Public Workshop on the Noncancer Reference Exposure Levels for

1,4-Dichlorobenzene

OEHHA Air Toxics Hot Spots Program

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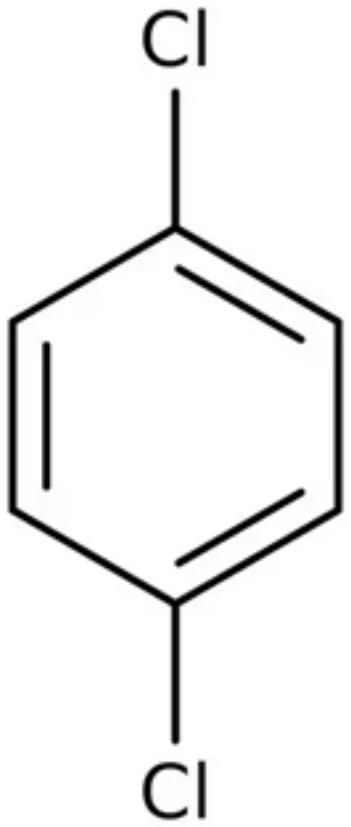
1,4-Dichlorobenzene (1,4-DCB)
Physical-Chemical Properties



- 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 Prop. 65 and Hot Spots programs
- Updated chronic REL will supersede current chronic REL of 800 $\mu g/m^3$

Airborne Concentrations

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 ppb
  - Below detection limit in most air monitoring measurements
- In 1987 California study, detectable in 59% of the initial breath samples and 77% of the personal air samples (mainly due to indoor exposure)

Toxicokinetics

Metabolism of inhaled 1,4-DCB in humans and rodents:

- In rats, inhaled 1,4-DCB peak tissue levels highest in fat but declines quickly to low levels in 24 hours - no long-term fat storage
- 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
- In humans, 5%–16% of absorbed 1,4-DCB eliminated via urine as 2,5-DCP in 9-11 hours – suggests a “long time” period to be removed from the body

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) correlated with urinary 2,5-DCP
  - No obvious illness in workers

Chronic/Subchronic Effects in Humans
Population Survey Studies in Adults

- Many studies examined associations between urinary 2,5-DCP and diseases using NHANES data
  - Limitation: Association does not mean causation; associations based on only one urinary sample
- Associations with increased 2,5-DCP levels have been found for:
  - 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

- Population survey data of 2,5-DCP urinary levels in children or pregnant women have also been used to look for associations with diseases or altered physiological states in infants and 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 mice)
  - **Kidney**: Papilla mineralization and pelvic urothelial hyperplasia (male rats)
  - **Nasal epithelium**: Degenerative changes in nasal olfactory epithelium (female rats) and respiratory epithelium (female rats and mice)
  - **Testis**: Mineralization (male mice)

Chronic Effects in Animal Studies

Main treatment-related findings in rats by Aiso et al. (2005)

Endpoint	Species Sex	0 ppm	20 ppm	75 ppm	300 ppm
Kidney: pelvic urothelial hyperplasia	Rat Male	7/50†	8/50	13/50	32/50**
Liver: hepatocellular hypertrophy	Rat Male	0/50†	0/50	0/50	5/50*
Nasal epithelium: olfactory degeneration	Rat Female	27/50†	29/50	39/50*	47/50**
Nasal epithelium: respiratory degeneration	Rat Female	11/50†	10/50	14/50	38/50**

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

Chronic Effects in Animal Studies

Main treatment-related findings in mice by Aiso et al. (2005)

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

† $p \leq 0.05$, positive trend; * - $p \leq 0.05$ and ** - $p \leq 0.01$, 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:
  - Decreased F_1 and F_2 pup litter size in 538 ppm group
  - Decreased F_1 and F_2 pup body weight and weight gain in 538 ppm group
  - Increased stillborn pups (F_2) and pup deaths on PND 1–4 (F_1 and F_2) in 538 ppm group

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
  - Decreased rat pup viability and body weights in a two-generation exposure study

Acute REL Derivation
US EPA BMC 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: RGDR* = 1 for systemic effects

    * RGDR – regional gas dose ratio

Acute 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 toxicokinetic differences between adults, infants, and children)
  - Intraspecies toxicodynamic ($UF_{H\text{-}d}$) = √10
- 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

