MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Dichloroacetic Acid (CAS # 79-43-6)

FROM: Keisha Williams, Air Quality Division

DATE: October 2, 2018

SUBJECT: Screening Level Derivation for Dichloroacetic Acid

The initial risk screening level (IRSL) for dichloroacetic acid (DCA) is 0.07 µg/m^3 (annual averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1231. The initial threshold screening level (ITSL) is 0.5 µg/m^3 (annual averaging time) based on Rule 336.1232 (1) (e) and (2) (c).

The following references or databases were searched to identify data to determine the screening level: United States (EPA's) Integrated Risk Information System (IRIS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels, International Agency for Research on Cancer (IARC) Monographs, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels (AEGLs) for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs), Spacecraft Maximum Allowable Concentrations (SMACs), California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Texas Commission on Environmental Quality (TCEQ) Effects Screening Levels (ESLs), and European Chemicals Agency Registered Substances Dossiers.

Background Information

DCA (Figure 1) has been used to produce chemicals like glyoxylic acid, to treat a number of metabolic pathologies, like lactic acidosis, and is also a byproduct of drinking water chlorination (ACGIH, 2005). At room temperature, DCA is a colorless or yellow liquid with a pungent acid-like odor. Chemical properties are listed in Table 1 and health benchmark values are listed in Table 2.

Figure 1. Chemical structure for DCA

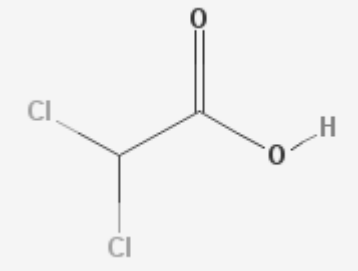

Table 1. Chemical properties of DCA

Molecular weight: 128.94 grams/mole
Melting point: 9.7 °C
Boiling point: 102 °C at 20 mm Hg
Vapor pressure: 0.179 mmHg at 25°C (extrapolated)
Vapor density: 4.45, where air=1

Reference: PubChem database, https://pubchem.ncbi.nlm.nih.gov/compound/6597

A number of benchmark values have been established to protect against adverse effects via inhalation or oral exposure (Table 2); however, all of these benchmarks have been derived using oral studies exclusively. When in aqueous solution, DCA exists in equilibrium with dichloroacetate ($C_2HCl_2O_2$-); thus, dichloroacetate is considered simultaneously with DCA, although the acid form is notably more reactive and corrosive.

Table 2. Benchmark values for DCA

Agency	Benchmark Value
United States Environmental Protection Agency (EPA)	Reference dose (RfD): 0.004 mg/kg-day (Cicmanec et al., 1991; EPA, 2003a) Oral slope factor: 0.05 per mg/kg-day (DeAngelo et al., 1999; EPA, 2003a)
American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold limit value (TLV): 2.6 mg/mg^3 (ACGIH, 2005) Classified as a confirmed animal carcinogen with unknown relevance to humans. NOTE: DCA was given a skin notation for dermal toxicity.
Texas Commission on Environmental Quality (TCEQ)	Health effects screening levels for long-term exposure: 2.6 µg/m^3 and for short-term exposure: 26 µg/m^3 (TCEQ, 2014)
Chemical Safety Program Protective Action Criteria (PAC)	PAC-1: 7.9 mg/m^3 PAC-2: 36 mg/m^3 PAC-3: 560 mg/m^3 (Chemical Safety Program, 2012)

No inhalation studies were found to consider possible toxic effects or even absorption efficiency. Furthermore, the EPA has declined to establish an RfC because, “DCA has a very low vapor pressure and is not expected to volatilize from drinking water or contaminated environmental media to any appreciable extent” (EPA, 2003b). However, per the AQD permitting process, DCA is known to be emitted into the ambient air in Michigan. Therefore, the inhalation route of exposure is of concern in Michigan. As far as absorption efficiencies across routes of exposure, the American Conference of Governmental Industrial Hygienists (ACGIH) has noted that DCA

may be absorbed at the same rate via oral or inhalation routes of exposure, especially as compared to the relatively rapid absorption via the dermal route of exposure (ACGIH, 2005). As a result, we will consider the inhalation and oral absorption efficiencies to be equal. Portal of entry effects are not critical effects with DCA toxicity, so route to route extrapolation was deemed appropriate.

Peripheral neuropathy and central nervous system (CNS) toxicity are critical effects observed in humans as soon as one month after oral administration of dichloroacetate at concentrations as low as 25 mg/kg per day in well-conducted human clinical studies (ACGIH, 2005; Kauffman et al., 2006; Kurlemann et al., 1995). However, a no observable adverse effect level (NOAEL) was not identified in the study where 25 mg/kg per day was given (Kauffman et al., 2006).

