

6/2/2010

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

**Profile Number:** 12

**Profile Title:** Formaldehyde/Formalin

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### Summary

Two out of three reviewers agree that there is inconclusive evidence on the systemic health hazards associated with exposure to formaldehyde. Reviewer 2 specifically points out that results of standard toxicity tests support this view. Reviewer 1 feels there is insufficient information to assign an SK:SYS notation. All reviewers agree on the clarity of the direct health hazards associated with skin exposure, but have varying opinions on whether immune-mediated responses were clearly outlined. All reviewers recommend acceptance of the manuscript; however, Reviewer 1 notes that the European classification of the chemical may challenge some of the conclusions in this review.

### Recommendations

- It is not clear why DIR (COR) is not assigned – presumed lack of data. This section could be clearer and could be missing information. (Q4, Reviewer 1)
- The section regarding immune-mediated responses is not easy to follow (particularly on page 9). The amount of detail on studies should be reduced. (Q5, Q11, Reviewer 1)
- The information on the uses seems to be incomplete – missing are tissue fixation, embalming fluids and uses as a biocide. (Q12, Reviewer 1)
- NB Add statement re data (or lack of) on:
  - a) Photoirritation
  - b) Photoallergic Contact Dermatitis
  - c) "Validity" of penetration algorithm (Q13, Reviewer 3)

### Suggested additional scientific data to review:

- The British Health and Safety Executive quote a dermal LD50 of 270 mg/kg from the OECD (see <http://www.hse.gov.uk/aboutus/meetings/iacs/acts/watch/130105/p6annex2.pdf>). (Q1, Reviewer 1)
- See several 2009 – 2010 (published "on-line" or available from author) publications by Anton De Groot (Q5, Reviewer 3)

### 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:

No. The discussion of systemic uptake begins with data that suggests formaldehyde is systemically absorbed, i.e. the animal data showing about 5% dermal uptake, with the comment "Although studies revealed that less than 10% of the applied amount of formaldehyde is absorbed, the low values may reflect that excess amounts of the compound were applied to skin...", and then the calculated SI of 3316. However, the remainder of the section paints a different picture and the conclusion is that there is insufficient information to assign a SK: SYS notation. How this conclusion is obtained is not clear as



there is no discussion of the reliability of the different evidence, e.g. why is the SI so clearly erroneous. Also no discussion of the difference in measured dermal uptake 319 mg/cm<sup>2</sup>/hr and that calculated in the Appendix.

The British Health and Safety Executive quote a dermal LD50 of 270 mg/kg from the OECD (see <http://www.hse.gov.uk/aboutus/meetings/iacs/acts/watch/130105/p6annex2.pdf> )

Reviewer 2:

Studies that relate to the possibility of systemic health hazards due to skin absorption of formaldehyde are extensively discussed in this document. There are no studies estimating dermal absorption in humans. Toxicokinetic data from in vivo animal studies showed limited potential for formaldehyde to be absorbed through the skin. Data regarding formaldehyde dermal absorption leading to carcinogenic promotion potential were inconclusive. There were no standard toxicity tests showing that formaldehyde absorption through the skin could result in systemic health effects.

Reviewer 3:

Yes

**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:

SYS(FATAL) not mentioned. As noted above the rationale for not assigning SYS notation is unclear.

Reviewer 2:

The rationale and logic behind not assigning the SK:SYS notation to formaldehyde is clearly discussed in this document.

Reviewer 3:

NA

**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 this is clear.

Reviewer 2:

This document clearly describes direct health hazards associated with exposure of skin to formaldehyde. Skin-patch tests showing direct skin effects of formaldehyde in humans and skin irritancy studies in animals are described.

Reviewer 3:

Yes

**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:

DIR(IRR) assignment is clear. No really clear why DIR(COR) not assigned, but I presume it is lack of data – one study is discounted because of inadequate information about the corrosive effects. In Europe the GHS classification for formaldehyde (>25%) is Skin Corr 1B, H314 and for 5 - 25% it is Skin Irrit 2, H315.



This section could be clearer and there may be missing information.

Mention is made of solutions with concentration >37%, but this is close to saturated concentration – not clear what is implied.

Reviewer 2:

This document clearly explains the rationale and logic behind the assignment of SK:DIR (IRR) notation to formaldehyde.

Reviewer 3:

No. Add best estimate of “NOEL”, as skin contact occurs daily – and is usually well tolerated.

Add vapor exposure.

**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:

It is not easy to follow the argument in this section, particularly on page 9. I think it might benefit from some editing to reduce the amount of detail about the studies.

The studies described in the first paragraph on page 8 all involve relatively small numbers of subjects with different methods and so it is unlikely that they have much power to accurately define the elicitation threshold. I think the final sentence in this paragraph while factually correct gives the wrong impression.

No need to define formalin on page 7 as this was done on page 1.

Reviewer 2:

Studies showing skin sensitization following dermal exposure to formaldehyde in humans and animals are extensively discussed in this document. Dermal allergic reactions in various worker groups are described. In addition, patch testing shows allergic response to formaldehyde contact with the skin. Predictive tests are described in animals showing the sensitizing potential of formaldehyde. The structure-activity relationship model, DEREK, which predicts formaldehyde to be a skin sensitizer, is outlined in this document.

Reviewer 3:

No. See several 2009 – 2010 (published “on-line” or available from author) publications by Anton De Groot – that permit clinical interpretation re dose, etc.

**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:

Yes, although note above it is not easy to follow the detail presented of information.

Note in Europe under GHS formaldehyde will be classified as Skin Sens 1, H317 - but only for C>=0.2%

Reviewer 2:

The rationale and logic for making the SK:SEN notation for formaldehyde is clearly presented in this document.

Reviewer 3:

No. As exposure is daily, reader needs clinical interpretation (and elicitation “NOEL”)



**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:

These notations were not assigned for formaldehyde.

Reviewer 3:

NA

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

Reviewer 1:

Yes.

Reviewer 2:

The conclusions in regards to systemic toxicity, direct irritant effects, and immune-mediated responses due to formaldehyde exposure of skin are all supported by the data presented. I agree with the skin notations made for formaldehyde.

Reviewer 3:

No. See #5 above.

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

Reviewer 1:

yes.

Reviewer 2:

The tables are clear and appropriate.

Reviewer 3:

Yes

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

Reviewer 1:

Yes.

Reviewer 2:

The document is well organized.

Reviewer 3:

Yes

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

Reviewer 1:

As notes above the text is not easy to follow and could be edited to reduce the amount of detail while still retaining the key messages.

Reviewer 2:

The manuscript is written using a clear and concise language.

Reviewer 3:

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:

The information on the uses seems to be incomplete – missing are tissue fixation, embalming fluids and uses as a biocide.

Reviewer 2:

I am not aware of any other scientific data that should be included within this document.

Reviewer 3:

Yes. See #5 above.

**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:

Yes, although I am not certain that the statements about GHS categorizations are correct. I have seen a document that indicates that in Europe formaldehyde will be classified under GHS as indicated above and this may challenge some of the conclusions arrived at in the document.

Reviewer 2:

I recommend that this document be accepted as the final SK profile for formaldehyde.

Reviewer 3:

Acceptable. Points noted in #5 would greatly increase usefulness.

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

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