Texas Commission on Environmental Quality (TCEQ) Response to Public Comments Received on the Proposed Development Support Document for Tetrachloroethylene (PCE) April 15, 2008

The public comment period for the proposed Development Support Document (DSD) for tetrachloroethylene (PCE) ended in March 2008. The Halogenated Solvents Industry Alliance (HSIA) submitted comments. The Toxicology Section (TS) of the Texas Commission on Environmental Quality (TCEQ) appreciates the effort put forth by HSIA to provide technical comments on the proposed DSD for tetrachloroethylene. The goal of the TS and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. A summary of HSIA comments are provided below, followed by TCEQ responses. The full comments of HSIA are in Appendix 1. Comments on issues that suggest a change in the DSD are addressed whereas comments agreeing with TCEQ's approach are not. TCEQ responses indicate what changes, if any, were made to the DSD in response to the comment.

Upon further review, the TS found that the proposed DSD inadvertently listed a unit risk factor (URF) of 5.6×10^{-8} per ppb both in the Footnote b of Table 1 and Section 4.4 (Long-Term ESL and Values for Air Monitoring Evaluation).The correct URF should be 2.6×10^{-6} per ppb.

Halogenated Solvents Industry Alliance (HSIA) Comments Regarding the TCEQ Development Support Document for Tetrachloroethylene (PCE) ReV and ESL Values

Comment 1:

The draft DSD presents a reasonable summary of the key information on the potential acute and chronic, non-cancer health effects of PCE. . . . HSIA encourages the Commission to include some additional discussions of other studies on central nervous system effects and the limitations of the two studies elected for establishing ESLs.

Response 1:

The TS appreciates HSIA's acknowledgment and encouragement. The TS has incorporated additional information reported in "Neurotoxicity of Tetrachloroethylene (Perchloroethylene): Discussion Paper" (USEPA 2003).

Comment 2:

The findings in the study TCEQ uses to establish the ESL_{odor} (Nagata 2003) are inconsistent with other available information on the odor threshold for PCE, generally considered to be between 5 and 50 ppm. HSIA comments that unless additional studies can be identified that are consistent with the findings of Nagata, HSIA does not believe that this study is an appropriate basis for establishing the ESL_{odor}.

Response 2:

The DSD was not revised based on this comment. "Inconsistency" among published odor threshold values is the unavoidable result of the fact that published odor thresholds for the same chemical commonly vary widely. In accordance with TCEQ Regulatory Guidance 442 Section 1.6.2.2 (Odor-Based ESLs), the Nagata (2003) study was chosen as the basis of the ESL_{odor} because it provides the lowest 50% detection threshold that meets the AIHA and USEPA's Evaluation Criteria. The proposed ESL_{odor} of 0.77 ppm is deemed appropriate and is not inconsistent with the odor threshold of 1 ppm reported by ATSDR (1997).

Comment 3:

HSIA is concerned about the Commission's decision to use a hazard quotient (HQ) of 0.3 to derive ESLs from the acute and chronic, non-cancer Reference Values (ReVs).

Response 3:

The DSD was not revised based on this comment. In order to develop ESLs for use in air permitting that adequately consider the potential for cumulative and aggregate exposures, the TS believes that it is prudent to use an HQ less than 1 for chemical effects whose dose-response relationships are known or assumed to be nonlinear (which generally consist of noncarcinogenic effects).

Consideration of cumulative risk is required by the Texas Water Code Subchapter D Section 5.130. Consideration of cumulative and aggregate concerns is also consistent with empirical evidence such as ambient air monitoring data that demonstrate the presence of multiple chemicals in the air at the same time and the repeated presence of the same chemical(s) over time, as well as the fact that multiple sources of the same chemical can contribute to the concentration of that chemical at a single location.

At the same time, the TS recognizes that the choice of a specific HQ less than 1 is a policy decision. TCEQ Regulatory Guidance 442 Section 1.4 Specific Risk Management Objectives (No Significant Risk Levels) states: "In consideration of cumulative and aggregate exposure, the Toxicology Section (TS) uses an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with a nonlinear dose-response assessment."

