

**IPCS**

**International Programme on Chemical Safety**

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

**Ottawa, Ontario, Canada: 29 October -1 November 2001**

**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 Aitio, on behalf of the Programme for the Promotion of Chemical Safety, World Health Organization, and Ms Meek, on behalf of Health Canada, opened the meeting and welcomed the participants. Dr Aitio expressed thanks for the support of Health Canada in making available the facilities for the meeting.

The meeting opened with the election of officers: Dr De Rosa was elected as Chair and Dr Dobson as Vice-Chair (Chair for polychlorinated biphenyls CICAD) and Dr Kielhorn and Mr Howe 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 9<sup>th</sup> Final Review Board (FRB) declared any conflict of interests.

## **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 and Observers, namely that Members are responsible for taking the formal decisions on the CICADs, whereas Observers are restricted to commenting on the factual content of the documents. Members were reminded 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**

The FRB systematically reviewed responses of the authors to each comment 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. The tables of peer-review comments are to be held by the Secretariat and made available, upon request.

### ***Acrolein***

The CICAD on *Acrolein* 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 IV.

### ***Bromoethane***

The CICAD on *Bromoethane* 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 IV.

### ***4-Chloroaniline***

The CICAD on *4-Chloroaniline* 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 IV and pending peer review and approval of the revisions in the evaluation section by a consultative group.

***Polychlorinated biphenyls (Human health aspects)***

The CICAD on *Polychlorinated biphenyls (Human health aspects)* 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 IV and pending the approval of authors' responses to the late comments by the Chair and Discussion leaders.

***Diethyl phthalate***

The CICAD on *Diethyl phthalate* 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 IV and pending peer review and approval of the revisions in the Section on the evaluation of human health effects by a consultative group and of the probabilistic environmental risk characterisation (to be formulated by the author) by another consultative group.

***Carbon disulphide***

The CICAD on *Carbon disulphide* 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 IV.

***Silver (Environmental aspects)***

The CICAD on *Silver* 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 IV.

***Ethylene glycol (Human health aspects)***

The CICAD on *Ethylene glycol (Human health aspects)* 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 IV and pending the verification of the reliability of the essential non-public source material used as well as approval of authors' responses to late comments by the Chair and the Discussion leader.

**OTHER BUSINESS****10<sup>th</sup> and subsequent Final Review Board meetings**

The 10<sup>th</sup> FRB is planned to take place in August-September 2002. The draft CICADs proposed for consideration at the 10<sup>th</sup> FRB are: Arsine, Asphalt, 1,1-Dichloroethylene, Ethylene oxide, Hydrogen cyanide and cyanides, Hydrogen sulphide, Thiourea, and 1,2,3-Trichloropropane. The closing date for the receipt of first draft of CICADs is the end of January 2002.

Other draft CICADs proposed for consideration at future FRB meetings are: Creosote; 2-Diethylaminoethanol; Crotonaldehyde; Glyoxal; 2-Mercapto benzothiazole.

**General issues for consideration by the Steering Group**

- Citation of unfinished documents, for example, EU documents.
- Dealing with papers with different information content and importance vis-a-vis risk characterization published beyond the cut-off date for the CICAD literature searches.
- Identifying conflicts of interest of peer reviewers and informing the FRB of such conflicts
- International evaluations included in Section 12.
- Informing the peer reviewers and CICAD readers of the availability of the supporting document
- Process and format of the response of authors to peer review comments
- The level of detail on a study or end-point specifically in relation to inclusion in CICADs vs reference to the source document.
- Process to deal with important changes in the CICAD caused by comments received in the international peer review, such as changes in critical end-points, key studies, approaches in hazard characterization, setting uncertainty factors, major changes in exposure scenarios for the sample risk characterization
- Coordination in time of FRB and Steering Group meetings; processes to get Steering Group advice on a very short notice
- Use of data from developing countries (including how to include data; a more formalized system for retrieving information)

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**APPENDIX II**

**Agenda**

**NINTH FINAL REVIEW BOARD ON CONCISE INTERNATIONAL CHEMICAL  
ASSESSMENT DOCUMENTS**

**Ottawa, Ontario, Canada: 29 October-1 November 2001**

**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. Draft CICAD on Acrolein
4. Draft CICAD on Bromoethane
5. Draft CICAD on Chloroaniline
6. Draft CICAD on PCB (Human health aspects)
7. Draft CICAD on Diethyl phthalate
8. Draft CICAD on Carbon disulphide
9. Draft CICAD on Silver (Environmental aspects)
10. Draft CICAD on Ethylene glycol (Human health aspects)
11. Future CICADs
12. Any other business
13. Closure of the meeting

= = =

**APPENDIX III**

**Terms of Reference**

**NINTH FINAL REVIEW BOARD ON CONCISE INTERNATIONAL CHEMICAL ASSESSMENT DOCUMENTS**

**Ottawa, Ontario, Canada: 29<sup>th</sup> October-1st November 2001**

**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 also by correspondence between meetings. It is guided in its work by the IPCS Programme Advisory Committee, and functions in collaboration with the newly-formed IPCS Steering Group on Risk Assessment.

