

IPCS

International Programme on Chemical Safety

**REPORT OF THE IPCS TWELFTH FINAL REVIEW BOARD
MEETING ON CONCISE INTERNATIONAL CHEMICAL
ASSESSMENT DOCUMENTS (CICADs)**

Hanoi, Vietnam: 28 September – 1 October 2004

Programme international sur la Sécurité des Substances Chimiques

**Internal Technical Report
Rapport Technique Interne**



United Nations Environment Programme
Programme des Nations Unies pour
l'Environnement



International Labour Organization
Bureau International du Travail



World Health Organization
Organisation mondiale de la Santé

**UNITED NATIONS ENVIRONMENT PROGRAMME
INTERNATIONAL LABOUR ORGANIZATION
WORLD HEALTH ORGANIZATION**

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Introduction

Dr M. Sweeney on behalf of the US Embassy in Hanoi, and Dr. A. Aitio, on behalf of the Programme on Chemical Safety, opened the meeting and welcomed the participants.

Dr M. Sweeney was elected as Chair and Dr K. Ziegler-Skylakakis as Vice-Chair and Mr. P Howe and Dr L. Fishbein as Rapporteurs. Following a brief introduction of each participant (List of participants, Appendix I), the agenda was adopted as proposed (Appendix II).

None of the members of the 12th Final Review Board (FRB) declared any conflict of interests with the subject matter of the meeting, and the potential conflicts of interest of two members with tobacco production/tobacco industry were considered not to present an impediment for their full participation in the meeting. The declaration of interest forms for each peer reviewer were considered in the context of separate CICAD drafts.

Background

Dr A. Aitio outlined the Terms of Reference for the meeting (Appendix III), and described the international peer-review process for the production of CICADs. He clarified the roles of Members, namely that Members are responsible for taking the formal decisions on the CICADs, and that they are selected to serve on the FRB for their individual scientific expertise and not, in any way, as representatives of their governments.

Document evaluation

After an introduction to and discussion of the key items brought up by the peer review process by the Discussion Leader, the FRB systematically reviewed responses of the authors to the comments submitted during the peer-review phase. Areas where additional changes were recommended are noted in Appendix IV. All other comments were considered to have been adequately addressed by the authors. Changes made in the main text of all documents have to be reflected in the Executive Summary.

Brominated phenols

The CICAD on Brominated phenols was approved by the Final Review Board as an international assessment and recommended it for publication subject to the requested changes being made as noted in Appendix 4, as approved by the Chair.

2-Butoxyethanol

The CICAD on *2-Butoxyethanol* was approved by the Final Review Board as an international assessment and recommended for publication subject to the requested changes being made as noted in Appendix 4, as approved by the Chair.

Butyl acetates

The CICAD on *Butyl acetates* was approved by the Final Review Board as an international assessment and recommended for publication subject to the requested changes being made as noted in Appendix 4, as approved by the Chair.

2-Ethoxyethanol

The finalisation process of the CICAD on *2-Ethoxyethanol* was referred to the Steering Group. The FRB recommendation was revision based on a further source document, consideration by a consultative group, another round of peer-review and ultimately approval in another FRB.

Heptachlor

The CICAD on *Heptachlor* was approved by the Final Review Board as an international assessment and recommended for publication subject to the requested changes being made as noted in Appendix 4, as approved by the Chair.

2-Methoxyethanol

The finalisation process of the CICAD on *2-Methoxyethanol* was referred to the Steering Group. FRB recommendation was a revision of the hazard characterization based on recently identified studies on adverse effects in humans, consideration by a consultative group, another round of peer-review and ultimately approval in another FRB.

Tetrachloroethene

The finalisation process of the CICAD on *Tetrachloroethene* was referred to the Steering Group. FRB recommendation was a revision of the hazard characterization noting especially the studies on neurotoxicity, carcinogenicity and reproductive toxicity, consideration by a consultative group, another round of peer-review and ultimately approval in another FRB.

Tin and inorganic tin compounds

The CICAD on *Tin and inorganic tin compounds* was approved by the Final Review Board as an international assessment and recommended for publication subject to the requested changes being made as noted in Appendix 4, as approved by the Chair.

General issues

Section 6

Section 6 structure and headings in guidelines should be reviewed.

