertise be brought to bear to develop it to a greater extent for circulation of the first draft?

The draft is then subjected to the second stage of the process. The second stage involves international peer review by scientists known for their particular expertise and by scientists from IPCS Contact Points and from IPCS Participating Institutions as well as scientists from Non-Government Organizations. Adequate time is allowed for the selected experts to undertake a thorough review. Peer reviewers must provide to the Secretariat copies of papers or reports they consider should be included in the CICAD. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with a table outlining the reviewers' comments and including the responses of the author.

Guidance to authors with respect to the tabulation of authors' responses to peer reviewers comments is provided in ANNEX 2.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review as recommended by the Steering Group;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to determine and document that the peer reviewers' comments have been addressed appropriately;
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology and risk assessment for chemical management. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers

may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

The final draft (including revisions requested by the Final Review Board) undergoes technical and language editing by the IPCS Secretariat, and publication by the World Health Organization on behalf of IPCS.

## **PREPARATION OF A CICAD**

Where the source document(s) upon which the CICAD is based is two or more years old, authors need to conduct updated literature surveys to ensure that the information presented in the CICAD is as up-to-date as possible. The author must specify which databases (with version date) were used to update the national document, and this should be provided to the peer reviewers. The cut-off date for this literature search is reported in the Executive Summary. In order to preserve the integrity of the review process, reference to work published after this date may only be included in the document (usually as foot notes) for information purposes and prioritisation of future work. The source document(s) should be provided to the Secretariat when the CICAD is accepted in the programme, preferably in electronic format. For critical data the original reference should always be provided. If the original article has not been seen, then it may be sufficient to state in the reference list that it was cited in the source document. Material that was taken from the source document (e.g. conclusions) should be referenced to the source document. Non-critical studies may be able to be grouped with one reference to source document. Guidelines on the use of non-public information in CICADs are given in ANNEX 4.

Documents are normally transferred electronically. As different wordprocessors are used it is essential that the format is as simple as possible, and that the same conventions are used. Detailed information on the formatting of draft CICADs is provided in ANNEX 1.

When a draft CICAD is forwarded (via e-mail) to the IPCS Secretariat for first stage review, the author should also send (by e-mail, if possible) copies of the national or regional source document(s) upon which the CICAD is based, as well as copies of key studies (only) that form the basis for the hazard identification and risk characterization, together with a report on the national peer review process. The Secretariat will be the repository for these source documents and key studies.

The IPCS Secretariat circulates the draft CICADs for international peer review to interested parties identified by IPCS after contact with IPCS Contact Points and Participating Institutions. However, authors of draft CICADs are encouraged to identify critical issues and where appropriate suggest specific experts to peer-review key issues in their draft CICADs. If possible appropriate industry contacts should be identified to the IPCS Secretariat.

The cut-off date for peer review comments is indicated in the letter requesting the comments, and is usually approximately 3 months before the Final Review Board Meeting. Comments received after the cut-off date are not taken into account.

Authors should cite the original publications in the reference list, especially for studies considered critical to the hazard identification and risk characterization. For areas not critical to risk characterisation (most often, information on physicochemical characteristics, analytical methods, sources of exposure), reference to the Source Document is sufficient.

While preliminary data (i.e., meeting abstracts) may be mentioned in the CICAD, they should not form the basis for the hazard identification and risk characterization. For more detailed information on the use of non-public information in the CICADs, see ANNEX 4

In cases where authors are aware of a critical study (e.g., carcinogenesis bioassay), the results of which were not available at the time the CICAD was prepared, they should indicate this in a footnote at the appropriate location within the text.

To facilitate rapid review and publication, authors should adhere carefully to these guidelines and observe the deadlines agreed with the IPCS. Authors should examine closely a recent CICAD before starting work.

### **CONTENTS AND LAYOUT OF A CICAD**

To provide guidance to authors in the preparation of draft CICADs, the specific guidance on the different sections of the CICAD is given here. It should be noted that the Guidance is expected to evolve with continued experience on the program. The author should therefore make sure that he/she uses the most recent version, to be found at the IPCS web site. To illustrate how CICADs may vary according to the relative importance of different end-points, and on the database available, an annotated example of a CICAD, based primarily upon the example of 1,1,2,2-tetrachloroethane, is also presented in at this web site. Authors are also encouraged to consult other, recently published CICADs for guidance.

**Standard format for CICADs.**

FOREWORD.....	
1. EXECUTIVE SUMMARY.....	
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES	
3. ANALYTICAL METHODS.....	
4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE	
5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION	
6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE	
6.1 Environmental levels.....	
6.2 Human exposure.....	
7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS.....	
8. EFFECTS ON LABORATORY MAMMALS AND <i>IN VITRO</i> TEST SYSTEMS	
8.1 Single exposure.....	
8.2 Short-term exposure.....	
8.3 Medium-term exposure.....	
8.4 Long-term exposure and carcinogenicity.....	
8.5 Genotoxicity and related end-points.....	
8.6 Reproductive toxicity.....	
8.6.1 Effects on fertility.....	
8.6.2 Developmental toxicity.....	
8.7 Other toxicity.....	
8.8 Mode of action.....	
9. EFFECTS ON HUMANS.....	
10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD	
10.1 Aquatic environment.....	
10.2 Terrestrial environment.....	
11. EFFECTS EVALUATION.....	
11.1 Evaluation of health effects.....	
11.1.1 Hazard identification and dose–response assessment.....	
11.1.2 Criteria for setting tolerable intakes and guidance values.....	
11.1.3 Sample risk characterization.....	
11.1.3.1 Exposure of the sample population.....	
11.1.3.2 Health risks in the sample population.....	
11.1.4 Uncertainties in the evaluation of health risks.....	
11.2 Evaluation of environmental effects.....	
12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES.....	
REFERENCES.....	
APPENDIX 1 — SOURCE DOCUMENTS.....	
APPENDIX 2 — CICAD PEER REVIEW.....	
APPENDIX 3 - CICAD FINAL REVIEW BOARD.....	
INTERNATIONAL CHEMICAL SAFETY CARD.....	
TABLES.....	
FIGURES	

Authors should adhere to the standard format to the extent possible, using the designated heading and subheadings in preparation of the draft CICAD. Alterations to the standard format may be undertaken only when warranted (for example, where there might be no data on environmental effects, the subsections 10.1, 10.2 and 11.2 need not be included).

Système International d'Unités (SI units) should be used throughout the CICAD. Where units of measurement are presented as ppm, ppb, etc, in the original citation, the appropriate conversion to SI units, followed by the original figures and units (in parenthesis) should be provided. For the conversion, the CEN recommendation (101 kPa and 20 °C, i.e., molar volume of ideal gas = 24.055 litre · mol<sup>-1</sup>) should be followed. The number of significant digits given for the converted numbers should not exceed two or that given for the original quantity, whichever is smaller.

Tables and Figures (numbered sequentially) should be grouped together at the end of the draft document and not presented within the body of the text.

Appendix 1 (*Source Documents*) should be included by authors in draft CICADs submitted for primary review by IPCS and international peer review. Appendix 2 (*CICAD Peer Review*) will be included by the Secretariat in subsequent drafts submitted for Final Review Board review and approval, and publication. Appendix 3 lists members of the Final Review Board, it is prepared by the Secretariat and inserted into the finalized CICAD prior to publication. The relevant International Chemical Safety Card/s will be inserted at the end of the document by the Secretariat.

