OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Goals

Cis- and Trans-1,2-Dichloroethylene in Drinking Water

July 2018

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Prepared by

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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LIST OF CONTRIBUTORS

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Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Author

Adrienne Bautista, Ph.D.

Reviewers

Francisco Moran, Ph.D.
Moira Sullivan, M.S.

Final Reviewers

Elaine Khan, Ph.D.
Melanie Marty, Ph.D.
David Siegel, Ph.D.
David Ting, Ph.D.

Director

Lauren Zeise, Ph.D.

PREFACE

The Public Health Goal (PHG) technical support documents provide information on health effects from contaminants in California drinking water. PHGs are developed for chemical contaminants based on the best available data in the scientific literature and using the most current principles, practices, and methods used by public health professionals. These documents and the analyses contained therein provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

Under the California Safe Drinking Water Act of 1996 (Health and Safety Code section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops PHGs for drinking water contaminants in California based exclusively on public health considerations. OEHHA periodically reviews PHGs and revises them as necessary based on the availability of new scientific data. This document presents an update for cis- and trans-1,2-dichloroethylene for which PHGs were published in 2006.

PHGs published by OEHHA are for use by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are based solely on scientific and public health considerations without regard to economic considerations, MCLs adopted by SWRCB consider economic factors and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory and represent only non-mandatory goals. Under federal law, MCLs established by SWRCB must be at least as stringent as the corresponding federal MCL if one exists.

In July 2014, responsibility for the state's drinking water regulatory program was transferred to SWRCB from the California Department of Public Health. References in this document to drinking water monitoring and regulation may cite either or both entities as appropriate.

TABLE OF CONTENTS

SUMMARY

This document presents updated public health goals (PHGs) for cis- and trans-1,2-dichloroethylene (cis-/trans-1,2-DCE). The 2006 PHG value of 100 micrograms per liter (µg/L) or 100 parts per billion (ppb) for cis-1,2-DCE was based on significant increases in relative kidney weight observed in a 90-day oral gavage study in rats (McCauley et al., 1990). This study is retained as the critical study and the updated PHG of 13 ppb is derived using benchmark dose (BMD) modeling, updated drinking water ingestion rates, dermal/inhalation exposure estimates from household tap water use, and an updated intraspecies variability factor. The 2006 PHG value of 60 ppb for trans-1,2-DCE was based on increases in relative liver weight and serum alkaline phosphatase observed in a 90-day drinking water study in mice (Barnes et al., 1985). The updated PHG of 50 ppb for trans-1,2-DCE is based on decreases in humoral immune response in mice (Shopp et al., 1985). Recent studies (Landics, 2007; Loveless et al., 2007) have noted that this endpoint is highly predictive of overall immunotoxicity and support its basis for the PHG. BMD modeling, updated drinking water intake rates, dermal/inhalation exposure estimates from household tap water use, and an updated intraspecies variability factor are also incorporated into the derivation of the updated PHG for trans-1,2-DCE.

Studies on genotoxicity and mutagenicity of cis-/trans-1,2-DCE are generally not positive and there are no data on carcinogenicity in any species, including humans. Thus, the carcinogenic potential of cis/trans-1,2-DCE cannot be evaluated due to lack of information at this time. These two compounds are not listed by the Proposition 65 program as either carcinogens or reproductive toxicants.[1]

INTRODUCTION

The Office of Environmental Health Hazard Assessment (OEHHA) performs health risk assessments and develops public health goals (PHGs) for drinking water contaminants in California. A PHG is the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water on a daily basis over a lifetime. This document presents PHG updates for cis- and trans-1,2-dichloroethylene (cis-/trans-1,2-DCE). This update incorporates a thorough review of the current scientific literature and the most current risk assessment practices and methods, as well as relevant chemical-specific toxicity data.

1,2-DCE, a volatile, chlorinated and highly flammable organic compound, exists in two isomeric states, cis and trans. 1,2-DCE has been used primarily as a solvent for waxes and resins, in the extraction of various industrial products such as rubber, and as a refrigerant. Although trans-1,2-DCE is the only isomer currently used in industry, both isomers can be found in the environment due to the anaerobic degradation of other commonly found chlorinated solvents such as tricholoroethylene (TCE) and

[1] https://oehha.ca.gov/proposition-65/proposition-65-list (January 27, 2017 Proposition 65 List)

tetrachloroethylene (PCE) (Mattes et al., 2010; US EPA, 2010b). In 2015, the US Environmental Protection Agency's (US EPA) Toxics Release Inventory (TRI)[2] reported that 27,689 pounds of 1,2-DCE were released to air, 5 pounds to surface water, and 46 pounds to on-site or off-site landfills, underground injection wells or other releases to land. Of the total, only 16 pounds were released in California. The California Maximum Contaminant Level (CA MCL) for cis-1,2-DCE is 6 ppb and for trans-1,2-DCE is 10 ppb.[3] These levels are lower than the federal MCLs of 70 ppb and 100 ppb for cis-1,2-DCE and trans-1,2-DCE, respectively, which were maintained in US EPA's second Six-Year Review of Drinking Water Standards in 2010 (US EPA, 2010a). Both isomers of 1,2-DCE have been detected in California public drinking water supply wells within the last three years.[4] Levels detected range from 0.097 to 40 ppb for cis-1,2-DCE and 1.8 to 33 ppb for trans-1,2-DCE.

BASES FOR THE 2006 PHGs

In 2006, OEHHA published a PHG of 100 ppb for cis-1,2-DCE in drinking water based on a 90-day oral gavage study in which Sprague-Dawley rats were dosed with 0, 32, 97, 291, or 872 milligrams per kilogram of bodyweight per day (mg/kg-day) of cis-1,2-DCE in corn oil (McCauley et al., 1990 as presented in McCauley et al., 1995). Significant increases in relative kidney weight (adjusted for body weight) were observed for males at all doses and a lowest-observed-adverse-effect level (LOAEL) for kidney effects was determined to be 32 mg/kg-day. A maximum combined uncertainty factor of 3,000 was applied, although the actual total combined uncertainty factor was up to 30,000 (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for extrapolation from subchronic to chronic exposure, 3 or 10 for extrapolation from a LOAEL to a no-observed-adverse-effect level [NOAEL] and 3 for database deficiency). It followed guidelines at the time which set the maximum cumulative uncertainty factor at 3,000 (US EPA, 2002 as cited in OEHHA, 2006). Exposure parameters included in the PHG calculation assumed an adult body weight of 70 kg, a water consumption rate of 4 liter-equivalents per day (L_{eq}/day) (to account for dermal, inhalation and oral routes of exposure), and a relative source contribution (RSC) of 60 percent.

The 2006 PHG of 60 ppb for trans-1,2-DCE was established from a 90-day drinking water study in CD-1 mice (Barnes et al., 1985). Based on water consumption, doses of trans-1,2-DCE were calculated to be 0, 17, 175 or 387 mg/kg-day for males and 0, 23, 224 or 452 mg/kg-day for females. A significant increase in relative liver weight and serum alkaline phosphatase was reported for males at 175 mg/kg-day. Thus a NOAEL

[2] http://iaspub.epa.gov/triexplorer/tri_release.chemical
[3] Available online at: http://www.swrcb.ca.gov/drinking_water/certlic/drinkingwater/MCLsandPHGs.shtml
[4] Based on monitoring data over the last three years for public water supply wells, accessed May 23, 2017 with GeoTracker GAMA (http://geotracker.waterboards.ca.gov/gama/). The data do not indicate whether the source is raw (untreated) water or treated water; therefore, the results in the dataset may not be representative of the water delivered to customers.

of 17 mg/kg-day was established. A total combined uncertainty factor of 3,000 was used (10 for interspecies extrapolation, 10 for intraspecies variability, 10 for extrapolation from subchronic to chronic exposure, and 3 for database deficiency). Exposure parameters included a 70 kg adult body weight, a 4 L_{eq}/day water consumption rate and an RSC of 60 percent to calculate the PHG.