Section 12

Change title to "... IOMC bodies" (general comment refers to all documents)

Other

Website to be added as source of OECD documents

Consider giving guidance on IUCLID referencing in the guidelines of CICADs

Propose to IPCS preparation of guidelines for harmonization of the species sensitivity-based probabilistic environmental risk assessment

Propose to IPCS prepare a guideline on risk assessments of groups of chemicals.

Bring the reported high concentrations of heptachlor in drinking water to the attention of the WHO Drinking Water Guideline group.

Other business

13th Final Review Board meeting

The 13th FRB is planned to take place in September-October 2005. The closing date for the receipt of first draft of CICADs is April 30, 2005. Chemicals likely to be considered include Organic tin compounds (other than tributyltin oxide and triphenyltin compounds), Chromium (III) compounds, Hydrogen cyanide: environmental aspects; DDT, human health aspects; and Resorcinol, as well as the revised documents on 2-Methoxy- and 2-Ethoxyethanol, a summary of 2-Alkoxyethanols (including available information on propoxyethanol in addition to 2-methoxy- 2-ethoxy- and 2-butoxyethanols), as well as the revised CICAD on Tetrachloroethene.

Acknowledgements

The International Programme on Chemical Safety (IPCS) wishes to express its gratitude to the Department of Health and Department for Environment, Food & Rural Affairs, UK, Environmental Protection Agency, Food and Drug Administration, and National Institute of Environmental Health Sciences, USA, European Commission, German Federal Ministry of Environment, Nature Conservation and Nuclear Safety, Health Canada, Japanese Ministry of Health, Labour and Welfare, and the Swiss Agency for Environment, Forests and Landscape for their generosity in providing financial support for the CICADs Project, which enabled the IPCS to convene this 12th Final Review Board. Thanks are also due to local organizing committee, chaired by Dr Marie H Sweeney for providing the meeting facilities and the practical arrangements of the meeting. Finally, appreciation is extended to the authors of the first draft documents, peer reviewers and FRB members, especially those who agreed to fulfil the roles of Chairman, Vice-Chairman and Rapporteurs, i.e., Drs Sweeney, Ziegler-Skylakakis, Fishbein, and Mr. Howe, respectively, as well as to those participants who acted as discussion leaders. They gave generously of their time and their expertise. The commitment of all the aforementioned has contributed to the success of the IPCS CICADs chemical risk assessment activity.

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Appendix I: Participants of the FRB Meeting

Members

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Appendix II: AGENDA

1. Opening of the meeting, election of officers and adoption of the agenda
2. Introduction to the Terms of Reference for Final Review Board members
3. Discussion of conflicts of interest
4. Draft CICAD on Brominated phenols¹
5. Draft CICAD on Butoxyethanol
6. Draft CICAD on Butyl acetates
7. Draft CICAD on Ethoxyethanol
8. Draft CICAD on Heptachlor
9. Draft CICAD on Methoxyethanol
10. Draft CICAD on Tetrachloroethene
11. Draft CICAD on Tin and inorganic tin compounds
11. Future CICADs
12. Any other business
13. Closure of the meeting

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¹ Consideration of each draft CICAD will be lead by the discussion leader

Appendix III: Terms of reference for a final review board

The Final Review Board is responsible for the following functions:

ensuring that each CICAD has been subjected to an appropriate and thorough peer review;

verifying that peer reviewers' comments have been addressed appropriately;

providing guidance to authors on how to resolve any remaining issues if, in the opinion of the Board, all comments of the reviewers have not been adequately addressed;

approving CICADs as international assessments.

The Final Review Board conducts most of its business at meetings, but when needed, also by correspondence after and before the meetings. It is guided in its work by the IPCS Programme Advisory Committee, and functions in collaboration with the IPCS Steering Group on Risk Assessment.

Appendix IV: Final review board comments on draft CICADs

For all CICAD drafts, the changes in the text to be reflected in the Executive summary.

Brominated phenols

Discussion leader: Dr J. Stauber

The FRB formally accepted the document as a CICAD given that changes would be made to reflect the points following. The redrafted document would be checked by the FRB Chair, primary reviewer and Rapporteurs.

General points

It was agreed that the title of the document should be changed to 2,4,6-Tribromophenol and other simple brominated phenols.

