Noncancer Reference Exposure Levels for

1,4-Dichlorobenzene

OEHHA Air Toxics Hot Spots Program

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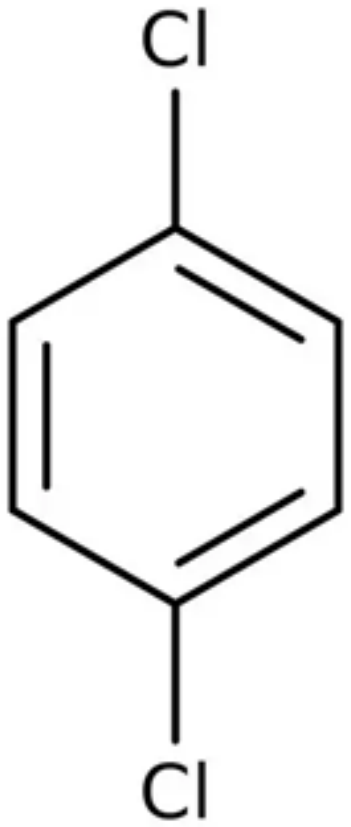
1,4-Dichlorobenzene (1,4-DCB)
Physical-Chemical Properties



- Also referred to as para-dichlorobenzene
- White crystalline solid that sublimes at ambient temperature
- Melting point: 52.7°C (127°F)
- Vapor pressure: 1.74 mm Hg (torr) @ 25°C
- Soluble in organic solvents
- Practically insoluble in water: 81 mg/L @ 25°C

Uses and Listings

- Uses include:
  - Active ingredient in mothballs and other pesticide products
  - Component in manufacture of polyphenylene sulfide thermoplastics
  - Minor uses as oil/fuel additive and in construction products
  - Banned in California for air freshener uses
- Listed as a carcinogen under California Proposition 65 and Hot Spots programs
- Updated chronic Reference Exposure Level (REL) will supersede current chronic REL of 800 $\mu g/m^3$ (133 ppb)

Airborne Concentrations

- In 1987 California study, detectable in 59% of the initial breath samples and 77% of the personal air samples (mainly due to indoor exposure)
- Current data on 1,4-DCB air concentrations in urban areas limited:
  - California urban ambient air monitoring up to 2007
    - Maximums of 0.4 to 3.1 parts per billion (ppb)
    - Below detection limit in most air monitoring measurements

Toxicokinetics

- Peak tissue levels were highest in fat but declined quickly to low levels in 24 hours following inhalation exposure in rats
- Oxidized mainly by CYP450 to epoxide, followed by further oxidation to 2,5-dichlorophenol (2,5-DCP)
    - CYP2E1 main isozyme involved in the metabolism of 1,4-DCB by humans
- 2,5-DCP primarily eliminated in urine as a GSH conjugate
- 5%–16% of absorbed 1,4-DCB eliminated via urine as 2,5-DCP in 9-11 hours suggests the half-life is greater than 10 hours in humans

Biomonitoring

National Health and Nutrition Examination Survey (NHANES)

- Since 1980s, NHANES collected urine samples from children and adults to assess chemical exposure, including 2,5-DCP (as a biomarker for 1,4-DCB)
- Surveys suggest wide-spread non-occupational exposure to 1,4-DCB
- Levels of urinary 2,5-DCP declining over time in both adults and children

Survey Years	Age (years)	Sample number	Geometric mean (µg/g Cr)	50th percentile (µg/g Cr)	95th percentile (µg/g Cr)
1988-1994	20-59	892	No data	24	670
2003-2004	All ages	2522	12.5	9.29	578
2015-2016	All ages	2650	3.02	2.03	133

Acute Effects of 1,4-DCB

- In humans: early occupational health surveys by Hollingsworth et al. (1956) suggest ≥ 50-80 ppm - irritation of nose and eyes
- In animals: acute effects observed during first day or days of 6-8-hour exposures
  - Tremors, weakness, eye irritation @ 798 ppm in rats, guinea pig and rabbits with 8-hour exposure(s) (Hollingsworth et al., 1956)
  - Tremors and signs of sensory irritation @ 571 ppm in rats with 6-hour exposure(s) (Tyl and Neeper-Bradley, 1989)
  - Microscopic damage to liver and kidney cells @ 125 or 500 ppm with 24-hour exposure (Umemura et al., 1989, 1990)

