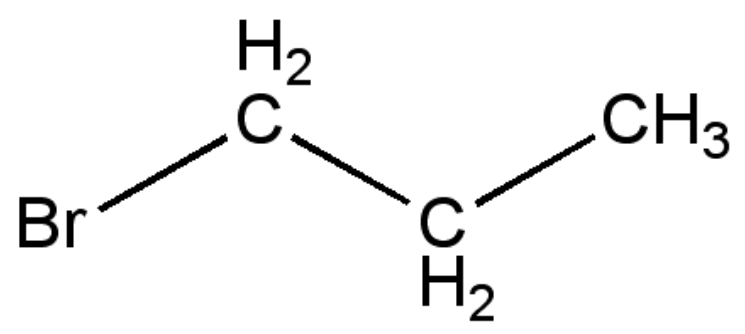
# *Air Toxics Hot Spots Program*

## *Cancer Inhalation Unit Risk (IUR)*

# *1-Bromopropane*




**Office of Environmental Health Hazard Assessment**

**Scientific Review Panel Meeting**

**October 15, 2021**

# *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 under California Prop. 65**
- **Listed by International Agency for Research on Cancer (IARC) as a Group 2B carcinogen, i.e., possibly carcinogenic to humans**

**Uses**

- **Solvent vehicle for adhesives in laminates and foam products**
- **Degreasing/cleaning agent for metals, plastics, optics, and electronics**
- **Promoted as an alternative to ozone-depleting CFCs**
- **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.**
- **The majority of absorbed 1-BP (40-71%) may be excreted unchanged 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 in the urine 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**
  - **Other metabolites in rodents include the mutagens α-bromohydrin and glycidol**

# *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 Vangard 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-Bromopropane Carcinogenicity Studies in Rodents*

**NTP performed 1-BP whole-body inhalation cancer bioassays in rats and mice in 2011**

- **F-344/N rats and B6C3F$_1$ mice (50 group/sex/species)**
- **Rats: 0, 125, 250 or 500 ppm for 6.2 hrs/day, 5 days/week for 105 weeks**
- **Mice: 0, 62.5, 125 or 250 ppm for 6.2 hrs/day, 5 days/week for 105 weeks**

# *1-Bromopropane*
# *Tumor Incidence - Rats*

**Increased tumor incidences in male and female rats:**

| Sex, species | Tumor type | Exposure conc. (ppm) | Tumor incidence |
|---|---|---|---|
| **Male rats** | **Skin**: Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma | 0<br>125<br>250<br>500 | 1/50‡<br>7/50*<br>9/50**<br>10/50** |
| **Female rats** | **Large intestine**: Adenoma | 0<br>125<br>250<br>500 | 0/50‡<br>1/50<br>2/50<br>5/50* |

*** $p < 0.05$, ** $p < 0.01$ difference from controls, poly-3 test**

**‡ $p < 0.01$ positive trend for tumor type**

# *1-Bromopropane*
# *Tumor Incidence - Mice*

**Increased tumor incidences in female mice only:**

| Sex, species | Tumor type | Exposure conc. (ppm) | Tumor incidence |
|---|---|---|---|
| **Female mice** | **Lung**:<br>Alveolar/bronchiolar adenoma or carcinoma (combined) | 0<br>62.5<br>125<br>250 | 1/50‡<br>9/50**<br>8/50*<br>14/50** |
| **Male mice** | None | | |

** $p < 0.01$ difference from controls, poly-3 test

‡ $p < 0.01$ positive trend for tumor type

# *1-Bromopropane*
# *Other Supporting Data*

- **Metabolism of 1-BP produces effects that other carcinogens are known for, such as oxidative stress via glutathione depletion and immunomodulation**
- **Structurally-related brominated hydrocarbon compounds (1,2-dibromoethane, tribromomethane, 1,2-dibromo-3-chloropropane, bromodichloromethane), cause tumors in the same organs and tissues as 1-BP**
- **1-BP metabolites formed by CYP-mediated oxidation (bromohydrin and glycidol) are direct-acting mutagens**

