MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

March 20, 2013

TO: File for Tetrachloroethylene (CAS No. 127-18-4)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Levels

The acute initial threshold screening level (ITSL) for tetrachloroethylene is 1400 µg/m³ (24-hr averaging time). The averaging time for the chronic ITSL of 40 µg/m³ (based on an EPA RfC) is being changed from 24-hr to annual.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), and the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH), Agency for Toxic Substances and Disease Registry (ATSDR) and California Office of Environmental Health Hazard Assessment (Cal OEHHA). The EPA has not established an acute or chronic non-cancer reference concentration (RfC) for tetrachloroethylene. The relevant health benchmarks available at this time are shown in Table 1 and Table 2.

EPA (2012) defines an Acute Reference Concentration (RfC) as follows:

> An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure for an acute duration (24 hours or less) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark concentration, with uncertainty factors generally applied to reflect limitations of the data used.

Physical Properties of Tetrachloroethylene (HSDB, 2013)

1. Molecular Weight: 165.8g
2. Form: Colorless liquid
3. Vapor Pressure
    a. 101.3 kPa (760 mmHg) at -19 °C (-2.2 °F)
    b. 52.6 kPa (395 mmHg) at -33 °C (-27 °F)
    c. 511.0 kPa (3833 mmHg) at 25 °C (77 °F)
4. Boiling point 121.3 deg C
5. Vapor Pressure: 18.5 mm Hg at 25 deg C
6. The odor threshold: 32 mg/m³.
7. Chemical Structure: 

Table 1. Health Benchmarks for Acute Exposures to Tetrachloroethylene

Benchmark	Organization Name	Benchmark Value (µg/m³)	Benchmark Value (ppm)	Averaging Time (hrs)
Short Term Exposure Limit (STEL)	Occupational Safety and Health Administration (OSHA)	678,000	100	0.25
STEL	American Conference of Governmental and Industrial Hygienists (ACGIH)	685,000	100	0.25
Immediately Dangerous To Life or Health (IDLH)	National Institute of Occupational Safety and Health (NIOSH)	1,017,000	150	0.5
Air Quality Guideline	World Health Organization (WHO)	8,000	1.2	0.5
Acute REL	California Environmental Protection Agency (Cal EPA)	20,000	2.9	1
8-hr TLV	American Conference of Governmental and Industrial Hygienists (ACGIH)	170,000	25	8
Permissible Exposure Limit	OSHA	678,000	100	8
Acute Minimal Risk Level (MRL)	Agency for Toxic Substances and Disease Registry (ATSDR)	1,360	0.2	24*

*ATSDR defines the exposure duration for acute MRLs as 1 - 14 days, however, the MDEQ Air Quality Division as well as others (e.g., NJ Dept. Environ. Protection) have interpreted the duration as 24 hours.

Table 2. Acute Exposure Guidance Level-1 (AEGL-1) for Transient, Reversible Effects (Nondisabling)

10 minute	30 minute	60 minute	4 hours	8 hours
35 ppm	35 ppm	35 ppm	35 ppm	35 ppm
240,000 µg/m³	240,000 µg/m³	240,000 µg/m³	240,000 µg/m³	240,000 µg/m³

As shown in Table 1 the acute health benchmarks range from 1,360 µg/m³ to 1,017,000 µg/m³, depending on the averaging time, the level of protection and the protected group. Typically benchmarks with short averaging times are higher than those with longer averaging times; however, this is not always the case. Benchmarks can differ based on the human population intended to protect (e.g., sensitive individuals, healthy workers), definition of "adverse effect", the level of protection, and other quantitative/qualitative adjustments (e.g., repeated exposures over lifetime, single short-term exposure, professional judgment). Occupational exposure limits (OELs) derived by OSHA, NIOSH and ACGIH have 15-minute, 30-minute- or 8-hr time weighted average (TWA) exposure durations. OELs are designed to protect healthy workers. Table 2 shows the interim EPA Acute Exposure Guidance Levels (AEGLs) for tetrachloroethylene.

An AEGL-1 is defined as

> AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

These are intended to protect against health effects from non-recurring exposures for the specified time periods, i.e., 10-minutes to 8-hours. All the interim AEGL-1 values for tetrachloroethylene are 240,000 $\mu g/m^3$. The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) provides additional information on AEGLs:

> Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

The AEGL-1 benchmark allows for the possibility that individuals could experience unique or idiosyncratic responses below the AEGL-1, and allows for the possibility that all individuals may experience sensory irritation or non-sensory effects. Therefore, the applicability of AEGLs in an air permit program, which allows facilities to emit the pollutant at levels for many years, typically 30 years or more, should also be scrutinized for protectiveness for long-term exposure durations or consider the ability of individuals to recover during non-exposed intervals. AEGLs were not included in Table 1 for the reason that benchmarks in Table 1 imply recurring exposures (e.g., OELs for occupational lifetime ≥ 40yrs) for the specified averaging times.