Chronic/Subchronic Effects in Humans
Cases of Substance Addiction

- Numerous case reports and reviews for substance addiction to 1,4-DCB lasting months or years
  - Main finding - nonspecific damage to white matter of the brain leading to functional neurological decline (leukoencephalopathy)
  - Symptoms include limb weakness, tremor, bradyphrenia, cognitive decline
- Dermatitis also a common finding
- Exposure confirmed by presence of 1,4-DCB in blood or 2,5-DCP in urine

Chronic/Subchronic Effects in Humans Occupational Exposure

- Worker exposures of 8 months to 25 years (Hollingsworth et al., 1956)
  - Spot air samples ranged from 5 to 725 ppm
  - Normal blood tests and urinalysis (no indication of liver or kidney injury), no eye damage
- Insect repellent factory worker mean exposure duration of 11.8 years, but no air sampling (Hsiao et al., 2009)
  - Increased white blood cell count and alanine aminotransferase (ALT) were observed
  - These correlated with urinary 2,5-DCP levels

Chronic/Subchronic Effects in Humans
Population Survey Studies in Adults

- Many studies examined associations between urinary 2,5-DCP and diseases using NHANES data
  - Limitations: Associations based on single urinary sample, multiple exposures
  - Associations with increased 2,5-DCP levels:
    - Decreased lung function
    - Increased prevalence of obesity, diabetes and metabolic syndrome
    - Higher prevalence of cancer and risk of cardiovascular disease
    - Decreased kidney function and increased vitamin D deficiency

Chronic/Subchronic Effects in Humans
Population Survey Studies in Children

- Associations with increased 2,5-DCP levels in children have been found for:
  - Increased prevalence of obesity and hypothyroidism
  - Earlier age of menarche in adolescent girls

- Associations of increased 2,5-DCP levels in pregnant women have been found for:
  - Decreased birth weight in male infants
  - Increase prevalence for asthma, and rashes, eczema, or hives in boys

Chronic Effects in Animal Studies

- Two-year study in rats and mice: 0, 20, 75 and 300 ppm, 6 hours/day, 5 days/week (Aiso et al., 2005)
- Main treatment-related non-cancer findings:
  - **Liver**: Hepatocellular hypertrophy but without hepatocellular injury (male rats and male mice)
  - **Kidney**: Papilla mineralization and pelvic urothelial hyperplasia (male rats)
  - **Nasal epithelium**: Eosinophilic globules in nasal olfactory epithelium and in respiratory epithelium (female rats); respiratory metaplasia (female mice)
  - **Testis**: Mineralization (male mice)

Chronic Effects in Animal Studies

Noncancer pathology findings in 2-year inhalation study (Aiso et al. 2005)

Endpoint	Sex Species	0 ppm	20 ppm	75 ppm	300 ppm
Kidney: papilla mineralization	Male Rat	0/50†	1/50	0/50	41/50**
Kidney: pelvic urothelial hyperplasia	Male Rat	7/50†	8/50	13/50	32/50**
Liver: hepatocellular hypertrophy	Male Rat	0/50†	0/50	0/50	5/50*

† $p \leq 0.05$ - positive trend; * - $p \leq 0.05$ and ** - $p \leq 0.01$, compared to control

Chronic Effects in Animal Studies

Noncancer pathology findings in 2-year inhalation study (Aiso et al. 2005)

Endpoint	Sex Species	0 ppm	20 ppm	75 ppm	300 ppm
Nasal epithelium: olfactory eosinophilic globules (moderate and marked combined)	Female Rat	27/50†	29/50	39/50*	47/50**
Nasal epithelium: respiratory eosinophilic globules (slight)	Female Rat	11/50†	10/50	14/50	38/50**
Nasal epithelium: respiratory metaplasia: nasal gland (slight)	Female Rat	5/50†	4/50	4/50	33/50**

† $p \leq 0.05$ - positive trend; * - $p \leq 0.05$ and ** - $p \leq 0.01$, compared to control

Chronic Effects in Animal Studies

Noncancer pathology findings in 2-year inhalation study (Aiso et al. 2005)

