Summary of the Basis of Cancer Risk Values for Tetrachloroethylene
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Introduction

In February 2012 the United States Environmental Protection Agency (US EPA) published its first cancer risk values[1] for tetrachloroethylene (PCE) on the Integrated Risk Information System (IRIS). In the IRIS supporting documents, US EPA provides documentation for two cancer inhalation unit risk (IUR) values[2] for PCE (US EPA 2012). One value was based on liver tumors and was ultimately selected by US EPA. The second was based on a type of leukemia. Both of these were derived using well established methods and were based on cancers observed in animals treated with PCE under controlled experimental conditions. The liver-based value is approximately 33 times lower (representing less potential carcinogenicity) than the leukemia-based value. While all of US EPA's previous draft documents used the leukemia endpoint (or leukemia and liver), US EPA adopted cancer risk values based on the liver tumor data, citing a National Research Council report (NRC 2010). NRC had convened a committee of scientists to review and provide recommendations on US EPA's evaluation of PCE's toxicity (US EPA 2008). A majority of this group recommended using the liver tumor data, while some concluded the leukemia data should be used.

MassDEP's Office of Research and Standards (ORS) conducted a further review of the scientific information on PCE's carcinogenicity. This review was undertaken because: 1) the cancer type serving as the basis of the value adopted by US EPA differed from that used for MassDEP's 2008 and 1990 values as well as from the type used by US EPA in previous draft toxicological assessments for PCE; 2) the NRC Committee did not reach a consensus position regarding which data should be used for quantitative assessment; 3) the two inhalation unit risk values derived by US EPA (2012) differed by more than an order of magnitude; and, 4) US EPA's final liver tumor-based inhalation unit risk value differed substantially from the liver and leukemia-based values initially proposed by US EPA in the public review draft (2008). The ORS review included a thorough toxicological assessment using all relevant available data, consideration of information provided by external risk assessors, consultation with US EPA experts on toxicology and risk modeling, and input from the MassDEP Health Effects Advisory Committee (the Advisory Committee).

Based on this work, ORS concluded that the leukemia data should continue to be used in the derivation of a unit risk value for PCE. The Advisory Committee concurred with this determination. ORS, with further input from the Advisory Committee, derived an updated IUR value for PCE using the leukemia

[1] The cancer risk values are the inhalation unit risk (IUR) and oral cancer slope factor (CSF). The cancer slope factor is derived from the inhalation unit risk, thus this document is written in terms of the inhalation unit risk. The IUR value is defined by US EPA as the excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 ug/m^3 of air. The CSF value is defined by US EPA as the excess lifetime cancer risk estimated to result from continuous oral exposure to an agent at a concentration of 1 mg/kg/day.
[2] Based on liver tumors 3 x 10^{-7} per ug/m^3 and based on leukemia 1 x 10^{-5} per ug/m^3.

data and the latest scientific approaches for estimating human cancer risk. While the Advisory Committee indicated that US EPA's leukemia-based value published in the IRIS file was reasonable, they suggested that the IUR value be based on the total dose of PCE metabolites as a more proximate measure of the active moiety than the total dose of PCE used by US EPA. Using total metabolized dose for dose extrapolation, ORS derived a range of scientifically supported IUR values based on the leukemia data and ultimately selected an IUR value of **3 x 10^{-6} per microgram/m^3**. [3] This decision was supported by the Advisory Committee. An oral cancer slope factor of **2 x 10^{-2} per mg/kg/day** was derived using the approach used for the IUR (details shown below).

ORS' new PCE IUR value falls between the two US EPA values published in the IRIS documentation based on the liver tumor and leukemia data and is about three times lower (meaning PCE is estimated to be less carcinogenic) compared to MassDEP's previous value of 1 x 10^{-5} per ug/m^3 (MassDEP 2008). The newly revised PCE cancer risk value equates to a target indoor air PCE concentration of 8 ug/m^3, about twice the indoor air background level, based on an excess cancer risk level of 1 X 10^{-5} over 30 years of exposure.

Decisions in the Derivation of the MassDEP PCE Cancer Risk Values

The following is a summary of the scientific rationale for MassDEP ORS' derivation of cancer risk values for PCE. These decisions were based on an in-depth review of the science with extensive input from the Advisory Committee and address a number of issues, including several raised in comments to MassDEP submitted by AMEC Earth and Environmental (Dec. 3, 2007), Arcadis U.S., Inc. (March 15, 2012) and the National Association for Industrial and Office Parks (NAIOP) (March 14, 2012).

