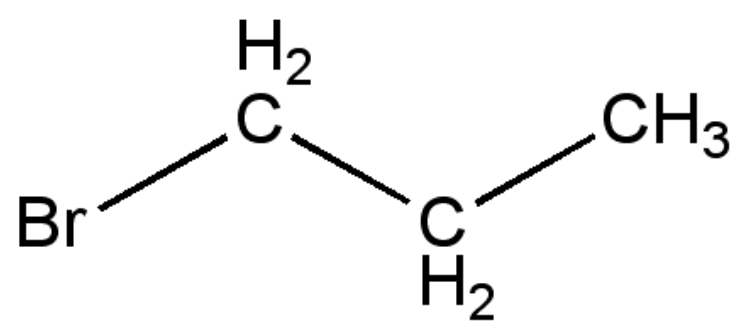
Air Toxics Hot Spots Program

Noncancer Reference Exposure Levels (REL)

1-Bromopropane



Office of Environmental Health Hazard Assessment

Scientific Review Panel Meeting

May 12, 2022

1-Bromopropane
Chemical-Physical Properties

- **Also referred to as n-propyl bromide**
- **Colorless liquid at room temperature**
- **Soluble in organic solvents**
  Slightly soluble in water: 2,450 mg/L @ 20°C
- **Boiling point: 71°C at 760 mm Hg (torr)**
- **Vapor pressure: 110.8 mm Hg (torr) @ 20°C**

1-Bromopropane Listings and Uses

- **Listed as a carcinogen and a developmental and reproductive toxicant (males and females) under California Prop. 65**
- **Draft Hot Spots cancer inhalation unit risk value has been reviewed by the Scientific Review Panel**

Uses

- **Solvent vehicle for adhesives in laminates and foam products**
- **Degreasing/cleaning agent for metals, plastics, optics, and electronics**
- **Alternate solvent in modified perchloroethylene dry-cleaning machines**

1-Bromopropane California Emissions

Limited data on 1-bromopropane (1-BP) emissions:

- **Statewide 2011 CA survey reported a total of 160.7 tons of 1-BP emissions in 2008 due to solvent cleaning operations**
- **As of March 21, 2022 – now quantitatively reportable under the Hot Spots Program**
- **As of Feb. 4, 2022 – US EPA amended the HAP list to add 1-BP**

1-Bromopropane Toxicokinetics

- **Metabolism of inhaled 1-BP in rodents primarily through oxidative metabolism via P450 enzymes, conjugation with glutathione and debromination.**
- **In rats, the majority of absorbed 1-BP may be excreted unchanged (40-71%) or as CO_2 (10-31%) in exhaled air within 4 hours.**
- **Radiolabeled [1-^{14}C]-1-BP recovered in urine ranged from 17 to 23%.**
- **Main urinary metabolite excreted is N-acetyl-S-propylcysteine (37% of total urinary metabolites)**
- **Metabolite found in urine of 1-BP workers and in national biomonitoring studies of pregnant women and children**

1-Bromopropane Toxicokinetics in Children and Adults

- **NIOSH observed a strong association between TWA inhalation exposure to 1-BP in workers and the urinary metabolite N-acetyl-S-propylcysteine**
  - **Considered N-acetyl-S-propylcysteine an effective biomarker for 1-BP workers**
- **National Children's Vanguard Study (2009-2010) found N-acetyl-S-propylcysteine in 99% of urine samples from ~ 500 3rd trimester pregnant women**
- **NHANES study (2011-2012) mean urinary levels of N-acetyl-S-propylcysteine was 2.6 ng/ml (boys) and 3.3 ng/ml (girls) in children's survey**
- **Surveys suggest wide-spread non-occupational exposure to 1-BP, although exposure to other chemicals could result in same urinary metabolite**

1-BP Acute Effects: Humans

- **Lack of data for an acute REL (≤ 24 hr exposure)**
- **Multi-day (several days to several weeks) occupational exposure result in neurotoxicity**
- **Neurotoxic effects noted in exposed patients include ataxic gait, hypoesthesia (partial or total loss of sense of touch), numbness, dizziness, ocular symptoms, and limb pain**
- **Occupational exposure levels hard to pin down. >50-200 ppm for days or weeks leads to severe neurological findings**