UPDATED TOXICOLOGICAL REVIEW

A thorough literature search on cis- and trans-1,2-DCE revealed no new toxicity studies in animals or humans published since the 2006 PHG. However, three epidemiological studies evaluated the health effects of drinking water contamination at Marine Corps Base Camp Lejeune, North Carolina (Rukart et al., 2013, 2014, 2015). The drinking water contaminants identified were TCE, PCE, benzene, vinyl chloride and trans-1,2-DCE.

A case-control study was conducted to determine if children born to mothers exposed to the contaminated drinking water at Camp Lejeune during pregnancy were more likely to have childhood hematopoietic cancers, neural tube defects or oral clefts (Ruckart et al., 2013). For neural tube defects and average first trimester exposures, the odds ratios (ORs) for any benzene exposure and for TCE exposure above 5 ppb were 4.1 (95% confidence interval (CI), 1.4-12.0) and 2.4 (95% CI, 0.6-9.6), respectively. For childhood cancers and average first trimester exposures, ORs for any PCE exposure and any vinyl chloride exposure were 1.6 (95% CI, 0.5-4.8) and 1.6 (95% CI, 0.5-4.7), respectively. Although several ORs were greater than 1, suggesting an association between exposure and outcome, the CIs were quite wide. The study found no evidence of associations between trans-1,2-DCE exposure and the health outcomes examined.

A cross-sectional study was also conducted to determine if prenatal exposure to Camp Lejeune's contaminated drinking water was associated with preterm birth, small for gestational age, and low birth weight (Ruckart et al., 2014). Modeling to provide monthly average estimates of concentrations of specific compounds was conducted to determine exposure levels to the various chemical contaminants for each individual included in the study. Overall findings suggested associations between in utero exposures to TCE and small for gestational age, term low birth weight and reduced mean birth weight, in utero exposures to benzene and term low birth weight, and in utero exposures to PCE and preterm birth. Results for trans-1,2-DCE were not presented in the study as the authors found they were highly correlated with PCE.

Another case-control study among Marines was conducted to determine if exposure to contaminated drinking water at Camp Lejeune was associated with male breast cancer (Ruckart et al, 2015). A total of 71 cases of male breast cancer were identified; 373 controls were used for comparison. Adjusted ORs for high cumulative exposures to PCE, trans-1,2-DCE and vinyl chloride were 1.20 (95% CI, 0.16-5.89), 1.50 (95% CI,

0.30-6.11), and 1.19 (95% CI, 0.16-5.89), respectively. Adjusted ORs for high cumulative exposures to TCE, benzene, and TVOC (the sum of the amount of exposure to PCE, TCE, trans-1,2-DCE, and vinyl chloride) were not elevated. The authors concluded that the ORs for high cumulative exposures to PCE, trans-1,2-DCE and vinyl chloride suggest a possible association with male breast cancer. However, the ORs for PCE and vinyl chloride were based on two cases and the OR for trans-1,2-DCE was based on three cases in the high cumulative exposure groups, resulting in large CIs.

PHG DERIVATION

Cis-1,2-dichloroethylene

Upon review of previously available studies on the toxicity of cis-1,2-DCE, OEHHA is retaining the study by McCauley et al. (1990, as presented in McCauley et al., 1995) for derivation of the updated PHG. Two candidate critical effects were identified in the McCauley et al. (1995) study: increased relative kidney weight and increased relative liver weight. The study did not report significant compound-related histopathological changes accompanying the increases in liver and kidney weight. However, several oral studies of trans-1,2-DCE and an inhalation study of 1,2-DCE as a mixture (Tables 4-13 and 4-14 in US EPA, 2010) provide support for the kidney and liver as the target organs.

Dose-response data from McCauley et al. (1995), which presents the data from the unpublished 1990 report, are presented in Table 1. Benchmark dose software (BMDS version 2.6, US EPA) is used to estimate the point of departure (POD). Continuous models were run with default parameters and a benchmark response (BMR) of one standard deviation (SD) from the control mean, which is typically used when there are no data to indicate what level of response is biologically significant (US EPA, 2012).

Table 1. Relative kidney and liver weights of rats exposed to cis-1,2-DCE by gavage for 90 days (McCauley et al., 1995)[d]

Dose[a] (mg/kg-day)	0	32	97	291	872
Relative kidney weight					
Males[b]	0.70 ± 0.06	0.80 ± 0.06[c]	0.83 ± 0.06[c]	0.83 ± 0.10[c]	0.89 ± 0.06[c]
Females[b]	0.69 ± 0.06	0.71 ± 0.05	0.82 ± 0.23	0.85 ± 0.21	0.85 ± 0.06
Relative liver weight					
Males[b]	2.85 ± 0.26	3.15 ± 0.27	3.28 ± 0.18[c]	3.34 ± 0.44[c]	3.75 ± 0.20[c]
Females[b]	2.82 ± 0.19	2.91 ± 0.18	3.21 ± 0.22[c]	3.36 ± 0.18[c]	3.67 ± 0.27[c]

[a] Administered doses in McCauley et al., 1995 were reported as 0, 0.33, 1, 3, and 9 mmol/kg-day. These doses were incorrectly converted to 0, 10, 32, 198, and 206 mg/kg-day in the 1995 publication. The doses presented here are the correctly calculated doses. For further explanation, see US EPA (2010b).

[b] Values are mean ± standard deviation (SD)
[c] Significantly different from control group; p≤0.05, Tukey's multiple comparison test.
[d] Adjusted for early gavage-related deaths, N were 9 (control), 10 (32 mg/kg-day), 10 (97 mg/kg-day), 7 (291 mg/kg-day) and 6 (872 mg/kg-day) in males, and 10 (control), 9 (32 mg/kg-day), 9 (97 mg/kg-day), 10 (291 mg/kg-day) and 10 (872 mg/kg-day) in females (US EPA, 2010b).

Table 2. Summary of BMD modeling results for organ weight changes in rats exposed to cis-1,2-DCE by gavage for 90 days (McCauley et al., 1995)

Sex/ Species	Endpoint	Model[a]	p-Value	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Male rat	Relative kidney weight	Hill	0.3423[b]	16.35[b]	**3.76[b]**
	Relative liver weight	Hill	0.1092	63.34	18.70
Female rat	Relative liver weight	Hill	0.3208	53.20	28.76

[a] All models were run with default parameters and set with adverse direction up, based on data.
[b] US EPA analysis used N=10 for this endpoint and produced different values: p=0.2257, BMD_{1SD}=16.35 mg/kg-day, $BMDL_{1SD}$=5.14 mg/kg-day; OEHHA used early gavage death-adjusted N values for consistency, as described in the footnote in Table 1.

Relative kidney and liver weights in male rats and relative liver weight in female rats were modeled (Table 2). The $BMDL_{1SD}$ of 3.76 mg/kg-day, derived from the Hill Model, for changes in relative kidney weight in male rats is chosen as the POD because it is the lowest BMDL derived from a model that fit the data well, in addition to being the most sensitive endpoint. Further details for the BMD analyses are presented in Table A1 and Figure A1 of Appendix I.