### **The title page**

The title page should indicate the programme, name of the chemical, the stage of preparation of the draft CICAD as well as the date of the draft document.

### **Foreword**

The FOREWORD outlines the function of CICADs and the process by which they are prepared and reviewed. The FOREWORD is inserted in the CICAD template provided by the Secretariat

### **Section 1 - Executive summary**

The Executive Summary provides a brief overview of the preparation of the CICAD, as well as the critical data and conclusions. Information presented in the first paragraph of this section should include:

- identification of the background source document(s) upon which the CICAD is based and the cut-off dates of literature review for the source document and for any subsequent literature review conducted in preparing the CICAD.
- reference to the nature of the peer review and availability of the source document(s), [outlined in Appendix 1 of the CICAD]
- reference to the list of individuals and institutions from which peer review comments were received [outlined in Appendix 2 of the CICAD]
- reference to the accompanying International Chemical Safety Card(s) reproduced in the CICAD

As appropriate, the use of standard text when referring in the Executive Summary, to Appendices 1 & 2 and the International Chemical Safety Card reproduced therein, is encouraged.

### **Section 2 - Identity and physical/chemical properties**

Section 2 provides a brief overview of the more relevant physical and chemical properties related to assessing the hazards and risks of the chemical to humans and environmental organisms.

Information presented in this section should include chemical name; CAS number; chemical formula; molecular mass; two to three common synonyms; information on properties relevant to prediction of fate in the environment (i.e., as applicable, volatility, aqueous solubility, Henry's law constant [dimensionless & with dimensions], octanol-water partition coefficient), conversion factor [ $\text{cm}^3/\text{m}^3$  (ppm) to  $\text{mg}/\text{m}^3$ ] at 20°C and 101 kPa; structural formula.

Additional relevant information such as data on the purity or chemical form (e.g., hydrochloride salt) of the chemical commonly examined in toxicological studies may also be mentioned here.

Additional physical/chemical properties are outlined in the International Chemical Safety Card. The use of the standard text (as shown) when referring to the International Chemical Safety Card in this section is encouraged

### **Section 3 - Analytical methods**

Section 3 provides a summary of the most commonly used methods to quantify the chemical in environmental and biological samples. The inclusion of detection limits is a key feature of the information provided in this section and an indication of the accuracy (trueness, precision, recovery) is useful.

### **Section 4 - Sources of human and environmental exposure**

Section 4 provides an overview on the occurrence (i.e., natural and anthropogenic), use patterns, production (including data on trends) and emissions of the chemical into the environment, quantified where feasible.

Data on production of the chemical should be summarized within the text in the following order; worldwide, region-wide or within specific countries. Data on releases into specific media that serve as sources of human and environmental exposure should similarly be summarised worldwide, region-wide or within specific countries.

Data should be expressed in kilograms (kg) or metric tonnes

### **Section 5 - Environmental transport, distribution, and transformation**

Section 5 provides an overview of the fate of the chemical in the environment including sinks, persistence and potential for bioaccumulation.

In cases where data on the distribution of the chemical are not available, the inclusion of predicted distributions derived from models cited in the published literature is encouraged

Where this is done, its limitations, as well as the assumptions and input data used in deriving the parameters reported, must be clearly outlined within the text. (See also the use of modelling to predict environmental concentrations in section 6.1)

In cases where the chemical is likely to accumulate, relevant data on bioconcentration factors (BCFs) should be summarized briefly. If no BCFs are available, an indication of accumulation tendency should be given, based on the  $\log P_{ow}$ .

### **Section 6 - Environmental levels and human exposure**

**Section 6.1 Environmental levels** provides an overview of the concentrations of the chemical that might be found in environmental media, and media through which humans may be exposed: ambient air (rural & urban), indoor air including occupational exposure, surface and ground water, soils, sediments, and biota, drinking-water.

When important in judging the concentrations reported, the methods should be indicated. For non-detectable concentrations, the detection limits should be specified.

Where available data are extensive, information from national surveys may be summarized in tabular format, with the general range of observed concentrations in air, water, etc., presented within the text (e.g., CICAD 5: Limonene).

Information on levels in source-dominated areas should also be included.

In cases where quantitative monitoring data are limited or are lacking entirely, concentrations of the chemical in environmental media predicted on the basis of modelling may be presented. However, the type of model and its limitations, as well as the assumptions and input data used in deriving the predicted concentrations, must be clearly outlined within the text

**Section 6.2 Human exposure** provides a summary of the principal routes of human exposure and an estimate of the daily intake of the chemical by the general public and occupationally exposed individuals. For assessing potential exposure of the general public, this section should include data on levels in indoor air, drinking water, foodstuffs and consumer products.

Where available data are extensive, information from national surveys may be summarized in tabular format, with the general range of observed concentrations presented within the text.

In calculating the estimated daily intake (presented as mg/kg body weight per day) for the general public, the information and assumptions used in such calculations should be outlined.

Generally, estimated intakes are calculated only for adults; however, where considered appropriate, estimated intakes for other age groups (e.g., infants, children) may also be provided.

Estimated daily intakes for the general public derived from exposure modelling may also be included; however, the type of model and its limitations, as well as the relevant input data and assumptions used, must be clearly identified.

Estimated daily intakes (presented as mg/kg body weight per day) for occupationally exposed individuals may also be included; however, the data and assumptions used in such calculations should be outlined within the text.

## **Section 7 - Comparative kinetics and metabolism in laboratory animals and humans**

Section 7 provides an overview of the kinetics and metabolism relevant to the assessment of human health hazards and risks. Where possible, likely similarities or differences in the kinetics and metabolism of the chemical between humans and laboratory animals should be highlighted.

In cases where data are available from studies conducted with humans, a very brief outline of the experimental conditions should be presented.

Information on the extent of absorption, critical metabolic pathways (including principal metabolites), and elimination from studies in animals, and where possible in humans, should be summarized briefly.

Where related to the characterization of human health risks, information on physiologically based pharmacokinetic (PBPK) models should include a brief summary of what the model describes, how it was developed and its limitations.

## **Section 8 - Effects in laboratory animals and *in vitro* test systems**

As the database and the relative importance of different findings varies widely between different chemicals, there is flexibility in the structure of this section: in specific instances approaches other than the present format will be more appropriate.

Normally studies on laboratory mammals are described in this section. However, studies on all species that are relevant to human health assessment are included.

In cases of exceptional complexity of a subsection in Chapter 8, a summary paragraph may be included at the end of such a subsection.

In general, the section should be subdivided as follows: 8.1 Single exposure, 8.2 Short-term exposure, 8.3 Medium-term exposure, 8.4 Long-term exposure and carcinogenicity. Single exposure generally should cover exposure up to 24 hours, short-term exposure up to 28 days, and medium-term exposure up to 50% of the life span, for example, 90-day studies).

**Section 8.1 Single exposure** provides a brief overview of the acute toxicity (low, moderate or high) following inhalation, ingestion and dermal exposure. Where data are extensive, only ranges of LC<sub>50s</sub> and LD<sub>50s</sub> for inhalation, ingestion and dermal exposure for major laboratory species should be presented. A brief summary of critical acute effects may also be presented.

The extent of the presentations in **Sections 8.2 Short-term exposure, Section 8.3 Medium-term exposure, and 8.4 Long-term exposure and carcinogenicity** depends primarily upon selection of the critical end-point(s) related to the assessment of human health and environmental effects, and the available dataset. In cases where critical information for hazard identification and risk characterization is derived from medium- or long-term studies, Section 8.2 provides only a brief overview of the effects and related effect levels derived from short-term studies.