# *1-Bromopropane Genotoxicity*

**Relatively small genotoxicity database**

- **DNA damage assay** (3 studies, +/-)
- **DNA adduct formation** (2, *in vitro* & *in vivo,* +)
- **Induction of DNA repair** (1 study, -)
- **Bacterial mutation assays** (3 studies, +/-)
- **Mammalian cell gene mutation test** (1 study, +)
- **Chromosomal damage** (2 *in vivo*, -)
- **Transgenic rodent mutation assay** (1 study, -)

# *1-Bromopropane Cancer Hazard Evaluation*

- **No epidemiology findings for carcinogenicity, although exposure data of sufficient size and duration may not yet exist**
- **One rodent lifetime inhalation study: 1) carcinogenic in multiple species, and 2) induced tumors at one or more sites in rats**
- **Some positive genotoxicity studies: 1) DNA adduct formation both *in vitro* and *in vivo*, 2) mutagenic in a closed system bacterial Ames assay, and 3) induced mutations *in vitro* in mouse lymphoma cells**
- **Structurally-related brominated compounds produce similar tumors in lifetime rodent studies**

**Combined, these factors point to a potential for 1-BP to induce tumors in humans.**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

**First step in IUR derivation is converting the NTP tumor incidence into "effective tumor incidence"**

- **Effective Tumor Incidence - The number of tumor-bearing animals over the number of animals alive at time of first occurrence of the tumor.**
- **Removes animals from the assessment that died before they were considered to be at risk for tumor development.**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

**Comparison of NTP tumor incidence with effective tumor incidence for rodents exposed to 1-bromopropane**

| Sex, species | Tumor type | Exposure Level (ppm) | NTP Incidence | Effective Tumor Incidence |
|---|---|---|---|---|
| Male rats | Skin tumors (combined) | 0 | 1/50† | **1/49†** |
| | | 125 | 7/50* | **7/49*** |
| | | 250 | 9/50** | **9/49**** |
| | | 500 | 10/50** | **10/44**** |
| | | | | |
| Female rats | Large intestine adenomas | 0 | 0/50† | **0/45†** |
| | | 125 | 1/50 | **1/43** |
| | | 250 | 2/50 | **2/41** |
| | | 500 | 5/50* | **5/36*** |
| | | | | |
| Female mice | Lung tumors (combined) | 0 | 1/50† | **1/41†** |
| | | 62.5 | 9/50** | **9/46*** |
| | | 125 | 8/50* | **8/42*** |
| | | 250 | 14/50** | **14/47**** |

Fisher exact test pairwise comparison: *$p < 0.05$, **$p < 0.01$
Cochran-Armitage trend test for dose response: †$p < 0.01$

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

- In male rats, survival was significantly reduced at 500 ppm ($p$ = 0.033, life table pairwise comparison)
- Decreased survival >15% compared to controls by week 85
- Most of these early deaths due to treatment-related chronic inflammation

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

- **To determine cancer potency, need to convert 1-BP air concentration to average daily dose, in mg/kg BW-day:**

**Dose (mg/kg BW-day) = IR × C / BW**

**Where:**

**C = time-adjusted concentration to annual average**

**(6.2 hrs / 24 hrs x 5 days / 7 days)**

**BW = body weight – average over 2-year exposures**

**IR = inhalation rate – equation based on BW of animal**

**IR calculation:**

- **rats: IR ($m^3$/day) = 0.702 × $(BW)^{2/3}$ (OEHHA, 2018)**
- **mice: IR ($m^3$/day) = 0.0345 × $(BW / 0.025\ kg)^{2/3}$ (Anderson, 1983)**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

**Dose (mg/kg BW-day) = IR × C / BW**

| **Species** sex | **1-BP Chamber Concentration ($mg/m^3$)** | | | | |
|---|---|---|---|---|---|
| | 0 | 314 | 629 | 1258 | 2515 |
| | **Daily Exposed Dose (mg/kg-day)** | | | | |
| **Rats** | | | | | |
| **Male** | 0 | - | 106.4 | 212.8 | 425.6 |
| **Female** | 0 | - | 123.2 | 246.4 | 492.8 |
| **Mice** | | | | | |
| **Female** | 0 | 64.3 | 128.6 | 257.2 | - |