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose (ADD) of the chemical from all sources is first calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime ADD that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

$$ADD = \frac{POD}{UF}$$

where,

ADD = acceptable daily dose, an estimate of the maximum daily dose that can be consumed by humans for an entire lifetime without adverse health effects;

POD = point of departure, in units of milligrams per kilogram of body weight per day (mg/kg-day); this can be the NOAEL, LOAEL, or lower limit of the 95% confidence interval of the benchmark dose estimated from the critical study (BMDL);

UF = uncertainty factor(s); for a list of default uncertainty factors, see Appendix III.

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for non-carcinogenic endpoints:

$$C = \frac{\text{ADD (mg/kg-day)} \times \text{RSC}}{\text{DWI}}$$

where,

RSC = relative source contribution (usually 20% to 80%, expressed as 0.20 to 0.80);

DWI = daily water intake rate expressed as liters or liter equivalents per kilogram of body weight per day (L/kg-day or L_{eq}/kg-day); liter equivalents represent the amount of tap water one would have to drink to account for the daily exposure to a chemical in tap water through oral, inhalation, and dermal routes.

To calculate the ADD for cis-1,2-DCE, a total UF of 3,000 is applied; 10 for interspecies extrapolation, 30 for intraspecies variability (10 for toxicokinetics and √10 for toxicodynamics), √10 for extrapolation from a subchronic study, and √10 for deficiencies in toxicity data. There are no chronic and no developmental and reproductive toxicity studies on cis-1,2-DCE. Therefore, the ADD is:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{3.76 \text{ mg/kg-day}}{3{,}000} = 0.00125 \text{ mg/kg-day}.$$

Due to its volatile nature, exposure to cis-1,2-DCE in drinking water is expected to occur through both inhalation and oral ingestion. Estimation of inhalation and dermal exposures to cis-1,2-DCE during household uses of tap water such as bathing and showering, are estimated using CalTOX[5] modeling. Detailed inputs and outputs used in CalTOX modeling are presented in Appendix II. The relative contributions from each route to the overall exposure to cis-1,2-DCE in tap water are presented in Table 3. Tap

[5] CalTOX 4.0 is a multimedia, multiple pathway exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory (available at https://eaei.lbl.gov/tool/caltox).

water exposure equivalencies (Table 4) are calculated for inhalation and dermal exposures using life-stage specific oral ingestion rates (OEHHA, 2012) and the relative contribution of each route.

Table 3. Relative contributions of multiple exposure routes to total cis-1,2-DCE exposure in tap water for individual life stages, determined by CalTOX[a]

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus[b] (Pregnancy)	54	44	2
Infant	98	0[c]	2
Child	43	55	2
Adult	58	39	3

[a] See Appendix II for exposure parameters used for CalTOX modeling.
[b] The fetus is assumed to have the same exposure as the pregnant mother.
[c] Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios; therefore the inhalation pathway is excluded for infants.

Table 4. Total liter equivalent values for multiroute exposure to cis-1,2-DCE in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation (L_{eq}/kg-day)[a,b]	Dermal (L_{eq}/kg-day)[a]	Total Exposure (L_{eq}/kg-day)
Fetus (Pregnancy)	N/A	0.047	0.019	0.0017	0.068
Infant	0-2	0.196	0	0.0040	0.200
Child	2-16	0.061	0.039	0.0028	0.103
Adult	16-70	0.045	0.015	0.0023	0.062
Time-weighted average over lifetime[c]					**0.075**

[a] Inhalation and dermal estimates are calculated using life-stage specific oral ingestion rates and relative contribution of the oral ingestion values.
[b] L_{eq} for inhalation assumes 50% absorption in the lung (OEHHA, 2006).
[c] Multiroute lifetime tap water exposure = (0.75 × 0.068 + 2 × 0.200 + 14 × 0.103 + 54 × 0.062)/70 = 0.075 L_{eq}/kg-day.

An RSC of 0.80 is applied because drinking water sources are anticipated to be the primary source contributor for exposures. In addition, use of cis-1,2-DCE is less common today (US EPA, 2010b) and exposure to residues on food and through inhalation from ambient air are expected to be minimal.

The public health-protective concentration, C, is:

$$C = \frac{0.00125 \text{ mg/kg-day} \times 0.80}{0.075 \ L_{eq}/\text{kg-day}} = 0.013 \text{ mg/L} = 13 \text{ µg/L or } 13 \text{ ppb}$$

OEHHA therefore proposes a PHG of 13 ppb for cis-1,2-DCE based on dose-related increases in relative kidney weight in male rats from a 90-day oral gavage study conducted by McCauley et al. (1995).

Trans-1,2-dichloroethylene

There are no new toxicity studies identified since the 2006 PHG. Most of the literature suggest that the liver and kidney are the primary organs affected by exposure to trans-1,2-DCE. For example, the 2006 PHG was based on liver effects in a drinking water study by Barnes et al. (1985), in which male and female mice were exposed to 0, 17, 175 or 387 mg/kg-day and 0, 23, 224 or 452 mg/kg-day trans-1,2-DCE, respectively, for 90 days. A significant increase in relative liver weight and an increase in serum alkaline phosphatase (SAP) in males were reported at ≥175 mg/kg-day and a significant decrease in relative thymus weight in females was reported at ≥224 mg/kg-day (Table 5). Similarly, a 2002 National Toxicology Program (NTP) study found significant increases in relative liver weight in male and female mice and female rats exposed to trans-1,2-DCE in feed for 14 weeks (Table 6). Hayes et al. (1987) exposed rats to trans-1,2-DCE in drinking water for 90 days at 0, 402, 1,314, or 3,114 mg/kg-day for males and 0, 353, 1,257 or 2,809 mg/kg-day for females. They reported a dose-dependent increase in kidney weights in females (Table 7).

Two studies have also looked at immune system effects as a toxicity endpoint (Munson et al., 1982; Shopp et al., 1985). The antibody forming cell (AFC) assay, which measures the response of antibody producing cells of the spleen (Landics, 2007), is highly predictive of overall immunotoxicity and has been well-validated as an immunotoxicity test (Luster et al., 1992, 1993; Loveless et al., 2007). Munson et al. (1982) conducted an assessment of immunotoxicity in 4-week-old male mice gavaged with 0, 22, and 222 mg/kg-day of trans-1,2-DCE for 14 days. Humoral immune function, as assessed by the AFC assay, showed a trend towards suppression of the number of AFCs when expressed as number of AFCs per spleen with significance at the $p<0.1$ level. However, no significant change was found when expressed as number of AFCs per 10^6 spleen cells. In another study, when male and female mice were exposed to 0, 17, 175 or 387 mg/kg-day and 0, 23, 224 or 452 mg/kg-day trans-1,2-DCE, respectively, for 90 days in drinking water, pronounced suppression of the AFC response was found in male mice (Shopp et al., 1985). In male mice, the number of AFCs per spleen were significantly reduced at all doses of trans-1,2-DCE and the number of AFCs per 10^6 spleen cells were significantly reduced at doses of 175 and 387 mg/kg-day (Table 8). In female mice, a significant reduction in AFCs per spleen was found only at the 23 mg/kg-day dose. Since the expression of AFCs per spleen can be affected by changes in the relative size of the spleen, the preferred measure is the number of AFCs per 10^6 spleen cells.

