

IPCS

International Programme on Chemical Safety

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

Nagpur, India: 31 October - 3 November 2005

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 T Chakrabarti on behalf of the National Environmental Engineering Research Institute, and Dr. A. Aitio, on behalf of the Programme for the Promotion of Chemical Safety, World Health Organization, opened the meeting and welcomed the participants.

Following a brief introduction of each participant (List of participants, Appendix I), Dr J. Stauber was elected as Chair and Dr T. Chakrabarti as Vice-Chair and Mr. P Howe and Dr L. Fishbein as Rapporteurs. The agenda was adopted as proposed (Appendix II).

None of the members of the 13th Final Review Board (FRB) declared any conflicts of interest with the subject matter of 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. The limitations of the participation of the observers in the meeting were likewise explained.

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.

Resorcinol

The CICAD on **Resorcinol** 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.

Cobalt and inorganic cobalt compounds

The CICAD on **Cobalt and inorganic cobalt 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.

2-Methoxyethanol

The CICAD on **2-methoxyethanol** 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 CICAD on **2-Ethoxyethanol** 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.

Selected alkoxyethanols including propoxyethanol

The FRB recommended that the documents on methoxyethanol, ethoxyethanol, propoxyethanol, and butoxyethanol be published as a single CICAD, titled Selected Alkoxyethanols, to comprise independent parts 1-4 on the individual alkoxyethanols, together with a Part 5 containing the assessment of the similarities and differences within the group, and a structure-activity analysis. Dr DeRosa indicated that ATSDR would author the first draft of the Part 5. In order that the preparation of the missing sections not delay the availability of the other parts, the FRB further recommended that the individual parts of the CICAD be made available on the web when they are finalized.

Tetrachloroethene

The CICAD on **Tetrachloroethene** 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.

Mono- and Di-methyl, -butyl and -octyl tins

The CICAD on **Mono- and Di-methyl, -butyl and -octyl tins** 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 Drs Chhabra, Hughes and Ziegler-Skylakakis.

Iodine and inorganic iodides

The CICAD on **Iodine and inorganic iodides** 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 FRB members.

CICADs and the Globally Harmonized System for the classification and labelling of chemicals

FRB 13 held a special session on the Globally Harmonised System of Classification and Labelling (the GHS). The session provided an overview of the GHS and identified how it is relevant to the IPCS work on CICADs. FRB also considered a discussion paper which looked at possibilities for using the information in 4 draft CICAD reports which were before the FRB (Resorcinol, Methoxyethanol, Ethoxyethanol and Tetrachloroethene) in order to classify the relevant hazard endpoints according to the GHS. It was noted that the GHS also had implications and opportunities for the IPCS International Chemical Safety Cards (ICSC) and similar discussions were taking place with that group. The FRB generally accepted that CICADs and the GHS had several points in common as communication tools, both aimed at conveying concise information about chemical hazards. CICADs went on to characterize exposure and risk, and the GHS went on to provide guidance on labelling and safety data sheets. It was therefore accepted that CICADs had the potential to provide GHS relevant information to provide assistance to countries in implementing the GHS. The scope and extent to which CICADs would be useful depended on several issues such as aligning terminology, the extent to which relevant information could be easily found in the CICADs and how conclusions regarding classification were presented. FRB13 welcomed the opportunity to discuss the GHS and agreed that a special consultation perhaps in combination with the ICSC and/or the RASG would be useful to determine policy and technical options. In the meantime the FRB wished to be kept informed about developments with implementation

of the GHS, to continue to improve awareness and to consider practical steps pending policy considerations being completed .

14th Final Review Board meeting

The 14th FRB is planned to take place in the fall in 2006. The closing date for the receipt of first draft of CICADs is April 30, 2006. Chemicals likely to be considered include 1-Bromopropane; Chromium (III) compounds; Cyclic acid anhydrides; DDT, human health aspects; Hydrogen cyanide, environmental aspects; Strontium and strontium compounds; the Parts 3 and 5 of the Selected Alkoxyethanols (propoxyethanol and the general section on alkoxyethanols including the SAR analysis).

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 13th Final Review Board.

Thanks are also due to the National Environmental Engineering Research Institute, notably Drs S. Devotta and T. Chakrabarti, and Mr Ram Huddar for providing the meeting facilities and the excellent 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 Stauber, Chakrabarti, 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.