Endpoint	Sex Species	0 ppm	20 ppm	75 ppm	300 ppm
Liver: hepatocellular hypertrophy	Male Mice	0/49†	0/49	0/50	34/49**
Testis: mineralization	Male Mice	27/49†	35/49	42/50**	41/49**
Nasal olfactory epithelium: metaplasia	Female Mice	7/50†	6/50	2/49	20/50**

† $p \leq 0.05$ - positive trend; ** - $p \leq 0.01$, compared to control

Developmental and Reproductive Studies in Animals

Developmental study in New Zealand white rabbits – 0, 100, 300 and 800 ppm
6 hours/day on gestational days 6-18 (Hayes et al., 1985)

- Treatment-related increase in retroesophageal right subclavian artery in 800 ppm fetuses

Endpoint	0 ppm	100 ppm	300 ppm	800 ppm
Total no. of fetuses with retroesophageal right subclavian artery (total litters)	1 (1)	0 (0)	1 (1)	6* (5)*

* Significantly different from control ($p < 0.05$)

Developmental and Reproductive Studies in Animals
Two-Generation Study

Two-generation study in rats 0, 66, 211 and 538 ppm 6 hours/day, 7 days/week (Tyl and Neeper-Bradley, 1989)

- Main treatment-related findings in F_1 and F_2 offspring in 538 ppm group:
  - Decreased F_1 and F_2 pup litter size
  - Decreased F_1 and F_2 pup body weight and weight gain
  - Increased stillborn pups (F_2) and pup deaths on PND 1–4 (F_1 and F_2)

Acute REL Derivation

- Developmental effects considered for acute REL derivation
- Exposure for just 1 hour during a critical period in development could result in developmental effects
  - Increased incidence of retroesophageal right subclavian artery in fetal rabbits (Hayes et al., 1985)
  - Decreased rat pup viability and body weights in a two-generation exposure study (Tyl and Neeper-Bradley, 1989)

Acute REL Derivation
Benchmark Concentration Methodology

- Benchmark concentration (BMC) analysis (US EPA, version 3.3.2) was performed on all adverse developmental endpoints
- The benchmark response (BMR) of 5% extra risk was used to derive the BMC for dichotomous data (pup viability).
- Continuous models with a BMR of 1 Standard Deviation (SD) of the control mean used to estimate the BMC for pup body weights.
- The BMCL (5% or 1SD) represents the 95% lower confidence limit of the BMC.

Acute REL Derivation

Summary of BMC results for decreased body weight and viability in F_1 and F_2 rat pups from the two-generation study by Tyl and Neeper-Bradley (1989)

Endpoint	Model	BMC (ppm)	BMCL (ppm)	*p*-value
F_1 pup decreased body weight (PND 0)	Polynomial deg3	547	431	0.12
F_2 pup decreased body weight (PND 0)	Polynomial deg2	452	345	0.82
F_2 Stillborn pups (PND 0)	Nested	546	476	0.21
F_2 Stillborn + dead pups (PND 0–4)	**Nested**	**464**	**288**	**0.11**

Acute REL Derivation

- Benchmark Dose Response of 5% = 464 ppm (BMC)
- 95% lower confidence limit ($BMCL_{05}$) = 288 ppm
  - 288 ppm is the Point of Departure (POD) for pup viability (and for REL derivation)
  - No time adjustment for exposure during gestation
  - Human Equivalent Concentration (HEC): RGDR* = 1 for systemic effects

    * RGDR – regional gas dose ratio

Acute REL Derivation

- Cumulative Uncertainty Factor (UF) = 200
  - Interspecies toxicokinetic UF = 2 (for toxicokinetic differences not addressed by RGDR)
  - Interspecies toxicodynamic UF = $\sqrt{10}$ (for lack of toxicodynamic data)
  - Intraspecies toxicokinetic ($UF_{H\text{-}k}$) = 10 (for interindividual variability in toxicokinetics, including in infants, and children)
  - Intraspecies toxicodynamic ($UF_{H\text{-}d}$) = $\sqrt{10}$ (for interindividual variability in toxicodynamics, with no reason to suspect additional susceptibility of children)
- Acute REL = 288 ppm / 200

= 1.5 ppm (8.7 mg/m^3 or 8,700 µg/m^3)