Background on Use of Acute ITSLs by the Air Quality Division

Because the MDEQ-Air Quality Division Air Permitting Program issues air pollution permits to install that do not expire, the acute ITSLs must take into account not only the effects from a single short-term exposure, but also those short exposures that may recur over a lifetime. Averaging times for acute ITSLs are 24-hours or less (e.g., 24-hr, 8-hr or 1-hr). With this in mind the acute benchmarks derived from several agencies were evaluated. The benchmarks that were given higher weight for a candidate ITSL were assessed based on how well they were derived, using criteria such as:

- Protect, including sensitive individuals, from acute adverse health effects
- Account for short-term exposures that may recur
- Provide analysis and discussion of the toxicological database of effects, and
- Use peer reviews for consensus benchmarks

OELs, as derived by ACGIH, NIOSH and OSHA, provide a suitable health benchmark with which to derive an acute ITSL (with the application of an uncertainty factor) only when higher quality benchmarks are not available.

Two benchmarks from Table 1 were found to best satisfy the criteria bulleted above:

1. Agency for Toxic Substances and Disease Registry (ATSDR)
2. California Environmental Protection Agency (Cal EPA)

ATSDR Acute Minimal Risk Level (MRL)

The Agency for Toxics Substances and Disease Registry (ATSDR, 1997) derived an acute Minimal Risk Level (MRL) for tetrachloroethylene.

Male volunteers were exposed to tetrachloroethylene at 10 or 50 ppm for 4 hours/day for 4 days. A total of 28 subjects were exposed; 12 at 10 ppm, 16 at 50 ppm. Altmann et al. (1992) state that faint odor was reported by 33% of the subjects at 10 ppm and 29% of the subjects at 50 ppm on the first day of testing, and by 15% of the subjects at 10 ppm and 36% of the subjects at 50 ppm on the last day of testing leading the investigators to conclude that only a few subjects could identify their exposure condition.

Pattern reversal and pattern onset visual-evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and tests of cognitive and psychomotor performance, and mood ratings were completed 72 hours before exposure, and during or after the exposure. VEPs and BAEPs were measured after 2 hours of exposure. Peak latencies of three components of VEPs (N75, Pl00 and N150) were measured. Measurements were made at the same time each day (10 AM-12 PM) to exclude circadian variations. The test battery completed included finger tapping, eye-hand coordination using a sine wave tracking test, simple reaction times, a continuous performance test, symbol-digit test, visual retention, pattern recognition test, digit learning, paired associates learning and retention, vocabulary test, and mood scales. Blood concentrations of tetrachloroethylene were measured before each day's exposure, in the middle of the exposure and at the end of the exposure. Effects noted in study and corresponding doses:

At 50 ppm, pattern reversal VEP latencies increased over the course of the exposure period, while at 10 ppm, pattern reversal VEP latencies decreased as a result of training. The difference-between the two groups was statistically significant ($p<0.05$). No effect on pattern onset VEPs or BAEPs were noted.

Using analysis of covariance, with pre-exposure baseline values as the covariates, significant performance deficits for vigilance ($p=0.04$), and eye-hand coordination ($p=0.05$) as well as a borderline increase in simple reaction times ($p=0.09$) at 50 ppm were found. For these tests, both exposure groups improved over the course of the experiment, but there was a greater improvement in the 10 ppm group compared to the 50 ppm group. No significant effects were noted for the tapping tests, or the learning and memory tests, or mood ratings.

Tetrachloroethylene in the blood increased with exposure duration. By the end of the last exposure period, tetrachloroethylene concentrations "exceeded 1.5 mg/L, and 0.3 mg/L" at 50 and 10 ppm, respectively.

The dose of 50 ppm was indicated as the lowest-observed-adverse-effect-level (LOAEL) for significant performance deficits for vigilance ($p=0.04$), and eye-hand coordination ($p=0.05$) as well as a borderline increase in simple reaction times ($p=0.09$). The dose of 10 ppm was indicated as the no-observed-adverse-effect-level (NOAEL). Extrapolation from animals to humans was not warranted because the study was performed in humans. The total Uncertainty Factor (UF) for derivation of the MRL was 10, for sensitive subpopulations.

To extrapolate from intermittent exposure to continuous exposure the 10 ppm concentration was multiplied by 4/24hrs.

