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solvents
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March 16, 2015

Division of Toxicology and Human Health Services
Agency for Toxic Substances & Disease Registry
1600 Clifton Road, NE (MS F57)
Atlanta, GA 30333

Re: ATSDR-2014-0001 (Tetrachloroethylene)

Dear Sir or Madam:

The Agency for Toxic Substances & Disease Registry ("ATSDR") recently announced the availability for review of a draft updated Toxicological Profile for Tetrachloroethylene (CAS No. 127-18-4). 79 Fed. Reg. 74094 (December 15, 2014). These comments on the Toxicological Profile are offered on behalf of the Halogenated Solvents Industry Alliance, Inc. ("HSIA"), which represents producers and users of tetrachloroethylene and other chlorinated solvents.

In its Federal Register announcement, ATSDR summarized the components of a Toxicological Profile, as follows.

> "Each profile will include an examination, a summary, and an interpretation of available toxicological information and epidemiological evaluations. This information and these data identify the levels of significant human exposure for the substance and for the associated health effects. The profiles must also include a determination of whether adequate information on the health effects of each substance is available (or in the process of development) in order to identify levels of significant human exposure."

The following comments address several areas where HSIA feels the current draft Toxicological Profile could be strengthened to better achieve those objectives. Some of the issues are general in nature, whereas others are more specific.

1) ATSDR should utilize emerging tools for systematic review in development of its Toxicological Profile for tetrachloroethylene.

Systematic review methodologies provide objectivity and transparency to the process of collecting and evaluating scientific data, however, it does not appear that ATSDR has utilized systematic review in the development of the current draft Toxicological Profile. In

fact, nowhere in the document is 'systematic review' even acknowledged. Although well established in clinical medicine (IOM, 2011)[1], systematic review has recently become popular in the evaluation of environmental health data which can typically involve human, animal and mechanistic data. In its recent evaluation of EPA's IRIS process, the NRC (2014)[2] made a series of recommendations for conducting a systematic review. Many of those recommendations mirror approaches contained in systematic review methodology developed by NTP's Office of Health Assessment and Translation (OHAT) (NTP, 2015)[3]. In its recommendations to EPA on overall evidence integration, the NRC states that "if EPA does move to a structured evidence-integration process, it should combine resources with NTP to leverage the intellectual resources and scientific experience in both organizations."

In a recent publication, ATSDR indicated that the agency has "entered into a collaborative effort with NTP OHAT to implement [systematic review] for updating and evaluating the scientific literature used to develop ATSDR Toxicological Profiles and Addenda."[4] As ATSDR has already used systematic review in at least one other profile/addendum[5], it would be our recommendation that the draft Toxicological Profile for tetrachloroethylene be revised to demonstrate, at a minimum, that it conforms to the NTP/OHAT systematic review paradigm.

Detailed Comment

There are several key components of the recommended systematic review process that are common to both the NRC and NTP approaches.

a) <u>Problem Formulation and Protocol Development</u>

NRC recommends a three-step process for problem formulation:

- Utilize a trained information specialist to conduct a broad literature search to identify possible health outcomes [Not to be confused with the comprehensive literature search conducted as part of evidence identification. No results are extracted or summarized during this stage];

[1] Institute of Medicine (IOM). Finding what works in health care: standards for systematic review. The National Academies Press, Washington, DC (2011).

[2] National Research Council (NRC). Review of EPA's Integrated Risk Information System (IRIS) Process. The National Academies Press, Washington, DC (2014).

[3] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences, Office of Health Assessment and Translation (OHAT), Research Triangle Park, NC (2015).

[4] Murray HE & Thayer KA. Implementing systematic review in toxicological profiles: ATSDR and NIEHS/NTP collaboration. J Env Hlth 76(8): 34-35 (2014).

[5] See: ATSDR. Addendum to the toxicological profile for titanium tetrachloride (2014)

- Construct a table to guide the formulation of specific questions that would be the subject of the systematic review [Organized by lines of evidence and various health outcomes to investigate]; and
- Determine from the table which outcomes warrant a systematic review and how to define the systematic review question(s). [The decision process should be documented and reviewed by relevant experts].

After the systematic review questions are defined, protocols for conducting the reviews to address the questions need to be developed. According to the NRC, the protocol "makes the methods and the process of the review transparent, can provide the opportunity for peer review of the methods, and stands as a record of the review. It also minimizes bias in evidence identification by ensuring that inclusion of studies in the review does not depend on the studies' findings. Any changes made after the protocol is in place should be transparent, and the rationale for each should be stated." The protocol is developed *a priori* and forms the basis for scientific judgments throughout the evaluation. Protocols should be included as appendices to the final document.