Chronic REL Derivation

- Two-year rodent 1,4-DCB exposure study by Aiso et al. (2005) used as the key study for the chronic and 8-hour RELs
- Primary organs affected in rats and mice included:
  - upper respiratory system
  - kidney
  - male reproductive system
- BMC modeling was used for treatment-related lesions
- The $BMCL_{05}$ used as the Point of Departure (POD) for REL derivation

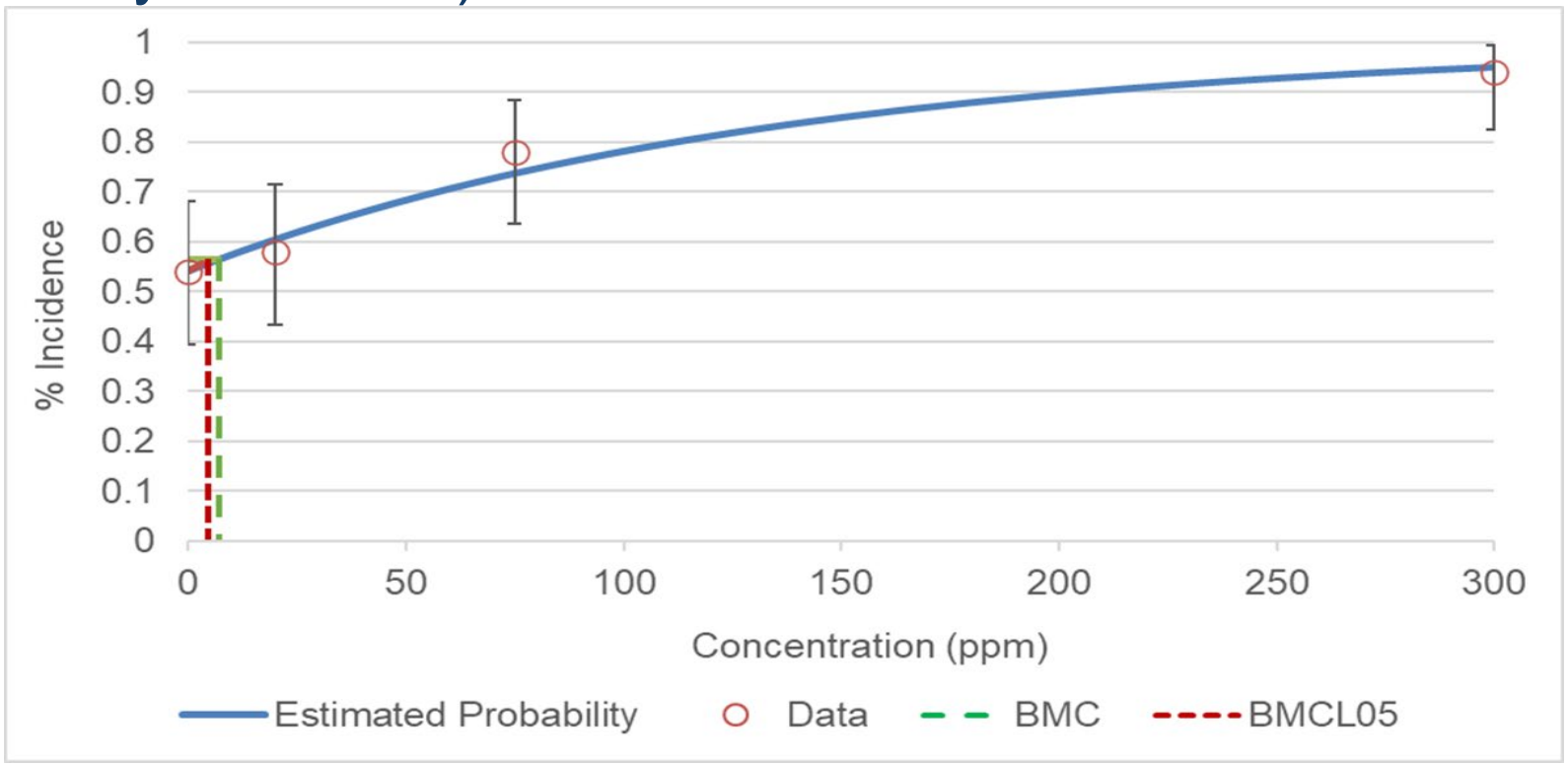
Chronic REL Derivation

- Most sensitive endpoints were nasal lesions in female rats and testis mineralization in male mice