1-BP Acute/Subacute Effects Experimental Animal Exposure

- Few acute (≤ 24 hrs) toxicity studies
- Multi-day (several days to several weeks) exposure protocols used to achieve neurotoxic effects
- Daily exposures in rats:
  - 1800 to 2000 ppm for <1 week results in ataxia
  - ≥ 800 ppm for 1 week resulted in axonal myelin sheath swelling of gracile nucleus and posterior tibial nerve
  - ≥ 200 ppm for 3 weeks resulted in decreased muscle strength

1-BP Acute/Subacute Effects Experimental Animal Exposure

- **Daily exposures in mice:**
  - **≥ 800 ppm for 6 hrs results in decreased sperm motility in males**
  - **≥ 500 ppm results in liver damage; higher concentrations can result in death on day 2**
  - **Respiratory airway lesions observed as low as 125 ppm after 2 week exposure**

1-BP Acute/Subacute Effects Developmental Studies

- Developmental abnormalities in newborn rodents resulting from 1-BP exposure during gestation considered to be acute exposure
- Huntingdon Life Sciences (2001): Maternal rat exposure to 1-BP 6 hrs/day to 0, 100, 498, 996 ppm 1-BP during GD 6-19
- In rat fetuses:
  - Reduced skull ossification at ≥498 ppm
  - Increase in bent ribs at 996 ppm
- Used as key study for the acute REL

Acute REL Derivation for 1-BP

Skeletal abnormalities in fetuses of 1-BP exposed rats

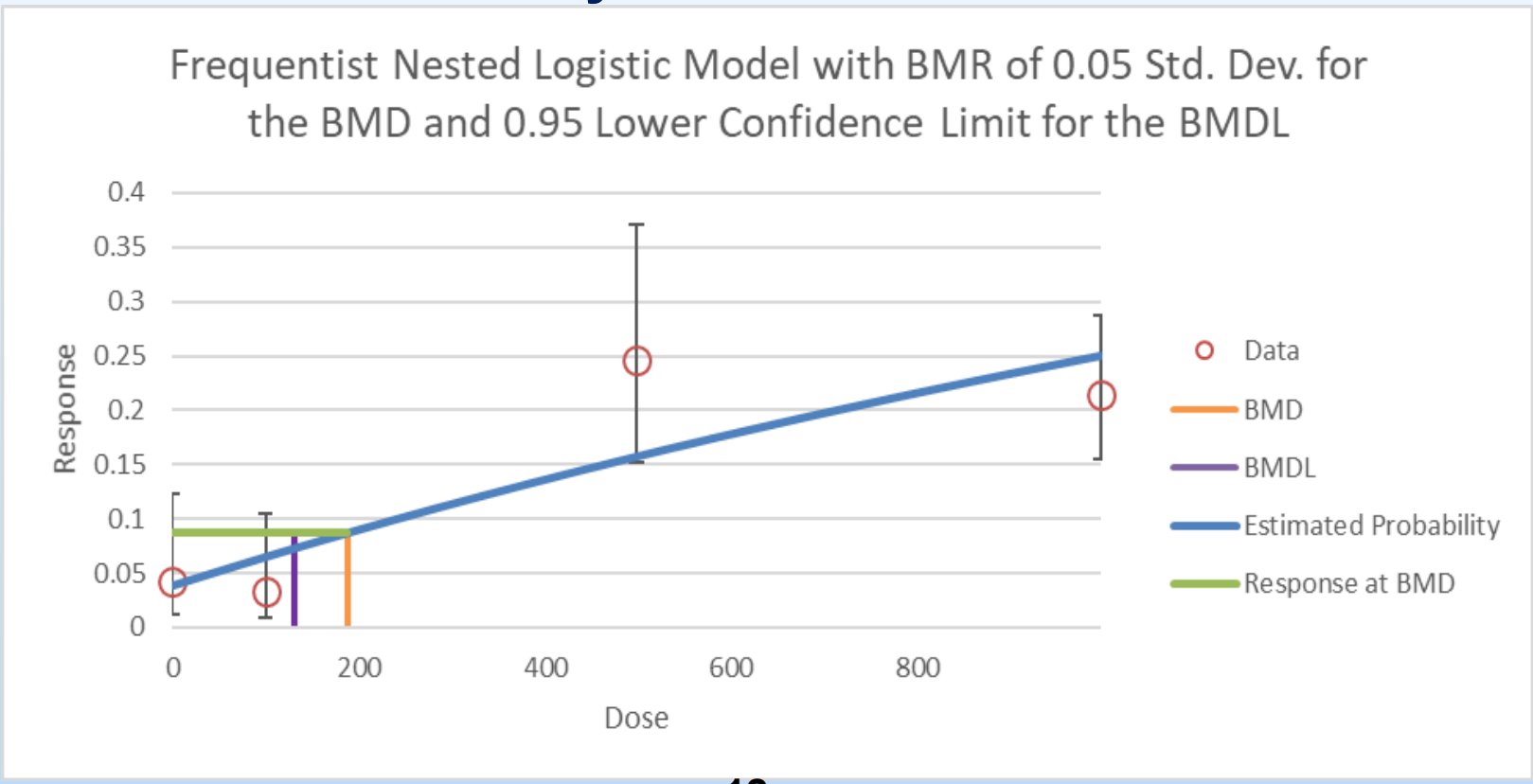
Exposure	**0 ppm**	**100 ppm**	**498 ppm**	**996 ppm**
Litters examined	23	23	25	24
Fetuses examined	145	146	153	151
Reduced skull ossification				
Fetal incidence	6	5	38	33
Litter incidence	**4**	**3**	**17***	**18***
Ribs bent				
Fetal incidence	0	0	7	26
Litter incidence	0	0	3	13*