In cases, in which effects observed in a medium-term study are considered to represent the critical end-point (and the dataset is more limited), the level of detail in the description of the key study is enhanced, including where appropriate, size of experimental and control groups, species and strain, dosing regime, including hours/days, days/week for designated period of exposure, route and vehicle of exposure, end-points examined at what periods of observation after dosing, results (i.e., incidence) for all important biological end-points examined, including assessment of exposure-response relationships and statistical analysis.

In cases where the critical end-point(s) is derived from long-term exposure and/or carcinogenicity bioassays, the type and extent of the presentation will depend upon the available dataset.

When data are relatively limited, information related to the critical end-point for human health hazard identification and risk assessment are presented in detail within the text; the description including information on size of experimental and control groups, species and strain, dosing regime, including hours/days, days/week for designated period of exposure, route and vehicle of exposure, end-points examined at what periods of observation after dosing, results (i.e., incidence) for all neoplastic end-points examined including assessment of exposure-response relationships and statistical analysis. Results of non-critical effects and the associated effect levels are presented in a tabular format, and only briefly summarized in the text.

In cases where critical data are extensive, the protocols and results may be summarized in tabular format, with only a brief overview of the more relevant findings and effect levels summarized within the text.

When describing carcinogenicity studies, actual tumour incidence data should be presented in text and/or tables, rather than simply the percentage of animals affected. Information from more limited carcinogenicity bioassays, providing less additional weight to the overall evidence for carcinogenicity than standard carcinogenicity bioassays, are only briefly summarized within the text.

In cases where non-neoplastic effects are considered to be the critical end-points, the protocols and results of relevant studies may be summarized in tabular format, with descriptions of the critical studies and end-points presented within the text.

The basis and selection of the critical end-point(s) and identification of no-observed-(adverse)-effect levels [NO(A)ELs], lowest-observed-(adverse)-effect levels [LO(A)ELs] or benchmark doses should be clearly outlined within the text. It is not necessary to report NOAEL/LOAEL values for individual studies. They should be presented for potentially critical effects related to repeated-dose toxicity.

**Section 8.5 Genotoxicity and related effects** . Summary only of data on genotoxicity and related end-points is presented; for individual studies, the reader is referred to the source document. Only when it is relevant, are highest effective or lowest ineffective concentration/dose levels given. Data are presented in phylogenetic order by end point, separated in sections on studies *in vitro* and *in vivo*. When extensive new data have become available since the preparation of the source document, data on genotoxicity may be presented in table form in an appendix.

Descriptions of *in vivo* genotoxicity studies (whether in a table or within the text) should include the species and exposure conditions.

This section should also include a summary of the weight of evidence concerning the genotoxic potential of the chemical.

**Section 8.6 Reproductive toxicity** is divided, where data are available, into subsections **8.6.1 Effects on fertility** and **8.6.2 Developmental toxicity**. In cases, in which such effects are not considered critical for the overall hazard identification and risk characterization, the results of the studies may be summarized within the text (including a brief description of the exposure conditions).

Where developmental effects are observed, these should be mentioned within the context of observed effect levels associated with maternal toxicity. In cases where reproductive or developmental effects are considered critical end-points for human health hazard identification, additional details on experimental design and end-points examined should be presented. Where reproductive toxicity is observed and existing data allow, NOAEL (or LOAEL) for reproductive effects should be given.

**Sections 8.7 Other toxicity**. Specific areas may be added as necessary if the information for the chemical warrants this, for example, dermal and ocular irritation, dermal and respiratory sensitisation, immunotoxicity, neurotoxicity. If no relevant other toxicity is identified, this section can be omitted.

**Section 8.8 Mode of action** is included only if sufficient relevant information is available and this assists in the risk characterisation. In cases, where such data are not considered critical to human risk assessment, the results can be summarized in sections 8.1 - 8.7.

## **Section 9 - Effects on humans**

The structure and subheadings in this section depend on the data available. Division into subsections is only needed when it increases the readability of the section

Information from case reports is often the first indication of an adverse health effect. However, it is not usually possible to draw causal inferences from such reports. In general, a very brief summary of such reports is sufficient. Emphasis should be on studies relevant to the hazard characterization and dose-response analyses

Studies on exposed volunteers may be used for hazard identification and dose-response analysis. However, almost always they are limited to short-term exposure and short-term follow-up. In general, a very brief summary of such reports is sufficient.

Cross-sectional studies (e.g., reports on clinical findings among exposed populations, or on biomarkers of exposure/ effect) often lack proper epidemiological design and long-term exposure assessment and are therefore difficult to interpret. In general, a brief summary of such reports is sufficient.

The extent of the presentation of epidemiological data is dependent on its contribution to hazard identification and dose-response analysis. In cases where this added value of epidemiological studies is limited, they are described very briefly in the text. In cases, where there are numerous relevant and valid studies, details of individual study design and results could be presented in tabular format, and summarized briefly in the text.

For epidemiological studies considered critical, descriptions should include the size of the population studied, study design, case identification, exposure and methods for its assessment, methods of analysis, possible sources of confounding and bias, and their treatment, results and interpretation, and comments on the reliability of the study.

## **Section 10 - Effects on other organisms in the laboratory and field**

The type and extent of the presentation on toxicity to aquatic and terrestrial organisms (other than those mentioned earlier sections) is dependent upon the size of the available dataset, and contribution to the overall assessment of environmental risks. In cases where available data are limited, the various end-points and associated effect levels may be summarized within the text. Where appropriate for chemicals having larger datasets, ranges of effect levels for various end-points and species may be summarized within the text.

In cases where extensive data are available for many species, the information (including species, end-point(s), range of effect levels and literature citation) may be presented in tabular format, and briefly summarized within the text. Where appropriate, the lack of identified data should be mentioned in the text.

If specific physicochemical properties (e.g., water solubility, vapour pressure) are expected to significantly influence the bioavailability and/or toxicity for aquatic species, this should be discussed, particularly if only results based on nominal test substance concentrations are available

## **Section 11 - Effects evaluation**

The first subsection **11.1.1 Hazard identification and dose-response assessment**, includes weight of evidence considerations for all identified hazards as a basis for delineation of those considered critical for dose-response analyses.

In cases where a dose-response parameter is based upon carcinogenic effects, the basis for the selection and derivation of this parameter should be clearly specified in the text. Similarly for any critical end-point, the selection of the dose-response parameter (e.g., NO(A)EL, LO(A)EL, benchmark dose) should be clearly described within the text.

In **Section 11.1.2 Criteria for setting tolerable intakes and guidance values**, the basis and rationale for the derivation of tolerable intakes and/or guidance values based upon the considered critical end-point(s) are described. Derivation of a tolerable intake or guidance value is dependent upon the critical end-point(s) selected, available dose-response parameters, as well as the predominant route of human exposure.

In cases in which the tolerable intake is derived on the basis of a NO(A)EL, LO(A)EL, or benchmark dose, the selection and application of uncertainty factors in the calculation of tolerable daily intakes or tolerable concentrations must be clearly outlined. Authors should indicate those cases in which the derivation of a guidance value may not be considered appropriate or feasible.