Table 5. Summary of effects in mice exposed to trans-1,2-DCE in drinking water for 90 days (Barnes et al., 1985)

Males				
Dose (mg/kg-day)	**0**	**17**	**175**	**387**
Liver weight[a] (mg) (% body weight)	2029 ± 206 (5.10)	2007 ± 240 (5.01)	2288 ± 232[b] (5.53)[b]	2022 ± 329 (5.17)
Serum alkaline phosphatase[a] (IU/L)	34.3 ± 8.82	37.6 ± 20.4	55.5 ± 21.6[b]	45.6 ± 9.6[b]
Females				
Dose (mg/kg-day)	**0**	**23**	**224**	**452**
Thymus weight[a] (mg) (% body weight)	71 ± 14.7 (0.22)	67 ± 16 (0.20)	61 ± 16 (0.18)[b]	54 ± 16 (0.17)[b]

[a] Values are mean ± SD
[b] Significantly different from control group; p≤0.05, Duncan's multiple range test (Barnes et al., 1985).

Table 6. Relative liver weight of rats and mice exposed to trans-1,2-DCE in feed for 14 weeks (NTP, 2002)

Relative liver weight[a] in rats						
Dose (mg/kg-day)	**0**	**190**	**380**	**770**	**1,540**	**3,210**
Males	3.465 ± 0.183	3.538 ± 0.101	3.658 ± 0.313	3.524 ± 0.158	3.492 ± 0.152	3.634 ± 0.177
Dose (mg/kg-day)	**0**	**190**	**395**	**780**	**1,580**	**3,245**
Females	2.937 ± 0.120	3.040 ± 0.164	3.220 ± 0.209[b]	3.100 ± 0.161[b]	3.132 ± 0.164[b]	3.216 ± 0.161[b]
Relative liver weight[a] in mice						
Dose (mg/kg-day)	**0**	**480**	**920**	**1,900**	**3,850**	**8,065**
Males	4.347 ± 0.177	4.552 ± 0.357	4.597 ± 0.364	4.745 ± 0.266[b]	4.736 ± 0.250[b]	4.979 ± 0.351[b]
Dose (mg/kg-day)	**0**	**450**	**915**	**1,830**	**3,760**	**7,925**
Females	4.621 ± 0.221	4.738 ± 0.215	4.970 ± 0.402	4.813 ± 0.158	5.115 ± 0.440[b]	5.117 ± 0.253[b]

[a] Organ-weight-to-body-weight ratio: g organ weight/g body weight as a percentage (mean ± SD).
[b] Significantly different from control group; p≤0.01, Williams' or Dunnett's test (NTP, 2002).

Table 7. Absolute and relative kidney weights of female rats exposed to trans-1,2-DCE in drinking water for 90 days (Hayes et al., 1987)

Dose (mg/kg-day)	0	353	1,257	2,809
Absolute kidney weight[a] (g)	2.20 ± 0.174	2.26 ± 0.179	2.37 ± 0.174[b]	2.40 ± 0.124[b]
Relative kidney weight[a]	0.87± 0.044	0.87 ± 0.045	0.91± 0.087	0.92 ± 0.041

[a] 17-20 animals per group. Values are mean ± SD.
[b] Significantly different from control group; p≤0.05 (Hayes et al., 1987).

Table 8. Humoral immune response to sRBC in mice exposed to trans-1,2-DCE in drinking water for 90 days (Shopp et al., 1985)

Exposure Group	Spleen weight (mg)	AFCs per spleen ($\times 10^{-5}$)	AFCs per 10^6 cells
Males[a]			
0 mg/kg-day	202 ± 104	4.48 ± 1.11	2,200 ± 433
17 mg/kg-day	164 ± 36.8	3.28 ± 0.80[b]	2,048 ± 430
175 mg/kg-day	178 ± 17.0	3.34 ± 1.10[b]	1,625 ± 385[b]
387 mg/kg-day	173 ± 28.3	2.87 ± 1.05[b]	1,618 ± 639[b]
Females[a]			
0 mg/kg-day	228 ± 45.0	4.38 ± 1.28	1,765 ± 381
23 mg/kg-day	176 ± 31.1[b]	2.97 ± 1.39[b]	1,478 ± 597
224 mg/kg-day	230 ± 34.0	4.51 ± 0.68	1,967 ± 252
452 mg/kg-day	191 ± 36.8[b]	3.47 ± 1.41	1,518 ± 520

[a] Values are mean ± SD for 12 mice in control group and 8 mice in treatment groups measured 4 days after antigen presentation
[b] Significantly different from control group; p≤0.05, Duncan's multiple range test.

The data in Tables 5-8 were analyzed for point of departure (POD) determination using BMDS (Version 2.6, US EPA). Continuous models were run with default parameters and a BMR of one SD from the control mean, which is typically used when there are no data to indicate what level of response is biologically significant (US EPA, 2012). Results of BMD modeling of the data are presented in Table 9.

Table 9. Summary of BMD modeling results for non-carcinogenic effects of trans-1,2-DCE in rodents

Reference	Sex/ species	Endpoint	Model[a]	p-value	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Shopp et al., 1985 (90-day drinking water study)	Male mouse	AFCs per 10^6 cells	Exponential 4	0.936	77.22	**14.5**
NTP, 2002 (14-week feeding study)	Female rat	Relative liver weight	Hill	0.232	201.82	108
	Male mouse		Hill	0.615	1348.69	396

[a] All models were run with default parameters and restricted up or down based on data.

The $BMDL_{1SD}$ of 14.5 mg/kg-day, derived from Exponential Model 4 for changes in humoral immune response observed in the Shopp et al. (1985) study, is chosen as the POD because it is the lowest BMDL. Further details for the BMD analyses are presented in Table A2 and Figure A2 of Appendix I. This endpoint is also supported by the decrease in absolute and relative thymus weight in female mice, with a NOAEL of 23 mg/kg-day, reported in the Barnes et al. (1985) study.

The AFCs per 10^6 cells data from this study were also used by US EPA (2010b) in deriving a chronic oral reference dose (RfD) of 0.02 mg/kg-day. In their BMD modeling, US EPA chose a second degree Polynomial Model with a $BMDL_{1SD}$ of 65.04 mg/kg-day. US EPA did not apply the non-positive restriction for this model, which resulted in a dip and then an upward curvature at the high dose (Figure A3 of Appendix I). OEHHA is concerned with the unusual shape of the curve and that it does not appear to accurately describe the responses at the two high doses. As shown in Table 8, the mean responses leveled off at 175 mg/kg-day and 387 mg/kg-day, though the standard deviations of the responses are relatively large. The AFC data were also modeled with the second degree Polynomial Model using the non-positive restriction and it did not fit the data as well as Exponential Model 4, thus the Polynomial Model is not chosen for POD derivation.

The Barnes et al. (1985) study used for the 2006 PHG is not retained as the critical study because a more sensitive endpoint has been identified. The Barnes et al. (1985) data showed that an increase in liver weight only at the mid dose (175 mg/kg-day), with liver weight returning to values similar to the controls at the high dose (387 mg/kg-day).

Although SAP values were increased at the two highest doses, the values are within normal physiological ranges for that species (Gad, 2016).

The Shopp et al. (1985) study was not chosen as the critical study for the 2006 PHG because the study authors concluded that the "immune system of random-bred CD-1 mouse does not appear to be overly sensitive to the effects of DCE." However, more recent studies by Landics (2007) and Loveless et al. (2007) have noted that the AFC assay is a well-validated and highly predictive test for immunotoxicity. The immunological endpoint of a decrease in the number of AFCs per 10^6 spleen cells from Shopp et al. (1985) showed a clear dose-response relationship and is supported by the decrease in relative thymus weight at the two high doses, with a NOAEL of 23 mg/kg-day. Therefore the Shopp et al. (1985) study replaces the Barnes et al. (1985) study as the critical study for determination of the POD for trans-1,2-DCE.