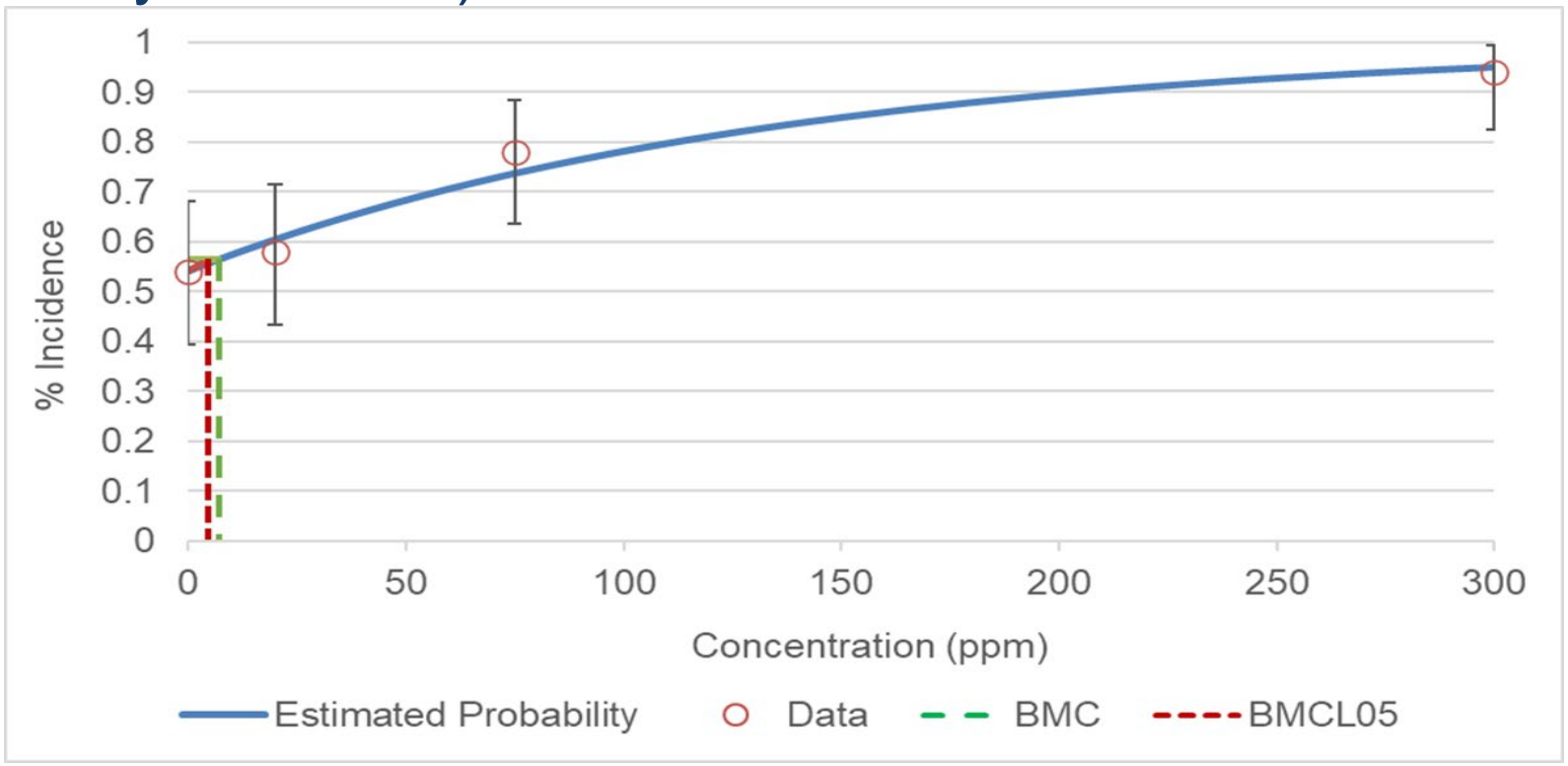
Chronic REL Derivation

- 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 toxicokinetic differences between adults, infants, and children
  - Intraspecies toxicodynamic ($UF_{H\text{-}d}$) = √10
- 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 occupational 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

- Comments may be submitted electronically through the following link: https://oehha.ca.gov/comments.
- Comments can also be submitted in writing to:

  Rima Woods, Chief of the Air Toxicology and Risk Assessment Section, at Rima.Woods@oehha.ca.gov