A few days after the meeting, we received the sad news that Dr Fishbein had unexpectedly passed away almost right after returning home from the meeting. Dr Fishbein was a long-time ardent supporter of the WHO chemical risk assessment programmes, and will be remembered with warmth and gratitude.

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Appendix I: Participants of the FRB Meeting

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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. Declarations of interests of the participants
4. Draft CICAD on Resorcinol *: Finalization and eventual approval
5. Draft CICAD on Cobalt and inorganic cobalt compounds: Finalization and eventual approval
6. Draft CICAD on Methoxyethanol: Finalization and eventual approval
7. Draft CICAD on Ethoxyethanol: Finalization and eventual approval
8. Draft CICAD on Alkoxyethanols and Propoxyethanol: Finalization and eventual approval
9. Draft CICAD on Tetrachloroethene: Finalization and eventual approval
10. Draft CICAD on mono- and di-methyl-, -butyl and -octyl tins: Finalization and eventual approval
11. Draft CICAD on Iodine and inorganic iodides: Finalization and eventual approval
12. CICADs and the Globally Harmonized System for the classification and labelling of chemicals
13. Future CICADs
14. Any other business
15. Closure of the meeting

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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.

Resorcinol**Discussion leader: Dr R. Hertel****General points**

This document was produced as a joint venture between IPCS and OECD.

- One reviewer requested extrapolation of higher occupational down to consumer exposure but this was not possible due to limited data.
- Justification for selection of key study should be improved in section 11.1.2. The key endpoint could be considered to be either on CNS or thyroid. No single study adequately covered both endpoints.
- Ecotoxicity and aquatic risk (choice of assessment factors) was discussed.
- It was agreed to retain both appendices 5 and 6.
- Add changes from ‘late’ comments provided by the Finnish Institute of Occupational Health (FIOH).

Specific points**Section 1**

Author to condense summary section where possible.

Para 15: Replace with

In bacterial mutagenicity assays, resorcinol showed mostly negative results. However, it induced mutations in the TK locus in mouse lymphoma cells. Resorcinol did not induce unscheduled DNA synthesis in hepatic cells or single strand DNA breaks in mammalian cells *in vitro*. Studies for SCE and chromosomal aberrations *in vitro* in isolated cells and cell lines gave both negative and positive results. Cytogenetic studies *in vivo* (micronuclei in bone marrow in rats and two strains of mice; SCE in male and female rats) gave consistently negative results.

Para 20: Modify second sentence with text from 11.1.1; para 24 (from FIOH comments).

“Dermal sensitization to resorcinol has been well documented but in practice is rare; the available data do not allow assessment of the sensitization potency”.

Section 2

Footnote to be added to section 2 regarding different commercial products (flaked and industrial) in older studies. Wording to be clarified with industry but based on the response text in the peer-review comments table (see comments in peer-review table of comments on section 8.1, para 7).

Section 3

No further changes.

Section 4

Para 4: Data from CEH (2005) not to be included.

Table 3: Add footnote to state that the European use of resorcinol in hair dyes is in fact 90 tonnes per annum rather than 150 tonnes per annum. Reference to be provided – personal communication from industry.

Section 5

5.2: Indian paper on biodegradation in water to be added if needed (Dr Chakrabati provided paper during FRB meeting).

5.2; para 8: Wording to be clarified by Dr Dobson.

Section 6

6.2.1; para 11b: Add quantitative exposure information for hairdressers if available. Remove reference to PPE.

Para 17: Add exposure estimates on anti-acne cream from stakeholder comments (Paul Ashford).

6.2.2.1; para 18: Figures to be checked.

6.2.2.1; para 22: Figures to be checked.

Section 7

No further changes.

Section 8

8.5; para 41: Delete paragraph and replace with paragraph from summary section.

Add as a footnote that we were aware of NTP (2005) studies [if these are provided to the authors].

8.6.1; para 53: Delete para. Add at the end of the para 52: "At the highest dose, decreased colloid in the thyroid was observed, but this was not statistically significant." Final version of the RTF 2005 report to be provided by Paul Ashford.

8.9.1; para 74: Define dermatitis (check whether paragraph refers to sensitization or irritation). Move paragraph to section 9.

8.9.3: Delete paragraphs 80 and 83.

