MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for 1,1'-Dichloroethylene (CAS # 75-35-4)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: July 26, 2022

SUBJECT: Screening Level for 1,1'-Dichloroethylene (CAS # 75-35-4)

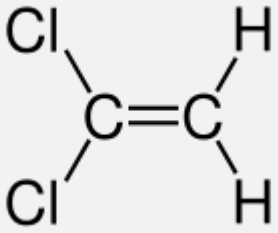
Summary

The initial threshold screening level (ITSL) is 7.3 µg/m^3 (annual averaging time). The initial risk screening level (IRSL) for 1,1'-dichloroethylene is 0.15 µg/m^3 (annual averaging time) and the secondary screening level (SRSL) is 1.5 µg/m^3 (annual averaging time).

Uses and Physical Chemical Properties

1,1'-Dichloroethylene is a simple unsaturated halogenated hydrocarbon that is used in the production of polyvinylidene chloride polymers, acrylonitrile, and acrylates; and in the production of silicon dioxide films for semiconductor devices. 1,1'-Dichloroethylene can be found in landfills because of the breakdown of polyvinylidene chloride products (OEHHA, 1999).

Table 1. Physical/Chemical Properties of 1,1'-Dichloroethylene

Structure	
CAS Number	75-35-4
Synonyms	DCE; 1,1'-dichloroethene; 1,1'-DCE; vinylidene chloride, VDC, Vinylidene dichloride
Appearance/Odor	Colorless liquid with mild, sweet odor resembling chloroform
Odor Threshold	500 ppm
Molecular Weight	96.95 g/mol

Melting Point	-122.5°C
Boiling Point	31.7°C @ 760 mmHg
Flash Point	-16°C (open cup); -10°C (closed cup)
Autoignition Temperature	570.0°C
Solubility: Water	2.5 g/L @ 25°C
Density	1.213 g/cm^3 @ 20°C
Vapor Pressure	500 mmHg at 20°C; 591 mmHg @ 25°C
Log Kow	1.32 at pH 7
Henry's Law Constant	0.19 atm-m^3/mole at 20-25°C

Literature Search

The literature was searched to find relevant data to assess the toxicity of 1,1'-dichloro-ethylene. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 7/21/2022), U.S. EPA ChemView, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

Key Study

In a two-year inhalation study conducted by the National Toxicology Program (NTP, 2015), mice and rats were exposed to 1,1'-dichloroethylene. Groups of 50 male and 50 female F344/N rats were exposed by whole body inhalation to 1,1'-dichloroethylene vapor at concentrations of 0, 25, 50, or 100 ppm (0, 99, 198, or 397 mg/m^3) for 6 hours plus 10 minutes per day, 5 days per week for 105 weeks. "In male rats, the incidences of malignant mesothelioma occurred with a positive trend and were significantly increased in all exposed groups compared to the chamber control group" (NTP, 2015). "The incidence of C-cell adenoma of the thyroid gland was significantly increased in 100 ppm females, and the incidence of C-cell carcinoma was significantly increased in 25 ppm females. The incidence of adenoma and carcinoma (combined) were significantly increased in 25 and 100 ppm females. The incidence of mononuclear cell leukemia was significantly increased in 100 ppm females" (NTP, 2015). "The only exposure-related primary nasal neoplasm observed in rats was adenoma in the respiratory epithelium. Exposure concentration-related increased incidences of turbinate atrophy and hypertosis, olfactory epithelium respiratory metaplasia, respiratory epithelium hyperplasia, and chronic active inflammation occurred in all exposed groups of male and female rats, and the severities of the lesions increased with increasing exposure concentration. The incidences of alveolar epithelium hyperplasia in the lungs were significantly increased in all exposed groups of male rats, the

severities increased with increasing exposure concentration. In the liver of rats, increased incidences of chronic inflammation, diffuse fatty change, and cystic degeneration in males and females and necrosis in females occurred" (NTP, 2015).