Comment 4:

HSIA comments that the DSD should include more consideration of substance-specific information in determining the appropriate HQ. The need for additional scrutiny is evidenced in the fact that the proposed $^{acute}ESL$ for PCE is higher than ATSDR's corresponding MRL and the proposed $^{chronic}ESL_{nonlinear(nc)}$ is lower than the corresponding MRL, even though the same studies are used.

Response 4:

The DSD was not revised based on this comment. It more appropriate to compare ATSDR MRLs with TCEQ ReVs than with ESLs. As stated in TCEQ Regulatory Guidance 442 Section 1.5.1 (ReVs for Nonlinear Dose-Response Effects), an inhalation ReV is an estimate of an inhalation exposure concentration for a given duration to the human population that is likely to be without an appreciable risk of adverse effects. The proposed acute and chronic ReVs for PCE are in agreement with similar types of toxicity values reported by other federal and state agencies (e.g.,

USEPA RfC, CalEPA REL, or ATSDR MRL). The proposed acute ReV (1 ppm) is within a factor of 10 but higher than the corresponding MRL (0.2 ppm), and the proposed chronic ReV (0.05 ppm) is nearly equal to the corresponding MRL (0.04 ppm).

Comment 5:

A recent epidemiological study by Lynge et al. (2006) provides strong evidence that the incidence of several important cancer types among dry cleaning workers in the Nordic countries was not related to PCE exposure. The results of the Nordic study strongly suggest that TCEQ should seriously reconsider whether the evidence supports establishment of an ESL for PCE based on potential human carcinogenicity.

Response 5:

The TS appreciates HSIA for providing two recent epidemiological studies (Mundt et al. 2003, Lynge et al. 2006). The Mundt et al. (2003) review of the epidemiological studies has been previously reviewed and cited in the proposed DSD (Section 4.2.1 Carcinogenic Weight of Evidence). The TS has incorporated the Lynge et al. (2006) study in the revised DSD. While both the Mundt et al. (2003) and Lynge et al (2006) studies indicate that the current epidemiological evidence does not support a conclusion that occupational exposure to PCE is a risk factor for cancer of any specific site including liver cancer, these authors acknowledge that there are severely limited by lack of valid exposure data or other adequate indicators of potential for exposure in the current epidemiological studies.

Additionally, tumor data observed from the NTP (1986) animal studies strongly show that PCE is carcinogenic in animals. Therefore, the TS believe it is necessary to conservatively use the results from the 1986 NTP inhalation bioassay to develop the $^{chronic}ESL_{linear(c).}$ Derivation of the $^{chronic}ESL_{linearc}$ based on results of the 1986 NTP inhalation bioassay is consistent with other federal and state agencies in developing PCE inhalation cancer unit risk factors and corresponding chronic toxicity values.

Comment 6:

While HSIA does not agree with TCEQ that establishment of an ESL based PCE's carcinogenic potential is appropriate, HSIA applauds the Commission's use of the data available for development of the proposed chronic toxicity benchmark dose. In particular, HSIA supports the Commission's selection of the PBPK model developed by Gerhart et al. (1993) which assumes that 1 to 3 percent of the PCE absorbed by humans is metabolized.

Response 6:

The TS appreciates HSIA's comments on carcinogenic potential issue. The TS believes that the Gearhart et al. (1993) model, which provided the closest predictions of the urinary excretion observed in low-concentration exposures, provides the most reliable dose metrics for a PCE risk assessment.

APPENDIX 1

Halogenated Solvents Industry Alliance (HSIA)
Proposed Development Support Document for Tetrachloroethylene (PCE), January 2008

HALOGENATED SOLVENTS INDUSTRY ALLIANCE, INC.
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March 17, 2008

Toxicology Section, MC 168
Texas Commission on Environmental Quality
12100 Park 35 Circle
Building F
Austin, TX 78753

Re: Proposed Development Support Document for Tetrachloroethylene (PCE), January 2008

To Whom It May Concern:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) appreciates the opportunity to submit comments on the draft Development Support Document (DSD) for tetrachloroethylene (perchloroethylene, PCE). HSIA represents manufacturers and some users of PCE and other chlorinated solvents.

