Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
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Air Toxicological Summary for: trans-1,2-dichloroethylene

CAS: **156-60-5**

Synonyms: 1,2-Dichloroethylene (trans); 1,2-trans-dichloroethylene; (E)-1,2-dichloroethene; (E)-1,2-Dichloroethylene; trans-1,2-Dichloroethene; trans-1,2-dichloroethylene; trans-1,2-dichloroethylene ; trans-1,2-DCE; trans-acetylene dichloride; trans-dichloroethylene

Air Exposure Durations:

Acute = dosing duration of 1-day or less

Short-term = repeated dosing for more than 1-day, up to approximately 30 days

Subchronic = repeated dosing for more than 30 days, up to approximately 10 percent of a lifespan in humans (more than 30 days up to approximately 90 days in typical laboratory rodent species)

Chronic = repeated dosing for more than approximately 10 percent of a life span in humans (more than approximately 90 days in typical laboratory rodent species

Acute Non-Cancer Risk Assessment Advice ($nRAA_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Risk Assessment Advice ($nRAA_{ShortTerm}$) = Not Derived (Insufficient Data)

Subchronic Non-Cancer Risk Assessment Advice ($nRAA_{Subchronic}$) = 200 µg/m^3

= RfD (mg/kg-d) x (70 kg/20 m^3) x (1000 µg/mg)

= 0.05 (mg/kg-d) x (70 kg/20 m^3) x (1000 µg/mg)

= 175 µg/m^3

= 200 µg/m^3

Reference Dose/Concentration(RfD/C):	HED/UF = 14.5/300 = 0.05 mg/kg-d (CD-1 mouse study)
Source of toxicity value:	Determined by MDH 2020
POD and Critical Effect:	14.5 mg/kg-d ($BMDL_{ADM-1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985);

	Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Dose Adjustment Factor (DAF):	DAF = 1 (USEPA 2011)
Human Equivalent Dose/Conc (HED/C):	POD x DAF = 14.5 mg/kg-d x 1 = 14.5 mg/kg-d
Total uncertainty factor:	300
Uncertainty factor allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, and 3 for database uncertainty due to lack of a multigenerational study and supplementing database with inhalation studies

Chronic Non-Cancer Risk Assessment Advice ($nRAA_{Chronic}$) = 20 µg/m^3

= RfD (mg/kg-d) x (70 kg/20 m^3) x (1000 µg/mg)

= 0.005 (mg/kg-d) x (70 kg/20 m^3) x (1000 µg/mg)

= 17.5 µg/m^3

= 20 µg/m^3

Reference Dose/Concentration (RfD/C):	HED/UF = 14.5/3000 = 0.005 mg/kg-d (CD-1 mouse study)
Source of toxicity value:	Determined by MDH 2020
POD and Critical Effect:	14.5 mg/kg-d ($BMDL_{ADM-1SD}$ based on 2018 OEHHA modeling of immunotoxicity data from Shopp et al 1985); Decreased ability to produce antibodies against sheep RBCs in male spleen cells
Dose Adjustment Factor (DAF):	DAF = 1 (USEPA 2011)
Human Equivalent Dose/Conc (HED/C):	POD x DAF = 14.5 mg/kg-d x 1 = 14.5 mg/kg-d
Total uncertainty factor:	3000
Uncertainty factor allocation:	10 for interspecies extrapolation, 10 for intraspecies variability, 10 for subchronic-to-chronic extrapolation due to clear and significant immunotoxicity in the subchronic study, and 3 for database uncertainty due to lack of a multigenerational study and supplementing database with inhalation studies

Cancer Risk Assessment Advice = Not Applicable

Cancer classification:	*"Inadequate information to assess the carcinogenic potential"* of trans-1,2-dichloroethylene (trans-1,2-DCE)
Inhalation Unit Risk (IUR):	Not Applicable
Source of IUR:	EPA IRIS 2010

Tumor site(s): Not Applicable

Volatile: Yes (High)

Summary of Guidance Value History:

In January 2019, at the request of the Minnesota Pollution Control Agency (MPCA), the Minnesota Department of Health (MDH) developed site-specific inhalation risk assessment advice (RAA) for trans-1,2-dichloroethylene (trans-1,2-DCE; CAS 156-60-5) for use at a specific high-priority site. This 2019 RAA was derived using route-to-route extrapolation from the 2010 Environmental Protection Agency's Integrated Risk Information System's (EPA IRIS) reference dose (RfD). Per EPA IRIS, the RfD was derived from the subchronic oral mouse study by Shopp et al. 1985. This study exposed mice to trans-1,2-DCE at concentrations of 0.1, 1.0, and 2.0 mg/mL in drinking water. The point of departure (POD) was the benchmark dose level ($BMDL_{1SD}$) of 65 mg/kg-d and based on a decrease in number of antibody forming cells against sheep red blood cells in male mice (decreased humoral immune response). A total uncertainty factor of 3,000 was applied by EPA IRIS; 10 for both intra- and interspecies variability, 10 for extrapolating from a POD for a subchronic to chronic exposure, and 3 to account for database deficiencies. This resulted in a trans-1,2-DCE RfD of 0.02 mg/kg/day, which was used to calculate the RAA of 70 $\mu g/m^3$.

