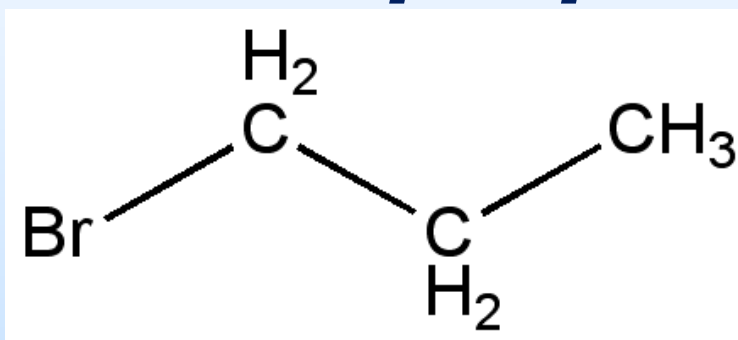


Air Toxics Hot Spots Program

Noncancer Reference Exposure Levels (REL)

1-Bromopropane



Office of Environmental Health Hazard Assessment

Public Workshop

January 26, 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/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:

- ◆ **Currently not reportable under the Hot Spots Program**
- ◆ **Statewide CA survey in 2011 reported a total of 160.7 tons of 1-BP emissions due to solvent cleaning operations**



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 (40-71%) may be excreted unchanged or as CO₂ (10-31%) in exhaled air within 4 hours.**
- ◆ **Radiolabeled [1-¹⁴C]-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*

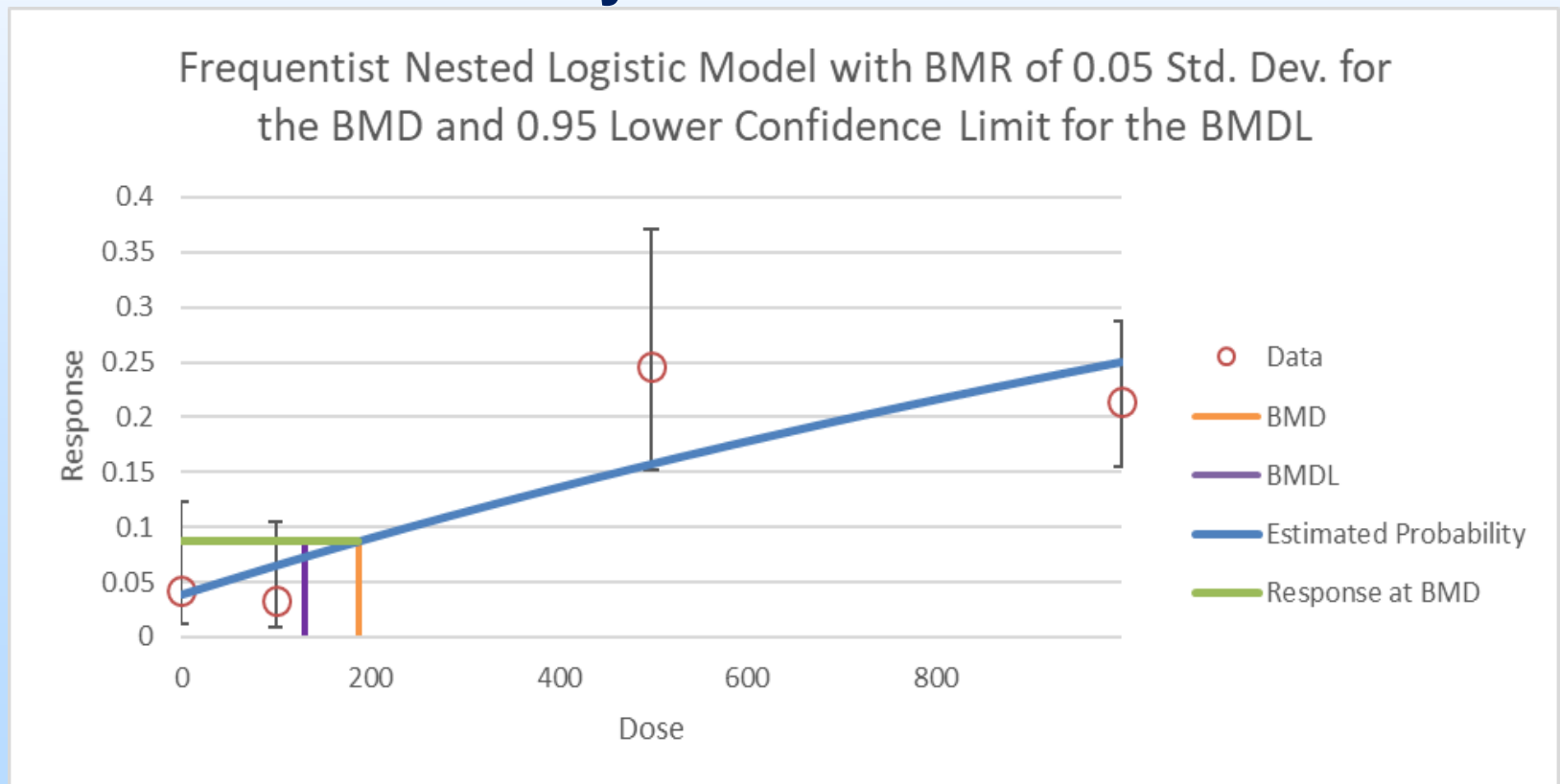
* $p < 0.01$

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 $3,300 \text{ } \mu\text{g/m}^3$



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 exposure for 1-BP workers:
14.13 mg/m³ (2.81 ppm)**



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/m³ (2.81 ppm)

◆ Time adjustment:

14.13 mg/m³ × 10/20 m³ × 5/7 d = 5.05 mg/m³

◆ 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**
= $1.7 \text{ } \mu\text{g/m}^3$ (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/m³ (2.81 ppm)**
- ◆ **Time adjustment is different:
14.13 mg/m³ × 5/7 d = 10.09 mg/m³
no 10/20 m³ factor: key study occupational**
- ◆ **All UFs are the same as the chronic REL derivation**
- ◆ **8-Hour REL = 3.4 µg/m³ (0.7 ppb)**



1-BP REL Summary

Proposed 1-BP RELs

Acute: 3,300 $\mu\text{g}/\text{m}^3$ (700 ppb)

Chronic: 1.7 $\mu\text{g}/\text{m}^3$ (0.3 ppb)

8-Hour: 3.4 $\mu\text{g}/\text{m}^3$ (0.7 ppb)



1-BP Draft RELs

- ◆ **Comments can be submitted in writing to: Dr. John Budroe
(John.Budroe@oehha.ca.gov)**