Acute and Chronic, Non-Cancer Effects

HSIA believes that the draft document presents a reasonable summary of the key information on the potential acute and chronic, non-cancer health effects of PCE. Although considerable additional information exists on non-cancer effects, we appreciate that the proposed DSD focuses on those studies used by the federal Agency for Toxic Substances and Disease Registry (ATSDR) in developing its minimum risk levels (MRLs). In light of the considerable amount of data available on central nervous system effects, however, HSIA encourages the Commission to include some additional discussion of other studies and the limitations of the two studies selected for establishing Effects Screening Levels (ESLs).[1]

HSIA is concerned, however, about the derivation of the acute ESL for odor. The findings in the study TCEQ uses to establish the ESL_{odor} (Nagata, 1983) are inconsistent with other available information on the odor threshold for PCE, generally considered to be between 5 and 50 parts per million (ppm). Unless additional studies can be identified that are consistent

[1] A discussion of the available human studies is included in a document developed by the US Environmental Protection Agency USEPA, Neurotoxicity of Tetrachloroethylene (Perchloroethylene) – Discussion Paper, EPA/600/P-03/005A (October 2003). (Available at http://www.epa.gov/ncea.)

with the findings of Nagata, HSIA does not believe that this study is an appropriate basis for establishing the odor ESL.

HSIA is also concerned about the Commission's decision to use a hazard quotient (HQ) of 0.3 to derive ESLs from the acute and chronic, non-cancer Reference Values (ReVs). The Commission's November 2006 Guidelines indicate that the use of an HQ of 0.3 to calculate short-term and long-term ESLs for chemicals with a nonlinear does-response assessment is in consideration of "cumulative and aggregate exposure" and is consistent with other TCEQ programs. HSIA believes that the DSD should include more consideration of substance-specific information in determining the appropriate HQ. The need for additional scrutiny is evidenced in the fact that the proposed ^{acute}ESL for PCE is higher than ATSDR's corresponding MRL and the proposed $^{chronic}ESL_{nonliner(nc)}$ is lower than the corresponding MRL, even though the same studies are used.[2]

Recent Epidemiological Evidence

Prior studies of dry cleaners, primarily from the United States, have indicated that PCE exposure might increase the risk of esophageal and cervical cancer, as well as non-Hodgkin's lymphoma (NHL). These earlier studies suffered from limitations, however, that included exposure to solvents other than PCE and the inability to take into account lifestyle factors (*e.g.*, smoking) known to affect the incidence of these cancers. As described in a 2003 review of the existing epidemiological literature by Mundt *et al.*,[3] the existing studies were limited by a "widespread lack of valid exposure measurements or other adequate indicators of potential for exposure." Based on these limitations, the Mundt review concluded that the "current epidemiological evidence does not support a conclusion that occupational exposure to [PCE] is a risk factor for cancer of any specific site." Specifically, the authors found that, based on existing evidence, a relationship between PCE and cancer of the oral cavity, liver, pancreas, cervix, and lung was considered unlikely. Scientific evidence was found to be inadequate for laryngeal, kidney, esophageal and bladder cancer. The article also stated, however, that because there had been a number of positive findings suggested in some of the studies (*e.g.*, for esophageal cancer) additional evidence was needed to elucidate if any real associations do exist.

A recent epidemiological study by Lynge *et al.*[4] provides strong evidence that the incidence of several important cancer types among dry cleaning workers in the Nordic countries was not related to PCE exposure. This study presents important information directly relevant to TCEQ's assessment of potential cancer risk from ambient PCE exposure.

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[2] TCEQ proposes ESLs of 300 ppb and 16 ppb, respectively, while ATSDR has established MRLs of 200 ppb and 40 ppb.