## APPENDIX IV FINAL REVIEW BOARD COMMENTS ON DRAFT CICADS

### Acrolein

*Discussion of the draft CICAD on Acrylonitrile was led by Mr. Richard Cary*

#### *Discussion leader notes*

Acrolein is a highly reactive molecule and does not seem to persist very long *in vivo* or in the environment. Aquatic organisms appear to be more sensitive to acrolein than terrestrial organisms. However, the information available to the authors indicates that the likely exposure levels do not result in a risk of adverse effects. There are no adverse effects anticipated for other environmental factors (e.g. ozone depletion, climate change or the formation of photochemical smog). In terms of human health, there are no immediate concerns of carcinogenicity and genotoxicity from the available data on acrolein, although these data are of limited quality. Hence, the main adverse health effects observed relate to upper respiratory tract irritation and these are the effects that form the basis of the guidance values that are derived.

#### *Specific comments*

- |                             |   |
|-----------------------------|---|
| Section 1                   | Summary section to be changed to reflect changes in main text.  |
| Section 1,<br>para 5        | Sentence on epidemiological data to be expanded to a paragraph of its own to indicate that available human data on systemic effects are very limited and did not enter into overall conclusions. A reference be made to effects on the respiratory tract and eye.<br>No need to include information on anti-cancer drug (reviewer 10 comment unaddressed in table of comments)  |
| Section 2,<br>para 2        | In response to the reviewer's comment; it would be possible to resolve the reasons for the considerable ranges on the physicochemical data. However, this would be time-consuming and is not relevant to determining risk for this compound. The current ranges can be left as they are.  |
| Section 4.3                 | Dr Kielhorn to provide production levels data.  |
| Section 5.2                 | Anaerobic and aerobic appear to be reversed since intuitively aerobic degradation should be greater - to be checked by author.  |
| Section 7                   | If there is no information on oral and dermal absorption, and the magnitude of binding, then it was suggested that it should be stated that there are no data.  |
| Section 8.1                 | Insert specific reference to source document for detail on signs of acute toxicity.   |
| Section 8.2                 | Add that limited data indicate that acrolein may be a skin sensitizer.<br>The EU document cannot be cited as the source since it is not yet complete. Citation of individual studies together with a footnote on the existence of the EU document.<br>The poor quality of the studies should be indicated.<br>Add sentence on effects on ciliary beat in the upper respiratory tract (reviewer 7 – comment on extra study from the BUA document). |
| Section 8.3                 | Deleted LOAELs to be retained or a description of the lowest effect concentrations to be added to the text.   |
| Section<br>8.3.1, para<br>6 | Number of animals to be added for the Cassee et al. (1996) study where it currently states these are not available – text in Chapter 11 (11.1.3.1 para 17) indicates numbers are available.   |
| Section<br>8.3.1 para<br>11 | Copy response statement on systemic effects from table of comments (reviewer 10) to section 8.3.1.  |

- Section 8.5    Extra material on genotoxicity to be provided by Dr Chakrabarti to update to 1998.  
Drosophila test not to be included in this section – leave as is.
- Section 8.8, para 33    Replace DNA adducts by the more general term DNA damage. (see also 11.1.1.2)
- Section 9    Add to Ott study: include confidence limits - if not possible then add p-value.
- Section 11.1.2, para 14    Check that first sentence is consistent with the main text (Sect 8.5)
- Section 11.1.3.1, para 19    Currently, the median figure has been used rather than the lower 95% confidence limit (note in bullet point 1 after equation). Indicate the value derived if the lower 95% limit was used instead either here in the text, in a footnote or an appendix.
- Figure 2    Interchange the names of S-(2-carboxyethyl)-mercapturic acid and S-(3-hydroxypropyl)mercapturic acid

Table of comments – list of reviewers

Replace C. Eichler with R. Hertel; correct Dr Ziegler-Skylakakis' affiliation; add Dr Ziegler-Skylakakis among reviewers (comments received on early document drafts)

## Bromoethane

*Discussion of the draft CICAD on Bromoethane was led by Dr Jun Sekizawa*  
Comments have been responded to in an appropriate manner.

### *Specific comments*

Section 2, Dimensionless Henry's Law discrepancy between Sec 2 and Sec 5. Check.  
para 1

Section 2, Check conversion factors  
para 2

Sec 4.2 Add production data (Jun Sekizawa to provide)

Sec 5 para 3 Check solubility

Sec 6.2.1 EASE Model: Introduce model e.g. This model is used to measure..... together  
para 5 with source where it can be obtained. Give input data either as footnote or  
appendix. Give reference to EU Technical Guidance Document.