In 2020, MDH's Health Risk Assessment Unit (HRA) re-evaluated the reference dose for trans-1,2-DCE using updated benchmark dose modeling techniques proposed by California EPA (OEHHA) in 2018. Per MDH's HRA 2020 Toxicological Summary Sheet, OEHHA was critical of EPA's decision to use an unrestricted polynomial model as it did not prevent the existence of a turning point, leading to a potentially unrealistic modeled dose-response curve; in general Benchmark Dose Software (BMDS) practice, restricted models are used whenever feasible to increase biological plausibility of resultant model curves. OEHHA performed their own BMDS analysis; the critical effect remained decreased humoral immune response in mice (Shopp et al., 1985). OEHHA's BMDS analysis was performed in BMDS 2.6 using restricted models, resulting in a $BMDL_{ADM\text{-}1SD}$ = 14.50 from the 4th degree exponential model. As part of HRA's more recent re-evaluation, HRA examined the EPA 2010 and OEHHA 2018 modeling results and attempted to replicate them. BMDS 1.4.1 was unavailable, and therefore EPA's results could not be directly replicated. OEHHA's analysis was performed in BMDS 2.6; HRA was able to replicate the results in BMDS 2.7. Using the two most recent versions of BMDS (3.1.1 and 3.1.2), the 4th degree exponential model recommended by 2.6/2.7 failed to compute a BMD and was considered unusable. Instead, the 2nd and 3rd degree exponential models were recommended by BMDS 3.1.2 and 3.1.1, respectively, with a $BMDL_{ADM\text{-}1SD}$ = 165, considerably higher than either EPA or OEHHA's POD; however, it must be noted that the visual fits of these models were extremely poor, fitting significantly worse than the OEHHA modeling in BMDS 2.6.

To investigate these apparent model fit discrepancies, HRA staff contacted the developers of BMDS at EPA for technical consultation. After internal discussion, EPA noted that, while the most recent versions (3.1.1/3.1.2) of BMDS typically perform better parameter optimization for the majority of datasets, this particular dataset was over-parameterized, resulting in an inappropriate model result.

EPA concluded that BMDS 2.6 and 2.7 arrived at a better optimization solution for this dataset and recommended use of those calculated BMDLs. Consequently, MDH has selected a $BMDL_{ADM\text{-}1SD}$ = 14.5 mg/kg-d as a point of departure for reference dose calculation. This POD was then used for a route-to-route extrapolation to derive a more up-to-date subchronic and chronic air value.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	No	Yes	Yes	No	No	Yes
Effects observed?	No	Yes[1]	Yes[2]	No[3]	No[4]	Yes[5]

Comments on extent of testing or effects:

[1]Shopp et al. (1985) measured depression in humoral immune status following 90 days of exposure via drinking water. These effects form the basis of the subchronic and chronic RAA.
[2]A single inhalation developmental study exists. Decreased fetal body weight was observed at doses estimated to be over 400-fold higher than the minimal short-term critical Human Equivalent Dose used by MDH HRA. A database uncertainty factor has been applied, in part, due to the lack of oral developmental/reproductive studies.
[3]Examination of the reproductive organs of animals in the 90-day study did not report any histological changes. A database uncertainty factor has been applied, in part, due to the absence of a multigenerational study.
[4]Neurological effects have not been adequately studied. Acute exposures (e.g., a single high dose) have reported effects.
[5]Changes in alveolar septal distension of the lungs following a subchronic inhalation study to a single trans-1,2-DCE exposure were observed (Freundt et al. 1977). Pathological changes in the lung consisted of pulmonary capillary hyperemia and alveolar septal distention in all six rats in all four-exposure duration groups. These changes in the lung were considered by the authors to be slight and evaluation of respiratory effects was very limited.

Resources Consulted During Review:

California Environmental Protection Agency OEHHA, Public Health Goals for Chemicals in Drinking Water: *Cis*- and *Trans*-1,2-Dicholorethylene (2018). URL: http://www.oehha.ca.gov/water/phg/allphgs.html

California Environmental Protection Agency, OEHHA Toxicity Criteria Database. URL: http://www.oehha.ca.gov/risk/ChemicalDB/index.asp

Freundt KJ, GP Liebaldt and E Lieberwirth. 1977. Toxicity Studies on Trans-1,2-Dichloroethylene. Toxicology 7:141-153.

Minnesota Department of Health. 2020. Toxicological Summary Sheet for: trans-1,2-dichloroethylene. See MDH Human Health-Based Water Guidance Table.

Shopp GM, VM Sanders, KL White, and AE Munson. 1985. Humoral and Cell-Mediated Immune Status of Mice Exposed to trans-1,2-Dichloroethylene. Drug Chem. Tox., 8(5):393-407.

U.S. EPA. 2011. Status Report: Advances in inhalation dosimetry for gases with lower respiratory tract and systemic effects. (EPA/600/R-11/067). Washington DC.