ORS has concluded that:

1) **The leukemia data should be used in the derivation of an inhalation unit risk value for PCE.** Highly experienced toxicologists have expressed differing views regarding the best basis for an IUR value for PCE. Atypically, the NRC did not reach consensus regarding the use of the leukemia data. In the IRIS PCE file US EPA states that,

> "A majority of the NRC peer review panel recommended that the mouse hepatocellular (liver) tumors be used for cancer risk estimation. Some members of the NRC peer review panel recommended that the leukemia data be used for cancer risk estimation. The inhalation unit risk would be 1 × 10^{-5} per ug/m^3 if it were based on the male and female rat leukemia data from the JISA 1993 bioassay."

[3] The revised ORS value was calculated using PCE metabolized dose in contrast to US EPA's leukemia-based cancer value, which used un-metabolized PCE levels in the blood as a measure of dose. Because PCE is known to be chemically transformed in the body by metabolic processes that can damage DNA and potentially lead to cancers, use of metabolized PCE in the derivation was deemed appropriate.

The bullets below summarize MassDEP's responses to issues raised by the NRC majority and others. See NRC (2010) and US EPA (2012) for more detailed discussion. US EPA scientists used the leukemia data in the IRIS Toxicological Review of PCE Interagency Science Discussion Draft (US EPA 2011a), which was the last draft before the document was finalized. US EPA ultimately selected liver tumors as the basis for its IRIS IUR value, making a decision to accept the NRC majority recommendation. However, for the reasons summarized below, ORS toxicologists and the Advisory Committee concluded that it was appropriate to use the leukemia data.

- **The rat leukemia (mononuclear cell leukemia or MCL)[4] is relevant to humans**. Leukemia classifications vary based on cell type, origin, etiology, and other characteristics. The exact cell type, origin and etiology of rat MCL is not fully resolved. Although this precludes definitive statements regarding its relevance, or lack thereof, to humans, Thomas et al. (2007) concluded that rat MCL shares numerous characteristics with, and is quite comparable on a morphological, functional and clinical basis, to an aggressive and lethal type of human leukemia. In addition, organ and tumor type concordance across species is not generally assumed or required in cancer risk value derivations, as exact concordance is frequently not observed across species. In light of these facts, ORS concluded, with the concurrence of the Advisory Committee, that it is appropriate to consider the MCL data to be relevant to people.

- **The leukemia dose response is statistically significant in both available animal bioassays.**

- **The leukemia rate was significantly elevated in rats exposed to PCE compared to concurrent controls, especially in the Japan Industrial Safety Association (JISA) bioassay, which ORS recommends as the preferred data set (see below)**. In addition, leukemia occurred sooner and was more severe in treated animals compared to controls.

- **The conditions under which high historical background rates would raise concerns about an endpoint were not observed in the leukemia data.** High historical cancer background rates are a particular concern if: 1) a study does not include an internal control (an untreated group of animals); 2) only one treated group exhibits an effect; or, 3) the test species/strain exhibits increased susceptibility through a documented mechanism of action that is not relevant to humans. Random fluctuations in the background cancer response rate can occur, which may either mask a positive effect or lead to a spurious false positive result. In the case of PCE, positive leukemia responses were observed in two independent studies, each with internal controls, and in several dose groups. Although the rat leukemia background rate may indicate that the test strain is sensitive to agents that increase this type of cancer, the mechanistic cause of this type of leukemia is unknown and people may also be sensitive.

- **The rat leukemia background rate in concurrent and historical controls is not consistently higher than the mouse liver tumor background rate and does not support rejection of the**

[4] The type of leukemia found in the NTP and JISA PCE cancer studies.

leukemia data. In the JISA study the rat leukemia rates in the control (untreated) animals were 22% for males and 20% for females. The mouse liver tumor background rates of 28% for males and 6% for females. The background rate of leukemia in the National Toxicology Program (NTP) study was much higher (56% in males and 36% in females). This contributed to ORS's decision to select the JISA study data as the preferred basis for deriving a PCE cancer value.

- **Although the National Toxicology Program decided to stop using the F344/N rat colony used in the study discussed here as of 2009, NTP did not conclude that cancer data previously generated using this strain should not be used. Additionally, the colony used in the JISA study exhibited lower background rates of MCL.** NTP's decision to stop using this rat strain was based on several reasons including reduced fertility, sporadic seizures and elevated background cancer rates (leukemia and testicular)(King-Herbert and Thayer 2006). NTP noted that "high background rates decrease the ability to detect an exposure-related effect. In addition, when a statistically significant tumor effect is found in test animals relative to concurrent controls the effect may not be considered exposure-related if it falls within the range observed in historical controls." In both studies evaluating PCE, the leukemia rates in the exposed groups were elevated compared to both concurrent and historical controls. Notably, the JISA F344DuCrj colony exhibits a background leukemia rate that is considerably lower than that of the NTP colony.