There is no documentation provided in the draft Toxicological Profile for tetrachloroethylene that ATSDR has developed or has utilized a protocol which delineates the steps a priori to be followed in its review. It appears that the agency has relied heavily on EPA's 2012 IRIS document for tetrachloroethylene[6] rather than conducting its own systematic review of the available literature. Unfortunately, the 2012 IRIS review was also conducted without the benefit of systematic review.

b) Evidence Identification

Searching for and identifying evidence are critical steps in conducting a systematic review and should utilize a standardized search strategy and reporting format. This should include a line-by-line description of the search strategy and statement of the inclusion/exclusion criteria for studies developed in collaboration with an information specialist trained in systematic review methodologies. The NRC encourages the use of at least two reviewers, working independently, to screen and select studies using standardized procedures and forms.

Without benefit of a protocol, there is no information provided in the draft Toxicological Profile describing either the search strategy used or the inclusion/exclusion criteria. Presumably a selection process was utilized; however, there can be little confidence that it was appropriate given the lack of detail or transparency. For example, given the reliance on epidemiological data for the derivation of MRLs, it is surprising that

[6] U.S. Environmental Protection Agency (EPA). Toxicological review of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in support of summary information on the Integrated Risk Information System (IRIS). (EPA/635/R-08/011F). Washington, DC (2012).

a recent epidemiological review, commissioned by HSIA[7], was apparently not selected for consideration in the ATSDR review.

c) Evidence Evaluation

Once studies are identified, relevant data are extracted and summarized using standardized approaches and evaluating human, animal and *in-vitro* data separately. Under the NTP OHAT approach, this activity is carried out by a two-person team, one performing the data extraction and the other quality assurance. Both the NRC and OHAT recommend the incorporation of risk-of-bias assessments for each outcome of interest on each individual selected reference. More specifically, the NRC recommends that "a risk-of-bias assessment should be conducted on studies that are used.……as primary data sources for the hazard identification and dose-response assessment." Although there are a number of approaches available for assessing risk-of-bias, there is agreement that both the assessment approach and the results should be fully documented. In addition to evaluation of risk-of-bias, the evidence evaluation step should result in a judgment of the quality of both the individual studies, which can be done using an approach such as the Klimisch scoring system (Klimisch *et al.* 1997)[8], and the overall body of evidence for each effect outcome. This can be accomplished through the use of confidence ratings. Although this process can be somewhat subjective, the advantage of the systematic review process is that it provides a framework to document and justify the decisions made.

It is perhaps in the area of evidence evaluation, that the lack of a systematic review approach is most apparent in the draft Toxicological Profile. There is no indication that risk-of-bias assessments were undertaken and the results of individual studies were included with little apparent consideration as to their individual or overall quality. For example, although the study by Cavalleri et al., (1994) was selected as a critical study by both EPA and ATSDR, there appear to be quality issues associated with that study that should have been evaluated in greater detail in the current review.

d) Evidence Integration for Hazard Identification

There are several approaches available for evidence integration. A qualitative approach, utilizing working groups to achieve consensus on a chemical's toxicity, is used by the International Agency for Research on Cancer (IARC). Several quantitative options are also available, including meta-analysis, probabilistic bias analysis and Bayesian analysis. It is essential that the protocol describe the specific approach to evidence integration that will be used in the evaluation. As part of its review of EPA's IRIS process, the NRC recommends

[7] Bukowski, J, Review of the epidemiologic literature on residential exposure to perchloroethylene. Crit Rev Toxicol 41: 771-782 (2011).

[8] Klimisch *et al.,* A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25: 1-5 (1997).

the development of templates for structured narrative justifications of the evidence-integration process and the hazard conclusions reached.

Although the draft Toxicological Profile does present summary tables of data from individual studies, there is really minimal integration of information from different evidence streams in developing conclusions on tetrachloroethylene hazard.

Health effects evaluations conducted following systematic review procedures have the potential to improve communication and transparency about hazard identification conclusions through documentation of the sources of data considered, the methods used to assess quality as well as the scientific judgments made during evidence integration. It is unfortunate that systematic review tools were not used in the current draft Toxicological Profile for tetrachloroethylene.