When the source documents do not derive a guidance value / tolerable intake, the *Section 11.1.2 Criteria for setting tolerable intakes and guidance values*" is limited to a sentence: See Footnote; and the foot note then reads:

The source document does not include derivation of tolerable intake or guidance value; rather, following the European legislation (European Commission, 1976), it states „substances are banned for consumer use“ / „exposure has to be avoided as low as technically attainable/feasible“.

**Section 11.1.3 Sample risk characterization** is intended to provide examples of how risks of certain populations might be characterized, based upon the toxicological and exposure information presented within the CICAD.

Thus the sample risk characterization(s) presented in a CICAD do not necessarily represent all possible exposure situations, but are provided as example and guidance only. Authors are encouraged to indicate within the text of this section that it is recognized that there are a number of different approaches to assessing the risks to human health posed by chemicals, and since exposure estimates vary as a function of use patterns, the risk characterization presented here is provided only as an example, primarily for illustrative purposes. In contrast to other sections of the CICAD, it is thus not necessarily applicable for populations elsewhere but is rather, as the heading implies, an example only.

Depending upon the available data, the sample risk characterization may encompass potential risks to the general public and/or occupationally exposed individuals. Where the available information allows, this section may be divided in two parts: , **11.1.3.1 Exposure of the sample population** and **11.1.3.2 Health risks in the sample population**

National Limits can be given in the sample risk characterization, provided that there is a full explanation of the process.

**Section 11.1.4 Uncertainties in the evaluation of health risks** describes the uncertainties in all stages of the health risk evaluation, i.e., hazard identification, exposure-response assessment, criteria for setting tolerable intakes/guidance values, and sample risk characterization

In **Section 11.2, Evaluation of environmental effects**, effects on organisms with the greatest potential for exposure (based upon the level and route of releases as well as fate within the environment) should be emphasized. Effects such as ozone depletion should also be addressed where possible. The data and assumptions used in the assessment of risks to environmental organisms should be clearly specified within the text.

In cases where relevant data are lacking, the text in this section should indicate that an assessment of possible effects on environmental organisms could not be conducted. Especially when the database is extensive, it may be advisable to present the evaluation in graphic form.

## **Section 12 Previous evaluations by international bodies**

The information presented in this section should refer to previous comprehensive international evaluations conducted by IOMC organizations (Inter-Organization Programme for the Sound Management of Chemicals, which includes WHO, FAO, UNEP, ILO, UNITAR, UNIDO and OECD).

The basis for the conclusions reached in the international evaluations mentioned in this section are very briefly summarized within the text of the CICAD.

## **Section 13 References**

References are listed in alphabetical order. Use of reference managing programmes is recommended, in order to ensure consistent reference formatting. For reference formatting, See ANNEX 1, formatting draft CICADs

### **Appendix 1**

Appendix 1 lists the source document(s) upon which the CICAD is based, its availability as well as the nature of its scientific peer review. Appendix 1 should be included in all drafts of CICADs.

### **Appendix 2**

Appendix 2 lists the individuals and institutions (and their locations; city & country) from which comments on the draft CICAD were received during the second-stage international peer review of the document, listed alphabetically. Appendix 2 will be prepared by the Secretariat and is included in draft CICADs submitted for Final Review Board review and approval.

### **Appendix 3**

The members of the CICAD Final Review Board, together with their affiliations, are listed, separately for members, observers, and secretariat. Appendix 3 will be prepared by the secretariat at the editorial stage.

### **International Chemical Safety Card**

The International Chemical Safety Card will be inserted by the IPCS Secretariat for reproduction within the CICAD.

### **Tables**

Examples of selected tabulated data included in CICADs are presented as guidance on types of presentations. When tables are used, all data should be in the tables and the text should only summarize what is in the tables.

Table 1: Levels of 1,1,2,2-tetrachloroethane in various media.

Medium	Location	Year	Concentrations	Reference
Ambient air	Canada	1989–1990	<0.1–0.25 µg/m <sup>3</sup> (means)	Environment Canada, unpublished data, 1992
Ambient air	USA	pre-1987	0.7 µg/m <sup>3</sup> (mean)	Shah & Heyerdahl, 1988
Surface water	Canada	1985	<1.0–4.0 µg/litre	COARGLWQ, 1986
		1981	<0.005–0.06 µg/litre	Kaiser & Comba, 1983
Surface water	USA	1980–1988	<10–180 µg/litre	ATSDR, 1994
Surface water	Japan	1976	<0.001, <0.002, <0.05 µg/litre	Environment Agency Japan, 1976
Surface water	Germany	1989–1990	<0.03–10 µg/litre	Wittsiepe, 1990
Sediment	Japan	1976	<0.05 µg/g, <1 µg/g	Environment Agency Japan, 1976

<sup>a</sup> Detection limit not specified.

Table 2: Concentrations of limonene in various media.

Medium	Concentration	Location and sampling date	Reference
Air, rural	0.036 µg/m <sup>3</sup> (6.4×10 <sup>-3</sup> ppb)	Whitaker's Forest, Sierra Nevada Mountains, California, June 1990	Helmig & Arey, 1992
	0.34 µg/m <sup>3</sup> (6.0×10 <sup>-2</sup> ppb)	Eastern Germany, July (forest site)	Ciccioli et al., 1993
	0.1–2.2 ppb (0.6–12.2 µg/m <sup>3</sup> )	Forest, Northwest Quebec, Canada, July 1989	Clement et al., 1990
Air, urban/suburban	nd <sup>b</sup> –0.36 µg/m <sup>3</sup> (nd–6.4×10 <sup>-2</sup> ppb)	Urban Riverside, California, June 1990	Helmig & Arey, 1992
	0.14 ng/litre (2.5×10 <sup>-2</sup> ppb)	Montelibretti, Italy (suburban site)	Ciccioli et al., 1992
Air, emissions	1.7–10 100 µg/m <sup>3</sup> (0.3–1.8×10 <sup>3</sup> ppb)	8 municipal solid waste composting facilities, USA	Eitzer, 1995
	1.9–14 µg/m <sup>3</sup> (0.34–2.5 ppb)	Emission plumes from kraft pulp industries, Sweden	Strömvall, 1992
Water, sea	2–40 ng/litre	Gulf of Mexico, <sup>d</sup> 1977	Sauer, 1981
	0.55 ng/litre (mean)	Barcelona, Mediterranean Sea, Spain, 1986	Gomez-Belinchon et al., 1991
Water, river	590 ng/litre (mean)	Llobregat River, Barcelona, Spain, 1985–1986	Gomez-Belinchon et al., 1991
	1600 ng/litre (mean)	Besós River, Barcelona, Spain, 1985–1986	Gomez-Belinchon et al., 1991
Water, estuary	25–633 ng/litre	Southampton Water estuary, UK	Bianchi et al., 1991
Water, groundwater	70 ng/litre (max.)	Otis Air Base, Massachusetts (sewage-contaminated water)	Barber et al., 1988
	1–130 µg/litre	Former site for production of charcoal and pine tar products, Gainesville, Florida	McCreary et al., 1983
Water, wastewater	nd–20 µg/litre	Influent waste water, sewage works, Göteborg, Sweden, 1989–1991	Paxéus et al., 1992
	10–220 ppb (10×10 <sup>3</sup> – 220×10 <sup>3</sup> ng/litre)	Kraft mill aerated lagoons, USA	Wilson & Hrutfiord, 1975
Sediment	105–807 ng/kg	Southampton Water estuary, UK	Bianchi et al., 1991
Soil	nd–920 µg/g	Former site for production of charcoal and pine tar products, Gainesville, Florida, USA	McCreary et al., 1983

Table 3: Investigations of non-neoplastic effects of 1,1,2,2-tetrachloroethane.