$NOAEL_{Adj} = NOAEL_{Exp}$ x 4hrs/24hrs
Where $NOAEL_{Adj}$ is the duration adjusted NOAEL, and
$NOAEL_{Exp}$ is the experimental exposure concentration

$NOAEL_{Adj}$ = 10 ppm x 4/24
$NOAEL_{Adj}$ = 2 ppm

The Minimal Risk Level was calculated by ATSDR as follows:
$MRL = NOAEL_{Adj} /(UF_1)$
Where:
UF_1 = Uncertainty Factor of 10 for human variability in order to protect potentially sensitive groups including children or the infirm.

MRL = 2 ppm/10
MRL = 0.2 ppm

Conversion of dose units in ppm to µg/m³:
µg/m³ = (ppm x Molecular Weight)/24.45 x 1000 µg/mg
= (0.2 ppm x 165)/24.45 x 1000 µg/mg
= 1356 µg/m³ (Rounding to 2 significant figure yields 1400 µg/m³).

CAL-OEHHA Acute REL
The following excerpts of text are taken directly from the CAL-OEHHA 2008 document for Derivation of the tetrachloroethylene REL (Recommended Exposure Level)(Cal OEHHA, 2008).

> Human subjects exposed to 100 ppm (700 mg/m³) PCE for 7 hours exhibited CNS effects as indicated by an abnormal modified Romberg test (a test of position sense) and symptoms including headache and light-headedness (Stewart et al., 1970). Symptoms were noted after the first 3 hours of exposure. Subjects exposed for 7 hours per day for 5 days reported decreased odor perception of PCE over the course of each exposure.

Table 4. CAL-OEHHA 1-hr REL: Key Study and Decision Points

Study	Stewart et al., 1970
Study population	3 human subjects
Exposure continuity	Single exposure per concentration
Exposure duration	3 hr
Extrapolated 1-hr concentration	1200 mg/m³ *(700^2 mg/m³ x 3 hr = C^2 x 1 hr)*
Critical effects	Abnormal CNS effects (modified Romberg test and symptoms with headache, irritation of the eyes, nose and throat, and light-headedness
LOAEL	700 mg/m³
NOAEL	Not observed
Human Equivalent Concentration	not applied
LOAEL uncertainty factor (UF_L)	6
Intraspecies	10
Cumulative uncertainty factor	60
Reference Exposure Level	20 mg/m³ (20,000 µg/m^3; 2.9 ppm)

Basis of AQD Acute ITSL

The ATSDR MRL for tetrachloroethylene was selected as the acute ITSL because the MRL was based on a study (Altmann et al., 1992) that observed subtle neurological effects at a lower level (50 ppm) than the level (100 ppm) used in the study to derive the Cal-EPA REL (Stewart et al., 1970).

The averaging time associated with the acute ITSL is 24-hrs, based on the definition of the MRL and the fact that ATSDR (1997) extrapolated from the 4 hour experimental exposures specifically to a 24 hour continuous exposure (i.e., experimental exposure x 4hrs/24hrs).

The chronic ITSL is being changed from 24-hr to annual at this time to reflect the long-term exposure assumptions explicit in the derivation of EPA's RfC for tetrachloroethylene (i.e., omission of subchronic to chronic UF if the exposure period of the critical study adequately addresses long-term or lifetime exposures).

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Michigan Department of Environmental Quality

Interoffice Communication

TO: Update to File for Tetrachloroethylene (CAS #127-18-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

SUBJECT: Update of Screening Levels for Tetrachloroethylene (CAS #127-18-4)

DATE: March 28, 2012

The initial risk screening level (IRSL) for tetrachloroethylene is 4 µg/m^3 based on an annual averaging time. The secondary risk screening level (SRSL) for tetrachloroethylene is 40 µg/m^3 annual averaging time. The initial threshold screening level (ITSL) for tetrachloroethylene is 40 µg/m^3 based on a 24-hour averaging time.

Tetrachloroethylene (also known as perchloroethylene or PCE) is widely used as a dry cleaner solvent. It is a common environmental contaminant and is designated a hazardous air pollutant. It is found in groundwater, drinking water, and at many hazardous waste sites. PCE is released to indoor air via vapor intrusion. Neurotoxicity is a critical effect and the EPA has classified PCE as a carcinogen.

The Environmental Protection Agency Integrated Risk Information System (IRIS) released a final assessment for tetrachloroethylene (EPA. 2012). A review of the IRIS assessment finds that the RfC is well supported. Two principle studies were used; Cavalleri et al., (1994) and Echeverria et al., (1995).

