MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

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To: File for Trichloroethylene (CAS# 79-01-6)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Cancer Screening Levels and Update of the Noncancer Screening Level

The screening levels for trichloroethylene (TCE) are:

- Initial Threshold Screening Level (ITSL) = 2 micrograms per cubic meter (µg/m³) with 24-hr averaging time
- Initial Secondary Risk Screening Level (IRSL) = 0.2 µg/m³ with annual averaging time
- Secondary Risk Screening Level (SRSL) = 2 µg/m³ with annual averaging time

In 2011, the Air Quality Division (AQD) established a chronic ITSL for TCE of 2 µg/m³ based on the US EPA (2011) Reference Concentration (RfC). At that time the ITSL was assigned an averaging time of 24-hrs pursuant to Rule 232(2)(b). The AQD also changed the IRSL to 0.2 µg/m³ from an existing IRSL of 0.6 µg/m³.

Then in 2012, an additional ITSL was established at 10,000 µg/m³ with 24-hrs averaging time, based on the acute Minimal Risk Level (MRL) from the Agency for Toxic Substances and Disease Registry; (ATSDR). Simultaneously, the chronic ITSL averaging time was changed from 2 µg/m³ with a 24-hr averaging time to 2 µg/m³ with an annual averaging time. At that time in 2012, it was reasoned that because an acute ITSL of 10,000 µg/m³ was being established with an averaging time of 24-hrs, the averaging time for the chronic ITSL should change from 24-hr to annual to reflect life-long exposures to TCE.

Recently it was learned that the ATSDR rescinded the acute MRL of 10,000 µg/m³ finding that the data on acute exposures to TCE no longer supported the relatively high acute MRL. Furthermore, after reviewing of the basis of the chronic ITSL it was shown to be based[1] on acute effects observed in a short-term developmental study (see below for description of the study; Johnson et al. (2003)). The effect of these findings make it necessary for the AQD to update the non-cancer screening level at this time.

[1] The RfC was based on two different studies that produced the same RfC, one of which was the acute developmental study. Both studies are equally valid; however, the developmental study produced adverse effects over a much shorter exposure duration (US EPA, 2011).

First, the AQD is dropping the acute ITSL of 10,000 µg/m³ based on now rescinded acute MRL. Second, the AQD is changing the RfC based ITSL of 2 µg/m³ with annual averaging time back to 2 µg/m³ with a 24-hr averaging time. The averaging time for the RfC based ITSL is supported by the basis of the RfC, specifically, short-term exposures observed during pregnancy caused adverse developmental effects (cardiac malformations) in an animal study (Johnson, 2003).
An RfC is considered applicable to chronic exposure scenarios; however, in this case, EPA defines chronic differently, stating that:

> For some reproductive and developmental effects, chronic exposure is that which covers a specific window of exposure that is relevant for eliciting the effect, and subchronic exposure would correspond to an exposure that is notably less than the full window of exposure. (US EPA, 2011, pg. 5-6)

Because the short-term exposure window occurs overs days and not years, it was deemed appropriate to use a 24-hr averaging time. Additionally, the protectiveness of using a long-term averaging time (e.g., annual) to protect for development effects from TCE exposure has been questioned, and EPA has begun to address this issue by stressing that:

> In most cases, it is assumed that a single exposure at any of several developmental stages may be sufficient to produce and adverse developmental effect, but the RfC for a single exposure hasn't been determined yet by EPA.

When EPA determines a single exposure risk value for TCE, the AQD will update the screening levels where appropriate. Until that time the averaging time for the RfC-based ITSL for TCE is set at 24-hr pursuant to Rule 232(2)(b).

US EPA Derivation of Chronic Non-Cancer Reference Concentration (RfC)
EPA's 2011 derivation of the RfC of 2 µg/m³ was based on the concurrence of two studies in drinking water given to rats (Johnson et al., 2003) and mice (Keil et al., 2009). The two critical effects are decreased thymus weight in mice and increased fetal heart malformations in rats.

The tables 1a. and 1b. below (Table 5-28 from EPA, 2011) summarize the Internal Dose Point of Departures (idPODs), uncertainty factors (UFs) and preliminary chronic RfCs (p-cRfCs) for the two critical studies/effects. Dose values were derived from route-to-route (oral to inhalation) extrapolation using a Physiologically-Based Pharmacokinetic (PBPK) model.