Study design	Effects	Effect level	Comments	Reference
<b>INHALATION</b>				
Male rats exposed to 50 mg/m <sup>3</sup> , 4 hours/day, 5 days/week, for 5 weeks; or to 130 mg/m <sup>3</sup> for 15 minutes, 4 times/day, separated by 40-minute intervals, for 5 weeks	Neurological effects; alterations in biochemical parameters and organ weights (although within ranges observed in controls); no "morphological changes"	Effects at 50 mg/m <sup>3</sup>	Strain and number of rats not specified; nature and extent of histopathological examination not specified	Schmidt et al., 1975
Fifty-five female Sprague-Dawley rats exposed to 560 ml/m <sup>3</sup> for 5 or 6 hours/day, 5 days/week, for 15 weeks; liver, kidneys, lungs, ovaries, uterus, and adrenal glands histopathologically examined	Transient increase in hepatic DNA synthesis, reversible histopathological changes in the liver; increase in relative liver weight	Effects at 560 ml/m <sup>3</sup> (equivalent to 130 ppm or 907 mg/m <sup>3</sup> , based on ATSDR [1994] conversion)	One exposure group only; uncertainty concerning exposure level based on unclear information in article (note: concentration more than approximately 10-fold higher than that at which effects were reported in other studies, no matter how converted)	Truffert et al., 1977
<b>INGESTION</b>				
Groups of 10 rats administered 3.2, 8.0, 20, or 50 mg/kg body weight per day by gavage for 2–150 days	Damage to liver, kidney, testicles, and thyroid gland (determined by histological, enzyme histochemical, and histoautoradiographic techniques)	Effects at 3.2 mg/kg body weight per day	Inadequate documentation of protocol and results; no quantitative data; not reported in which dose groups effects were observed (some groups were also concomitantly exposed to high temperatures); not possible to verify effect level	Gohlke et al., 1977
Five male or female B6C3F <sub>1</sub> mice administered 0, 32, 56, 100, 178, or 316 mg/kg body weight per day by gavage, 5 days/week, for 6 weeks, followed by 2 weeks of observation	No effects on body weight gain or mortality	No effects at highest dose of 316 mg/kg body weight per day	No end-points other than body weight and mortality appear to have been examined	NCI, 1978
Five male or female Osborne-Mendel rats administered 0, 56, 100, 178, 316, or 562 mg/kg body weight per day by gavage, 5 days/week, for 6 weeks, followed by 2 weeks of observation	Decrease in body weight gain in males at 178 mg/kg body weight per day and in females at 100 and 178 mg/kg body weight per day; all females exposed to 316 mg/kg body weight per day died; one male exposed to 100 mg/kg body weight per day died	Effects at 100 mg/kg body weight per day; no effects at 56 mg/kg body weight per day	No end-points other than body weight and mortality appear to have been examined; no data presented on effects on body weight gain at two highest doses or on mortality for other dose groups	NCI, 1978

Table 4: Genotoxicity of 1,1,2,2-tetrachloroethane *in vitro*.

Species (test system)	End-point	With activation	Result		Reference
			Without activation		
Saccharomyces cerevisiae D7	Mitotic gene conversion	nt	+	Callen et al., 1980	
	Recombination	nt	+		
Saccharomyces cerevisiae XV185-14C	Gene conversion and reversion	nt	–	Nestmann and Lee, 1983	
		nt	–		
Salmonella typhimurium TA1530 TA1535 TA1538	Reverse mutations	nt	+	Brem et al., 1974	
		nt	+		
		nt	–		
		–	–		
Salmonella typhimurium TA100	Reverse mutations	–	–	Warner et al., 1988	
Salmonella typhimurium BA13/BAL13	Forward mutations	–	–	Roldan-Arjona et al., 1991	
Escherichia coli (polymerase deficient pol A/pol A)	DNA damage	nt	+	Brem et al., 1974	
Escherichia coli PQ37	Gene mutation	–	–	Mersch-Sundermann et al., 1989b	
Escherichia coli	Induction of prophage lambda	+	–	DeMarini & Brooks, 1992	
Aspergillus nidulans	Mitotic malsegregation	nt	+	Crebelli et al., 1988	
Chinese hamster ovary cells	Chromosomal aberrations	–	–	Galloway et al., 1987	
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Galloway et al., 1987	
BALB/c3T3 cells (mouse)	Sister chromatid exchange	+	+	Colacci et al., 1992	
Mouse hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983	
Mouse hepatocytes	DNA repair	nt	–	Milman et al., 1988	
Rat hepatocytes	DNA growth, repair, or synthesis	nt	–	Williams, 1983	
Rat hepatocytes	DNA repair	nt	–	Milman et al., 1988	
Human embryonic intestinal cells	Unscheduled DNA synthesis	–	–	McGregor, 1980	

nt = not tested

Table 5: Cross-sectional epidemiological studies — respiratory effects

Protocol	Results	Reference
Study population composed of 40 workers from two factories who were exposed to methyl methacrylate for >5 years and 45 controls engaged in similar job categories but without exposure to methyl methacrylate. Mean atmospheric concentrations of methyl methacrylate at the two factories were 18.5 ppm (75.8 mg/m <sup>3</sup> ) (range 9–32 ppm [36.9–131.1 mg/m <sup>3</sup> ]) and 21.6 ppm (88.6 mg/m <sup>3</sup> ) (range 11.9–38.5 ppm [48.8–157.9 mg/m <sup>3</sup> ]). Smoking history and information on the presence of respiratory symptoms were gathered by means of a questionnaire. Respiratory measurements (maximum expiratory flow volume [MEFV], forced vital capacity [FVC], forced expiratory volume [FEV]) were performed by means of a spirometer: one before the working shift, and the second in the last 2 hours of the 8-hour shift.	An increase in the prevalence of chronic cough was observed in exposed workers compared with controls (p = 0.04). This difference remained significant after adjustment for smoking (p = 0.03). Airway resistance increased during the 8-hour work shift in workers exposed to methyl methacrylate (as measured by MEF <sub>50</sub> (p = 0.04) and MEF <sub>50</sub> /MEF (p = 0.01). The obstruction was mild, and forced expiratory volume in one second (FEV <sub>1</sub> ) did not decrease during the work shift.	Marez et al., 1993
Ninety-one exposed and 43 non-exposed workers were evaluated at five plants manufacturing polymethyl methacrylate sheets. For exposed workers, 8-hour time-weighted-average concentrations of methyl methacrylate were between 4 and 49 ppm (16.4–200.9 mg/m <sup>3</sup> ). Evaluation of chronic effects was conducted through an extensive questionnaire, a comparison of mean blood pressure values with predicted values from the 1971–1972 US National Health Survey, and results of pulmonary function tests, haemoglobin and white blood cell counts, urinalysis, and blood chemistry.	No significant differences were observed for respiratory function, chronic liver and gastrointestinal effects, skin and allergic problems, blood pressure and pulse rate, white blood cell count, and haemoglobin values. The only parameters for which effects were observed were serum glucose, blood urea nitrogen, cholesterol, albumin, and total bilirubin values, although the implication of these effects remains unclear. Although not statistically significant, the data also “suggested possible alterations in skin and nervous system symptomatology, urinalysis findings, and serum triglycerides.”	Cromer & Kronoveter, 1976

## ANNEX 1 - FORMATTING OF DRAFT CICADS

Documents are transferred almost invariably by electronic means, and authors are requested to follow these guidelines as far as possible in order to minimise problems in transferring documents from one format to another.