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

**We now have the fraction affected (effective tumor incidences) and the dose (in mg/kg BW-day)**

- **Multistage Cancer Model in the Benchmark Dose Software (U.S. EPA, 2017) used to determine the cancer potency for female rat and female mouse tumor data**
- **Multistage Weibull model used for male rat tumor data due to decreased survival in 500 ppm group**
- **Potency values derived using a Benchmark Response (BMR) of 5% (5% extra risk) to calculate the Benchmark Dose (BMD)**
- **The 95% lower confidence bound on the effective dose producing 5% response ($BMDL_{05}$) is used to calculate cancer potency**
- **0.05 / $BMDL_{05}$ = Cancer Slope Factor (CSF)**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

- **Cancer slope factors were calculated for tumors with a statistically significant tumor incidence on pair-wise comparison to controls and a positive trend for dose-response:**
  - **Skin tumors of epithelial origin (combined) in male rats**
  - **Large intestine adenomas in female rats**
  - **Lung alveolar/bronchiolar adenoma or carcinoma (combined) in female mice**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

- **Final calculation is to convert the animal CSF values (CSF(a)) to CSF human equivalents (CSF(h)) using body weight ($BW^{3/4}$) scaling:**

$$CSF(h) = CSF(a) \times (BW(h) / BW(a))^{1/4}$$

- **This interspecies scaling factor accounts for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), and for pharmacodynamic considerations (*i.e.*, tissue responses to chemical exposure).**

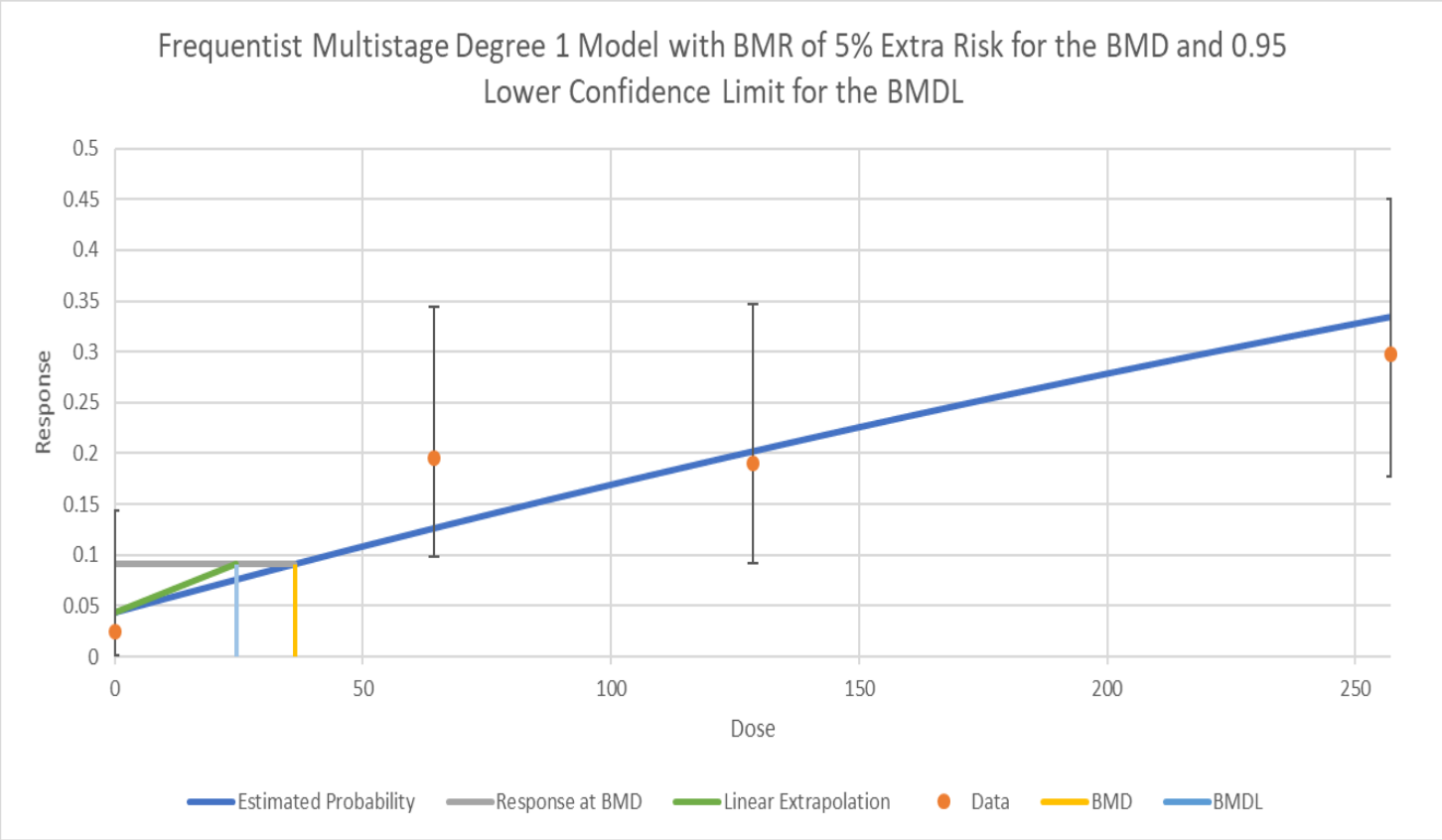
# *1-Bromopropane*
# *Unit Risk Factor Derivation*