Sec 7 Para 1 The authors are to consider Paper from Thier et al., which Jun Sekizawa will  
provide (response to Reviewer 7)

Sec 7 p. 9. Line 6 change bromine to bromide  
para 2

Sec 8.1.1 Check conversions mg/L - ppm.  
Paras 2 and  
3

Sec 8.2. Para Delete para  
9

Sec 8.4 paras Recheck incidence figures. Add information about historical tumour incidence  
15 & 17 data from tabulated comments page 9 Sec 8.4 para 17 reviewer 10.

Paras 19 & Change order of the paragraphs 19 & 20  
20

Section Weight of evidence for carcinogenicity. Put together information from Section  
11.1.4 11. Para. 6,11 and 12 (Is bromoethane a genotoxic carcinogen or not?  
Bromoethane is a direct-acting alkylating agent but induces tumours not at the  
site of entry but rather at distant sites, such as the uterus) into new para 21.  
Delete old para 21

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Table of comments & responses: P.4 Sec 6.2 Reviewer 9. Change in response: Not usual to  
add occupational exposure limits in a CICAD.

## 4-Chloroaniline

*Discussion of the draft CICAD on 4-chloroaniline was led by Dr Raj Chhabra in a teleconference*

The FRB considered the document to be well written and that the authors had made considerable effort to deal with reviewers comments.

The critical end-point and key study have been changed following proposals received in the peer review. While the FRB endorsed these changes, it considered it essential that the revised evaluation of health effects be reviewed by peers, and suggests the consultative group approach.

### *Specific comments*

Section 1	Changes in the text (especially in section 11) to be reflected in the executive summary.
Section 1, para 2	Include MAK document as source document.
Section 1, para 17	To be changed to reflect the wording in section 11.2
Section 4.2	Mr Howe to provide US EPA release data..
Section 4.3, para 5	Delete 'can affect human health' in last sentence.
Section 5.1, para 1	Comma missing in sentence, which makes the meaning ambiguous.
Section 5.2, para 4	Terminology (half-time vs. half-life) to be verified.
Section 5.2, 5.3	Not degradation – adsorption. Dr Dobson to aid with making the conclusion clearer.
Section 6.1, para 3	Analytical methods – explain where limits of detection refer to analytical equipment and where to method. (current text gives the impression that some reported concentrations are below the limit of detection).
Sections 6.2.1, para 12 & 6.2.2, para 15	Calculations need to be checked.
Section 6.2.2, para 19	Add 'because products may contain PCA as a residual'.
Section 8.1.1, para 2	Uncertainties – possible contribution of dermal adsorption of vapour to body burden. Author to check paper (Russian)
Section 8.4, para 10	Replace NOEL with NOAEC(L)
Section 8.5.2, para 17	Add author's response to reviewer 10 to section 8.9 (Mode of Action Section).
Section 8.6.2	Dr Chhabra to provide further data on MN from NTP to author.
Section 8.6.2, para 23b	Paragraph to be deleted.
Section 8.7, para 24b	Delete paragraph.
Section 8.9, para 28	Second sentence to be reworded to indicate that there is one positive in vivo study on MN, but this was only positive at a dose level in the range of the LD <sub>50</sub> .
Section 9, paras 1 & 3	Replace resorption with adsorption.

Section 9, para 2	Dr Gibb to check the studies in this paragraph with view on the interpretation of causal link between exposure to chloroaniline and methaemoglobinaemia in humans.
Section 9, para 4	Replace 'traced to' with 'reported to be associated with'.
Section 9, paras 4b & 4c	Paragraphs to be revised by Drs Sweeney and Gibb to verify the causality and exposure-response relationships reported.
Section 9, para 4c	Last sentence of paragraph to be deleted.
Section 10.1 & Table 10.1	Common names of organisms to be provided by Mr Howe.
Section 11	Ms Meek to aid author with reorganizing hazard identification, exposure-response assessment and criteria for setting guidance values: Reorganize order and remove subheadings Delete first paragraph (summary). Emphasize the methaemoglobin formation (critical endpoint). Remove more detailed descriptions of the data throughout. Animal data in paragraphs 4 and 5 to be moved before the human data. Delete LD50 values. Cross-reference between animal and human data.
Section 11.1.1, para 7	Paragraph needs to be revised subsequent to the NTP study being reviewed.
Section 11.1.2	Animal data should be used to set the guidance value with human data being used to bound the animal data.
Section 11.1.2 para 8g	Delete second sentence and emphasise that the human data is based on a sensitive population.
Section 11.1.2 para 9	Delete paragraph.
Section 11.1.3, para 19	Delete paragraph.
Section 11.1.4	Add uncertainties regarding human exposure data (possibility of dermal exposure) to this subsection. Note the weaknesses of the human study design)
Section 11.1.4, para 22b	Paragraph to be deleted.
Section 11.2	Add scattergram
Section 12	Delete second paragraph (one line).
Figure 7.3	For the 4-aminophenol replace Cl with OH