2) The epidemiology dataset relied upon for development of tetrachloroethylene MRLs has limitations

Consistent with ATSDR guidelines, the draft Toxicological Profile for tetrachloroethylene is intended to provide an examination, summary, and interpretation of available toxicological and epidemiological information. During that process, MRLs are derived when ATSDR determines that "reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure to the substance" (ATSDR, 2015)[9]. MRLs are based on non-cancer health effects only and are not based on a consideration of cancer effects. Both the oral and inhalation MRLs for tetrachloroethylene are based on a study by Cavalleri *et al.* (1994)[10] with additional consideration given to a follow-up study by Gobba *et al*. (1998)[11]. However, a closer evaluation of the Cavalleri *et al*. study suggests that it has a number of limitations which should have been discussed in greater detail.

Detailed Comment

This Cavalleri *et al.* (1994) which was selected by ATSDR as the primary study for the development of oral and inhalation MRLs. The study examined the loss of color vision in 35 dry-cleaning workers in 12 small dry-cleaning shops in Modena, Italy. To be included in the study all workers were required to be "apparently healthy" with "a daily average alcohol intake under 50 g/day, smoking fewer than 30 cigarettes /day and with a visual acuity of 6/10 or more (with lenses)." An equal number of controls were matched by sex, age (± 3

[9] See at http://www.atsdr.cdc.gov/mrls/index.asp

[10] Cavalleri *et al.* Perchloroethylene exposure can induce color vision loss. Neuro Letters 179: 162-166 (1994).

[11] Gobba *et al.*, Two-year evolution of perchloroethylene-induced color-vision loss. Arch Env Hlth 53(3): 196-198 (1998).

yrs), alcohol consumption (± 10 g/day) and cigarette smoking (± 5 cigarettes/day). The authors state that tetrachloroethylene was "the main solvent used in all shops" which does raise the concern that other solvents might have been used in lesser amounts.

Color vision was evaluated with the Lanthony 15 Hue desaturated panel, which was repeated 10 times. Results were expressed as a color-confusion index (CCI) with a focus on errors in blue-yellow color vision. Tests were performed monocularly, and the mean CCI for both eyes was used in the analyses.

The authors segregated the 35 workers into two subgroups [i.e., drycleaners (n=22) and ironers (n=13)] based on their job responsibilities and presumed different solvent exposure levels. Personal passive sampling conducted over a single 1 day work shift produced a mean time-weighted average (TWA) for all workers of 6.23 ± 6.66 ppm (range: 0.38 - 31.19 ppm), for drycleaners of 7.27 ± 8.19 ppm (range: 0.38 - 31.19 ppm) and for ironers of 4.80 ± 3.45 ppm (range: 0.52 - 11.28 ppm). HSIA is concerned about the segregation of the workers, a concern apparently shared by EPA in Section I.B.2 of their 2012 IRIS Summary (EPA, 2012)[12], where they noted that "[a]lthough no apparent CCI deficit was observed in ironers, their reported exposure range (0.52 - 11.28 ppm, or 3.5 - 76 mg/m^3) was completely contained within the range of exposures for dry cleaners (0.38 - 31.19 ppm, or 2.6 - 210 mg/m^3)."

The paper reported that the mean CCI for all workers was significantly higher (1.143 ± 0.128) than that of controls (1.083 ± 0.104). The mean CCI for the drycleaner subgroup was also significantly higher (1.192 ± 0.133) than that of controls (1.089 ± 0.117), whereas the mean CCI for the ironer group was not significantly greater than its control group.

These results have been used in the current draft Toxicological Profile as evidence that a dose-response relationship exists between inhalation exposure to tetrachloroethylene and color-vision loss. A closer examination of the paper raises several questions. Given the importance of establishing a dose-response relationship, predicting a chronic inhalation exposure level for a 9 year plus period (106 ± 92 months) based on TWA air concentrations measured during a single sampling event appears to be a problem. No exposure data were provided for previous years, nor was any information provided linking measured TWA exposure levels to actual years of exposure (i.e., ppm-yrs) for individual workers, although the authors do state that "CCI was not related to the duration of previous PCE exposure, nor to an integrated index of exposure as TWA levels of the solvent per year." Unfortunately, no data were presented in the paper to support that contention.

The authors affirm that the "hypothesis that PCE exposure is the specific cause of the color vision loss is supported by the observed relationship between exposure levels and values of CCI (Fig. 1), and by the results of multivariate analysis." A closer examination of

[12] See at http://www.epa.gov/iris/subst/0106.htm

Figure 1 (reproduced below) indicates that there appear to be only two outlier individuals with exposure levels that exceed 12.5 ppm. The highest exposed individual has a TWA exposure level of 31.2 ppm and the second highest exposed individual appears to have an exposure level between 21 and 22 ppm (see Figure 1).

Figure 1 from Cavalleri *et al.*, (1994).