8.9.3; paras 84, 85 & 86: Delete reference to study by Baubaund et al. in para 84. Move paragraphs to section 9.

Section 9

Change all references of 'case studies' to 'case reports'.

Extra subsection on sensitization to be added (see section 8.9.3). Subsection 9.3, para 15c to be taken into account.

9.2.1; para 3: Delete 'may act as antithyroidal drug' from end of paragraph. Author to check paragraph for inconsistency – 'hyperactivity' would normally reflect **hyper**-thyroidism.

Section 10

10.1.1; para 4: Delete 'numerous' from the first sentence.

Table 7: Delete acute study on water fleas by Lima (2004).

Section 11

References to be included for key studies in this section.

11.1.1; para 1: Dermatitis is not sufficiently specific (also check section 8, para 74). Separate sensitization and irritation.

11.1.1; para 2b: Reverse the order of the second and third sentences. Rephrase the 3rd sentence to avoid the impression of 'transient death'.

11.1.1; para 6: Delete first sentence. Clarify that the difference in response at < and >2% solution is not a measure of potency. The text could read e.g.:

Several case reports describe sensitization to resorcinol through the use of medicinal products and anti-acne cream. In several patch test studies with large collectives the prevalence of sensitivity to resorcinol was less than 2% when the tested at resorcinol concentrations of $\leq 2\%$. With increasing resorcinol concentrations there was an increase in the number of persons tested positive. As no information is available of the levels of exposure in the studied populations, no estimate of the sensitizing potency of resorcinol can be made. In practice, however, the incidence of sensitization seems to be low.

11.1.4; para 24: Delete.

11.1.2 & 11.1.3: Author to redraft providing justification for using the CNS as the key endpoint by comparing NOAELs for CNS and thyroid. Discuss no effect on thyroid histopathology but emphasize no measurement of T3/T4 ratios. Make comparison between acute effects on CNS and possible long-term effects on thyroid. Make appropriate changes in summary (1; para 22).

11.2: Dr Kielhorn and Dr Dobson to discuss the different approaches to environmental risk assessment and add information to uncertainties section (11.2.3)

Cobalt and Inorganic Cobalt Compounds**Discussion leader: Dr MH Sweeney****General points**

The uncertainties section should be expanded with more explanation on whether cobalt is a sensitizer which might imply a lower risk.

Environmental risk assessment needs to be reviewed and the alternative assessment approach noted in the uncertainties section.

It was decided after much discussion that it was not necessary to tabulate data from sections 8 and 9.

Specific points**Section 1**

Make changes consistent with changes in main text.

Sections 2-4

No further changes.

Section 5

5; para 4: Correct the chemical species names (undissociated CoCO_3 and CoSO_4 not carbonate and sulphate ions)

Section 6

No further changes.

Change response to peer-reviewer comment in table of comments: Section 6, para 3 (reviewer 1) – replace ‘Don’t know’ with ‘None identified’.

Section 7

7; para 18: Truhaut paper in French to be checked by Dr Dobson (see peer-reviewer comment in table of comments).

Section 8

8; para 1: Author to check FDRL (1984a), FDRL (1984b), FDRL (1984c) and Speijers et al. (1982) to address comments by reviewer 17 on Section 8, para 1.

8; para 4: Author to check Johansson et al. (1987), Johansson et al. (1984), Johansson et al. (1991), Kyono et al. (1992), and Palmes et al. (1959) as regards comments by Reviewer 17 on Section 8, para 4.

8; para 5: Author to check Bucher et al. (1990) as regards comments made on Section 8, para 5.

8.5; para 9: Wehner et al. (1977) paper now checked and salt not specified there either.

8.5; para 16: Move to section 9

Change response to peer-reviewer comment in table of comments: Section 8, para 9 (reviewer 17) – replace ‘Not provided in ATSDR or IARC source documents’ with ‘Not in original paper’.

Section 9

9; para 2: Delete last sentence with reference to the LOAEL.

Section 10

No further changes.

Section 11

11.1.2: State that the guidance value is based on non-cancer endpoint and the value is then compared to cancer risk estimate for reassurance.