## **Polychlorinated biphenyls (Human health aspects)**

*Discussion of the section 9 of the draft CICAD on Polychlorinated biphenyls (Human health aspects) was led by Dr MH Sweeney, and of the other sections, by Ms ME Meek*

### **General**

The draft has vastly improved since presentation at 8<sup>th</sup> Meeting. It is more explicit and inclusive. It should be made sure that the executive summary accurately reflects the body of the text and the evaluation section. It should be clearly stated what is the object of evaluation and what is our explicit approach. For different exposure scenarios there are different approaches, notably because of different isomer composition, e.g., in the environment the profile of the mixture changes. This CICAD concentrates on situations where the mixtures approach is valid. Other approaches should not be described in detail but should be noted with an indication of the special circumstances where these approaches might be more appropriate (with reference where possible).

The Secretariat had received additional comments on the document from a stakeholder organisation, mostly on details in the section on human health effects. Because of the late arrival of these comments, it was not possible for the author or the FRB to consider these comments by the time of the meeting. Furthermore, the health evaluation section of the document is mainly based on experimental studies, rather than on epidemiological findings. Thus the FRB considered it sufficient that the author considers these new comments after the meeting, and revises the document where needed. The adequacy of the author's response to these comments will be verified by the discussion leaders, and the Chair.

### **Specific comments**

- Add list of abbreviations and acronyms used.
- Section 1 Changes in the text to be reflected in the Section 1.
- Section 1 Remove description of history of the document (Executive summary, para 1) to para 1 the Appendix.
- Section 1 (which will become para 3 in the final Section 1, see below). Put into historical para 2 context the sentence on risk management.
- Section 1 Paragraph 14 should be subsumed in a new para 2 in the Executive summary, which identifies the PCB mixtures that are discussed in this CICAD (commercial PCB mixtures and mixtures generated from them, e.g. in the environment and food chain), and makes explicit the hazard characterization approach chosen as the basis in this document. The other approaches should be briefly mentioned with a reference (and thus deleted from Section 10, para 17-18).  
It should be stated that there is much more data in the source document.  
It should be stated that this document does not deal with heating-induced contaminants of PCB, but describes, however, briefly the studies on Yusho and Yucheng patients. It should also be made clear that, in many instances of both epidemiological and experimental studies, the exposure has been to a mixture not only of PCBs with varying and unknown composition, but also to PCDD /PCDF, and even other POPs.  
Ongoing work at WHO should be mentioned, perhaps as a foot-note.

Section 1 para 10	Delete reference to mink
Section 1 para 12	the first part refers to exposure in the US; this should be indicated
Section 2 para 1	Add at the end of the para that the subject of the present CICADs is commercial mixtures of PCB, and mixtures generated from them in the environment and food chain.
Section 3 para 3	Check detection limit
Table 6	Move to Section 6 (with reference to table in para 5).
para 6 and elsewhere	When describing a study, remove the term "recent".
Section 5. para 6	Delete last sentence.
Section 5 para 7	Combine with para 8. Add "in tuna.", after "of PCB congeners 84"
Section 5 para 9	Line 1. PCBs <u>generally</u> .....
Section 5 para 10	Reinstate the Geyer study. Provide reference for the PCB concentrations in the adipose tissue in the sentence after (Geyer et al., 1986); move this information to Section. 6.2.
Section 6.1	Dr Dobson to condense by removing information only relevant to environment (such as soil, sediment and sludge).
Section 6.2	Order more logically e.g. by putting breast-milk samples together.
Section 6 para 7	Delete ..."the NIOSH recommended exposure limit" ..[keep figure 1000 µg/m <sup>3</sup> ].
Para 11	Clarify [These?]. Add which tissues of the fish (muscle?).
Para 12	Delete.
Table 8	Reword the title to indicate that this is US data from 1982-1984. Emphasize this in para 9 and para 12 of Executive Summary.
Section 7 Para 5	line 5 Delete sentence ..."Metabolites are found..."
Para 7	Delete :.. this may..... children.
Section 8 para 3	Delete sentence ...The NOAEL...
Table 9	Heading: "dose-response observed". Check the accuracy of the footnotes.
Section 8.3	In toxicological animal studies in particular long-term carcinogenicity studies, indicate purity of Aroclor samples, to what extent they are likely to contain PCDD/PCDF contamination. Identify studies, where the contamination was small (Meyes & Brunner?).
Para 6 and para 11	Brunner & Meyer. Put together (same study).
Section 8.4 para 18	Delete.
para 21& 22	Combine the paras.
Section 8.5	Delete paras on mink.
para 28 and 30	Delete.
Sec 8.5.1 and 8.5.3	Add information on parental toxicity.
para 40	Clarify that this study deals with developmental effects.
para 43	Replace by "In a range of experimental animals including primates, PCB induces fetal mortality, neurological defects, immunological changes at doses not causing parental toxicity."
Para 46	Delete: "At relatively.....immunological effects."
Para 47	Specify that in all species studied, immunological effects were observed at high doses. In some species they were also observed at low dose levels; primates are among the sensitive general. Replace "The effects of..... to development" by "See section 8.5.3".
Section 8.7	Change title to read: Neurochemical effects.