Currently the "master documents" are held by the IPCS Secretariat in Word 97 format (authors will be informed of any changes). If possible, authors are asked to prepare documents in this format. Apple Macintosh files cannot be handled. If the author cannot use Word, he/she should discuss the best alternative with the Secretariat.

In order to streamline the process, the author should use the "CICAD-template" that the Secretariat provides. Details of this style are described below.

### Header / Footer; Page numbering

The file name and version should be identified in the header. Pages should be numbered consecutively starting from the first page, in the header at the right upper corner of the page.

### Abbreviations

Abbreviations are presented in parenthesis where they are first introduced. The full name of the chemical should be used throughout the document; the use of non-standard abbreviations for chemical names should be avoided. Presentation of the abbreviations and acronyms in tabular format is encouraged.

### Font

The text should be in Times New Roman 12pt (with 10pt allowed for tables).

### Tabs

Set at every 0.5 inch (12.5 mm). They should not be changed within the document.

### Paragraphs

For ease of reference during peer-review, paragraphs should be numbered manually (not using the automatic paragraph numbering facility, which causes loss of paragraph identification in the editing of the document), restarting with each main section.

The paragraphs should be left-justified, with no special treatment for the first line. A single carriage return only should be used between paragraphs.

### Headings

The first three levels are in **bold**. The first level should be in **CAPITALS**, the second level in **bold**, the third in **bold italics**, the fourth in *italics (not bold)*. It would be optimal if no more levels of headings were needed, but if this is the case, the fifth level should be in **SMALL CAPITALS**, and the sixth in normal text font. Do not use the WORD automatic heading numbering system (which often produces unexpected results) but rather, number headings manually. This formatting is provided in the CICAD Template.doc provided. Examples:

## 11. EFFECTS EVALUATION

### 11.1 Evaluation of health effects

#### 11.1.3 Sample risk characterization.

##### 11.1.3.1 Estimated population exposure

###### 1.1.3.1.1 GENERAL POPULATION

###### 1 Children

#### **Table of contents**

This should be located at the beginning, showing section/subsection headings at 3 levels, and should be done using the 'table of contents'-facility of WORD. (see Annex 1)

#### **Tables**

Tables should be generated using the Table-facility of WORD, not by using tabulation. If possible, they should be fitted within the normal margins, and preferably be orientated in portrait mode. They should be placed after the main text. 10 pt font size is acceptable for the tables. As complex table formatting may greatly increase the file size, the formatting should be kept as simple as possible.

#### **Figures/Diagrams**

The use of figures and diagrams should be avoided as, generally, conversion between formats is not possible. When use of a figure or diagram is essential, it should be provided as a separate file from the programme that was used to generate it, rather than as a converted (e.g., Word) file. It should be further noted that figures and diagrams may easily reach a size that exceeds the capacity of the email systems in general use. The total file size of the document in the pdf format [which is usually about 1/2 - 2/3 of the size of the corresponding word document] must not exceed 0.5 Mb. At draft stages, especially, colour graphs and pictures should be avoided.

#### **Page size and margins**

Draft documents should be preferably submitted in A4 (8.27 x 11.69 inches; 210 x 297 mm); if this is not feasible, letter size (8.5 x 11 inches; 215 x 279 mm) can be used. One inch (25 mm) margins should be used all round.

#### **Literature citation and list of references**

For citations in the text, the name-and-year system is used; two different styles are possible:

- a) Renberg et al. (1980) have used reversed phase TLC to determine TCP in edible oil.
- b) Capillary GLC is frequently used for analysing TAPs in environmental samples (Lebel et al., 1981, 1982; Lebel & Williams, 1983a,b; Ofstad & Sletten, 1985).

Where a report has more than two authors, the first author is followed by "et al.". It should be noted that "et al." is not underlined or italicized, "&" replaces "and", the punctuation must be correct, and that several references to the same statement [including more than one by the same author(s)] are placed in chronological order.

Citations in the list of references are listed in alphabetical order. Some examples of presentations for various types of cited documents are provided in below.

**Journal article**

Davis A, Bailey DR (1969) Metrifonate in urinary schistosomiasis. *Bulletin of the World Health Organization*, 41:209-224.

**Chapter in a book**

Pawlowski ZS. Control of ascariasis within primary health care. In: Crompton DWT et al., eds. *Ascariasis and its public health significance*. London, Taylor & Francis, 1985:245-252.

**Book**

Jordan P. *Schistosomiasis - the St Lucia project*, 2nd ed. Cambridge, Cambridge University Press, 1985.

**Foreign language reference**

Jordon JR. Desarrollo psicomotor del niño. [Psychomotor development of the child.] In: *Temas de pediatría. [Aspects of pediatrics.]* Havana, Editora Universitaria, 1976.

**Meeting reports**

WHO's revised drug strategy. In: *Thirty-ninth World Health Assembly, Geneva, 5-16 May 1986. Volume 1. Resolutions and decisions, and list of participants*. Geneva, World Health Organization, 1986 (unpublished document WHA39/1986/REC/1), Annex 5:93-105.

**Databases and Electronic publications**

Harrison CL, Schmidt PQ, Jones JD. Aspirin compared with acetaminophen for relief of headache. *Online Journal of Current Clinical Trials*, 2 January 1992.

CANCERNET-PDQ [database online]. Bethesda, National Cancer Institute, 29 March 1996.

**Information obtained on the World Wide Web**

*Food safety from the farm to table: a new strategy for the 21st century*. Washington, DC, United States Department of Agriculture, Department of Health and Human Services, and United States Environmental Protection Agency, 1997 (Internet communication of 21 February 1997 at web site <http://um.crsan.fda.gov/dms/fs-draft.html>).

For details on further types of publications, see <http://intranet.who.int/homes/PUB/guides/references/exempleref.shtml>

All authors of the citation should be listed; journal names should be written in full and *italicized*. All main words in journal titles should be Capitalised. The names of authors are not always provided, in which case the name of the organization associated with the data, followed by the year, should be cited; for example, (IARC, 1983) or (WHO, 1976).

For personal communications, the name of the author, the recipient, and the date should be given. If the original recipient was not the World Health Organization, the submitter of the communication to WHO should be included.

**ANNEX 2 - AUTHORS' RESPONSES TO PEER REVIEW COMMENTS**

As part of the CICAD review and approval process, authors are required to provide a summary of the responses to comments received during the international peer review of the draft document. The basis of this summary is a tabulation of author's responses to individual comment.

Where the author has changed the text because of the comment, a standard response "e.g., see revised text in para 35" is sufficient. Alternatively, a sentence in the narrative summary of the responses (see below) to the effect that all comments except those for which there is a specific response in the appropriate column, have been taken into consideration, and the text has been changed accordingly. Where the author has not made the changes requested, a brief justification should be provided. Substantive comments having an impact on the hazard/risk characterization may be ideally dealt with using a narrative, where the responses to similar comments have been dealt with in a summary fashion. Comments responded to already in the national peer review stage need not be considered, but for the information of the FRB, it is useful to identify them with a standard phrase, e.g., "dealt with in national peer review".

The revised draft CICAD and responses to comments are forwarded by authors to the Secretariat for distribution to members of the Final Review Board for final review and approval of the CICAD as an international assessment.