11.1.2; para 12: Change “reassurance” to “context”

11.1.2; para 13: Delete middle sentence “a study of 6 human”. Final sentence becomes a footnote: “From a short-term study, ATSDR derived an intermediate duration”

11.2: The Australian approach is an example approach and this needs to be made more explicit in the text. A discussion of an alternative approach to assessing the aquatic risk to be included in the uncertainties section.

11.2; para 8: Delete ‘and then converted.....Appendix 4’ from third sentence.

Section 12

The text is verbatim from IARC and so remains.

Peer-review comments table

Change ‘Refer to FRB’ to ‘No change’ where appropriate.

2-Methoxyethanol**Discussion leader: Dr O. Sabzevari****General points**

2-methoxyethanol was previously reviewed at the 12th FRB meeting.

Secretariat to contact American Chemical Council for further information on uses and volume produced. Does the information cover all producers?

Dermal exposure in the occupational setting should be emphasized (particularly in the summary).

Caveats should be included in the summary, table 2 (section 6) and evaluation stating that exposure estimates are extreme worst case.

Specific points**Section 1**

Make changes consistent with changes in main text.

Add a new paragraph after para 4 emphasizing exposures from dermal route as well as the inhalation route.

1; para 6: expand paragraph especially for information on key studies (reprotoxic and haematological effects).

Section 2

No further changes.

Section 3

Table 1: check units for analytical method for blood (Smallwood et al., 1984).

Sections 4-5

No further changes.

Section 6

Table 2: Emphasize that the information provided is worst case and has not been verified (to be included in the uncertainties section).

Section 7

Add paragraph on biological monitoring.

Check Fig 1: The metabolite generated by dealkylase carboligase is missing

Paras 6 & 7: author to check papers for the accuracy of the MAA concentrations in serum and estimated total uptake at 5 ppm exposure.

Delete para 19.

Section 8

Author to check NOAELs for consistency throughout this section and section 11.

8.7.2; para 21: Check for consistency on reprotoxicity between this para and para 18

8.7.2; para 21: Move last sentence (not reprotoxicity). New para and heading "Haematological effects"

Section 9

Para 3: Modify first sentence to read ‘described by the authors as extensive’. Add a full stop after (El-Zein et al., 2002). Move paragraph up to become para 2

Para 3: Delete ‘intensively’ from last sentence.

Para 6: Author to check reference (were the exposure levels for the controls reported?). Indicate ‘male’ workers.

Para 7: Confirm what the NOAEL is here (1.7 or 8.4). NOAEL = 1.7 but provide rationale for both.

Section 10

No further changes.

Section 11

A reference to dermal exposure and biological monitoring should be added.

Para 7: Mention haematological effects.

11.1.2; paras 5 & 6: author to clarify rationale for using 1.7 and/or 8.4 as NOAEL (but do not use the terms NOAEL/LOAEL).

11.1.4; para 10: Delete ‘reproduction’ from last sentence.

Section 11.2: Dr Dobson has checked that there are no new data in the background document of the source document: no changes needed here.

2-Ethoxyethanol

Discussion leader: Dr J. Kielhorn

General points

2-ethoxyethanol was previously reviewed at the 12th FRB meeting.

Secretariat to contact American Chemical Council for further information on uses and volume produced (including the acetate). Does the information cover all producers?

Dermal exposure in the occupational setting should be emphasized (particularly in the summary and evaluation (11.1.1)).

Caveats should be included in the summary, table 2 (section 6) and evaluation stating that exposure estimates are extreme worst case.

Specific points

Section 1

Make changes consistent with changes in main text.

Para 5: add 'inhaled' to the last sentence.

Para 6: Delete 'weak' and 'at most' from the 5th sentence.

Para 8: In the first sentence replace 'not robust enough' with 'too limited'. Delete the last sentence.

Section 2

No further changes.

Section 3

Table 1: check units for analytical method for blood (Smallwood et al., 1984).

Sections 4-5

No further changes.

Section 6

Tables 4, 5 and 6: Clarify how the means and percentile figures were derived (dependent on how the non-detectables were handled)

Para 6, penultimate sentence: Clarify that the >30 to 100% is a **category** for reporting and not an indication of up to pure ethoxyethanol (reporting category >30%)

Section 7

Add paragraph on biological monitoring.

Section 8

8.4.1; paras 8 & 11: Harmonize content; check information on platelet count.

8.5; para 16: Delete paragraph. Replace with 'No adequate long-term studies were available'.