The unreliable Industrial Biotest study should be referred-to in a footnote only with no details of the results.

All reference to the abstracts from Lyubimov et al. to be removed from the text. The problems with the published study from Lyubimov et al. to be more emphasised in the text.

The test design of the OECD 422 study from Japan to be discussed in the text and reasons given why it should not be used to set guidance values; all text in Chapter 11 relating to guidance values to be deleted.

The uncertainties section to be expanded to cover the difficulties with the dataset.

QSAR data to be referred-to in a sentence in the text but not used for environmental risk assessment.

Check text to remove any suggestion that the OECD SIDS was a source document. OECD SIDS document to be referenced in an appendix. Add that UK document is being developed concurrently as a source document.

Specific points

Section 1

To be adapted to reflect the changes in the main text.

Lack of information on the possibility of presence of bromphenol in flame-retarded products to be included.

Para 3: “through waste streams “ to be deleted.

Para 11: delete following semicolon.

Para 18: delete last sentence

Para 20: see general comments

Para 21: rewrite to reflect extra data in chapter 10

Add paragraph on possible general population exposure from wood preservatives.

Section 2

No changes required

Section 3

Specify what the limits of detection apply to and add units (/litre?)

Section 4

Add information on use as a wood preservative and the possibility of human exposure (relate to Section 6).

Add qualitative information on the possibility of exposure from leaching following use in plastics although amounts unknown.

Section 5

Add extra information on the input data and the nature of the models used.

Section 6

See Section 4. Discuss human exposure from use as a wood preservative.

Section 7

No changes required

Section 8

Details of body weight changes to be added to the oral study in rats (paras 10 and 20).

para 19 – *per os* to be added

See general comments above.

Section 9

No changes required

Section 10

Response in comments table – marine data in 1978 book unusable.

Section 11

Delete final sentence of 11.1.1 para 6

11.1.2 delete guidance values and state that none could be determined.

Add mention of terrestrial data to evaluation in 11.2

Para 27: add year following EU TGD

See general comments above

Section 12

Change title to "... IOMC bodies" (general comment refers to all documents)

Website to be added as source of OECD documents

2-Butoxyethanol**Discussion leader: Dr R. Chhabra**

The FRB formally accepted the document as a CICAD given that changes would be made to reflect the points following. The redrafted document would be checked by the FRB Chair, primary reviewer and Rapporteurs.

General points

Make clear at the start of the Executive Summary why the CICAD is being updated to include extra studies (carcinogenicity), mechanism of action and extra information on exposure and harmonization of chemical-specific adjustment. The document will be a stand-alone new CICAD replacing the original.

When checking original CICAD, correct errors but this need not involve going back to all the original papers.

Check for consistency in the description of the weight of evidence of carcinogenicity (specific to mode of action).

Environmental effects sections to be added from previous CICAD, making clear that these have not been updated. Check Canadian document to ensure that no update is necessary and inform FRB if it is considered necessary.

Specific points**Section 1**

See general comment.

Make changes consistent with changes in main text.

Para 4: delete from beginning of paragraph to "...bioaccumulation is low".

Summarise evaluation and mode of action information from Chapter 10.

Section 2

No changes needed.

Section 3

No changes needed.

Section 4

No changes needed.

Section 5

No changes needed.

Section 6

Para 4: add information on input data used in the model.

Table 2: check figures in the 'concentration column'. Why is concentration in air greater than in the product (units wrong?).

Section 7

Para 1: detail on vehicle used in experiments and what the effect of different vehicles is.

Section 8

Addition of quantitative data considered adequate. No changes required.

Section 9

No changes needed.

Section 10

See general comment on description of carcinogenic mode of action.

Para 20: Make clear that the TC for fore-stomach effects is based on non-neoplastic lesions (irritancy) and not tumours. Better discussion on the mode of action here.

Clarify why the guidance value is based on rats and not mice with reference to the US EPA document on mode of action.

Section 11

Reference to the IARC evaluation in 2004 to be as footnote because post-cutoff date.

Appendix 1:

Add the dose response curve on haematological effects only (benchmark dose) here.

Appendix 3:

Introduction required for this outlining its origin, process and use in the evaluation.