Both peripheral neuropathy and CNS toxicity have been observed in animal studies as well (Cicmanec et al., 1991; Calcutt et al., 2009). Since animal studies can reproduce comparable critical effects to those observed in humans, utilization of animal studies is appropriate for screening level development. Furthermore, screening levels based on animal studies that use lower DCA doses than human studies may better characterize the LOAEL and NOAEL, and produce a more health protective screening level value.

Detailed mechanisms of action toward neurotoxicity or carcinogenesis have not been identified. However, oxidative stress, altered hepatic metabolism, and decreased cell death are hypothesized to play a role in the DCA-induced hepatic carcinogenesis (Hassoun and Cearfoss, 2011; Carter et al., 2003; EPA, 2003b).

Evaluation of Cancer Risk and Derivation of Cancer Slope Factor

The EPA used DeAngelo et al.'s 1999 oral study, where mice were administered dichloroacetate, as the key study for slope factor derivation (EPA, 2003b). In this study, a significant increase in hepatocarcinomas and hepatoadenomas was seen after a lifetime of exposure (100 weeks) (Table 3 taken from EPA, 2003b). Benchmark dose (BMD) modeling software (EPA, Version 1.3.1) was used to determine the benchmark dose lower bound confidence limit (BMDL) given that the benchmark dose response (BMR) level was 10%, and subsequently, the cancer slope factor (Equation 1).

Table 3. Cancer dose-response data evaluated using BMD modeling: male mice after 100 weeks

Conc. in water (g/L)	No. of animals entering study	Mean body weight (g) at 100 weeks	Dose (mg/kg-day)		Mice with hepatocarcinomas		Mice with hepatoadenomas	
			Mice	HED*	%	N	%	N
0	50	43.9	0	0	26	13	10	18
0.05	33	43.3	8	1.3	33	11	3	11
0.5	25	42.1	84	13.2	48	12	20	14
1	35	43.6	168	26.5	71	25	51	30
2	21	36.1	315	47.5	95	20	43	21
3.5	11	36.0	429	64.6	100	11	45	11

NOTE: The highest dose group was excluded because decreased body weights in that group suggested that the dose was approaching the maximum tolerable dose.
*Human Equivalent Dose (HED) was calculated using a dose scaling factor of $BW^{0.75}$

Equation 1.

$$Slope\ Factor = BMR/BMD$$

$$Slope\ Factor = \frac{0.1}{(2.1\frac{mg}{kg}\ per\ day)} = 0.048\ per\frac{mg}{kg}per\ day$$

≈0.05 per mg/kg per day

Pursuant to AQD Rule 336.1231, the initial risk screening level (IRSL) is 0.07 µg/m^3, annual averaging time as shown in Equations 2 and 3.

Equation 2.

$$Inhalation\ unit\ risk = oral\ slope\ factor\ x\frac{20\ m^3}{70\ kg}\ x\frac{mg}{1000\ \mu g}$$

Where:

20 m^3 is the daily inhalation rate
70 kg is the body weight of a person
mg/1000 µg is the conversion factor

$$Inhalation\ unit\ risk = 0.05\ per\frac{mg}{kg}per\ day\ x\frac{20\ m^3}{70\ kg}\ x\frac{mg}{1000\ \mu g} = 1.4286\ x\ 10^{-5}\left(\frac{\mu g}{m^3}\right)^{-1}$$

Equation 3.

$$IRSL = \frac{1\ x\ 10^{-6}}{inhalation\ unit\ risk}$$

$$IRSL = \frac{1\ x\ 10^{-6}}{1.4286\ x\ 10^{-5}\left(\frac{\mu g}{m^3}\right)^{-1}} = 0.06856\ \mu g/m^3$$

IRSL≈0.07 µg/m^3, annual averaging time

It is important to note that both the EPA and ACGIH have distinguished DCA as being "a confirmed animal carcinogen with unknown relevance to humans" because of little to no human data indicating DCA's carcinogenicity and DCA-induced tumors in animals only being observed at relatively high doses (ACGIH, 2005; EPA, 2003b). However, using AQD's definition of a carcinogen, increased malignant and/or benign tumors in a well conducted animal study is sufficient for classification as a potential human carcinogen.

Review of Relevant Studies on Noncarcinogenic Effects

The EPA RfD of 0.004 mg/kg per day was derived using the study by Cicmanec et al., 1991 (EPA, 2003a). With this, the lowest observable adverse effect level (LOAEL) was found to be 12.5 mg/kg for critical effects of neurological changes, hepatic vacuolization, testicular effects and increases in liver weight. A total uncertainty factor of 3,000 was given (10 for intraspecies variability, 3 for interspecies extrapolation, 10 for LOAEL to NOAEL extrapolation, 3 "for use of a

less than-lifetime study in which frank effects were noted", and 3 for database deficiencies. In the chemical assessment summary, it was further noted that Benchmark Dose Modeling had been performed but was determined to be less reliable than the NOAEL/LOAEL approach. Overall, the confidence in the RfD was considered medium with high confidence in the study and medium confidence in the database.