Table 1a. Summary of Keil et al. (2009)

Decreased thymus weight in female $B6C3F_1$ mice exposed for 30 wks by drinking water.

- idPOD = 0.139 mg TCE metabolized/$kg^{3/4}$/d, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/d (continuous) (no BMD modeling due to inadequate model fit) HEC_{99} = 0.033 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- UF_L = 10 because POD is a LOAEL for an adverse effect.
- UF_A = 3 because the PBPK model was used for interspecies extrapolation.
- UF_H = 3 because the PBPK model was used to characterize human toxicokinetic variability.
- p-cRfC = 0.033/100 = 0.00033 ppm (2 µg/m^3).

Table 1b. Summary of Johnson et al. (2003)

Fetal heart malformations in Sprague-Dawley rats exposed on GDs 1–22 by drinking water.

- idPOD = 0.0142 mg TCE metabolized by oxidation/kg^{¾}/d, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest dose group (1,000-fold higher than next highest dose group) dropped, pup as unit of analysis, BMR = 1% (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation. HEC_{99} = 0.0037 ppm (lifetime continuous exposure) derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- UF_A = 3 because the PBPK model was used for interspecies extrapolation.
- UF_H = 3 because the PBPK model was used to characterize human toxicokinetic variability.
- p-cRfC = 0.0037/10 = 0.00037 ppm (2 µg/m^3).

Derivation of the Cancer Inhalation Unit Risk Value

Cancer effects of TCE exposure are addressed by application of the IRSL and SRSL of 0.2 and 2 µg/m³ (respectively) based on an inhalation unit risk (IUR) of 5 x 10^{-6} (µg/m³)$^{-1}$. This IUR is the result of an adjustment for increased early life susceptibility using EPA (2005) Age-Dependent Adjustment Factors (ADAFs). However, the ADAFs were applied only to the kidney component of the total cancer risk, and not for the liver or non-Hodgkin's lymphoma components of TCE cancer risk. Rule 232(4) designates and annual averaging time for an IRSL/SRSL.

The IRSL was calculated based on the IUR, pursuant to Rules 229 and 231.

IRSL = (1 x 10^{-6})/IUR
IRSL = (1 x 10^{-6})/(5 x 10^{-6})((µg/m³)$^{-1}$)
IRSL = 0.2 µg/m³

Summary of EPA's (2011) Cancer Risk Quantitative Risk Assessment

> "TCE is characterized as 'carcinogenic to humans' by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for non-Hodgkin Lymphoma [NHL] but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. Less human evidence is found for an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Further support for the characterization of TCE as 'carcinogenic to humans' by all routes of exposure is derived from positive results in multiple rodent cancer bioassays in rats and mice of both sexes, similar toxicokinetics between rodents and humans, mechanistic data supporting a mutagenic mode of action for kidney tumors, and the lack of mechanistic data supporting the conclusion that any of the mode(s) of action for TCE-induced rodent tumors are irrelevant to humans." (U.S. EPA, 2011, page 6-42)

For total cancer risk, the adult-based unit risk is 4.1 x 10^{-6} per µg/m³ (2 x 10^{-2} per ppm), based on an adjusted risk of human kidney renal cell carcinoma (RCC) from occupational exposure to TCE reported by Charbotel et al. (2006). This unit risk is the result of an adjustment, using human epidemiological data, for potential risk for non-Hodgkin's lymphoma (NHL) and liver cancer. An adjustment factor of 4 was applied to the unit risk of RCC alone to account for the total risk to all three cancer types. This factor of 4 was based on human surveillance data on the background risk of these cancers, and human epidemiologic data on the relative risk (RR) of these cancers associated with TCE exposure. US EPA (2011) calculated a "lowest effective

concentration corresponding to an extra risk of 1%" (LEC_{01}) using Charbotel et al. (2006) and background RCC rates from United States cancer registry. Conversion between occupational TCE exposures and continuous environmental exposures was made to account for differences in the number of days exposed per year (240 vs. 365) and in the amount of air inhaled per day (10 vs 20 m^3). The calculation of the LEC_{01} using a linear cumulative exposure model is complex and beyond the scope of this summary.