External peer-review part of this Appendix to be moved to front as part of the description of the process.

Safety card to be updated.

Exposure information from EU document to be referenced in an appendix.

Butyl acetates

Discussion leader: Debbie Willcocks

The FRB formally accepted the document as a CICAD given that changes would be made to reflect the points following. The redrafted document would be checked by the FRB Chair, primary reviewer and Rapporteurs.

General points

IRIS to be added to the source documents.

Specific points

Section 1

Add a paragraph summarizing exposure concentrations.

Para 5: needs rewording to emphasize that t-butyl acetate is not readily metabolized.

Para 6: In second sentence delete 'moderately toxic' and replace with indication of data range.

Para 7: delete second sentence.

Para 11: Replace second sentence with 'Sensitivity to odour occurs at concentrations several orders of magnitude lower than levels at which nose and throat irritation are reported.'

Section 2

Para 1: clarify which isomer the odour thresholds refer-to where possible.

Table 1: To be modified in accordance with CICAD guidelines (only include the list of properties indicated there and refer to the card for all others)..

Section 3

Add NIOSH method.

Section 4

Para 16: combine text with Table 2.

Para 18: Reference to be checked to confirm figures; release seems high compared with production.

Section 5

Check references and cite originals where possible (for example the EPIWIN model as source of volatilisation from a river).

Section 6

Section 6 headings in guidelines should be reviewed (general point for consideration by the Steering Group).

6.2; Para 7: Author to clarify that this should be a minor source of exposure.

Section 7

Para 16: Delete 'template'

Section 8

Detail addressed.

Table 5: OK as it is.

8.2; Para 13: author to check value for LC50

8.6; Para 41: replace 'clean' with 'negative' for description of genotoxicity profile in last sentence.

8.7; Check against MAK data

Section 9

Paras 2 & 8: Paragraphs to be condensed. Discussion of study limitations to be added (subjects aware of exposure etc.) with less emphasis on multiple chemical sensitivity. Subheadings to be removed.

Section 10

No further changes.

Section 11

Para 2: Author to modify text.

11.1.2; Para 7: Move paragraph to uncertainties section (11.1.4).

11.1.3; Para 11: Author to clarify the use of the guidance values derived in 11.1.2; indicate that reported exposure value is close to the guidance value (also add to summary). Specify that the studies refer to n-butyl acetate.

11.1.3; Para 12: Move paragraph to section 12.

11.1.4: Author to bring together various bits of text on uncertainties from throughout Section 11.

Section 12

Para 3: Delete last sentence.

IRIS to be added as a source document.

2-Ethoxyethanol

Discussion leader: Dr J. Kielhorn

Another round of peer-review is needed and document to be reviewed again at an FRB for approval.

General points

Author to check the draft EU document and extract extra studies on effects and data on exposure.

MAK document to be cited as a source document to help identify the critical study to derive a guidance value for consumers.

Indicate that consumer products should not contain the substance.

Text in evaluation on the “worst case” approach used in the Canadian source document to be removed.

Acetate to be added to title; to be revised following literature search for more information on the acetate particularly regarding physico-chemical properties.

Specific points

Section 1

Not discussed – to be modified in accordance with changes in the new draft.

Section 2

Add physicochemical data following the guidelines (including that for the acetate).

Section 3

Para 1: detail in table adequate – fill in comments table response.

Table – update the NIOSH reference and add limits of detection.

Check EU document for analytical methods.

Section 4

Extra information on presence in consumer products to be added (EU document)

Comment on discrepancy between production and use figures.

Possible reduction in coverage of Canadian data if global data available.

Section 5

No changes required

Section 6

Add extra information on workplaces and extra data from EU document on exposure.

No further detail required on locations of monitoring (add to response column in table of comments)

Paras 7, 8: Extra information on consumer products

Paras 9, 11, 14: add detail on modelling

Extra information on exposure of Chinese workers (Dr Liang) to be included.

Section 7

Level of detail now OK.

Check against EU document.

Para 12: author to check papers and modify text on PBPK modelling as required.

Para 13: delete detail but retain first sentence with “...however does not consider dermal exposure...” added.

Add metabolic pathways figure.

Section 8

Check EU document for extra studies and relevant detail but bear in mind that the detail requested by some reviewers is too much for a CICAD.