- Section 8.7 Replace the paras 48, 49, 50, 51, 52 with:  
"PCB isomers 153 and 128 and Aroclors 1254 and 1260 induced changes in neurotransmitter levels in different areas in the central nervous system in the rat. Levels of dopamine were also lowered in several anatomical locations of the brain in monkeys fed Aroclor 1016 (ATSDR 2000)."
- Section 9 Dr Sweeney to assist in selecting, and condensely describing the studies to be presented in the CICAD, with reference to studies important in assessment of the weight of evidence of causality. Not all studies are to be presented, reference to be made in this section specifically to source document Studies on Yusho and Yucheng to be kept, but with an opening qualification that the exposure was not only to PCB but also to PCDF (PCDD). Add blood levels of PCB /PCDD/PCDF in Para 10 p.46.  
The studies may be presented in tabular form if this is expedient and not likely to lead to misleading conclusions.  
Summary paragraphs (such as para 17, 31, 36, 40): delete the words "weight of evidence"; present the essential contents of the section, not an evaluation.  
The whole of Section 9, especially the Sections 9.1, 9.3, 9.4 and the description of Yusho & Yucheng in all sections, should be markedly condensed as the human data are not used in the hazard characterization.
- Para 18 *fes* should read *fos*; Delete last sentence of the para
- Para 31 See general comments on summary paragraphs above; Delete However.
- Section 10.1 Open by brief description of the approach selected (which also appears as the second para in the executive summary, see above) and the circumstances where it is most appropriate. This opening will subsume the bulleted list in para 12, which thus will disappear.  
As a second para, introduce a short recapitulation of data from humans and their limitations, i.e., why they were not used in the hazard characterization.  
Delete the last sentence in para 1.
- Section 10, para 9 Rephrase the last sentence to reflect the new section 9.
- Section 10.3 State clearly that risk characterization is from US data.
- paras 11-12 Delete the notion that the mixtures approach is well suited for assessing PCB-related hazards from environmental / dietary exposure.
- para 11. Delete reference to US EPA.
- para 12 Delete reference to US EPA RfD.  
Delete ...(from leaking..... to end of para.
- Para 13 (first of the two) Add as a new para a brief summary of the results of the other approaches (as presented by Dr Faroon to the FRB)
- Para 13 (first of the two) Provide reason for only using Factor 3. Add to uncertainties section.
- Section 10.4 Delete "environmental" on the third line up; indicate instead that environmental/dietary exposure is qualitatively different from the commercial mixtures used as the basis of risk characterization in this CICAD
- Para 16
- Section 10.4 Delete.
- Para 17, 18

## Diethyl phthalate

*Discussion of the draft CICAD on diethyl phthalate was led by Dr Janet Kielhorn*

### General

Authors for environmental effects section to be added to author list on front page.

Body weight to be added to mg/kg/day wherever applicable.

As the critical end-point and key study have been changed at a proposal from the peer review (and the human health effects evaluation in its present form thus has not been peer reviewed), a consultative group is to be set up to discuss and peer review Section 8.9 and Section 11.1 on evaluations; including the selection of end-point and of critical studies, setting of uncertainty factors and the use of the biological monitoring approach.

It was noted that if the biological monitoring approach outlined in section 11.1.3 is used then the studies should be described in detail in the comparative kinetics section.

As an alternative to the present, a probabilistic environmental risk characterization to be written and then reviewed by experts in the area.