*** p < 0.01**

Reduced skull ossification is the critical effect for the acute REL

Acute REL Derivation for 1-BP

Individual data for fetuses from each litter available for Benchmark Dose (BMD) nested dichotomous analysis.



Acute REL Derivation for 1-BP

- Benchmark Dose Response of 5% = 187 ppm (BMD)
- 95% lower confidence limit (BMDL) = 131 ppm
- 131 ppm is the Point of Departure (POD)
  - No time adjustment for exposure during gestation
  - Human Equivalent Concentration: RGDR = 1 for systemic effects

Acute REL Derivation for 1-BP

- **Interspecies Uncertainty Factor (UF):**
  - **Toxicokinetic UF = 2**

    For residual toxicokinetic differences not addressed by the RGDR
  - **Toxicodynamic UF = $\sqrt{10}$**

    For lack of toxicodynamic data

Acute REL Derivation for 1-BP

- **Intraspecies Uncertainty Factor (UF):**
  - **Toxicokinetic UF = 10**

    No information on pharmacokinetic differences for 1-BP among adults, infants, and children
  - **Toxicodynamic UF = $\sqrt{10}$**

    For using a sensitive endpoint (development) as the POD
- **Cumulative UF = 200**
- **Acute REL = 659 mg/m^3 (131 ppm) / 200**

  = 3.3 mg/m^3 (0.7 ppm) or 3,300 µg/m^3

1-BP Chronic/Subchronic Effects in Experimental Animals

Neurological studies in rats

- **12 week exposure (6-8 hrs/day, 5-7 days/week**
- **≥400 ppm**
  - **increased distal latency sciatic nerve**
  - **decreased forelimb strength**
  - **axonal degeneration and demyelination**
- **≥800 ppm**
  - **decreased motor nerve conduction velocity**

1-BP Chronic/Subchronic Effects in Experimental Animals

National Toxicology Program (NTP) 2-year study in rats and mice

- **No apparent lesions in the nervous system were found (pathological exam of brain and spinal cord)**
- **Respiratory tract lesions in mice at the lowest dose (62.5 ppm)**
- **Splendore Hoeppli material (abscesses) primarily in the nose and skin of exposed rats – evidence of immunosuppression**

1-BP Chronic/Subchronic Effects: Humans

- **Similar to occupational reports with shorter duration/higher 1-BP concentrations, neurological effects dominated: numbness in the lower limbs, decreased pallesthesia (vibratory sensation), unstable gait, and difficulty walking**
- **Several occupational studies performed nerve conduction tests**
- **Most common finding: reduced conduction velocity (CV) and increased distal latency (DL) in peripheral motor and sensory nerves of the lower limbs**