Groups of 50 male and 50 female mice were exposed by whole body inhalation to 1,1'-dichloroethylene vapor at concentrations of 0, 6.25, 12.5, or 25 ppm (0, 25, 50, or 99 mg/m^3) for 6 hours plus 10 minutes per day, 5 days per week for 105 weeks. "Survival of 25 ppm males and 6.25 and 25 ppm females was significantly less than that of the chamber control groups. Mean body weights of 12.5 and 25 ppm males were at least 10% less than those of the chamber control group after weeks 17 and 13, respectively, and those of 25 ppm females were at least 10% less after week 21. Exposure related clinical findings included thinness and abnormal breathing in 25 ppm males and abnormal breathing, thinness, and ventral torso mass in all exposed groups of females. The incidences of renal tubule adenoma, renal tubule carcinoma, and renal tubule adenoma or carcinoma (combined) were significantly increased in all exposed groups of males; the incidences of renal tubule hyperplasia were also significantly increased in all exposed groups of males. The incidences of hemangioma (all organs) in all exposed groups of females were increased compared to that in the chamber controls, and the incidence of hemangioma or hemangiosarcoma (combined) in 25 ppm females was significantly greater than that in the chamber controls. The incidences of hepatocellular adenoma in 12.5 ppm females, hepatocellular carcinoma in 25 ppm females, and hepatocellular adenoma or carcinoma (combined) in 12.5 and 25 ppm females were significantly greater than those in the chamber control group. In addition, hepatocholangiocarcinoma occurred in all exposed groups of females. The incidences of hepatocholangiocarcinoma in exposed groups of males were increased compared to that in the concurrent chamber control group and exceeded the historical control range for inhalation studies" (NTP, 2015). "In 25 ppm females, the incidence of carcinoma of the small intestine (ileum) exceeded the historical control ranges for inhalation studies and all routes of administration. Turbinate atrophy, hyperostosis, and olfactory epithelium respiratory metaplasia occurred in the nose of the vast majority of exposed male and female mice, and the severity of these lesions increased with increasing exposure concentration. The incidences of olfactory epithelium hyaline droplet accumulation in 12.5 and 25 ppm males and 25 ppm females and respiratory epithelium hyperplasia in 25 ppm females were significantly increased compared to chamber controls" (NTP, 2015).

ITSL Derivation

The NTP (2015) study was used to derive an ITSL. Benchmark Dose Software [BMDS] (version 3.2) was used to calculate the many statistically significant non-neoplastic effects. Statistically significant changes due to exposure to 1,1'-dichloroethylene were entered into the BMDS program. Table 2 shows the most statistically significant critical effects from several effects evaluated during this review. The calculated model predictions for significant changes in adult rats and mice are listed in Table 3.

Table 2. Significant Changes in F344/N Rats and B6C3F1/N Mice Exposed to 1,1'-Dichloroethylene

		Concentration (mg/m^3)	Incidence/number of animals tested	
Male Rat				
Critical Effect	**0**	**99**	**198**	**397**
Nasal inflammation chronic, active	9/49	36/50	45/50	48/50
Liver – Cystic degeneration	2/50	5/50	7/50	12/50
Female Rat				
Critical Effect	**0**	**99**	**198**	**397**
Olfactory epithelium metaplasia, respiratory	1/50	50/50	50/50	50/50
Liver – Cystic degeneration	0/50	2/50	4/50	7/50
Female Mouse				
Critical Effect	**0**	**25**	**50**	**99**
Turbinate atrophy	0/50	46/50	50/50	49/50
Olfactory epithelium metaplasia, respiratory	3/50	29/50	49/50	50/50

Table 3. Model Predictions for Significant Changes in F344/N Rats and B6C3F1/N Mice Exposed to 1,1'-Dichloroethylene

Critical Effect	Model	p-Value	Chi^2	AIC	BMDL
Male rat nasal inflammation, chronic active	Log-probit	0.8860	0.2421	159.6	14.26
Male rat liver cystic degeneration	Weibull	0.8708	0.0265	150.9	19.04
Female rat olfactory epithelium metaplasia, respiratory	Probit	0.9505	0.3495	12.43	10.29
Female rat liver cystic degeneration	Gamma	0.9986	0.0303	87.20	173.8
Female mouse turbinate atrophy	Probit	0.9977	0.0422	66.80	5.686
Female mouse olfactory epithelium, respiratory	Probit	0.9880	0.0241	104.6	5.858

To better describe the information given in Table 3 for the BMDS results above, the EPA (2020) states the p-value must be greater than 0.1, such that the greater the p-value, the better the model fits the data. The chi-square statistic is a test that measures how a model compares to the actual observed data. The lower the value of chi^2, the better the model fits the data. Also, the lower the Akaike Information Criterion (AIC), the better the model fits the available data. The AIC is used to compare different possible models to determine which model is the best fit for the data. The lower-bound confidence limit on the benchmark dose (BMDL) is the point of departure value determined by the model. If the available BMDLs are within 3-fold range, the model with the lowest AIC is selected. If the BMDLs are not within 3-fold range, the model with the lowest BMDL is selected.

Of the many effects seen in the NTP (2015) study, the most critical effect was the female mouse olfactory turbinate atrophy. This effect will be used to calculate the ITSL.