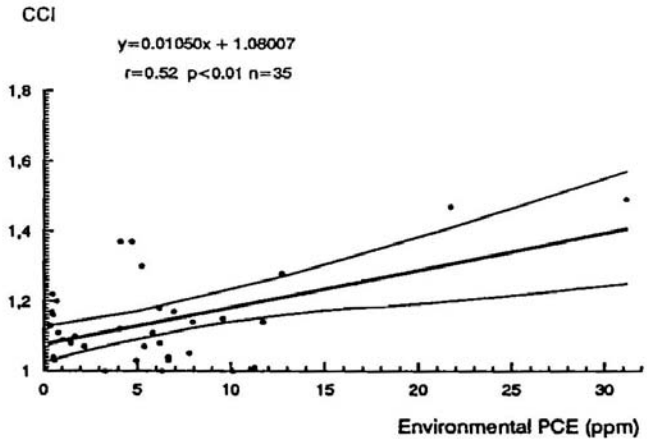

Fig. 1. Correlation and 95% confidence interval for the predicted mean values of the dependent variable between Time-Weighted Average (TWA) environmental levels of PCE and values of the Colour Confusion Index (CCI).

Without those two outliers, HSIA contends that there does not appear to be any correlation between dose and response across the remaining 33 'exposed' workers. The authors apparently come to a similar conclusion stating that "by excluding these data [i.e., the three data points 12.5 ppm and greater] the significance of the correlation between exposure and effect disappeared."

In stating that "we documented current exposure but have no evaluation of previous exposure", the authors concede a degree of uncertainty about the strength of the dose-response relationship between tetrachloroethylene and color vision loss. In our view, the study does suggest the existence of a threshold for color vision loss and, based on the current exposure levels and the results shown in Figure 1, that threshold could lie between 12 and 20 ppm. That range is slightly higher than the value selected by ATSDR in the current review.

3) Estimation of MRLs for tetrachloroethylene.

Although available epidemiological data, as cited in the draft Toxicological Profile, do suggest that high-level exposure to tetrachloroethylene (>40-50 ppm) may be associated

with subtle neurobehavioral effects, the data on lower-level exposures are much more difficult to interpret. The general solvent literature suggests that sensory tests involving visual pathways (*e.g.*, color discrimination and contrast sensitivity) could provide the most sensitive endpoints, but the inconsistent and potentially flawed nature of much of the literature preclude such a determination for tetrachloroethylene. The subtle nature of these effects makes it difficult to tease out risks related to tetrachloroethylene from those related to other factors. A risk assessment based on such subtle, and potentially temporary, effects should be health protective while providing a margin of error against uncertainty or short-lived departures above the MRL.

While no single study stands out of sufficient quality as being the basis for developing a MRL (See Comment 2), two studies appear to be to adequate. Adequacy is based on the inclusion of a measure of exposure, comparison to a defined control group, no known co-exposure to other solvents in the workplace, chronic exposure duration, and the use of accepted testing procedures for neurological endpoints. The LOAELs are 7.3 ppm based on ATSDR's interpretation of color discrimination effects in dry-cleaners (Cavalleri *et al.*, 1994) and 12 ppm based on neurobehavioral changes in dry-cleaners (Seeber, 1989)[13]. The quality of these two studies does not appear to be sufficiently different to allow for the selection of one study over the other as the critical endpoint. Furthermore, no indication was found that either study identified a more sensitive endpoint, given that both reported effects at similar levels of exposure. Thus, we recommend that the arithmetic mean of the LOAEL values from the two studies be used to represent an average point of departure (POD) for the MRL. This would result in an average exposure level of 10 ppm. We recognize, however, that the LOAEL may lie within a range of exposures (i.e., approximately 5-30 ppm) rather than at a single mean concentration.

4) Application of uncertainty factors in the derivation of MRLs is overly conservative.

ATSDR used a total UF of 300 to derive the MRLs: 10 for variability of sensitivity in the human population; 10 for extrapolating from a LOAEL to a NOAEL; and 3 for database deficiencies. The evidence from the Cavalleri *et al*. study would suggest, however, that a factor of 10 for the uncertainty in extrapolating from a LOAEL rather than a NOAEL is overly conservative and that a factor of 3 would be more appropriate.

5) Proposing the same value for the acute, intermediate and chronic MRL is generally inconsistent with the historical approach adopted by ATSDR for existing MRLs.