8.6; para 17: Delete last sentence of paragraph and 'weak' and 'at most' from remaining text

8.6; para 19: A bit more detail to be added to allow better definition of the 'equivocal and mixed results'.

Sections 9-10

No further changes.

Section 11

A reference to dermal exposure and biological monitoring should be added.

11.1.2; para 6: Add that it was mixed exposure in Welch et al. study

11.1.4; para 14: Remove 'Whilst' and start sentence with 'There is a moderate.....'. At the first comma add 'as haematology and reproductive effects'. Start a new sentence with 'There is some.....'

11.1.4; para 15: Delete Canada from the first sentence. Add Canada to the third sentence after 'Windsor'.

11.1.4; para 16: Add In countries that have reduced or discontinued its use.

Tetrachloroethene**Discussion leader: Dr H. Gibb****General points**

Tetrachloroethene was first discussed at the 12th FRB meeting in Hanoi, Vietnam. Due to conflicting views on interpretation of data on critical endpoints the draft CICAD was referred to a WHO consultative group which met at CEH Monks Wood, UK. Therefore, the discussions at the 13th FRB were mainly related to the evaluation and summary sections of this document.

Specific points**Section 1**

Make changes consistent with changes in main text.

Para 9: Delete 'repeatedly' from 4th sentence.

Para 11: Delete 'or postulated metabolites' from the last sentence.

Para 13: Add 'Some....' to the start of the first sentence. Delete 'repeatedly' from the same sentence.

Para 14: Clarify that the tolerable concentration is derived from neurotoxicity and the Mutti study used for comparison only.

Para 17: delete paragraph.

Sections 2-9

No further changes.

Section 10

To be checked by Environment Sub-group.

Section 11

11.1.1; para 17: Delete 'repeatedly' from 4th sentence. Delete last sentence and replace with 'The risk of non-Hodgkin's lymphoma among workers who used tetrachloroethene was found to be elevated in three studies, but the risks were not statistically significant. Furthermore the workers may have had multiple solvent exposure.' (sections 1 and 9 to be modified accordingly)

11.1.1; para 23: The third sentence beginning 'Accordingly, the IPCS.....' needs to be clarified (i.e. it is not clear what the consultative group meant by this sentence). State that the Consultative Group used the new IPCS framework for assessing the mode-of-action.

11.1.1; para 27: Add 'Some....' to the start of the first sentence. Delete 'repeatedly' from the same sentence.

11.1.2; para 29: Outline why the occupational cohort study by Seeber (1989) was chosen as the key study (quality, size of groups, sensitivity of tests etc). Outline the reasoning behind the numbers chosen for the derivation of the Tolerable Concentration (rationale from consultative group).

11.1.2; para 34: Keep first two sentences and delete from 'On this basis.....'

11.1.2; para 45: Delete 'though' from last sentence.

APPENDIX IV

11.1.2; para 46: Replace the stated change for 11.1.2, para 46 with a change to 11.1.4 (new para 46): “It is unknown whether the neurological effects observed in the key study (Seeber et al., 1989) are the result of short or long-term exposure. It is also unknown whether the neurological effects are transitory.”

11.1.4; para 47; In the last sentence replace ‘real’ with ‘this holds true for humans’.

11.2: To be checked by environment sub-group.

Appendix 6

Figures 1, 2, 3, 4, 5 and 6 to be deleted (author to check that no useful information is being lost).

Appendix 7

The apparent discrepancies between the text in the para starting "According to the Rao & Brown... and the legend of figure 1 need to be clarified. See comments from Primary Reviewer.

Mono- and Di-methyl, -butyl and -octyl tins**Discussion leader: Dr J. Stauber****General points**

Two minor issues were raised by the reviewers

- The level of detail required for the toxicity studies such as doses, animal species, numbers, route of exposure, exposure vehicle etc.
- Is there a WHO standard for calculating worst case exposure to organotins for children?
No – the factor of 4 was retained

Harmonize the use of ‘endpoint’ in Tables throughout the document.

Author now provided with extra papers from Dr Sekizawa.

Drs Chhabra, Hughes and Ziegler-Skylakakis to review changes to sections 8, 9 and 10.

Specific points**Section 1**

Make changes consistent with changes in main text.