Endpoint	BMC (ppm)	$BMCL_{05}$ (ppm)
Mineralization of testis (Male mice)	**5.67**	**2.29**
Nasal olfactory epithelium degeneration (Female rats)	**6.89**	**4.65**
Nasal respiratory epithelium degeneration (Female rats)	28.79	23.19
Kidney pelvic urothelial hyperplasia (Male rats)	36.10	29.36
Nasal gland respiratory metaplasia (Female rats)	111.95	44.35
Nasal olfactory epithelium metaplasia (Female mice)	151.40	74.77
Kidney papilla mineralization (Male rats)	246.91	91.80

Chronic REL Derivation

- BMC model fit to incidence data for nasal olfactory epithelial lesions (moderate or marked severity combined) in female rats



Chronic REL Derivation

- Benchmark Dose Response of 5% = 6.89 ppm (BMC)
- 95% lower confidence limit ($BMCL_{05}$) = 4.65 ppm
- POD = 4.65 ppm for nasal olfactory degeneration
    - Time adjustment:

      4.65 ppm × 6 hrs/24 hrs × 5 days/7 days = 0.83 ppm
    - HEC: 0.83 ppm × 0.2 (RGDR) = **0.166 ppm**

Chronic REL Derivation

- Cumulative UF = 200
  - Interspecies toxicokinetic UF = 2 (for toxicokinetic differences not addressed by RGDR)
  - Interspecies toxicodynamic UF = √10 (for lack of toxicodynamic data)
  - Intraspecies toxicokinetic ($UF_{H\text{-}k}$) = 10 (for interindividual variability in toxicokinetics, including in infants, and children)
  - Intraspecies toxicodynamic ($UF_{H\text{-}d}$) = √10 (for interindividual variability in toxicodynamics, with no reason to suspect additional susceptibility of children)
- Chronic REL = 0.166 ppm / 200

= 0.0008 ppm (0.8 ppb, 5.0 µg/m^3)

8-Hour REL Derivation

- Based on same exposure endpoint as chronic REL
- Same POD of 4.65 ppm
- Time adjustment includes:

  20 m^3 /10 m^3 factor for worker exposure

- All UFs are the same as used for the chronic REL derivation
- **8-Hour REL = 1.7 ppb (10 µg/m^3)**

Public Comments
Draft Hot Spots RELs for 1,4-Dichlorobenzene

- OEHHA released the draft document for public comment on November 29, 2024
  - Held two public workshops: December 16, 2024 and January 7, 2025
  - Public comment period ended January 13, 2025
- OEHHA received one public comment submission from CleanEarth4Kids.org

OEHHA's Responses to Public Comment 1

"Children are particularly vulnerable to airborne toxins like 1,4-DCB. Their respiratory systems are still developing and they have higher respiratory rates relative to their body weight, which creates a higher health risk."

- OEHHA's methodology explicitly considers possible differential effects on the health of infants and children, in accordance with the mandate of the Children's Environmental Health Protection Act (SB 25).
- Both acute and chronic REL derivations applied a full factor of 10 for interindividual differences in toxicokinetics, to account for infants and children
- Age-specific breathing rates and body weight are applied while conducting exposure assessment and risk characterization

OEHHA's Responses to Public Comment 2

"*The current REL proposals (5 µg/m³ for chronic exposure and 10 µg/m³ for repeated 8-hour exposure) do not sufficiently address the risk posed by higher exposure scenarios and should be further reduced to account for the significant indoor and occupational exposure documented globally.*"

- Exposure scenarios and exposure assessment are accounted for while characterizing the risk
- The Hot Spots program assesses risk to off-site workers but does not cover occupational exposures within Hot Spots facilities

OEHHA's Responses to Public Comments 3 & 4

"There should be more comprehensive educational campaigns about the risks of 1,4-DCB exposure, and information about safer, non-toxic alternatives."

- The draft TSD focuses on the scientific basis and derivation of RELs for 1,4-DCB by the inhalation route of exposure. Educational campaigns are outside the scope of this draft.

"Additionally, there should be stronger air quality monitoring programs in vulnerable communities to identify and mitigate sources of 1,4-DCB."

- Risk management approaches are beyond the scope of the draft TSD for 1,4-DCB.

Thank you!