2) **Data from the Japan Industrial Safety Association cancer bioassay study should be used in preference to the National Toxicology Program study.** While both studies found positive findings for leukemia, the JISA study included an additional dose group compared to the NTP study, improving the study's ability to delineate the dose response relationship. The results from this study are also statistically stronger. The Advisory Committee supported the use of this study.

3) **Extrapolation of cancer data from the animal cancer bioassays to humans should be conducted using the latest US EPA harmonized physiologically based pharmacokinetic (PBPK) model.** This model, which US EPA used to develop both the liver tumor-based and leukemia-based IUR values, is the most up-to-date available. The application of this improved model addresses issues raised by various groups about prior models used by US EPA, ORS and others. The Advisory Committee supported use of this model.

4) **Total PCE internal blood dose and total metabolized dose metrics (outputs of the harmonized PBPK model) provide reasonable approaches to relate PCE exposure to cancer risk.** Metabolites of PCE are known to be genotoxic (an effect well associated with carcinogenicity), while the parent compound is not. Thus, basing risk on total metabolized dose was ultimately selected as the dose metric to calculate the PCE cancer risk value. This decision was supported by the Advisory Committee and relied on PBPK modeling by US EPA using the harmonized model to derive the metabolized dose values used in the dose response models.

Derivation of Cancer Toxicity Values for PCE

The inhalation unit risk (IUR) of **3 x 10^{-6} per ug/m^3** and oral cancer slope factor (CSF) of **2 x 10^{-2} per mg/kg/day** for PCE were both derived by ORS from an inhalation animal bioassay because the one available oral animal bioassay had significant limitations.

The cancer toxicity values were estimated using:

- the male and female rat MCL incidence data adjusted for early deaths from JISA (1993);
- the harmonized PBPK model (Chiu and Ginsberg 2011) to extrapolate animal exposure to human internal dose units based on total metabolized PCE dose;
- the multi-stage dose response model from the BMDS software (USEPA 2011b)with linear extrapolation from point of departure;
- the lower confidence level of the benchmark dose at the 10% response level ($BMDL_{10}$) of 2.26 mg metabolized PCE/$kg^{3/4}$/day as the point of departure to estimate the risk per total metabolized dose, i.e., risk per 0.0442 mg metabolized PCE/$kg^{3/4}$/day;
- the inhalation and oral dose metric conversion factors (DMCF), 0.473 mg metabolized PCE /$kg^{3/4}$/day per ppm and 0.563 mg metabolized PCE/$kg^{3/4}$/day per mg/kg/day, respectively, for total metabolized dose using the harmonized PBPK model (Chiu and Ginsberg 2011) to adjust the internal cancer risk value to the external exposure concentration for the inhalation and oral pathways.

The derivation is summarized in the table below.

Summary of the Quantitative Derivation of Inhalation and Oral Cancer Risk Estimates for PCE

Extrapolation of Human **Internal** Concentration to Human **External** Concentration		
Human Internal Concentration - Unit Risk per Total Metabolism dose metric (mg/$kg^{3/4}$-d)[a] 0.0442		
Steps in the Derivation Process from Human Internal Concentration	**Inhalation Unit Risk**	**Oral Slope Factor**
PBPK factor[b] –Dose Metric Conversion Factor (DMCF) (mg/$kg^{3/4}$-d per ppm or per mg/kg-day)	PBPK factor ($DMCF_{ppm}$) 0.473	PBPK factor ($DMCF_{mg/kg/day}$) 0.563
Unit risk or slope factor per external dose (=UR or SF in human internal concentration*PBPK factor DMCF in appropriate units)	2.12 x 10^{-2} per ppm	2.49 x 10^{-2} per mg/kg-day
Convert to units used in Risk Assessment and rounded to 1 sig. fig.	**3 x 10^{-6} per ug/m^3**	**2 x 10^{-2} per mg/kg-day**

[a] Based on survival adjusted incidence of MCL in male and female rats exposed by inhalation to PCE (JISA 1993).

[b]DMCF were derived by Weihsueh Chui (Chiu 2012). Dr Chiu provided DMCF to MassDEP for dose metrics that were not presented in the USEPA Toxicological Review of Tetrachloroethylene (2012), e.g., total metabolized PCE.

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