Dragon, Karen E. (CDC/NIOSH/EID)

From: Paul Dugard [pdugard@mindspring.com]
Sent: Friday, June 11, 2010 4:33 PM
To: NIOSH Docket Office (CDC)
Subject: Docket Number: NIOSH-153-A. Skin Notation Profile for Trichloroethylene
Attachments: TCE Skin Notation HSIA Comments 2010-06.docx; TCE S-J Kamijima rev 2007.pdf; TCE S-J Genetics Li 2007.pdf; TCE S-J US case Bond 1996.pdf

Dear Sir or Madam:

Please find attached the comments of the Halogenated solvents Industry Alliance (HSIA) on the Skin Notation Profile for Trichloroethylene (TCE). Also attached are papers referred to in the comments that were not included in the Profile itself.

Sincerely,

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Director of Scientific Programs

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Trichloroethylene: Skin Notation Profile

(Response to Request for Technical Review, 75 Fed. Reg. April 27, 2010)

Comments of the Halogenated Solvents Industry Alliance

Submitted by Paul H. Dugard, PhD

Docket Number: NIOSH-153-A

General

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents the producers and users of trichloroethylene (TCE). HSIA has a strong tradition of involvement in the toxicology and epidemiology of TCE and has sponsored many research projects as well as standard toxicity testing.

NIOSH is to be congratulated on a comprehensive review of the available information relevant to the assignment of the skin notation to TCE. Nevertheless there are elements in the interpretation of the data that are of concern. HSIA agrees that the "SK: DIR (IRR)" is an appropriate designation but we do not consider that designations for systemic effects (SK: SYS) or skin sensitization (SK: SEN) are supported by the evidence.

Systemic Toxicity

The conclusion that "The available dermal absorption data from studies of humans and animals demonstrate that the degree of absorption of TCE through the skin is limited in comparison with uptake via inhalation" is valid. And the SI ratio of 0.02 emphasizes that the skin absorption component is small when inhalation exposure occurs (as will almost always be the case when bare skin contact is extant). [Note that the Appendix, on p.15 states "The calculated SI ratio was 0.02. On the basis of these results, TCE is predicted to represent a skin absorption hazard." – we assume this should say "…predicted NOT to represent a skin absorption hazard."]

In terms of the effects, it is not clear that general liver or kidney toxicity occur even with many years' high inhalation exposures. Observed neurotoxicity may well be an anesthetic effect rather than a degenerative condition and, again, intake by inhalation will dominate. Considering the widespread use of TCE over many decades with high levels of exposure it is clear that systemic effects have not been of great concern.

The decision to apply the "SYS" notation appears to have been driven largely by the case reports of Liu (2009). These reports of severe effects on liver or kidney with extensive skin involvement have been coming from the Far East, especially China, for a number of years. We have been

unable to find any reports of such reactions in the Western Hemisphere apart from a single mild case in the USA (Bond, 1996) that appears to be similar to cases in the Far East. The ethnicity of this patient discussed by Bond has not been established by us. To understand the nature of these responses, we recommend reading the publication by Kamijima et al. (2007) that we include with this submission. The genetic basis to these diseases, and an explanation for the geographic pattern of occurrence, is provided by Li et al. (2007), also included. These related reactions are systemically mediated immune reactions and are probably the same as idiosyncratic reactions seen for pharmaceutical products. We suspect, but cannot prove, that the initial induction of immune sensitivity requires a high exposure level. Once sensitivity has been induced, lower exposures would be likely to cause reactions. Since these immune responses are systemically mediated, the balance between inhaled and percutaneous doses applies, and a skin notation is not indicated.

Skin Sensitization

The information for TCE is striking in the absence of reports of skin sensitization reactions despite very large numbers of workers over many decades who have routinely experienced skin contact with undiluted TCE. Of the human cases cited by NIOSH, those reported by Nakayama et al. (1988) and Phoon et al. (1984) clearly fall in the category of reactions described by Kamijima et al. (2007) and thus the skin reactions are secondary to a systemic immune response. These are not examples of skin sensitization *per se*. The sole example (Conde-Salazar et al. 1983) does appear to indicate sensitization but whether to TCE or to a biologically active stabilizer (such as epichlorohydrin – TCE always contains stabilizers) cannot be established. The existence of this one case is insufficient to consider TCE to be a skin sensitizer.

The results obtained by Tang et al. (2002, 2008) show a clear positive for TCE in the guinea pig maximization test and suggest that TCE is a strong skin sensitizer. Human experience clearly refutes this finding. It is not clear why the results of the guinea pig test are not predictive of human responses in this case.

Overall, there is no basis for the designation "SK: SEN" for TCE.

Conclusions

The designation "SK: DIR (IRR)" is appropriate. The evidence does not support notation for systemic effects or skin sensitization.

References

Are as in the Profile except for the papers included with this submission.

(Correction: ACGIH now classifies TCE as "A2 – suspected human carcinogen")

PD 06/11/2010