| Tumor type | AIC | *p*-value | $BMD_{05}$ (mg/kg-day)[a] | $BMDL_{05}$ (mg/kg-day) | CSF Rodent $(mg/kg\text{-}day)^{-1}$ | CSF - Human $(mg/kg\text{-}day)^{-1}$ |
|---|---|---|---|---|---|---|
| **Male Rats** Skin tumors combined | 151.75 | NA | 57.57 | 33.43 | 0.001496 | **0.0053** |
| **Female Rats** Large intestine | 56.84 | 0.95 | 202.43 | 119.07 | 0.000420 | **0.0017** |
| **Female Mice** Lung Tumors combined | 159.53 | 0.26 | 36.34 | 24.54 | 0.00204 | **0.013** |

**Lung tumors in female mice provided the highest CSF(h) value, establishing this tumor as the most sensitive endpoint for 1-BP-induced carcinogenicity**

# *1-Bromopropane*
# *Unit Risk Factor Derivation*

**BMDS Multistage Cancer Model plot fit for alveolar/bronchiolar lung tumors in female mice exposed to 1-bromopropane**



# *1-Bromopropane*
# *Inhalation Unit Risk (IUR) Derivation*

- **1-BP unit risk factor = IUR** $= \left(\frac{CSF \times BR}{BW \times CF}\right)$
  - **CSF (human) is 0.013 $(mg/kg\text{-}day)^{-1}$**
  - **Human breathing rate (BR) of 20 $m^3/day$**
  - **Average human body weight (BW) of 70 kg**
  - **mg to µg conversion factor (CF) of 1000**
- **1-BP IUR = $3.7 \times 10^{-6}$ $(\mu g/m^3)^{-1}$**
  - **Lifetime exposure to 1 $\mu g/m^3$ 1-BP results in an extra cancer risk of 3.7 chances in a million.**

# *1-Bromopropane*
# *Changes from Public Comment Draft*

**No public comments were submitted**

**Additions following public comment period:**

- **US EPA (2020) TSCA Reference – comments on N-acetyl-S-propylcysteine as a biomarker (p. 15, lines 410 - 415) and advantages/limitations of several 1-BP genotoxicity studies (p. 19, lines 547 – 559)**
- **Comment regarding $N^7$-guanine adducts (p. 17, lines 484 – 489)**
- **BioReliance (2015) bacterial mutation study (p. 18, lines 526 - 537), and removed Elf Atochem (1994) bacterial mutation study**

# *1-Bromopropane Inhalation Unit Risk*

- **Questions?**