Para 3: do not include the requested information on renal toxicity (respond to comment in table)

Add mode of action section if information is available from the EU document beyond the modelling in Section 7.

Section 9

Do not include the extra study suggested on renal effects (comments table)

For more general text on case studies check EU document. Paras 1 and 2 to be replaced with condensed text.

Add extra information on other exposures, where possible, to epidemiological studies.

Section 10

Tabulation/plotting of effects data including any extra information from the EU document (SD to assist the author).

Check additional study on seed germination (reviewer's comment).

Section 11.1

See general comments. Screening assessments in sample risk characterization to be removed. Succinate dehydrogenase material not to be included – change comment table response.

Section 11.2

Worst case risk assessment from additional monitoring data to replace modelled data where possible. Use additional material from EU document if available.

Heptachlor

Discussion leader: Dr C. DeRosa

The FRB formally accepted the document as a CICAD given that changes would be made to reflect the points following. The redrafted document would be checked by the FRB Chair, primary reviewer and Rapporteurs.

General points

Comments addressed very well by the authors so specific comments only.

Specific points

Section 1

Summarise evaluation.

Add summary of effects on humans

Para 21: delete.

Section 2

Para 1: Information on formulations not required.

Section 3

No changes required.

Section 4

No changes required.

Section 5

Para 5: add definition of ThOD and BOD.

Section 6

Para 7: revise sentence and remove “although”.

Para 25: add text from reviewer as a base line for adipose tissue levels pre-restrictions (plus reference) and compare to modern data. Fill in response in comments table.

Make new para 25.

Current paragraph 25: Paragraph removed from here and moved to Section 9.

Para 30: Split text on food (final sentence) into two sentences to clarify.

Section 7

Add footnote to figure equating different terminology for compounds.

Para 2: replace storage factor with “bioaccumulation factor” (BAF).

Section 8

Para 22: describe fertility and developmental effects from these studies in appropriate sections (8.6.1 or 8.6.2)

Para 22: “compound-related” - author to check if can add “dose-related” too.

Para 31: editorial decision needed on how to cite studies cited in secondary document (Antero Aitio to clarify with editor).

Section 9

Para 6: delete.

Para 14a: add a paragraph on sensitive populations exposed via the diet to high doses (developing foetus at risk; cover possible physiological sensitivity).

Section 10

No changes needed.

Section 11.1

Para 23: Delete or author check why text is here. Add response to comments table.

Section 11.2

Author to work with Jenny Stauber to develop probabilistic approach to add to environmental risk assessment.

Section 12

Para 1: replace “carcinogenic risk” with “carcinogenicity”.

Add that heptachlor is on PIC and POPs.

Delete para 5.

2-Methoxyethanol**Discussion leader: Prof Y. Liang**

Further peer-review of the document will be required followed by discussion at the next FRB.

General points

Significant extra information is available on both exposure and epidemiology from recent Taiwanese studies to be added. The possibility of deriving a guidance value from the Shih et al. (2002) study to be assessed. Study to be looked at by epidemiologists (Herman Gibb and Marie Sweeney).

Information from SPIN database to be added on presence in consumer products together with extra Canadian survey of products. Check whether used as a component of insecticidal formulations.

Include acetate in the title.

Specific points**Section 1**

Reflect changes in text.

Make clear that substance still being used in parts of the world despite risk management being in place in many countries.

Section 2

Add structure for acetate.

Section 3

NIOSH method to be added.

Section 4

See general comments (SPIN and Canadian data).

Section 5

No changes needed.

Section 6

Section 6.2: Reviewer's comment on possible synergy/additive interaction to be discussed in overview document on alkoxyethanols in general.

Para 15: add reference provided by reviewer 4 with some detail (less than proposed by reviewer).

ara 15: justify use of high dermal absorption figure (100%).

Section 7

Add metabolic pathway figure.

Section 8

Add detail for critical studies only. However, bear in mind that critical study might change (Taiwanese information).

Current additions of quantitative information considered adequate.

Para 10: delete last part of final section to remove conclusion.

Para 19: more detail to be added on monkey study if it remains key.

Section 9

Para 9: Marie Sweeney to check the El-Zein study on female workers.

