

6/2/2010

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**Review:** NIOSH Skin Notations Review - Group A

**Profile Number:** 18

**Profile Title:** Trichloroethylene (TCE)

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### Summary

Reviewers did not find the document to clearly outline the systemic health hazards associated with dermal exposure to TCE. Reviewer 1 notes confusing and possible contradicting data. Reviewer 2 also notes that data quality is unclear. The reviewers also agree that more information is needed to emphatically state that direct health hazards are clearly described. Regarding clarity of immune-mediated responses, both reviewers agree there could be health hazards associated, but more study is needed. Reviews on notation assignments are both positive and negative, and in some cases state insufficient evidence to determine. The many recommendations in this review are listed below.

### Recommendations

- Provide concentrations in the same units (e.g., micro-g vs. nanomoles). (Q1, Reviewer 1)
- Provide clarity on the concentrations, uptake rates, etc., derived from studies, whether they are averages or some other summary measure. (Q1, Reviewer 1)
- Provide clarity in the description of the Poet et al study in paragraph 1. (Q1, Reviewer 1)
- It would be less confusing if the second paragraph did not mix up animal and human studies. (Q1, Reviewer 1)
- In the 3rd paragraph there should be some more description of what data was used to calculate the SI ratio. (Q1, Reviewer 1)
- In the 7th paragraph it should be made clear that there is evidence of dermal exposure to TCE and cancer that is being discussed. (Q1, Reviewer 1)
- Make clear the fact that there is no evidence in dermal exposure to TCE causing death. (Q2, Reviewer 1)
- Focus more on skin cancer risks and dermal exposure. (Q3, Reviewer 1)
- Do not describe the use of TCE as a "detergent" (ref. page 5, first paragraph). (Q 3, Reviewer 1)
- Add need for quantitative human data to determine "NOEL." (Q3, Reviewer 2)

### Suggested additional scientific data to review:

- Dai et al. Effects of genetic polymorphisms of N-acetyltransferase on trichloroethylene-induced hypersensitivity dermatitis among exposed workers. *Industrial Health* (2009) vol. 47 (5) pp. 479-486
- Kamijima et al. Trichloroethylene causes generalized hypersensitivity skin disorders complicated by hepatitis. *Journal of Occupational Health* (2008) vol. 50 (4) pp. 328-338

- Kamijima et al. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. International Archives of Occupational and Environmental Health (2007) vol. 80 (5) pp. 357-370

### Verbatim Reviewer Comments

**1. Does this document clearly outline the systemic health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

Reviewer 1:

I found the section of systemic health effects confusing. The first five paragraphs make a fairly convincing case for limited uptake via the skin, but the next couple of paragraphs describing a very limited case series seem to overturn the previous data resulting in the assignment of SK: SYS. I believe that the weight of evidence presented and in fact supports there being no important systemic uptake of TCE via the skin. The Liu et al paper does not describe the exposure circumstances (other than metal degreasing) and I am certain that the majority of exposure in these situations would be by inhalation. The observation that the workers had dermatitis associated with the solvent does not justify the conclusion that skin exposure was the primary pathway.

Minor comments:

1. Provide concentrations in the same units, e.g. don't switch from micro-g /cm<sup>2</sup>/min to nanomoles/cm<sup>2</sup>/min
2. In describing concentrations, uptake rates etc derived from studies say whether these are averages or some other summary measure, e.g. is the flux of 430 nanomoles/cm<sup>2</sup>/min the average flux?
3. The description of the Poet et al study in para 1 is unclear, e.g. what is a "water-patch", how long was the hand immersion for and how much of the hand?
4. The second paragraph mixes up animal and human studies, which is a little confusing.
5. In the 3rd para there should be some more description of what data was used to calculate the SI ratio - I realize this is in the Appendix but it would not take much effort to say what assumptions were made, particularly what k<sub>p</sub> value was used.
6. In the 7th para it should be made clear that there is evidence of dermal exposure to TCE and cancer that is being discussed.

Reviewer 2:

Partially. Document is not clear re data quality for systemic effects if these are real, estimate "NOEL" and frequency

**2. If the SYS or SYS (FATAL) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

There is no statement about SYS: FATAL. I don't think it should be assigned but it should be made clear that there is no evidence for dermal exposure to TCE causing fatalities.

Reviewer 2:

NA How is reader to interpret?

**3. Does this document clearly outline the direct (localized) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

Reviewer 1:

Yes, although I think the information about carcinogenicity (3rd para on page 5) could be more clearly focussed on skin cancer risks and dermal exposure.