In the draft Toxicological Profile for tetrachloroethylene, ATSDR is proposing a single oral MRL value (i.e., 0.008 mg/kg/day) and a single inhalation MRL value [i.e., 0.006 ppm (0.04 mg/m^3)] for acute, intermediate and chronic exposure scenarios. Examination of the

[13] Seeber, A, Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. Neurotoxicol Teratol 11: 579-583 (1989).

current MRL table indicates that the proposed approach is relatively rare (ATSDR, 2015)[14]. Typically, as noted in the following, the acute MRL for a given chemical is higher than the intermediate and/or chronic MRL value.

There are currently 28 organic chemicals, excluding tetrachloroethylene, which have acute inhalation MRLs as well as intermediate and/or chronic inhalation MRLs. From this list of 28 chemicals, there are only two (i.e., trans-1,2-dichloroethene and hexachloroethane) where the acute inhalation MRL is not higher than the intermediate or chronic MRL. No chronic inhalation MRL was derived for either of those two chemicals.

There are currently 57 organic chemicals, excluding tetrachloroethylene, which have acute oral MRLs as well as intermediate and/or chronic oral MRLs. From this list of 57 chemicals, there are only five (i.e., cyhalothrin; p,p'-DDT; 4,6-dinitro-o-cresol; ethylene glycol and naphthalene) where the acute oral MRL is not higher than the intermediate or chronic MRL. No chronic oral MRL was derived for any of those five chemicals.

In the case of tetrachloroethylene, ATSDR has relied on a PBPK-based argument to support using the chronic MRL as the acute MRL. With the advances in PBPK modeling, we feel that such an approach is certainly reasonable and anticipate that it will become even more common place in the future. However, we also feel that ATSDR needs to do a better job of explaining the process in the Toxicological Profile. For example, we have identified the several uncertainty issues with the Cavalleri *et al.* study (see following) and, although the issues are common to many epidemiology studies, the Profile does not do a very good job of explaining how these uncertainties are integrated into the decision to use the chronic MRL as the acute MRL.

a) Without worker histories (e.g., number of years employed at the specific facilities), the uncertainty surrounding actual chronic exposure levels would appear to be quite high.

b) Whether or not a dose-response relationship actually exists between tetrachloroethylene exposure and loss of color vision is unclear. In the key study, the authors indicate that when three outliers out of 35 points were removed from the dataset, correlation between exposure level and severity of effect seemed to disappear.

c) No robust mode (mechanism) of action is provided within the draft for the selected toxicity endpoint (i.e., loss of color vision).

d) Whether or not the loss of color vision following tetrachloroethylene exposure is reversible is unclear.

e) No pharmacokinetic data are presented within the draft to clarify if the loss of color vision is caused by tetrachloroethylene or one of its metabolites.

[14] See MRL list at: http://www.atsdr.cdc.gov/mrls/pdfs/atsdr_mrls_december_2014.pdf.

6) Minor Comments.

a) Near the bottom of Page 9 (Section 2.1) it is reported that levels of tetrachloroethylene in water samples at Camp Lejeune were as high as 30,000 mg/L. This value needs to be discussed, as Table 4-2 reports that the water solubility of tetrachloroethylene is 206 mg/L.

b) ATSDR should be consistent within the document in its use of alpha-2u-nephropathy; it is not alpha-2μ-nephropathy[15].

c) In evaluating the identification of data needs for the tetrachloroethylene database (Section 3.12.2), there is a section titled 'Chronic-Duration Exposure and Cancer' which for some reason summarizes data on vision effects.

d) In Section 3.12.2 under 'Developmental Toxicity', it is stated that the study by Fredriksson *et al.* (1993)[16] "serves as the basis for the acute oral MRL". Although this was the case in the previous Toxicological Profile for tetrachloroethylene, it needs to be corrected in the current draft.

e) In Section 6.5, reference is made to the Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2012). This section needs to be updated to reflect the recent release of the updated tables (CDC 2015)[17] which provide an ongoing assessment of the exposure of the U.S. population to environmental chemicals by the use of biomonitoring.

Thank you in advance for consideration of HSIA's comments. If you have any questions or need clarification on any of our comments, please contact me at 703-875-0683 or at fgraul@hsia.org.

Respectfully submitted,

Faye Graul

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Executive Director

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[15] See, for example, the incorrect citation title for Swenberg, J, *et al.*, (1989) in the Reference Section of the draft. The correct title should read: "The comparative pathobiology of a α2u-globulin nephropathy".

[16] Frederiksson *et al.*, Altered behavior in adult mice orally exposed to tri- and tetrachloroethylene as neonates. Tox Letters 66: 13-19 (1993).

[17] See at: www.cdc.gov/biomonitoring/pdf/FourthReport_Updated Tables_Feb2015.pdf