Para 4: Delete ‘organotin’

Para 8: Clarify 5th sentence beginning ‘There are few measured.....’.

Para 17: Clarify paragraph on endocrine disruption.

Para 18: Reword second sentence to include ‘unintentional exposure’ and delete "accidental".

Para 18a: Delete ‘Working’ from the beginning of the sentence and specify medium term exposure.....

Para 20: Paragraph to be modified to take into account that baking papers containing organotins have been discontinued (author to check if this is a worldwide action). Reword penultimate sentence on exposure of children relating to exposure via baking paper.

Carcinogenicity and genotoxicity to be added to summary.

Sections 2-3

No further changes..

Section 4

Para 13: Industry to provide information on the range of tin concentrations in the finished PVC product.

Section 5

Table 8: Clarify the meaning of ‘c’ in the table. (= *circa*)

Sections 6-7

No further changes.

Section 8

Section to be reorganized by chemical as far as possible.

Table 21: Delete ‘endpoint’ from headings and replace with other term.

8.2; para 3: Separate sensitization and irritation, add some more detail and include statement on sensitization from 11.1.1.

8.3.1; para 6: Delete NOAEL from middle of paragraph. Start a new paragraph at ‘The Elf Atochem NA (1996) study.....’.

8.3.1; para 7: Move to first paragraph and reword as an introduction (see comments table).

8.3.1; Table 22: Delete table.

8.3.2; para 8a: Add study to table 24.

8.3.2; para 9: Check whether information can be added to table 24.

8.3.2; para 10: Clarify author of report's NOAEL and the NOAEL agreed by FRB

8.4; para 30: No non-neoplastic endpoints seen in NCI study; range of non-neoplastic endpoints should be given here. State that a comprehensive range of endpoints were monitored.

Third line up, add "statistically" [significant...]

8.4; para 31: Delete 'industry-sponsored' from first sentence. Delete 'Slightly but' from last sentence and begin sentence 'Significant increases.....'

8.5: Summary to be added at beginning of subsection

Section 9

Para 1: Delete 'permanently' from 4th sentence. What type of memory loss (short-term or long-term memory) is referred-to in 5th sentence? (i.e. 'The remaining survivors experienced memory loss'). And check whether this endpoint was subjectively assessed or measured.

Para 2: Delete paragraph but retain T-cell study if useful.

Section 10

Table 23: Concentration values for 21 day NOEC (ABC Study) to be checked..

Section 11

11.1.1; para 1: Reword last sentence and replace 'organotins' (Reworked sentence to be copied to 8.2).

11.1.1; para 2: Clarify that endocrine disruption is an issue for TBT (and possibly DBT) but not for other compounds

11.1.1: Name the two most potent sensitizers.

Add information on carcinogenicity, genotoxicity

Table 24: Table to be moved to section 8. Doses to be added to table (range of doses used).

'Toxic effects' heading to be modified.

11.1.2; para 3: Delete 'working' from 2nd sentence.

Table 26: Change heading to 'Estimates of medium-term tolerable daily intake (TDI) for use in the risk assessment on the basis of medium term exposure results. Replace the 'endpoint' heading.

11.1.2; para 3a: Replace 'standard 100' in the 2nd sentence with 10 for intraspecies variation and 10 for interspecies variation. Reword 3rd paragraph as follows 'For DBT a factor of 10 was applied together with factors of 5 for lack of information and 5 for a substantially smaller research base'.

Table 27: Add a footnote regarding baking sheet.

Tables 27 & 28: Clarify what is meant by 'via the environment' in these tables.

11.3: Split uncertainties section between human health and environment.

11.1.3; para 7: Reword extra text added to the end of this paragraph on exposure of children.

Section 12

Secretariat to check WHO drinking water guidelines to find information on DBT from PVC pipes.

Iodine and inorganic iodides

Discussion leader: Dr Raj Chhabra

Specific points:**Section 1:**

Reviewer 2, page 3 Comments Table: Add the suggested new paragraph 7 to the Summary

Para 1: Refer to a source of information on the radioisotopes (ATSDR Report) [Secretariat to check if a WHO document exists – otherwise refer to the ATSDR report alone]

Para 6: Add a footnote that the added material is from other WHO sources (make clear that it is not a conclusion of the FRB)

Paras 7,8: Combine these two paragraphs

Para 13: First sentence should be “Doses toxic to the dams administered in the latter part of gestation induced” but author to check that this is true.