[3] Mundt *et al.*, Critical Review of the Epidemiological Literature on Occupational Exposure to Perchloroethylene and Cancer, *International Archives of Occupational and Environmental Health* 76: 473-491 (2003). (Enclosed)

[4] Lynge *et al.*, Cancer in Persons Working in Dry Cleaning in the Nordic Countries, *Environmental Health Perspectives* 114: 213-219 (2006). (Enclosed)

The Nordic study, conducted by five prominent European epidemiologists, responded to most of the shortcomings identified by Mundt *et al.* The Nordic study was undertaken as a series of case-control studies nested in groups of laundry and dry cleaning workers identified from 1970 census data in Denmark, Norway, Sweden and Finland – a total of over 46,000 persons. It covers a period when PCE was the dominant solvent and included all persons working in dry cleaning in the four countries in 1970. The nested case-control design allowed the researchers to compare the cancer risks of dry cleaners with those of laundry workers, a similar group apart from the use of PCE. In particular, cigarette smoking was equally frequent among exposed and unexposed subjects.

Lynge *et al.* found that the risks of esophageal, liver, kidney, pancreatic, and gastric cardia cancer and NHL were not increased among the Nordic dry cleaners. An elevated incidence of cervical cancer was not observed in women directly involved in dry cleaning, and was determined by the researchers not to be related to PCE exposure. The authors observed a small increase in bladder cancer that also was not associated with the extent of exposure to PCE, consistent with previous studies where incidence of this cancer was not increased in the study populations exposed only to PCE.

In light of some of the previous findings, perhaps the most significant finding in the Nordic study is the absence of an increase in esophageal cancer. Prior studies of smaller groups of U.S. workers reported an increase in esophageal cancer, which is associated with smoking, alcohol consumption, and poor nutrition. The Nordic researchers note that, while the U.S. studies compared cancer incidence among dry cleaners with that of the national population, the current study controlled for the possible effects of smoking and other lifestyle factors by comparing incidence between two similar groups – dry cleaning and laundry workers. In sum, the Nordic study methodology significantly improved the ability to detect the potential for an increase in cancer incidence as the result of PCE exposure, and found no increases in cancer associated with PCE exposure using that improved methodology.

The results of the Nordic study strongly suggest that TCEQ should seriously reconsider whether the evidence supports establishment of an ESL for PCE based on potential human carcinogenicity.

Carcinogenic Potential

While HSIA does not agree with TCEQ that establishment of an ESL based on PCE's carcinogenic potential is appropriate, we applaud the Commission's interpretation of the data available for development of the proposed chronic toxicity benchmark. In particular, the Commission's selection of the physiologically-based pharmacokinetic (PBPK) model developed

by Gearhart et al,[5] which assumes that 1 to 3 percent of the PCE absorbed by humans is metabolized.

As noted in the proposed DSD, and as described by the US Environmental Protection Agency (USEPA), one "significant contributing factor" to the differences in the risk estimates that have been developed is the variability in the "characterization of human metabolism of [PCE]."[6] USEPA's 1985 Health Assessment Document (HAD),[7] notes that experimental studies indicate that PCE metabolism in humans is "very limited" and amounts to "only about 1 to 3 percent of the estimated amounts absorbed." The basis for this conclusion is human volunteer studies and several empirical studies of occupationally exposed workers published in the scientific literature. In generating its URF for PCE, however, California's Environmental Protection Agency (CalEPA) assumed that a much higher fraction of the dose (18.5 percent) is metabolized in humans. CalEPA's assumption is based on the inclusion of data from a study of Japanese workers in a kimono manufacturing facility[8] suggesting that PCE may be more readily metabolized than predicted by the volunteer studies, particularly at low ambient concentrations.