To calculate the ADD, a total UF of 3,000 is applied; 10 for interspecies extrapolation, 30 for intraspecies variability (10 for toxicokinetics and √10 for toxicodynamics), √10 for extrapolation from subchronic to chronic exposure and √10 for deficiencies in toxicity data for trans-1,2-DCE as described in Appendix III. There are no chronic or reproductive toxicity studies. Therefore, the ADD is:

$$\text{ADD} = \frac{\text{POD}}{\text{UF}} = \frac{14.5 \text{ mg/kg-day}}{3{,}000} = 0.0048 \text{ mg/kg-day}.$$

Due to its volatile nature, exposure to trans-1,2-DCE in drinking water is expected to occur through both inhalation and oral ingestion. Estimation of inhalation and dermal exposures to trans-1,2-DCE during household uses of tap water, such as bathing and showering, are estimated with the CalTOX 4.0 model. Detailed inputs and outputs used in CalTOX modeling are presented in Appendix II. The relative contributions from each route to the overall exposure to trans-1,2-DCE in tap water are presented in Table 11. Tap water exposure equivalencies (Table 12) are calculated for inhalation and dermal exposures using life-stage specific oral ingestion rates (OEHHA, 2012) and the relative contribution of each route.

Table 11. Relative contributions of multiple exposure routes to total trans-1,2-DCE exposure in tap water for individual life stages, determined by CalTOX[a]

Life Stage	Oral Ingestion (%)	Inhalation (%)	Dermal (%)
Fetus[b] (Pregnancy)	53	43	4
Infant	97	0[c]	3
Child	42	54	4
Adult	57	39	4

[a] See Appendix II for exposure parameters used for CalTOX modeling.
[b] The fetus is assumed to have the same exposure as the pregnant mother.
[c] Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios; therefore the inhalation pathway is excluded for infants.

Table 12. Total liter equivalent values for multi-route exposure to trans-1,2-DCE in tap water

Life Stage	Age range (years)	Oral Ingestion (L/kg-day)	Inhalation (L_{eq}/kg-day)[a,b]	Dermal (L_{eq}/kg-day)[a]	Daily Water Intake (DWI, L_{eq}/kg-day)
Fetus (Pregnancy)	N/A	0.047	0.019	0.0035	0.070
Infant	0-2	0.196	0	0.0061	0.202
Child	2-16	0.061	0.039	0.0058	0.106
Adult	16-70	0.045	0.015	0.0032	0.063
Time-weighted average over lifetime[c]					**0.076**

[a] Inhalation and dermal estimates were calculated using life-stage specific oral ingestion rates and relative contribution of the oral ingestion values
[b] L_{eq} for inhalation assumes 50% absorption in the lung (OEHHA, 2006)
[c] Multiroute lifetime tap water exposure = (0.75 × 0.070 + 2 × 0.202 + 14 × 0.106 + 54 × 0.063)/70 = 0.076 L_{eq}/kg-day

An RSC of 0.80 is applied because drinking water sources are anticipated to be the primary source contributor for exposures. According to the US EPA's TRI data[6] California has had few releases of trans-1,2-DCE and it is not heavily used in California, therefore exposure to residues on food and through inhalation from ambient air are expected to be minimal.

The public health-protective concentration, C, is:

$$C = \frac{0.0048 \text{ mg/kg-day} \times 0.80}{0.076 \ L_{eq}/\text{kg-day}} = 0.050 \text{ mg/L} = 50 \text{ µg/L or } 50 \text{ ppb}$$

OEHHA therefore proposes an updated PHG of 50 ppb for trans-1,2-DCE based on dose-related decreases in humoral immune response as measured by decreased AFCs per 10^6 spleen cells in male mice from a 90-day drinking water study conducted by Shopp et al. (1985).

RISK CHARACTERIZATION

Cis-1,2-dichloroethylene

The PHG of 13 ppb is calculated based on the adverse non-carcinogenic effect of cis-1,2-DCE on the kidney. Although cis-1,2-DCE has been found at levels as high as 22 ppb in California public water systems, it is likely a product of the incomplete anaerobic degradation of more highly chlorinated chemicals such as TCE and PCE (Mattes, 2010) since cis-1,2-DCE is not commercially available in the United States (US EPA, 2010b).

[6] http://iaspub.epa.gov/triexplorer/tri_release.chemical

No chronic, developmental, or reproductive toxicity studies have been identified for cis-1,2-DCE, which are significant data gaps in the literature. Thus, a database UF of √10 was added to account for this. Studies on genotoxicity and mutagenicity are generally not positive and there are no data on carcinogenicity in any species, including humans. Thus, the carcinogenic potential of cis-1,2-DCE cannot be evaluated due to lack of information at this time. No new toxicity studies have been identified for cis-1,2-DCE since the publication of its PHG in 2006. This PHG incorporates updated risk assessment methodology, including the use of a more sophisticated estimation of a POD through BMD modeling, updated age-specific drinking water intake rates, modeling to estimate dermal and inhalation exposures and an updated intraspecies variability factor.

Trans-1,2-dichloroethylene

The PHG of 50 ppb for trans-1,2-DCE is calculated based on adverse effects on the immune system. Trans-1,2-DCE has been found at very low levels in California public water systems (4.8 ppb). No chronic toxicity studies exist and one limited study has been conducted on the developmental toxicity of trans-1,2-DCE. A 1993 inhalation study conducted by Hurtt et al. showed marginal maternal toxicity evidenced as a decrease in food consumption starting at 2,000 ppm trans-1,2-DCE in air for 6 hours per day during days 7-16 of gestation. Fetal toxicity noted as a decrease in fetal weight was observed at 12,000 ppm. The concentrations of trans-1,2-DCE used on a mg/kg-day basis in the Hurtt et al. study were more than 85 times the concentration identified as the POD from the Shopp et al. (1985) study. A database UF of √10 was used in the derivation of the ADD to account for the lack of chronic and reproductive and developmental toxicity studies. Similar to cis-1,2-DCE, studies on genotoxicity and mutagenicity are generally not positive and there are no data on the carcinogenicity of trans-1,2-DCE in any species, including humans. Thus, the carcinogenic potential of trans-1,2-DCE cannot be evaluated due to lack of information at this time (US EPA, 2010b).

No new toxicity studies for trans-1,2-DCE have been found since the PHG publication in 2006. Reevaluation of previously published studies and acknowledgment of immunotoxicity as a critical endpoint resulted in changing the critical study for risk characterization. In addition, the current risk assessment methodology used in this PHG incorporates the use of a more sophisticated estimation of a POD through BMD modeling, updated age-specific drinking water intake rates, modeling to estimate dermal and inhalation exposures and an updated intraspecies variability factor.

OTHER STANDARDS AND CRITERIA

Cis-1,2-dichloroethylene

US EPA's MCL and Maximum Contaminant Level Goal (MCLG) for cis-1,2-DCE are both 70 ppb. The current California MCL is 6 ppb.

In their 2010 review of cis-1,2-DCE, US EPA calculated a chronic oral RfD of 0.002 mg/kg-day, derived from a $BMDL_{10}$ of 5.1 mg/kg-day based on effects in the kidney found in the McCauley et al. (1995) study and applying an uncertainty factor of 3,000 (10 for intraspecies variability, 10 for interspecies extrapolation, 10 for extrapolation from a subchronic exposure and 3 for database deficiencies) (US EPA, 2010b).