Exposure to TCE results in an adult-based Renal Cell Carcinoma (RCC) LEC_{01} of 1.82 ppm.

Convert to µg/m^3 using this equation: $mg/m^3 = (ppm \times MW)/24.45$,
where MW = 131.39g

$mg/m^3 = (ppm \times MW)/24.45$
$mg/m^3 = (1.82 \times 131.39g)/24.45$
$mg/m^3 = 9.78\ mg/m^3$ or $9780\ \mu g/m^3$

Next, find the Total Cancer Risk, using the adjustment factor of 4.

Total (adult-based) Cancer Risk LEC_{01} = adult-based RCC $LEC_{01}/4$
Total (adult-based) Cancer Risk LEC_{01} = 9780 µg/m^3/4
Total (adult-based) Cancer Risk LEC_{01} = 2445 µg/m^3

Unit Risk (for total adult based cancer risk) = 0.01/2445 µg/m^3
Unit Risk (for total adult based cancer risk) = 0.00000409 per µg/m^3
Unit Risk (for total adult based cancer risk) = 4.1×10^{-6} per µg/m^3

US EPA decided to separate the risk into the three organ specific cancer types: kidney, NHL and liver cancer. In order to do this EPA calculated the ratio of relative risk (RR) of kidney cancer to the RR of NHL and RR of kidney cancer to the RR of liver cancer. These two ratios of RR for NHL and liver cancer relative to that of kidney cancer extra risk were obtained from 2 calculations: (1) the meta-analysis of 15 epidemiologic studies and (2) using the RRs from Raaschou-Nielsen et al. (2003). Using these two calculations, a geometric mean of the ratios of RR of NHL and liver cancer to kidney cancer were rounded to 1 significant figure. The RR ratio of kidney cancer was assigned a value of 1 (relative to kidney cancer), RR ratio of NHL to kidney cancer was calculated to be 2, and RR ratio of liver cancer to kidney cancer was calculated to be 1. US EPA calculated the adult-based individual unit risks (rounded to 1 significant figure) to be:

1×10^{-6} per µg/m^3 for kidney cancer (i.e., renal cell carcinoma)
2×10^{-6} per µg/m^3 for NHL, and
1×10^{-6} per µg/m^3 for liver cancer

Application of Age Dependent Adjustment Factors

When there is sufficient weight of evidence to conclude that a carcinogen operates through a mutagenic mode of action, and in the absence of chemical-specific data on age-specific susceptibility, EPA recommends the application of default Age-

Dependent Adjustment Factors (ADAFs) to adjust for potential increased susceptibility from early-life exposure. The current US EPA (2005) ADAFs, and their age groupings are:

10: for 0 to 2 years,
3: for 2 to 16 years (14 years), and
1: for ≥ 16 years (54 years; age 16 to 70)

EPA concluded, by a weight-of-evidence evaluation, that TCE is carcinogenic by a mutagenic mode of action for induction of kidney tumors. EPA also concluded that there is an, "absence of a mode of action for the lymphoid and liver cancers associated with exposure to TCE." Therefore, only the kidney cancer was adjusted for early life exposure; the NHL and liver cancer risk were not adjusted. Assuming a 70-year exposure from age 0 to 70, the kidney cancer risk was adjusted as follows:

Early-Life-Exposure-Adjusted Kidney Cancer Risk

$$= \text{Adult-based Unit Risk} \times \frac{(10 \times 2 \text{ years}) + (3 \times 14 \text{ years}) + (1 \times 54 \text{ years})}{70 \text{ years}}$$

$= 1.02 \times 10^{-6}$ per µg/m³ x 1.657
$= 1.69 \times 10^{-6}$ per µg/m³

Summing the 3 cancer types for TCE inhalation risk:

1.69×10^{-6} per µg/m³ for age-adjusted kidney cancer
2.05×10^{-6} per µg/m³ for NHL, and
\+ 1.02×10^{-6} per µg/m³ for liver cancer
4.76×10^{-6} per µg/m³ for total cancer (including early-life exposures)

Rounding to 1 significant figure yields a total unit risk for all life stages of 5×10^{-6} per µg/m³.

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