According to the EPA (1994, 2009), 1,1'-dichloroethylene can be classified as a category 1 gas, as its main effects are in the respiratory tract, though it does have effects in more remote regions of the body. The critical effects from 1,1'-dichloroethylene exposure were nasal olfactory epithelial metaplasia, turbinate atrophy, and chronic active nasal inflammation, but critical effects also included cystic degeneration in the liver. As the most critical effects were generally seen in the nasal cavity, 1,1'-dichloroethylene is considered to have the greatest effect in the extrathoracic (ET) region. The EPA (2009) equation 9 on page 2-17 was used to calculate 1,1'-dichloroethylene effects on the nasal epithelium.

The EPA (2009) equation 9 on page 2-17 was used to determine the human equivalent concentration point of departure using a dosimetric adjustment factor and a regional gas dose ratio (RGDR) for a chemical that causes effects in the extrathoracic region.

$$POD_{(HEC)}\left({}^{mg}/_{m^3}\right) = POD_{(ADJ)}\left({}^{mg}/_{m^3}\right) \times RGDR_{ET}$$

Where:
$POD_{(HEC)}$ = The human equivalent external air concentration of the animal point of departure that has been dosimetrically adjusted to a human equivalent concentration (HEC) though application of the appropriate dosimetric adjustment factor for the respiratory tract region, in this case for gases, using the regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) (EPA, 2009).

$POD_{(ADJ)}$ = The air concentration used as the Point of Departure corresponding to an effect level obtained from analysis of a chemical in a laboratory animal inhalation study (EPA, 2009).

EPA (2009) Table 2-4 on page 2-16 states that the $RGDR_{ET}$ for the extrathoracic region in a mouse is 0.21. The BMDL of 5.6863 mg/m^3 for the female mouse turbinate atrophy is the POD. The following equation was used to calculate the $POD_{(ADJ)}$ which is equivalent to the $BMDL_{(ADJ)}$:

$$BMDL_{(ADJ)}\left({}^{mg}/_{m^3}\right) = BMDL \times \frac{6\ hours\ 10\ minutes}{24\ hours} \times \frac{5\ days}{7\ days}$$
$$= 5.686\ {}^{mg}/_{m^3} \times \frac{6.167}{24} \times \frac{5}{7} = 1.044\ {}^{mg}/_{m^3}$$

To calculate the $POD_{(HEC)}$ which is equivalent to the $BMDL_{(HEC)}$, the first stated equation on page 5 of this document will be used.

$$BMDL_{(HEC)}\left({}^{mg}/_{m^3}\right) = 1.044\ {}^{mg}/_{m^3} \times 0.21 = 0.2192\ {}^{mg}/_{m^3}$$

According to Rule 336.1232(1)(a) in Part 2 of Act 451, an ITSL can be derived from an inhalation reference concentration (RfC). The RfC can be calculated from the $BMDL_{(HEC)}$ using the following equation:

$$RfC = \frac{BMDL_{(HEC)}}{UF_A \times UF_H}$$

Where:
UF_A = Extrapolation from animal data to humans. The uncertainty factor of 3 will be used to account for the quality of data and statistics used in the determination of the critical effect.

UF_H = Extrapolation to account for sensitive human populations. The uncertainty factor of 10 will be used to account for the lack of data to determine the effect in sensitive populations.

$$RfC = \frac{0.2192\ {}^{mg}/_{m^3}}{3 \times 10} = 0.007305\ {}^{mg}/_{m^3} = 7.305\ {}^{\mu g}/_{m^3} \cong 7.3\ {}^{\mu g}/_{m^3}$$

The ITSL for 1,1'-dichloroethylene equals the inhalation RfC. According to Rule 336.1232(2)(b), the averaging time is annual. Therefore, the ITSL for 1,1'-dichloroethylene is 7.3 µg/m^3 based on an annual averaging time.

IRSL Derivation

The NTP (2015) 2-year inhalation study found clear evidence of carcinogenic activity of 1,1'-dichloroethylene "in male F344/N rats based on increased incidences of malignant mesothelioma. Increased incidences of renal tubule carcinoma and respiratory epithelium adenoma in the nose of male rats were also considered to be related to vinylidene chloride" (NTP, 2015). "There was some evidence of carcinogenic activity of vinylidene chloride in female F344/N rats based on increased incidences of C-cell adenoma or carcinoma in the thyroid gland and systemic mononuclear cell leukemia" (NTP, 2015). "There was clear evidence of carcinogenic activity of vinylidene chloride in male B6C3F1/N mice based on increased incidences of renal tubule adenoma and carcinoma. Increased

incidences of hepatocholangiocarcinoma may have been related to vinylidene chloride exposure. There was clear evidence of carcinogenic activity of vinylidene chloride in female B6C3F1/N mice based on increased incidences of systemic hemangioma or hemangiosarcoma (combined). Hepatocholangiocarcinoma and hepatocellular adenoma or carcinoma (combined) in the liver of female mice were also considered to be related to vinylidene chloride exposure" (NTP, 2015).