In 2014, Gattone and Bacallao performed a study to evaluate DCA-induced toxicity in rats from the PCK rat model, a model of the polycystic kidney disease observed in people. 0 or 75 mg/l DCA was administered in drinking water to 4-week old groups of rats: normal, male Sprague-Dawley rats, and males and females from the PCK rat model. The drinking water was given ad libitum for 30 days. Immediately following the 30-day administration, the rats were weighed, and samples were collected. Stereology was used to determine cystic size in the kidney and fibrocystic pathology in the liver. Results were analyzed using ANOVA. Gattone and Bacallao observed increased cyst size and proteinuria in male PCK rats as compared to controls. As shown in Equation 2, the 75 mg/L DCA concentration in drinking water is estimated to be approximately 10 mg/kg per day based on the assumptions referenced by EPA (1988).

Equation 2.

$$\frac{liters\ of\ H_2O\ consumed}{day}\ x\ [DCA]\ x \frac{1}{body\ weight} = DCA\ administraion\ in \frac{mg}{kg\ per\ day}$$

where:

$$\frac{liters\ of\ H_2O\ consumed}{day} = 0.10\ x\ bodyweight^{0.7377}$$

The average body weight of the Male PCK rats in study was 340 grams

[DCA] is 75 mg/liter

$$water\ consumption\ in \frac{liters}{day} = 0.10\ x\ 0.34^{0.7377} = 0.04512 \frac{liters}{day}$$

$$0.04512 \frac{liters\ H_2O}{day}\ x\ 75 \frac{mg}{liter} x \frac{1}{.340\ kilograms} = 9.95 \frac{mg}{kg\ per\ day} \approx 10 \frac{mg}{kg\ per\ day}$$

While there are human studies available to use for screening level derivation, both the Cicmanec et al. study that was used for US EPA's RfD derivation and the Gattone and Bacallao study showed effects at doses lower than those used in the human studies. As a result, the animal studies will be used for screening level derivation. And while the doses in both animal studies are similar, the human equivalent dose seen in the rat study is relatively lower; see Table 4. Therefore, the Gattone and Bacallao study will be used for ITSL derivation. Since there was only one treatment dose in the Gattone and Bacallao study, Benchmark Dose Modeling will not be done.

Table 4. HEDs from Potential Key Studies compared to LOAEL from Human Study

Study	Species Used	LOAEL in Study (mg/kg per day)	Body weight (kg)	DAF[A]	HED (mg/kg per day)
(Gattone and Bacallao, 2014)	Rat	10	0.34	.26	2.6
(Cicmanec et al., 1991)	Dog	12.5	2[B]	.41	5.1
(Kauffman et al., 2006)	Human	25	70	1	25

A) DAF is the dosimetric adjustment factor, where DAF= (animal body weight/human body weight)$^{0.25}$

B) This bodyweight is recommended for use with male/female beagles in subchronic studies when the bodyweight from the actual study is not known (EPA, 1988)

It may be noted that a potential ITSL based on EPA's RfD would be 14 µg/m^3, annual averaging time (as shown in Equation 4).

Equation 4.

$$Potential\ ITSL = Oral\ RfD\ x \frac{70\ kg}{20\ m^3}$$

$$Potential\ ITSL = 4\ x \frac{10^{-3} mg}{kg} per\ day\ x \frac{70\ kg}{20\ m^3} x 1000 \frac{\mu g}{mg} = 14 \frac{\mu g}{m^3}, annual\ averaging\ time$$

Per rule 232 (1) (e), the ITSL is derived as shown in Equation 5.

Equation 5.

$$ITSL = \frac{LOAEL}{20\ x\ 100\ x\ UF} x \frac{W_A}{I_A}\ x \frac{b}{a}$$

where

LOAEL is *10 mg/kg per day*

A factor of *20* is used instead of *35*, as written in Rule 232 (1) (e), to reflect the decrease in uncertainty when using a 28-day study versus a 7-day study

W_A is the body weight of the rat in kilograms (kg); which is 0.34 based on the male rat body weight (EPA, 1988; MDEQ, 1996)

I_A is the daily inhalation rate of the rat in cubic meters/day; which is 0.33 based on the general rat inhalation calculation outlined by EPA (EPA, 1988)

b is the absorption efficiency by the oral route of exposure

a is the absorption efficiency by the inhalation route of exposure, and assumed to be equal to *b*

UF is uncertainty factor for LOAEL to no observable effect level extrapolation

$$ITSL = \frac{10 \frac{mg}{kg} per\ day}{20\ x\ 100\ x\ 10}\ x \frac{0.34}{0.33} x\ 1$$

$$ITSL = 0.000515 \frac{mg}{m^3}\ x \frac{1000\ \mu g}{mg}$$

$$ITSL \approx 0.5 \frac{\mu g}{m^3}, annual\ averaging\ time$$

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