The responses to comments is not part of the published CICAD; however it is retained by the IPCS Secretariat as part of the record of the CICAD, and the peer reviewers are sent the summary of key comments.

To facilitate the review with respect to the way in which peer-review comments were dealt with by authors during their revision of the draft CICAD, the Secretariat will provide to authors an electronic file containing a tabulated list of the peer review comments received (see the example outlined below), as well as copies of all correspondence received from peer reviewers. Authors are required to indicate (in the "RESPONSE" column of the electronic file) how the peer review comments were dealt with.

### **ANNEX 3 - ROLES AND RESPONSIBILITIES OF AUTHORS, PEER REVIEWERS, FINAL REVIEW BOARD CHAIRPERSON AND MEMBERS, AND IPCS SECRETARIAT**

All individuals participating in the process of IPCS Risk Assessment document preparation, are required to fill in and sign a statement on Declaration of interests.

#### **Author**

Authors serve in their personal capacity as scientists, not as a representative of any government or other organization.

Authors are responsible for:

- producing drafts of CICADs within agreed time scales, including a description of:
  - i. the provenance of the source (peer reviewed public domain, internal reports, commercial in confidence, etc.);
  - ii. national review processes (e.g. in-house, independent national committee of experts, bilateral/international);
  - iii. the time frame and data sources covered by the literature cited in the source document and complementing literature searches thereafter;
  - iv. the contentious issues discovered in the national peer review process, and, consequently, the areas of expertise likely to be useful in the IPCS peer review process;

- revising the document in light of the secretarial comments in the first-stage acceptance review;
- revising the document based on comments from the IPCS peer-reviewers;
- indicating how the comments from reviewers have been dealt with by providing a distillation of the salient comments fortified where needed by specific responses to the most pertinent individual comments;
- revising the document as requested by the Final Review Board in collaboration with the secretariat and the discussion leader;
- assisting the editor to finalise the document;
- giving consideration, particularly for some end-points (*e.g. genotoxicity and carcinogenicity*) to alternative viewpoints, even though these may or may not impact on the final conclusions;
- when presenting the rationale for risk assessment from the primary reference source, also giving consideration to alternative approaches adopted by other authorities/jurisdictions.
- informing the IPCS Secretariat if at anytime a conflict of interest, whether actual or potential, could be perceived in their work.

### Peer reviewers

The primary objective of CICADs is to characterize health and environmental hazards and the dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based. When reviewing the document, the reviewer should note therefore that omission of a study does not necessarily mean that it was not considered but that it may not have been related to the key end-point or among the key studies related to that end-point.

A prerequisite of the integrity of the peer review process of a CICAD is that information that became available after the closing date of the literature searches (for which dates are given in the first paragraph of the executive summary) is not added.

As conciseness is a target of a CICAD, the review and critique of the document should focus on the following points.

- Have all *critical* studies, published prior to the cut-off date, which are relevant to the risk assessment, been included? If not, a copy of the reference(s) omitted will have to be provided.
- Are the *critical* studies presented in sufficient detail to support the conclusions concerning the characterization of risk?
- Is the presentation of the information sufficiently concise or can the descriptions (of the non-critical studies) be condensed?
- Are there any limitations of the *critical* studies which have not been presented?
- The Section 11 on the evaluation of the health and environmental hazards is the most important part of the document. Is there sufficient critical discussion of issues relevant to the risk characterization, and, based on the data presented, are the conclusions sound?
- Is the exposure scenario obviously unrealistic, so that the example risk characterization is significantly misleading? If this is the case, information supporting this conclusion should be provided

Comments of general nature can seldom be interpreted to specific changes in the text, and are thus not very productive. The peer reviewers are therefore urged to be as specific as possible in the commenting, and indicate clearly, what passage of text they wish to have changed, how and why. Comments on presentation are not required, as the document will undergo a thorough

linguistic editing afterwards. However, modifications of the presentation which would clearly improve the understanding, are welcome.

The Secretariat is in possession of the source document and its supporting documentation. Thus, if a meaningful review of the draft requires information contained therein, the Secretariat will provide assistance.

### **Final review board**

The participation in the Final Review Board meetings is by IPCS invitation only. Invited people may include members of the FRB, representatives of international organisations, and observers. The Secretariat may, at the proposal of the Chair, decide to hold parts of a meeting as closed, i.e., limit the participation to the members only.

FRB members are selected by the Secretariat separately for each FRB meeting using criteria set by the Steering Group. Board Members serve in their personal capacity, not as representatives of any organization, government, or industry. Board members are required to fill in and sign the Declaration of interest-form. The FRB will strive to reach a consensus. In the event that a consensus is not reached, the CICAD will list the name(s) of the FRB member(s) who wish to dissent from it. The functions of the FRB are:

- To ensure that each CICAD has been subjected to an appropriate and thorough peer review.
- To verify that peer reviewers' comments have been addressed appropriately.
- To provide guidance to CICAD producers on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers.
- To approve CICADs as an international assessment.

The work of the FRB normally ends with the closure of the meeting. However, when the approval of a document as a CICAD remains conditional pending important changes, the FRB may decide that the final approval is sought by written procedure involving some identified (e.g., Chair, Discussion leader, Rapporteur), or even all, FRB members.

### **Chairperson**

The Chair oversees the smooth running of the meeting, ensures that enough time is available for the evaluations and that the allotment of available time is in proportion to the importance of the points discussed. In doing this, the Chair may have to decide that one or more of the documents scheduled for a meeting will have to be postponed to later FRB meetings. The Chair makes sure that observers do not unduly influence the evaluation or the proper course of the meeting. The Chair finally approves the revisions performed after the meeting by the author, Secretariat, and discussion leader, The Chair may propose to the FRB that a wider partnership for the final approval is established.

### **Discussion leader**

A discussion leader will be nominated from amongst the members of the FRB for each CIDAD under discussion at the meeting. The role of the discussion leader is to:

- identify scientific issues where there is lack of consensus between peer reviewers or peer reviewers and the author of the document on key questions relevant to the risk assessment
- identify areas where he/she considers that peer review comments have been inadequately or incompletely covered by the author in the post-peer review draft
- based on the peer-review comments, identify conflicts between specialist areas, highlight significant gaps in coverage of the document etc.
- assist the author in the finalisation of the synopsis of the response to the peer reviewer comments

- where important changes are requested by the FRB, to collaborate with the author and the Secretariat to make sure that these will be done in an appropriate fashion and in compliance with the FRB requirements.

### **Observers**

Observers, in contrast to the members of the FRB, may have a declared interest in the outcome of the evaluation. The main role of the observers in the process is to serve as sources of first-hand information from the meeting to the organizations they represent. However, the observers are expected to provide factual information on the chemicals they have special expertise in, when asked by the Chair. Observers must not try to influence the FRB or its individual members or disturb the course of the meeting. Thus, e.g., *ex cathedra* presentations by observers in an FRB meeting may only be allowed following prior request, after careful consideration by the Chair, discussion leader, authors, and secretariat. If needed, the Secretariat, at the proposal of the Chair, may revoke the invitation to attend the meeting at any time.

### **Risk Assessment Steering Group**

The Risk Assessment Steering Group consists of eight members. Members should be senior managers with expertise in, and responsibilities for, chemical risk assessment work in their respective agency.