Interpretation of these occupational data is complicated by several factors, as noted in EPA's 1985 HAD and draft 1986 HAD Addendum. These factors include: (1) the difficulty of accurate measurement of the dose of PCE received from the exposure, (2) imprecision of older methodologies used to quantify the products of metabolism, (3) the possibility that metabolites other than those monitored may be excreted, and (4) the very long half-life of PCE urinary metabolites that necessitates extended collection of samples. In particular, the study of Japanese kimono workers included in the CalEPA analysis used the older (Fujiwara) method for measuring the metabolite and did not account for dermal exposures resulting from the workers' handling of PCE-laden cloth.[9] The authors of the original paper have, in fact, subsequently acknowledged a much lower rate of metabolism in humans.[10]

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5 Gearhart *et al.*, Variability of physiologically-based pharmacokinetic (PBPK) model parameters and their effects on PBPK model predictions in a risk assessment for perchloroethylene (PCE), *Toxicology Letters* 68: 131- 144 (1993).

6 70 *Federal Register* at 75889.

7 USEPA, Health Assessment Document for Tetrachloroethylene (Perchloroethylene), Office of Health and Environmental Assessment, EPA/600/8082/005F (July 1985).

8 Ikeda *et al.*, Urinary Excretion of Total Trichloro Compound, Trichloroethanol, and Trichloroacetic Acid as a Measure of Exposure to Trichloroethylene and Tetrachloroethylene, *British Journal of Industrial Medicine* 29: 328-333 (1972).

9 Reitz *et al.*, *In Vivo* and *In Vitro* Studies of Perchloroethylene Metabolism for Physiologically Based Pharmacokinetc Modeling in Rats, Mice, and Humans, *Toxicology and Applied Pharmacology* 136: 289-306 (1996).

10 Ohtsuki *et al.*, Limited Capacity of Humans to Metabolize Tetrachloroethylene, *International Archives of Occupational and Environmental Health* 51: 381-390 (1983). The authors conclude that "less than 2 percent of [PCE] would be metabolized."

The article by Clewell *et al*.[11] referenced in the proposed DSD summarizes the various estimates of human metabolism that have been used in risk assessments of PCE. Clewell *et al*. consider more recent experimental data from human subjects exposed to relatively low concentrations of the solvent.[12] The authors conclude that the fraction of PCE metabolized following inhalation and oral exposure is 1.1 percent and 2.6 percent, respectively.

Clewell *et al*. also compare the estimate of the exposure level that would result in the public health goal (PHG) of one-in-a-million (10^{-6}) risk developed by CalEPA in a 2001 assessment[13] for drinking water exposure to one derived using a preferred model by Gearhart *et al*. that includes the generally accepted estimates of human metabolism. The preferred model yields a URE of 3.8×10^{-7} per ug/m^3, which is very similar to the URF derived by EPA in its last Agency-wide assessment for PCE. The article concludes that the PHG developed by CalEPA is 240-fold lower (*i.e*., more stringent) than that predicted by the Gearhart *et al* model. Clewell *et al*. conclude that this difference "is primarily due to the different estimates of fractional metabolism in the human." Most significantly, Clewell *et al.* conclude that the CalEPA model "greatly overestimates fractional metabolism in humans at the low exposures of interest for risk assessment. Therefore, the upper bound estimates of fractional metabolism obtained with [the CalEPA] model must be considered highly suspect."

Please feel free to contact me if you have any questions about the information discussed above.

Sincerely,

Steve Risotto

Stephen P. Risotto
Executive Director

Enclosures

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[11] Clewell *et al*., Evaluation of Physiologically Based Pharmacokinetic Models in Risk Assessment: An Example with Perchloroethylene, *Critical Reviews in Toxicology* 35: 413-433 (2005).

[12] Völkel *et al*., Biotransformation of Perchloroethene: Dose-Dependent Excretion of Trichloroacetic Acid, Dichloroacetic Acid, and N-acetyl-S-(trichlorovinyl)-L-Cysteine in Rats and Humans after Inhalation, *Toxicology and Applied Pharmacology* 153: 20-27 (1998). The results of this study are consistent with the earlier volunteer studies used by EPA in the 1985 and 1986 assessments.

[13] CalEPA, Public Health Goal for Tetrachloroethylene in Drinking Water, Office of Environmental Health Hazard Assessment (August 2001). The analysis of human metabolism in the 2001 document is consistent with the 1991 CalEPA analysis.