	List of acronyms and abbreviations to be produced.
Section 1	Changes in the text to be reflected in the Section 1.
Section 1	Cut off date in summary should be changed to reflect the most recent systematic literature survey.
	The summary section will have to be revised following the reporting of the conclusions from the consultative group.
	Human data on irritancy to be reflected in the summary.
Section 1, para 3	Replace 'level' with 'concentration'.
	Replace 'bioaccumulate' with 'biomagnify' in the last sentence.
Section 1, paras 4 & 12	Incorporate information regarding the differing exposures in different countries (see also comment for section 11.1.4).
Section 1, para 6	Author to reword 3 <sup>rd</sup> sentence beginning 'However, no clinical.....' to reflect the main text.
Section 2	Dimensionless Henry's Law Constant to be added (see table of comments).
Section 2, table 1	Replace HSDB with primary references.
Section 3	Remove ATSDR 1995 from the title.
Section 3, paras 2, 4 & 5	Add method of detection to these paragraphs.
Section 3, para 6	Add detection limit for analytical method.
Section 3, para 6	The following changes suggested in the table of comments should be incorporated: 'preferred' should be deleted 'than is ECD' should be deleted
Section 2, para 2	Insert a dot after (MS) and thereafter: 'MS is preferred before ECD' Amend last sentence to accommodate a further study: although no diethyl phthalate was observed in blood infusion or dialysis tubings in a limited study in Germany, there may still be.... and add to references: Wahl et al., 1999) (Wahl HG, Hoffmann A, Häring H-U, Liebich HM (1999) Identification of plasticizers in medical products by a combined direct thermodesorption-cooled injection system and gas chromatography-mass spectrometry. J Chromatography A 847: 1.7.

Section 4, para 3	Production data to be provided by industry observer. Api (2000) reference to be checked to determine the scope of the survey. In other words to find out if the use data are worldwide or just for the U.S.
Section 5, para 7a Section 5.2	Release data from US EPA to be moved to section 4. Dr Dobson to help author with checking this section. Extra information on degradation and adsorption to be provided by industry observer. Chinese papers provided by Dr Chen related to fate in soil, water and rubbish to be considered for inclusion.
Section 6.1, para 4	Move paragraph to section 5. Check the accuracy of the figure 0.00039.
Section 6.1, para 9	Check sediment concentration values.
Section 6.2, para 12	Delete last 3 sentences of this paragraph.
Section 6.2, para 15	Last sentence needs clarifying.
Section 6.2, para 17	Concern was raised about the level of DEP in cosmetics. It was felt that if levels of 50% were correct then this should be flagged in the uncertainties section. However, it was also pointed out that there is limited uptake via the dermal route. The DEP content of cosmetics, and especially perfumes, to be checked by industry observer.
Section 7.1, para 1	Add study by Blount et al. (2000) (see table of comments).
Section 7.1, para 4	The last sentence should be deleted.
Section 8.2	Dr Hertel to check EU documentation regarding irritation to eyes, respiratory system and skin.
Section 8.2	Author to check if there are any standard dermal irritation studies and to state in the text if there are not.
Section 8.2, para 3	Local irritation at what grade? (see table of comments).
Section 8.2, para 4	Doses to be added for lymph node assay (see table of comments).
Section 8.4, para 8	Last 2; sentences check NOAEL.
Section 8.5, para 9B	Paragraph to be deleted.
Section 8.5, para 9c	Replace last sentence with an explanation that due to the small group size the study is inadequate for evaluation of carcinogenicity, and remove the two references at the end of the paragraph. Dr Kielhorn to check API studies.
Section 8.5, para 11	Replace 'usual' with 'unusually' in the sentence beginning 'The authors considered.....'
Section 8.5, para 14	Delete sentence beginning 'The ranges of the concentration used were.....'
Section 8.6, para 14a	Delete from the sentence beginning 'The studies were conducted in two laboratories.....' to the end of the paragraph.
Section 8.7.1, para 17	Delete the sentence beginning 'The authors speculated.....'. Reword the last sentence 'The toxicological significance of the decreased intratesticular testosterone level is unknown'.
Section 8.7.1, para 20	Replace 'indexes' with 'indices'.
Section 8.9	This section needs to be checked and all studies that are not directly related to mode of action of critical effects should be moved.
Section 8.9, para 26b	Delete second half of paragraph starting 'Although positive trend.....'. Move paragraph to section 8.5 (carcinogenicity).
Section 9, para 1	Delete 1 <sup>st</sup> and last sentences. Paragraph to be checked for limitations of study and a statement made regarding the level of reaction.
Section 9, para 2	Replace first sentence with .... 'In a skin patch test, none of the 25 healthy adult volunteers showed a

	positive reaction to 10% diethylphthalate (purity not specified) (Greif, 1967).’
Section 9, para 2b	Last sentence is unclear. To be checked by author.
Section 9, para 3	Delete paragraph.
Section 10.1, para 1	Replace marine alga <i>Skeletonema costatum</i> with marine dinoflagellate <i>Gymnodinium breve</i> .
Table 10.1	Check secondary reference (US EPA) and replace with primary reference if possible.
Section 11.1.1, paras 0 & 1	Author to check both paragraphs with regard to irritation following any changes to 8.2 (see above).
Section 11.1.1, para 1c	Second sentence to be moved to paragraph 1b. The malformations should be characterized and the Singh references removed.
Section 11.1.1, para 1d	Delete paragraph.
Section 11.1.2, para 2	Specify the species used in the Gray et al. (2000) and Lamb et al. (1987) studies. Move paragraph to section 11.1.1.
Section 11.1.3	Author to integrate this paragraph with paragraph 1b in section 11.1.1. Industry observer offered to provide details of CDC information as ε back up to the Blount et al. (2000) study.
Section 11.1.4	Move paragraph 8b to 11.1.3 and add to paragraph 5 of this section to reflect the differing DEP exposure in different countries. Discussion of DEP in medical devices to be included in the uncertainties section.
Section 11.2	There was a short discussion regarding environmental risk assessment and the probabilistic approach outlined by one of the commenters. It was decided to include both the safety factor approach and the probabilistic approach. The revised section will have to be peer reviewed.
Section References	13: Blair et al. (2000) to be added to reference list.