Para 13: Replace the final sentence “However by....” Human cases of neonatal hypothyroidism have been reported after in utero exposure to pharmacological doses of iodine administered to the mother.

Add para 15 from the circulated sheet (from author)

Insert paragraph on irritation/sensitization.

Section 2:

Physico-chemical properties information to be put in a table as in other CICADs

Section 3:

No further changes

Section 4:

Section 4 para 4,8 Reviewer 2, page 5 Comments Table: Add material on production and geographic areas deficient of iodine and on uses provided by the reviewers to Section 4

Para 7: Replace “may also be used” with “is being used”

Add paragraph on iodine deficiency here.

Section 5:

Section 5 para 2 Reviewer 2, page 5 Comments Table: Add the suggested material to the document after checking.

Section 6:

Section 6.2 Reviewer 18, page 6 Comments Table: Make a statement in the document that no specific data on occupational exposure could be located. Add that occupational exposure is expected.

Section 6 para 5, Reviewer 2, page 7 Comments Table: Add the text “Pederssen et al. (1991) ...” to the document

Section 6 para 7, Reviewer 11, page 8 Comments Table: Explain DRI for non-US readers 6.2; para 3: Clarify the exposure value (outdoors/indoors exposure value)

Para 7: Not consistent with para 8. Author to make consistent.

Table 6.2: Remove table but cover the material in the text. Tabulate intake data from various sources and include ranges if possible. Extra data from Germany provided to authors.

Para 13: Delete material in square brackets

Para 15: Note that what is typical for a diet will vary geographically. Delete the phrase "...with the conclusion that..."

Add a note that there are no data on occupational exposure but this is likely to occur.

Section 7:

7.1, para 4: Delete.

7.3, para 16: Move added material in the beginning of the para to the beginning of section 7 as an introduction.

Section 8:

Detail should be given for key studies only (FRB response to Reviewer 17)

Para 2: Create separate section for irritancy/sensitization

8.2, para 3: Delete

8.4, paras 19,20: Clarify and reorganize so that similar material is together. More detail for Ames test in para 20. Remove reference to povidone-iodine.

8.5, para 21: Add Arrington et al. (1987) to reference list. Replace 'rodents' with 'laboratory animals'.

In Section 8.5, clarify whether effects are developmental/reproductive/fertility where this can be done.

Section 9:

General: Effects on thyroid should be brought together.

9.2, para 2: Delete.

Para 5: Move to 9.3 "other systemic" as last paragraph in 9.3. Delete Last two sentences "A fourth case ...was discontinued"

Para 9: Move to Section 8 and redraft to reflect observations not author's conclusions. Delete final point 3. Delete reference to Table 1.

9.3.1, Para 10: Explain origin of the 70 kg body weight (average male/female for US population at this time). Matching of body weight to be checked by Dr Gibb.

para 12: Expand since this is the key study (include information on statistical significance, robustness etc. and move key study to start of the paragraph).

Para 15: Delete the final two sentences.

Paras 23, 24, 29, 39: Delete.

Para 42, 43: Redraft to reflect observations rather than author's conclusions. Delete last sentence of para 42.

Para 44: Delete.

9.3.3 para 45: Clarify what bold figures and the range are. Redraft to reflect observations rather than author's conclusions; delete from "...The authors concluded...".

Para 48: Inconsistency with study details in para 26 to be checked.

Para 52: Delete the added text.

Para 53: Delete.

Para 56: check the Text starting "The RR for papillary thyroid cancer...Delete added text "Overall....discussed"

Para 61: Move to beginning of section 9.

paras 62 to 64: Delete.

Section 10:

10.2 paras 5, 6 and 7: Combine

para 8: Check for consistency with the revised section 9 “The prevalence of clinical
respectively”. Delete last sentence “Linear extrapolation”

Para 9: Delete

Merge the new text in the author’s circulated paper with the existing text for hazard
identification (Note: the circulated paper is headed “Sample risk characterization”
incorrectly)

Delete the added last sentence in para 13

Section 10.4: Additional uncertainties relating to increased awareness-induced reporting bias in
the epidemiology studies (text to be provided by Dr Sweeney). Delete the last two
sentences.

Additional uncertainties relating to geographical variability and exposure