1-BP Chronic/Subchronic Effects Human Exposure

Case report by Sclar (1999)

- **Patient hospitalized following 2 months of occupational exposure to 95.5% 1-BP**
- **First nerve conduction exam of a patient poisoned by 1-BP**
- **Sural and peroneal sensory nerve conduction velocity (CV) of 29 - 36 m/sec well below range of normality of 40 - 41 m/sec**
- **Motor nerve distal latencies (DL) of 8.0 - 9.6 ms well above normal range of 6.1 - 6.5 ms**

Chronic REL Derivation for 1-BP

- **Li et al. (2010b) key study for the chronic and 8-hour RELs**
- **71 female workers from 4 Chinese 1-BP manufacturing plants – largest cohort of 1-BP workers studied thus far**
- **Compared to a control group of 71 female workers from the same region**
- **Geometric mean for 1-BP workers: 14.13 mg/m^3 (2.81 ppm); mean duration: 38.8 months**

Chronic REL Derivation for 1-BP

Results of nerve conduction velocity and distal latency tests (Li *et al*. 2010b)

Exposure Group	N	Tibial nerve DL (ms)	Tibial motor nerve CV (m/s)	Sural sensory nerve CV (m/s)
Control	71	6.7 ± 1.8	50.1 ± 10.3	48.3 ± 5.2
1-BP-exposed	71	7.5 ± 2.1*	44.8 ± 8.7*	45.5 ± 4.9*
Cut-off for normality		6.1[a]	42[b]	40[c]

*** P < 0.05 compared to the control group**

[a] Upper limit - 97th percentile, all ages combined (Chen *et al*., 2016)

[b] Low limit – 3rd percentile (Chen *et al*., 2016)

[c] Low limit – 3rd percentile (Benatar *et al*., 2009)

Chronic REL Derivation for 1-BP

Results of the pallesthesia (vibratory perception) tests (Li *et al*. 2010b)

Exposure Group	N	Right foot vibration threshold (dB)	Left foot vibration threshold (dB)	Right foot vibration delay (s)	Left foot vibration delay (s)
Control	63	15.9±7.0	15.4±7.2	3.3±4.3	2.9±4.3
1-BP-exposed	63	16.1±6.8	18.3±7.5*	6.2±4.4*	5.7±4.4*

* ***p*<0.05 compared to the control group**

Chronic REL Derivation for 1-BP

POD = 14.13 mg/m^3 (2.81 ppm)

- **Time adjustment:**

14.13 mg/m^3 × 10m^3/20m^3 × 5d/7d

= 5.05 mg/m^3

- **LOAEL UF = $\sqrt{10}$ (subclinical findings)**

- **Subchronic UF = 10 (mean 38.8 month exposure - <8% of estimated lifetime)**

Chronic REL Derivation for 1-BP

- **Total interspecies UF = 1 (human study)**
- **Intraspecies toxicokinetic (UF_{H-k}) = 10**
  (protect infants and children)
- **Intraspecies toxicodynamic (UF_{H-d}) = 10**
  (neurotoxicity critical effect)
- **Cumulative UF = 3000**
- **Chronic REL = 5.05 mg/m^3 (1.00 ppm) / 3000**
  = 1.7 µg/m^3 (0.3 ppb)

8-Hour REL Derivation for 1-BP

- **Based on same occupational study by Li et al. (2010b)**
- **Same POD of 14.13 mg/m^3 (2.81 ppm)**
- **Time adjustment is different:**
  14.13 mg/m^3 × 5d/7d = 10.09 mg/m^3
  no 10/20 m^3 factor: key study occupational
- **All UFs are the same as the chronic REL derivation**
- **8-Hour REL = 3.4 µg/m^3 (0.7 ppb)**

1-BP REL Summary

Proposed 1-BP RELs

Acute: 3,300 µg/m^3 (700 ppb)

Chronic: 1.7 µg/m^3 (0.3 ppb)

8-Hour: 3.4 µg/m^3 (0.7 ppb)

Public Comments/Workshop

- The 1-BP RELs document was released for a 45-day public comment period on January 8, 2022.
- A virtual public workshop was held on January 26, 2022.
- No public comments were received on the document.