## Carbon disulphide

*Discussion of the draft CICAD on Carbon disulphide was led by Dr. Herman Gibb.*

The author and the discussion leader identified two main points for consideration by FRB.

1) Should plot for regression model for Benchmark Dose Concentration be included in the CICAD? Answer. Yes, - for the key endpoint (peroneal conduction velocity) specifying confidence limits.

2) Should effects of CS<sub>2</sub> on the atmosphere (global warming, acidification, ozone depletion) be added? Answer. Yes. to Sec 5.1

Most comments adequately answered.

### *Specific comments*

Section 1	Changes in the text to be reflected in the Section 1
Section 1, para 1	Cite also WHO, 1979
Section 3, para 1	The term captation, proposed by a reviewer does not seem to be standard terminology (and certainly does not specify cold trapping). Proposed wording "cryogenic trapping".
Sec 4.	Tonnes are metric throughout.
Section 4.2 para 4	Check Crookes et al (1993) . Assuming 75% release or 75% use?
Section 6.	Add Exposure likely in laboratories using CS <sub>2</sub> as a solvent and as desorbent. Check whether concentration data in air have been normalised.
Sec 6.1.6	para 16 line 5. Delete 'other'.
Sec 6.3	para 24 Add data from China (Dr Chen): The average CS <sub>2</sub> concentrations in workplace in China have decreased to around 10mg/m <sup>3</sup> in the recent decade. (Lü & Wang, 1999; Yang et al., 1996; Sun et al., 1998, Wang & Shiu, 2000, Wang et al., 1999). In one Chinese study based on the monitoring data of 1503 samples, the average CS <sub>2</sub> concentrations in workplace was 5.13±3.17 mg/m <sup>3</sup> (Wang et al., 1999).
Sec 7	Add to para 2. "Different studies show a constant, close correlation between 8-h TWA airborne exposure to CS <sub>2</sub> and urinary TTCA concentrations."
Sec. 8.2.1	Delete paragraph 8b
Sect 8.4, para 14	At beginning of last sentence. Add: "In one study it has been reported"
Sec 8.5 para 22	Add fetal effects and statistical significance observed at the lowest dose.
Sec 8.6	Mode of action. Add ... of critical effect.
Sec 9.2.1 para 4	Add: H <sub>2</sub> S is not a known neurotoxic chemical.
para 5	Add the absolute difference (m/s) in MCV values for exposed and unexposed populations.
para 6	Delete from While Reinhart.et al (1997)... to end of para.
Sec 9.2.3 Para 24b	Delete last sentence: There is some....
Sec 9.2.4 Para 26	Add, as a footnote, that we were aware of Austrian study but it was published after cut-off date.
Sect 9.2.6	Review Chinese studies and include their results if pertinent. Dr De Rosa will have them translated.
Sec 10 para 6	Delete 'of ammonium'.
Sec 11.1.4	Add uncertainty in genotoxicity.
Sec 12	Add WHO air quality guideline based on sensory effects or annoyance reactions (20 µg/m <sup>3</sup> , 30 min averaging time).

Note that in the list of reviewers, reviewers 5 and 6 have been mixed up. Add Response to ACC. Comments on the selection of the metric of MCV (relative change vs absolute decrease in m/s).

## **Silver (Environmental aspects)**

*Discussion of the draft CICAD on Silver (Environmental aspects) was led by Dr H. Temmink*

### **General**

There was agreement by the FRB that the comments from the 5 Reviewers (Package 1) and from Eastman Kodak (Package 2) had been adequately answered by the author and any relevant new papers included.

Late comments by Temmink were still to be dealt with. Chair to verify the adequacy of these responses.

Editorial proposals such as printing errors found in text by Observer should be given to author for inclusion in the text, with a copy to the Secretariat.