- The Risk Assessment Steering Group will give strategic direction to the IPCS work on risk assessment within the policy framework agreed by the Programme Advisory Committee noting the recommendations of the IPCS/OECD coordinating group. As derived from its terms of reference, the main tasks of the Steering Group are to
- further develop criteria and determine priorities for the selection of chemicals for evaluation by IPCS, particularly with respect to Environmental Health Criteria (EHC) monographs and Concise International Chemical Assessment Documents (CICADs)
- act as a gatekeeper for each particular chemical consistent with decisions made in the Joint IPCS/OECD Coordinating Group
- provide oversight and guidance on the process for development and finalisation of IPCS documents, i.e., on
  - selection of chemicals to the programme and on whether a CICAD or an EHC is more appropriate pathway for each entry
  - selection of authors /author institutions
  - design of the peer review process for specific chemicals
  - assessment for the need of consultative groups at any stage of the process
- promote sharing and use of information resulting from other activities of the IPCS, particularly those related to harmonized methodologies for risk assessment
- ensure continuous development of the risk assessment process

### **Secretariat**

The IPCS Secretariat is responsible for:

- overseeing and managing the process, including distributing progress reports;
- distributing information on the IPCS risk assessment programme, including the continuous updating of the web site
- ensuring overall quality control of the process, including smooth flow of information between, the Programme Advisory Committee, Steering Group, and the Final Review Boards;
- carrying out the first stage acceptance review of draft CICADs;
- distributing drafts for peer-review and collating returned comments;

- choosing members of the Final Review Board and Consultative groups, when needed, and arranging meetings;
- in collaboration with the author(s), and the discussion leader, ensuring that the final version is consistent with the wishes of the Final Review Board;
- maintaining documentation of the review process, including a record of all comments; overseeing the editing and publishing of the CICADs.

#### **ANNEX 4 USE OF NON-PUBLIC INFORMATION IN THE CICADS.**

The CICAD risk assessments are based on information that is publicly available, and preferably - but not necessarily - published in peer reviewed scientific series. In cases where information not published in peer reviewed journals is used, it is the responsibility of the author and the Final Review Board to verify that the information is reliable.

Because of transparency, it is of great importance that the documents used in the CICAD, and especially those describing the key studies, are publicly available, and only in specific instances can other information be used. When considering the use of such information, the following situations have arisen:

*Full reports where the whole text is available to the CICAD author, and others:*

These can be used without problems (noting the added responsibility of the author and the FRB for the quality of non-peer reviewed studies)

*Full reports where the whole text was available to the author of the source document, but not to the CICAD author (for example, was provided under confidentiality provisions):*

These reports should not be used to provide information on critical end-points. For other, non-critical end-points they can be used, and should be cited as being referenced in the source document. If the data had been reviewed in another international forum (e.g., JECFA, JMPR) then it may be acceptable to use them, as long as the process is fully explained.

*Only the abstract of the full report is available to the CICAD author:*

Generally not to be used, but can be used for non-critical end-points, as long as there is a clear statement about its status. Summary information (as opposed to an abstract) can be satisfactory, usually only for environmental data.

*Unpublished reports / communications which are only available to the CICAD author:*

These should be examined by a case-by-case basis. Generally they should not be used unless they refer to a non-critical end-point or are the only information available on a critical end-point, in which case they must be made available to the reviewers. Personal communications, which are publicly available, can be used.

*Summary reports and/or other evaluations (for example, the source document on which the CICAD is based)*

Can be used, but access and reference the original studies for critical endpoints.

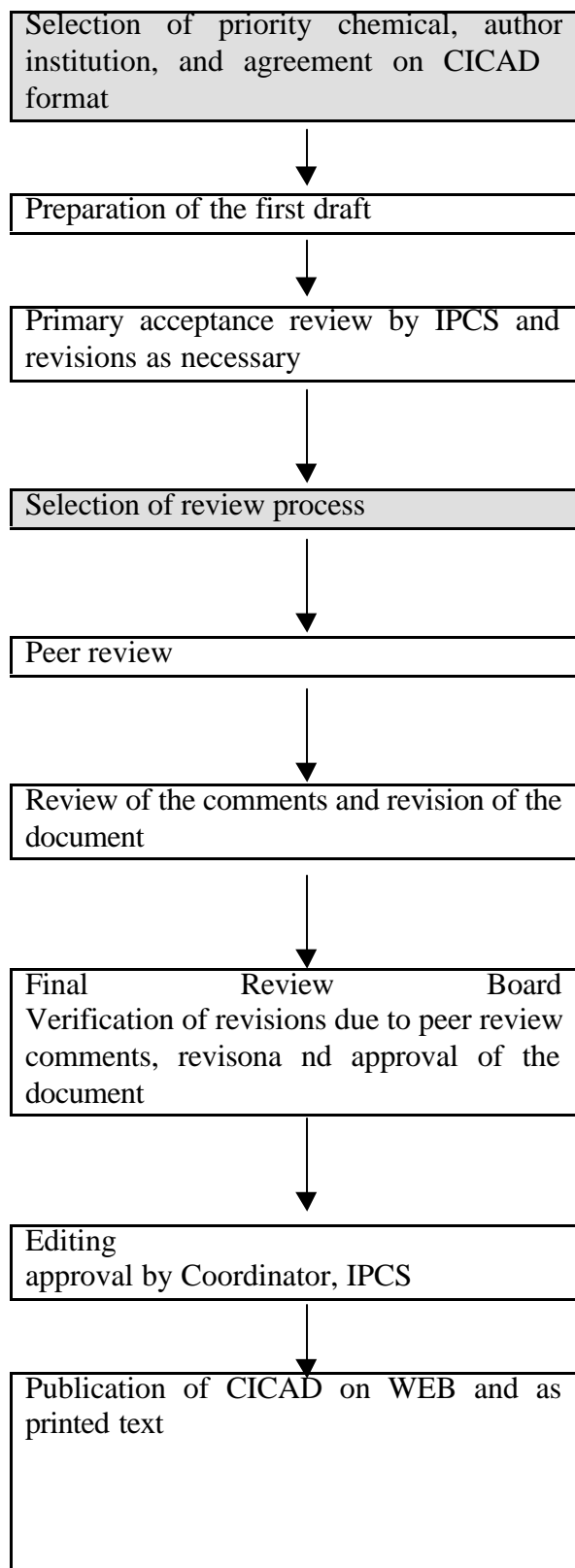
*Summaries of data (for example, IUCLID), which do not go through any peer-review process:*

Generally do not use, although they are valuable sources of information on what studies to look at. There may be some data (e.g., production volumes) for which they are the only source available; in this case it should be made clear that this may be "poor" information.

*Preliminary and/or ongoing study reports:*

Not to be used, although there can be a problem where there is no other information available. There is a need to be pragmatic, and these data can be used to flag issues for future consideration.

## ANNEX 5. CICAD PREPARATION FLOW-CHART



Advice from Risk Assessment Steering Group  
Criteria of priority:

- there is the probability of exposure, and/or significant toxicity/ecotoxicity

Thus it is typical of a priority chemical that

- it is of transboundary concern
- it is of concern to a range of countries (developed, developing and those with economies in transition) for possible risk management
- there is significant international trade
- the production volume is high
- the use is dispersive

A CICAD is normally only produced when the available information allows a meaningful hazard characterization, as well as a sample risk characterization.

Special emphasis on avoiding duplication of effort by WHO and other international organizations. A prerequisite of the production of a CICAD is the availability of a recent high-quality national/ regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced *de novo*, provided it is not controversial. If no source document is available, IPCS may produce a *de novo* risk assessment document if the cost is justified.