Section 10

Suggested *Xenopus* study not to be added.

“Toxicity threshold” to be checked (reviewer’s comment)

Tabulate/plot information (Stuart Dobson to assist).

Section 11

Section 11.1 may change substantially – see general comments.

Dermal absorption to be added to ‘uncertainties’.

Tetrachloroethene

Discussion leader: Bette Meek

The major re-draft of the document will be looked at by a Consultative Group and re-considered at the next FRB meeting.

General points

Conflicting comments had been received from reviewers many of which the author had started to address in the latest draft. However, there were outstanding issues relating to:

- The weight of evidence regarding human carcinogenicity
- Animal carcinogenicity studies (mode of action)
- Neurotoxicity (implication of epidemiology)
- Reproductive toxicity (human studies)

The EU process will possibly have a re-drafted text on carcinogenicity by the end of 2004 and a re-draft of neurotoxicity by early 2005. A US EPA discussion and conclusion is available on neurotoxicity.

The proposal is for a Consultative Group to be convened to discuss these issues, particularly from an epidemiological perspective.

The document will be redrafted with an attempt to derive guidance value based on neurotoxicity.

The environmental sections of the document were considered adequate but a sub-Group of the FRB would consider how they might be condensed.

Specific points

Section 2

OK

Section 3

Section 3.2 (biological monitoring) to be condensed with some indication of the appropriateness/utility of each method. Occupational hygienists to help.

Section 4

Para 4: 2nd sentence: check the definition of ‘demand’; this cannot be production plus exports.

Para 4: Add emissions data.

Section 5

Condense (Environment sub-Group)

Section 6

Summarise and give overview (trends, groundwater contamination from waste sites etc.) if possible (Environment sub-Group)

Section 6.3: Add NIOSH data on trends in occupational exposure (Chuck Geraci to provide)

Section 7

Section 7.3 ‘biotransformation’ condense to ranges over several studies; keep the message in this Section of species differences in metabolism and extrapolation to humans. Check summary in source document (EU).

Section 8

Consultative Group

Section 9

Consultative Group

Section 10

To be checked by Environment sub-Group

Section 11

Consultative Group

Tin & Inorganic tin compounds**Discussion leader: Dr R. Hertel**

The FRB formally accepted the document as a CICAD given that changes would be made to reflect the points following. The redrafted document would be checked by the FRB Chair, primary reviewer and Rapporteurs.

General points

Editorial: tin terminology needs to be standardized throughout the document.

Specific points**Section 1**

Para 2: Replace 'silver-white' in first sentence with 'grey-white'.

Para 8: insert 'food or juice containing...' into fourth sentence after 'In humans, the acute ingestion of.....'

Para 8a: delete '...unmeasured, but probably high, levels...' from the first sentence.

Para 10: Modify according to changes in section 11.

Para 11: Summarise exposure of environmental organisms (opening statement of para 11) and summarise evaluation.

Section 2

No further changes.

Section 3

No further changes.

Section 4

No further changes.

Section 5

No further changes.

Section 6

Para 16: JECFA covers the whole world; CMI covers only the USA but agrees that the value for lacquered cans is OK; therefore, no changes necessary.

Section 7

Para 5: Japanese article on levels of urinary tin to be checked by Dr Ishimitsu

7.2; Para 11: At the beginning of the paragraph replace 'In unexposed humans' with 'In humans with no occupational exposure'.

7.4; Para 24: After the second sentence insert percentages for faecal excretion.

Section 8

8.4; Para 19: Add to fifth sentence ‘...not found in the NTP study using higher doses’.

Paras 34 & 35: ‘good quality’ to be replaced with ‘NTP’.

8.6.1; Para 40: In the last sentence delete ‘...of the females..’.

Para 52: More detail now provided from the Dimitrov study. Comment adequately addressed.

Section 9

No further changes.

Section 10

No further changes.

Section 11

Check the papers in para 7 of section 9 and if necessary delete ‘high concentrations’ from the first sentence of para 1.

Section 11.1.3.2: Author and discussion leader to revise text. Comparison with the JECFA PTWI to be removed and replaced by comparison with the toxic effects reported in the text.

Section 12

Change title to ‘IOMC bodies’

Footnote that JECFA will re-assess acute effects but not change PTWI.