### **Specific comments**

Title	The title of the CICAD should be changed to Silver & Silver compounds.
Section 1	Changes in the text to be reflected in the Section 1.
Section 1	Add reference to ATSDR for effects on humans.
Section 2	Add sentence similar to that of Sec 6 Para 1, last sentence, concerning contamination and reliability of analytical results.
Section 5	Observer to provide further data on anaerobic studies. Sequestration as a means of disposal and detoxification should be considered (as exemplified by metallothionein binding in para 16).
Sec7. Table 2.	Check Calabrese et al., 1984. Histopathology and add details in a footnote.
Section 7.2 para 4 (old 2)	Change 'poults' to 'young turkeys'.
Sec 8. para 2.	Move the added second sentence to the end of the para and reword the present last sentence to accommodate this change. Add cautionary note on analytical accuracy.
Section 8 para 3	Delete toxic and check 'bioreactive' for wording.
Section 8 para 6	Add validation of model BLM.
Section 8. Fig 1	Add text to indicate that all data presented in Table 2 are in the figure.

## Ethylene glycol (Human health aspects)

*Discussion of the draft CICAD on Ethylene glycol (Human health aspects) was led by Dr Rolf Hertel.*

### **General**

The primary reviewer identified major items for discussion:

- Availability of suggested extra material for inclusion
- The cut-off date of January 2000 and its implications for extra material
- The predictive power of the TDI – is the author's response to reviewers comments adequate?
- The relative merits of the DePass et al. (1986) and Gaunt et al. (1974) as critical studies for the setting of guidance values – although the DePass study is published in outline, the crucial material remains unpublished and the Gaunt study is also unpublished. Issues raised during discussion included dose regimes, time period and strain of rat.
- The limitations of exposure data – critical to completion of the national source document but less important for the CICAD since only an example risk characterisation is needed
- The large number of personal communications within the CICAD

Comments from a stakeholder organisation that had arrived late had not been distributed to the FRB participants (but the salient points had been covered in the authors' summary of responses to comments). The adequacy of authors' responses to these comments will be verified by the Secretariat, discussion leader and Chair; they will likewise verify that the studies that have a direct impact on the risk characterization, which are cited in the document, but are not publically available (notably the Gaunt et al. study and the personal communications) are reliable enough for use in the CICAD<sup>1</sup>.

### **Specific comments**

Section 1	Changes in the text to be reflected in the Section 1
Section 1, para 10	The wording of the last sentence which seems to combine two separate ideas need to be checked.
Section 5.1.5, paras 1, 2 & 4, table 4	Industry observer to provide documentation (Material Safety Data Sheet) from the manufacturer regarding the ethylene glycol content of tub & tile cleaner and windshield washer specifically referred to in these paras. The author to further verify if ethylene glycol is found in these products in Canada.
Section 5.1.5, para 4	Delete paragraph if the document to be provided by the observer demonstrates that the published source of information is misleading and these specific products do not contain ethylene glycol.
Section 5.3	Extra study to be included on theatrical smoke (NIOSH, 1994).
Section 7.3	Authors to give further consideration to adding more detail of kidney effects from the short-term studies (comments on pages 5 & 6 of the comments table) or to insert general text stating that results from short-term studies confirm long-term observations.
Section 7.6	Two extra NTP reproductive toxicity studies from the 1980s to be

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<sup>1</sup> Following the policy of IPCS, the Secretariat will archive these documents for two years after the publication of the CICAD and make them available to persons with a *bona fide* interest in them.

	included.
Section 7.6, para 10	Extra reference from Nagano et al. (1984) to be added – more recent coverage of the same study as the earlier Nagano reference.
Section 7.8	The publication date of McMartin & Cenac to be checked; if after January 2000 then data to be deleted from text.
Section 8	Extra study from China (2001) regarding the measurement of urinary microalbumin in exposed workers to be incorporated as a footnote.
Section 9.2, paras 1 & 2	NOAEL/LOAEL for critical studies on kidney effects to be incorporated.
Section 9.3, para 2	To be checked and reference to tub and tile cleaner deleted if appropriate (see above).
Section 9.4	Information on uncertainties from the national source document to be incorporated.
Table 2	Industry observer to provide information regarding daily intakes via inhalation and ingestion of soil for consideration for possible inclusion or changes in Table 2 (to be judged by the Secretariat, discussion leader, and Chair).
Table 5	Personal communication (Brantom) to confirm incidence in Gaunt study to be referenced in this table.
Table 7	To be deleted. Information to be incorporated into the text in section 9.2.1, para 7.
Figure 2	Title to be revised to indicate not only metabolism but also mechanism of action.

## ACKNOWLEDGEMENTS

The International Programme on Chemical Safety (IPCS) wishes to express its gratitude to the Japanese Ministry of Health and Welfare and the United States Environmental Protection Agency for their generosity in providing financial support for the CICADs Project, which enabled the IPCS to convene this 9th Final Review Board. Thanks are also due to Health Canada for providing the meeting facilities. Finally, appreciation is extended to those FRB members who agreed to fulfil the roles of Chairman, Vice-Chairman and Rapporteur, i.e., Drs De Rosa, Dobson and Kielhorn, as well as 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 further development of the IPCS CICADs Project.

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