The NTP (2015) study was used to determine an IRSL for 1,1'-dichloroethylene. The statistically significant neoplastic effects were entered into the BMDS (version 3.2). Table 4 shows the lifetime adjusted exposure concentrations for 1,1'-dichloroethylene vapor at concentrations of 0, 25, 50, or 100 ppm (0, 18, 36, or 73 mg/m^3) adjusted from 6 hours plus 10 minutes per day, 5 days per week for 105 weeks for rats to 24 hours over a lifetime dose. The lifetime adjusted exposure concentrations to 1,1'-dichloroethylene vapor at concentrations of 0, 6.25, 12.5, or 25 ppm (0, 5, 9, or 18 mg/m^3), which was adjusted from 6 hours plus 10 minutes per day, 5 days per week for 105 weeks for mice to a continuous exposure over a lifetime. The adjusted incidence of tumors was calculated to account for the animals that died before the occurrence of the first visible tumor. The most statistically significant critical neoplastic effects from the many effects evaluated during this review. The calculated model predictions for significant changes in adult rats and mice are listed in Table 5.

Table 4. Significant Neoplastic Changes in F344/N Rats and B6C3F1/N Mice Exposed to 1,1'-Dichloroethylene

		Lifetime Adjusted Concentration (mg/m^3)	**Adjusted Incidence/Adjusted number of animals from time of first tumor**	
		Male Rat		
Critical Effect	**0**	**18**	**36**	**73**
Respiratory epithelium adenoma	0/49	0/50	1/50	4/50
		Female Rat		
Critical Effect	**0**	**18**	**36**	**73**
Thyroid adenoma	3/46	4/41	6/39	11/44
Mononuclear cell leukemia	10/50	11/49	13/48	25/48
		Female Mouse		
Critical Effect	**0**	**5**	**9**	**18**
Hepatocholangiocarcinoma	0/50	1/50	1/50	2/50
Small intestine(ileum) carcinoma	1/46	1/43	1/47	3/38

Table 5. Model Predictions for Significant Neoplastic Changes in F344/N Rats and B6C3F1/N Mice Exposed to 1,1'-Dichloroethylene

Critical Effect	p-Value	Chi^2	AIC	Multi-stage Cancer Slope Factor
Male rat respiratory epithelium adenoma	0.9685	0.2539	40.18	0.0001649
Female rat thyroid adenoma	0.9571	0.08775	135.5	0.004720
Female rat mononuclear cell leukemia	0.9545	0.09319	228.9	0.007291
Female mouse hepatocholangiocarcinoma	0.9674	0.2596	38.63	0.005592
Female mouse small intestine (ileum) carcinoma	0.9598	0.08216	53.89	0.006539

Even though mononuclear cell leukemia is listed as a significant neoplastic change in the NTP (2015) study, there is no evidence that mononuclear cell leukemia is relevant to humans. Caldwell (1999) reviewed the incidences of mononuclear cell leukemia in the F344 rat and found that mononuclear cell leukemia is a common neoplasm in the F344 rat. It was also found that "mononuclear cell leukemia occurs in untreated aged F344 rats at a high and variable rate and is uncommon in most other rat strains (e.g., Sprague-Dawley, Osborne-Mendel)" (Caldwell, 1999). It should also of be noted that "mononuclear cell leukemia has not been found in other mammal species (e.g., mice and hamsters) and no histologically comparable tumor is found in humans" (Caldwell, 1999).

After reviewing the benchmark dose data generated from the multi-stage cancer model using dichotomous data, the most sensitive endpoint from the table above is the female mouse small intestine (ileum) carcinoma for determination of the IRSL. The carcinogenic risk from inhalation exposure with an inhalation unit risk of 6.539×10^{-3} per mg/m^3 using the benchmark dose software dose-response data from Table 5. Rule 231(1) is used to develop the IRSL using the equation below:

$$IRSL = \frac{1 \times 10^{-6}}{6.539 \times 10^{-3}} = 0.0001529\ {}^{mg}/_{m^3} = 0.1529\ {}^{\mu g}/_{m^3} \approx 0.15\ {}^{\mu g}/_{m^3}$$

Rule 231(3) states that the averaging time for IRSLs and SRSLs in an annual averaging time. Therefore, the IRSL for 1,1'-dichloroethylene (CAS# 75-35-4) is 0.15 $\mu g/m^3$ and the SRSL is 1.5 $\mu g/m^3$ based on an annual averaging time.

References

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