Minor comments:

1. Page 5 1st para, I would not describe the use of TCE as a "detergent". It's sufficient or say "used TCE to clean metal surfaces".
2. page 6, "undiluted TCE ... at extremely high concentrations" - what does this mean?

Reviewer 2:

Partially. Add need for quantitative human data- to determine "NOEL"

**4. If the DIR, DIR (IRR), or DIR (COR) notations are assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

Yes, seems appropriate to assign DIR (IRR) and the text justifies why DIR (COR) was not appropriate.

Reviewer 2:

NA

**5. Does this document clearly outline the immune-mediated responses (allergic response) health hazards associated with exposures of the skin to the chemical? If not, what specific information is missing from the document?**

Reviewer 1:

I think this assignment is quite controversial and to be honest I do not think I am sufficiently expert in this area to give an authoritative opinion about whether there is a sensitisation risk from TCE skin exposure. There does seem to be some relevant human literature that has not been discussed, i.e.

Dai et al. Effects of genetic polymorphisms of N-acetyltransferase on trichloroethylene-induced hypersensitivity dermatitis among exposed workers. *Industrial Health* (2009) vol. 47 (5) pp. 479-486

Kamijima et al. Trichloroethylene causes generalized hypersensitivity skin disorders complicated by hepatitis. *Journal of Occupational Health* (2008) vol. 50 (4) pp. 328-338

Kamijima et al. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. *International Archives of Occupational and Environmental Health* (2007) vol. 80 (5) pp. 357-370

There may be other references but these do seem to highlight some of the difficulties in attributing an association to TCE. It also seems worth noting that this mainly seems to be an issue reported in the literature from Asia.

Reviewer 2:

Partially. Review ACD refs re data quality (see Benezra, J Invest Derm)

**6. If the SEN notation is assigned, is the rationale and logic behind the assignment clear? If not assigned, is the logic clear why it was not (e.g., insufficient data, no identified health hazard)?**

Reviewer 1:

See comments above.

Reviewer 2:

Partially. See #5 (above)

**7. If the ID<sup>(SK)</sup> or SK were assigned, is the rationale and logic outlined within the document?**

Reviewer 1:

Neither of these were assigned or discussed.

Reviewer 2:

NA

**8. Are the conclusions supported by the data?**

Reviewer 1:

No. I think the first sentence of the summary contradicts much of the first part of the document. I do not agree that there is sufficient evidence to assign SK: SYS notation (as discussed above). The assignment of the SK: SEN notation seems controversial and I think it needs some more careful justification.

It is said that under GHS TCE would be assigned Skin Irritation category 2 and Skin Sensitization Category 1, but this is not the view of the European industry (see <http://www.eurochlor.org/qandatrienglish> )

Reviewer 2:

Yes

**9. Are the tables clear and appropriate?**

Reviewer 1:

Yes.

Reviewer 2:

Yes

**10. Is the document organized appropriately? If not, what improvements are needed?**

Reviewer 1:

Yes.

Reviewer 2:

Yes

**11. Is the language of the manuscript acceptable as written? If not, what improvements are needed?**

Reviewer 1:

Yes, I think it is generally clearly written in appropriate language.

Reviewer 2:

Yes

**12. Are you aware of any scientific data reported in governmental publications, databases, peer reviewed journals, or other sources that should be included within this document?**

Reviewer 1:

I think the data on uses of TCE is wrong (page 1). In Europe there are two major categories of use for TRI:

- Used as an intermediate, mainly as a feedstock for the production of fluorinated hydrocarbons and fluorinated polymers
- Used as a solvent in various applications, mainly industrial surface cleaning with minor uses in industrial adhesives, ceramic production, wool scouring, asphalt testing, and other minor uses.

TRI is not used in dry cleaning clothes or in consumer products. I suspect the picture is not so different in the USA. I am not sure of an appropriate reference to cite for this but this is the information I was able to obtain from the European industry (CEFIC).

Reviewer 2:

No

**13. What is your final recommendation for this manuscript? (Do you agree with the scientific rationale that serves as a basis for the skin notation assignments?)**

Reviewer 1:

No, as noted above I think the case for the SYS designation is wrong and the SEN designation needs to be more carefully considered and argued.

Reviewer 2:

Acceptable. Points above would help reader

NB Add statement re data (or lack of) on:

- a) Photoirritation
- b) Photoallergic Contact Dermatitis
- c) "Validity" of penetration algorithm