Trans-1,2-dichloroethylene

US EPA's MCL and MCLG for trans-1,2-DCE are both 100 ppb. The current California MCL is 10 ppb.

In their review of trans-1,2-DCE, US EPA calculated a chronic oral RfD of 0.02 mg/kg-day, derived from a $BMDL_{1SD}$ of 65 mg/kg-day based on adverse effects on the immune system found in the Shopp et al. (1985) study and applying an uncertainty factor of 3,000 (10 for intraspecies variability, 10 for interspecies extrapolation, 10 for extrapolation from a subchronic exposure and 3 for database deficiencies) (U.S. EPA, 2010b).

In June 2015, US EPA updated its Human Health Ambient Water Quality Criteria for trans-1,2-DCE based on the 2010 RfD to 100 ppb (U.S. EPA, 2015).

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APPENDIX I. BMD Modeling

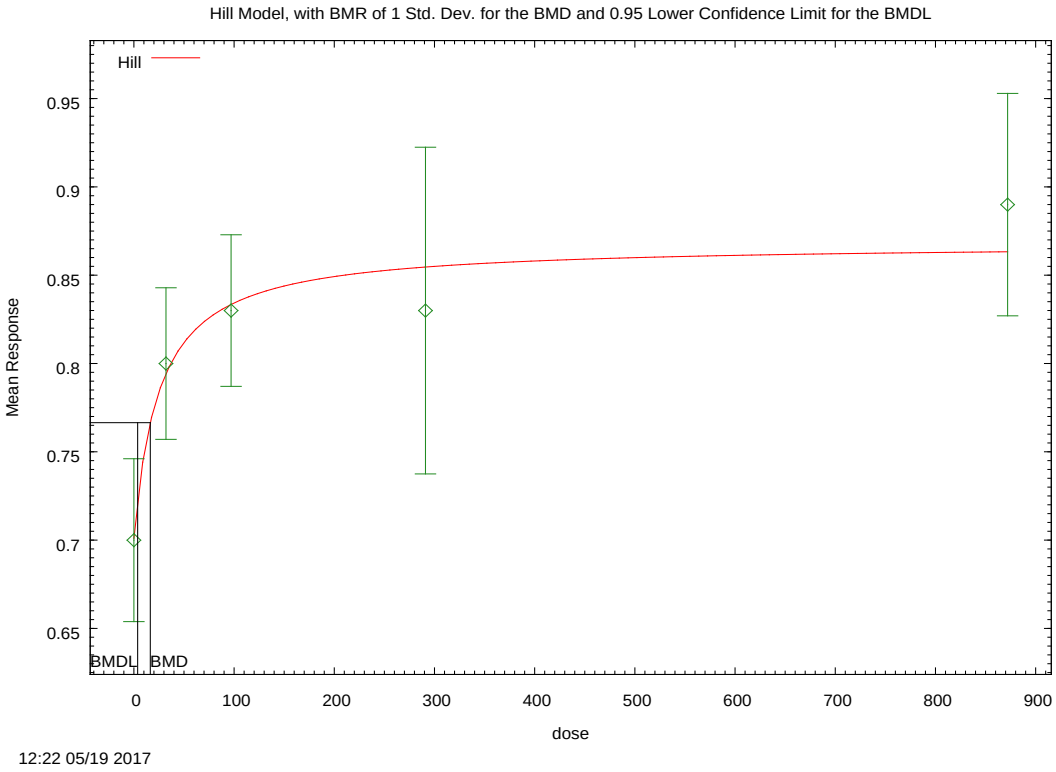
This appendix provides the BMD modeling outputs for cis-1,2-dichloroethylene and trans-1,2-dichloroethylene where data were amenable to dose-response modeling. All models were run with default parameters and a benchmark response of 1 standard deviation from the control mean. Model selection criteria when comparing outputs of different models for the same endpoint/dataset were: the lowest Akaike's information criterion (AIC), goodness of fit p-value ≥0.05, scaled residual ≤ the absolute value of 2, and visual inspection of the dose-response curve. When using BMD modeling, the BMDL, which is the lower limit of the 95 percent confidence interval of the BMD resulting in the benchmark response, is selected as the POD. The model selected to derive the POD is presented here.

Table A1. Benchmark dose modeling results for relative kidney weight data in male rats exposed to cis-1,2-DCE by gavage for 90 days (McCauley et al., 1995)

Model Name	AIC	p-value[a]	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$[b] (mg/kg-day)	Scaled Residual[c]
Exponential2	-167.83	0.00167	532.94	370.56	0.52
Exponential3	-167.83	0.00167	532.94	370.56	0.52
Exponential4	-177.66	0.18700	19.38	6.98	0.26
Exponential5	-177.66	0.18700	19.38	6.98	0.26
Hill	**-178.87**	**0.34230**	**16.35**	**3.76**	**0.28**
Linear	-168.07	0.00187	505.96	341.97	0.46
Polynomial2	-168.07	0.00187	505.96	341.97	0.46
Polynomial3	-168.07	0.00187	505.96	341.97	0.46
Power	-168.07	0.00187	505.96	341.97	0.46

[a] p-values ≥0.05 indicate the model adequately fits the data.
[b] The BMDL is the lower limit of the 95% confidence interval of the BMD resulting in the benchmark response.
[c] Scaled residual for the dose group near the BMD; this provides a measurement of how close the modeled response is to the actual data point. A scaled residual greater than the absolute value of 2.0 indicates poor fit to the data point.

Figure A1. Hill model output for cis-1,2-DCE; increased relative kidney weight in male rats from McCauley et al. (1995)




```
=================================================================
        Hill Model. (Version: 2.17;  Date: 01/28/2013)
        Input Data File: K:/BMDS
analysis/hil_12DCE_McCauley1995_m_90d_kidney%_Opt.(d)
        Gnuplot Plotting File:  K:/BMDS
analysis/hil_12DCE_McCauley1995_m_90d_kidney%_Opt.plt
                                          Fri May 19 13:05:59 2017
 =================================================================

 BMDS Model Run
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 5
```

Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

alpha =	0.00463784	
rho =	0	Specified
intercept =	0.7	
v =	0.19	
n =	0.362485	
k =	33.6	

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	alpha	intercept	v	k
alpha	1	6e-007	2.5e-007	1.4e-007
intercept	6e-007	1	-0.66	0.38
v	2.5e-007	-0.66	1	0.29
k	1.4e-007	0.38	0.29	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
alpha	0.00429971	0.000938273	0.00246073	0.00613869
intercept	0.700967	0.0220441	0.657761	0.744173
v	0.167151	0.0301254	0.108106	0.226195
n	1	NA		
k	25.3284	18.2121	-10.3668	61.0235

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	9	0.7	0.701	0.06	0.0656	-0.0442
32	10	0.8	0.794	0.06	0.0656	0.276
97	10	0.83	0.834	0.06	0.0656	-0.169
291	7	0.83	0.855	0.1	0.0656	-0.998
872	6	0.89	0.863	0.06	0.0656	0.994

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	94.505433	6	-177.010866
A2	96.257592	10	-172.515183
A3	94.505433	6	-177.010866
fitted	93.433354	4	-178.866707
R	81.095902	2	-158.191804

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	30.3234	8	0.0001853
Test 2	3.50432	4	0.4772
Test 3	3.50432	4	0.4772
Test 4	2.14416	2	0.3423