Cavalleri et al., (1994) tested 35 dry cleaning and laundry workers and 35 controls matched in age, alcohol consumption, and smoking. There was a 6% decrease on a test of color vision compared to controls. "The LOAEL for all workers in this study was 42 mg/m^3 [$LOAEL_{HEC}$ = 15 mg/m^3] (time-weighted average mean concentration). Controls were not matched on education or intelligence, but these factors have not been shown to be associated with color vision. Exposure was assessed for individual subjects from personal monitoring over the full work shift and represented an 8-hour time-weighted average." (EPA, 2012).

"Echeverria et a., (1995) examined 65 dry cleaners in Detroit, MI, using a standardized neurobehavioral battery and found changes in cognitive and visuospatial function. A LOAEL of 156 mg/m^3 [$LOAEL_{HEC}$ = 56 mg/m^3] (time-

weighted average mean concentration) was identified, based on comparison of the two higher exposure categories with an internal referent group comprising mainly counter clerks, who were matched to exposed dry cleaners on age and education. Changes of 4-14% from internal referent levels, depending on subtest, were observed at the LOAEL. The study had a high quality exposure-assessment approach and appropriate statistical analysis that adjusted for covariates including alcohol. A potential selection bias may have resulted from the 18% participation rate among dry-cleaning shop owners, if the low participation could be explained by the health status of employees. The study also lacked an unexposed control group, the exposure level for the lowest exposure group (i.e., the internal referent group) cannot be classified as a NOAEL or a LOAEL. This study was of relatively good quality in terms of the comparability of referent and exposed groups, measurement of effect, and measurement of exposure and, although there are concerns about the lack of an unexposed referent group, this study was used to derive a candidate RfC." (EPA, 2012).

The EPA's final non-cancer inhalation reference values were derived from the two principal studies of occupational exposure listed above, and are protective of the most sensitive effects which are supported by multiple studies and endpoints. The EPA used physiologically based pharmacokinetic (PBPK) modeling to estimate blood PCE and metabolism of PCE in their RfC derivation. The EPA used an uncertainty factor (UF) of 1,000: a UF of 10 for human variability in the population; a UF of 10 for extrapolation from a LOAEL to a NOAEL; a UF of 10 for critical data gaps based on deficiencies on neurological, developmental, and immunological effects. The candidate RfCs are 0.056 mg/m^3 (derived from Echeverria et al., 1995) and 0.015 mg/m^3 (derived from Cavalleri et al., 1994). "The RfC is supported by the two principal studies, as the midpoint of the range of available values (then rounded to one significant figure)." (EPA, 2012). The EPA's inhalation RfC is 0.04 mg/m^3. According to Rule 232(1)(a),

$$ITSL = RfC = 0.04\,{}^{mg}\!/_{m^3} = 40\,{}^{\mu g}\!/_{m^3}$$

Rule 232(2)(a) the averaging time is 24 hours, therefore the ITSL for tetrachloro-ethylene is 40 µg/m^3 based on a 24-hour averaging time.

EPA used a JISA (1993) PCE inhalation study on male and female Crj:BDF1 mice and in male and female F344/DuCrj rats to derive the inhalation unit risk (IUR) for PCE . The JISA study demonstrated dose-related increased incidence of mononuclear cell leukemia (MCL) in male and female F344/DuCrj rats as well as reduced MCL latency in females. In male and female mice, PCE inhalation exposure significantly increased the incidence of hepatocellular adenomas and carcinomas. Increases in hemangiomas or hemangiosarcomas in liver, spleen, fat, and subcutaneous skin were reported in male mice. The EPA derived an inhalation unit risk of 2.6 x 10^{-7} per µg/m^3 from the $BMCL_{10}$, the 95% lower bound on the exposure associated with a 10% extra cancer risk based from

hepatocellular adanomas or carcinomas in male Crj:BDF1 mice. "Route-to-route extrapolation from the inhalation PODs developed from the JISA study (1993) was carried out using the human pharmacokinetic model." (Chiu and Ginsberg, 2011). The cancer risk discussion does not include a finding of a mutagenic mode of action, therefore no age-dependent adjustment factors (ADAFs) need to be used to estimate the age-specific cancer risks for PCE. According to Rule 231(1) the IRSL is determined using the equation below:

$$IRSL = \frac{1\times10^{-6}}{unitrisk} = \frac{1\times10^{-6}}{2.6\times10^{-7}} = 3.8\,{}^{\mu g}/_{m^3}$$

The result is rounded to one significant figure, therefore the IRSL is 4 µg/m^3. The SRSL is 40 µg/m^3. Rule 232(4) states that the averaging time for an IRSL and SRSL is annual.

References:

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