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels

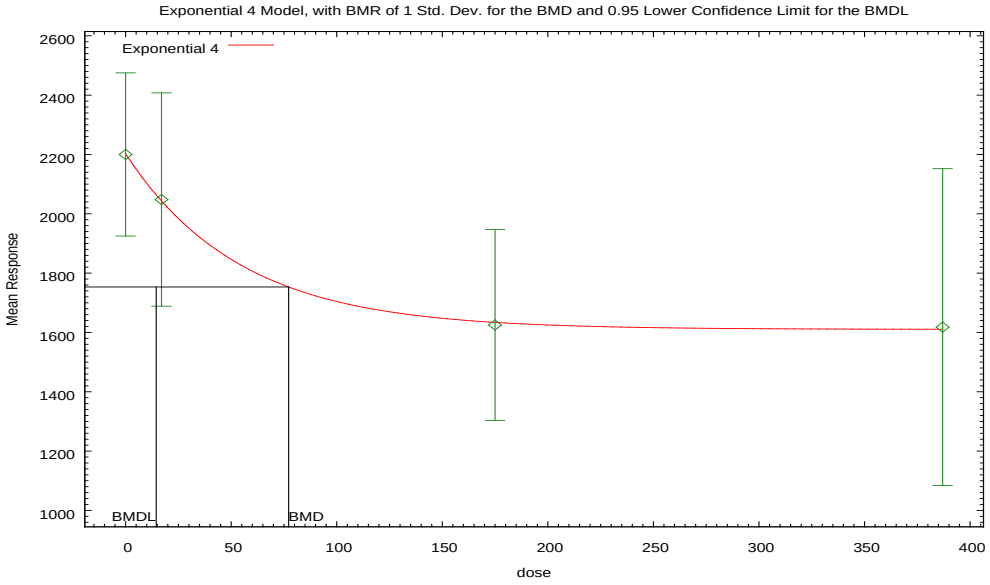
```
It seems appropriate to model the data

The p-value for Test 2 is greater than .1.  A homogeneous variance
model appears to be appropriate here


The p-value for Test 3 is greater than .1.  The modeled variance appears
 to be appropriate here

The p-value for Test 4 is greater than .1.  The model chosen seems
to adequately describe the data


        Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD =        16.3503

            BMDL =       3.75749
```

Table A2. Benchmark dose modeling results for decreased humoral immune response (AFCs per 10^6 spleen cells) in male mice exposed to trans-1,2-DCE in drinking water for 90 days (Shopp et al., 1985)

Model Name	AIC	p-value[a]	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$[b] (mg/kg-day)	Scaled Residual[c]
Exponential2	484.00	0.3137	284.06	164.57	0.6255
Exponential3	484.00	0.3137	284.06	164.57	0.6255
Exponential4	**483.69**	**0.9360**	**77.22**	**14.50**	**-0.01638**
Linear	434.38	0.2596	309.21	195.02	0.721
Polynomial2	434.38	0.2596	309.24	195.02	0.721
Polynomial3	434.38	0.2596	309.19	195.02	0.721
Power	434.38	0.2596	309.21	195.02	0.721

[a] p-values ≥ 0.05 indicate the model adequately fits the data.
[b] The BMDL is the lower limit of the 95% confidence interval of the BMD resulting in the benchmark response.
[c] Scaled residual for the dose group near the BMD; this provides a measurement of how close the modeled response is to the actual data point. A scaled residual greater than the absolute value of 2.0 indicates poor fit to the data point.

Figure A2. Exponential Model 4 output for trans-1,2-DCE; decreased humoral immune response in male mice (AFCs per 10^6 spleen cells) from Shopp et al. (1985)




```
================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File: C:/BMDS260/Data/1-Shopp-AFC-ExpCV-1SD-4d.(d)
        Gnuplot Plotting File:
                                              Tue Oct 20 15:46:58 2015
================================================================

 BMDS Model Run
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   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = MeanResponse
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
   A constant variance model is fit.
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

Variable	Model 4	
lnalpha	12.2133	
rho	0	Specified
a	2310	
b	0.0071112	
c	0.667079	
d	1	Specified

Parameter Estimates

Variable	Model 4	Std. Err.
lnalpha	12.2135	47491.8
a	2202.12	125.226
b	0.018397	0.0233506
c	0.731228	0.0677852

Table of Stats From Input Data

Dose	N	Obs Mean	Obs Std Dev
0	12	2200	433
17	8	2048	429.9
175	8	1625	384.7
387	8	1618	639.2

Estimated Values of Interest

Dose	Est Mean	Est Std	Scaled Residual
0	2202	448.9	-0.01638
17	2043	448.9	0.03045
175	1634	448.9	-0.05618
387	1611	448.9	0.04579

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)

```
            Var{e(ij)} = Sigma(i)^2

  Model A3:        Yij = Mu(i) + e(ij)
            Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

  Model  R:        Yij = Mu + e(i)
            Var{e(ij)} = Sigma^2
```

Likelihoods of Interest

Model	Log(likelihood)	DF	AIC
A1	-237.8397	5	485.6794
A2	-236.5346	8	489.0692
A3	-237.8397	5	485.6794
R	-243.1589	2	490.3178
4	-237.8429	4	483.6859

Additive constant for all log-likelihoods = -33.08. This constant added to the above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)

Test 6a: Does Model 4 fit the data? (A3 vs 4)

Tests of Interest

Test	-2*log(Likelihood Ratio)	D. F.	p-value
Test 1	13.25	6	0.03925
Test 2	2.61	3	0.4557
Test 3	2.61	3	0.4557
Test 6a	0.006449	1	0.936

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

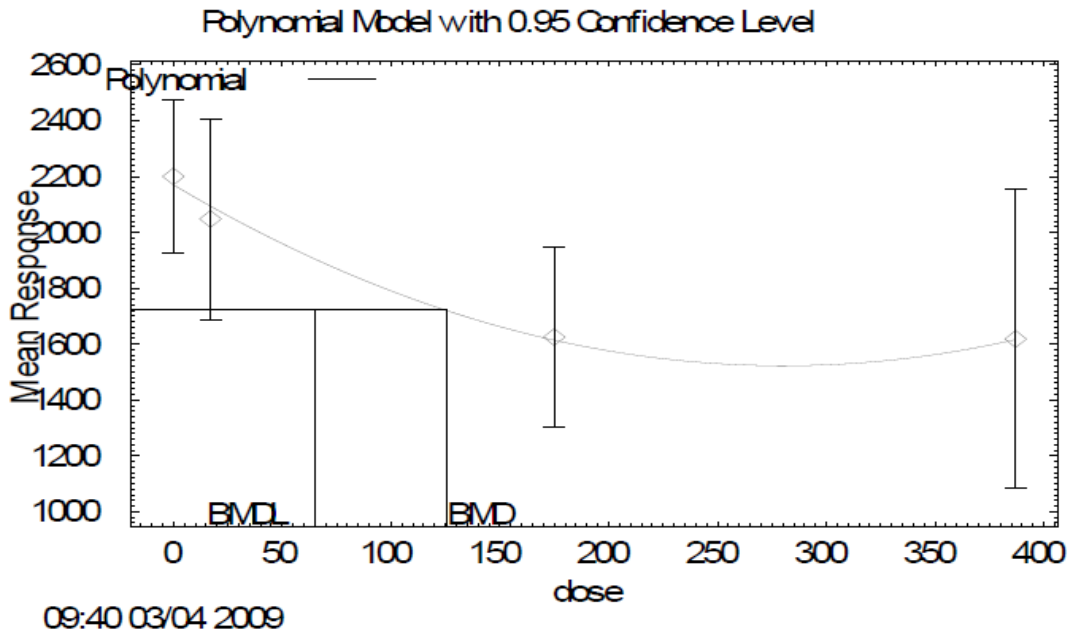
The p-value for Test 6a is greater than .1. Model 4 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

```
        Risk Type = Estimated standard deviations from control
Confidence Level = 0.950000
              BMD =      77.2136
             BMDL =      14.4979
```

Figure A3. Unrestricted second degree Polynomial Model output for decreased humoral immune response in male mice (AFCs per 10^6 spleen cells) exposed to trans-1,2-DCE in drinking water for 90 days (Shopp et al., 1985); figure is from US EPA (2010b)



APPENDIX II. CalTOX Modeling

This appendix describes the multi-route exposure assessment of cis- and trans-1,2-dichloroethylene in drinking water using CalTOX modeling. CalTOX 4.0 is a multimedia, multiple pathway exposure model developed for the California Department of Toxic Substances Control by Lawrence Berkeley National Laboratory (available at https://eaei.lbl.gov/tool/caltox). In addition to oral ingestion, exposure to chemical contaminants in tap water can occur via inhalation or dermal contact while performing common household activities, such as bathing, showering, or flushing toilets. OEHHA applies the CalTOX model to assess these exposures and calculate the relative contribution of each exposure pathway to the total daily exposure to this tap water contaminant.

Exposure pathways included in CalTOX modeling:

- All inhalation exposures indoor active
- All inhalation exposures indoor resting
- Inhalation exposure in shower/bath
- Use of contaminated water as tap water
- Ingestion of tap water
- Dermal exposure during shower/bath

Table A3 provides OEHHA-derived human exposure parameters for various life stages that are applied during CalTOX exposure modeling of contaminants in drinking water (OEHHA, 2012).

Table A3. OEHHA-derived 95th percentile exposure parameters for various life stages used for CalTOX modeling

Life Stage	Age Range (years)	Drinking Rate (L/kg-day)	Inhalation rate (m^3/kg-hr)	Body Surface Area (m^2/kg)	Reference
Fetus (Pregnancy)	N/A[a]	0.047	0.015	0.029[b]	OEHHA (2012)
Infant	0-2	0.196	0[c]	0.059	
Child	2-16	0.061	0.031	0.045	
Adult	16-70	0.045	0.012	0.029	

[a] Not applicable

[b] The adult body surface area parameter is used for pregnant women in the 3rd trimester. Fetuses in the 3rd trimester are assumed to be exposed to the same dose as the pregnant mothers.

[c] Infants are expected to be exposed to negligible levels of chemicals in tap water via inhalation (compared to other pathways) because they typically do not shower or flush toilets. These are the dominant inhalation exposure scenarios; therefore the inhalation pathway is excluded for infants.

CalTOX estimates the relative contributions of oral ingestion, inhalation, and dermal exposure to total exposure to contaminants in water based on the input parameters in Table A3 and the exposure pathways selected for inclusion. Liter equivalents for inhalation and dermal exposure are calculated for each life stage using the age-specific drinking water ingestion rate and relative contribution of the oral ingestion value. Examples of CalTOX outputs are presented below. For the sake of brevity, only the results using adult exposure parameters are included here.

Table A4. Cis-1,2-dichloroethylene CalTOX output, adult exposure scenario

PATHWAYS	**Air (gases & particles)**	**Surface soil**	**Root-zone soil**	**Ground water**	**Surface water**	**Totals**	**%**
INHALATION	3.45E-263	0.00E+00	0.00E+00	7.64E-01	0.00E+00	7.64E-01	**39.18**
INGESTION:							
Water				1.14E+00	0.00E+00	4.37E+00	56.16
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	1.14 E+00	0.00 E+00	1.14 E+00	**58.36**
DERMAL UPTAKE		0.00E+00	0.00E+00	4.79E-02	0.00E+00	4.79E-02	**2.46**
Dose SUM	3.45E-263	0.00E+00	0.00E+00	1.95E+00	0.00E+00	1.95E+00	**100.0**

Table A5. Trans-1,2-dichloroethylene CalTOX output, adult exposure scenario

PATHWAYS	**Air (gases & particles)**	**Surface soil**	**Root-zone soil**	**Ground water**	**Surface water**	**Totals**	**%**
INHALATION	3.31E-263	0.00E+00	0.00E+00	7.67E-01	0.00E+00	7.67E-01	**38.50**
INGESTION:							
Water				1.14E+00	0.00E+00	1.14E+00	56.16
Exposed produce	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Unexposed produce			0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Meat	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Milk	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Eggs	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00E+00	0.00
Fish					0.00E+00	0.00E+00	0.00
Soil		0.00E+00	0.00E+00			0.00E+00	0.00
Total ingestion	0.00 E+00	0.00 E+00	0.00 E+00	1.14 E+00	0.00 E+00	1.14 E+00	**57.11**
DERMAL UPTAKE		0.00E+00	0.00E+00	8.74E-02	0.00E+00	8.74E-02	**4.39**
Dose SUM	3.31E-263	0.00E+00	0.00E+00	1.99E+00	0.00E+00	1.99E+00	**100.0**

APPENDIX III. Default Uncertainty Factors for PHG Derivation

This appendix describes the default uncertainty factors OEHHA generally uses to calculate the Acceptable Daily Dose when deriving PHGs. When scientific evidence is compelling these defaults are supplanted by alternative factors or modeled results. Table A6 below is adapted from OEHHA's "Technical Support Document for the Development of Noncancer Reference Exposure Levels" (OEHHA, 2008).

Table A6. **Default uncertainty factors for PHG derivation, adapted from OEHHA (2008)**

LOAEL uncertainty factor (UF_L)		
Values used:	10	LOAEL, any effect
	1	NOAEL or BMD modeling used
Interspecies uncertainty factor (UF_A)		
Combined interspecies uncertainty factor (UF_A):	1	human observation
	√10	animal observation in nonhuman primates
	10	where no data are available on toxicokinetic or toxicodynamic differences between humans and a non-primate test species
Toxicokinetic component (UF_{A-k}) of UF_A:	1	where animal and human PBPK models are used to describe interspecies differences
	√10	non-primate studies with no chemical- or species-specific kinetic data
Toxicodynamic component (UF_{A-d}) of UF_A:	1	where animal and human mechanistic data fully describe interspecies differences (*This is unlikely to be the case.)*
	2	for residual susceptibility differences where there are some toxicodynamic data
	√10	non-primate studies with no data on toxicodynamic interspecies differences

Intraspecies uncertainty factor (UF_H)	
Toxicokinetic component (UF_{H-k}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children), or where a PBPK model is used and accounts for measured inter-individual variability √10 for residual susceptibility differences where there are some toxicokinetic data (e.g., PBPK models for adults only) 10 to allow for diversity, including infants and children, with no human kinetic data
Toxicodynamic component (UF_{H-d}) of UF_H:	1 human study including sensitive subpopulations (e.g., infants and children) √10 studies including human studies with normal adult subjects only, but no reason to suspect additional susceptibility of children 10 suspect additional susceptibility of children (e.g., exacerbation of asthma, neurotoxicity)
Subchronic uncertainty factor (UF_S)[1]	
Values used:	1 study duration >12% of estimated lifetime √10 study duration 8-12% of estimated lifetime 10 study duration <8% of estimated lifetime
Database deficiency factor (UF_D)	
Values used:	1 no substantial data gaps √10 substantial data gaps including, but not limited to, developmental toxicity

[1]Exposure durations of 13 weeks or less are subchronic regardless of species (OEHHA, 2008)