OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Air Toxics Hot Spots Program

1-Bromopropane

Cancer Inhalation Unit Risk Factor

Technical Support Document for
Cancer Potency Factors
Appendix B

Public Comment Review Draft

May 2021

Air, Community, and Environmental Research Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Technical Support Document for Cancer Potency Factors
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List of Acronyms

AIC	Akaike Information Criterion	GSH	Glutathione
ANOVA	Analysis of Variance	GST	Glutathione-S-transferase
1-BP	1-Bromopropane	IL	Interleukin
BMD	Benchmark dose	iNOS	Nitric Oxide Synthetase
BMD_{05}	BMD 5% response rate	IUR	Inhalation unit risk
$BMDL_{05}$	The 95% lower confidence bound at the 5% response rate	IR	Inhalation rate
		IARC	International Agency for Research on Cancer
BMDS	Benchmark dose modeling software	IV	Intravenous
BMR	Benchmark dose response	NO	Nitric Oxide
BR	Breathing rate	NTP	National Toxicology Program
BW	Body weight	OEHHA	Office of Environmental Health Hazard Assessment
CEBS	Chemical Effects Biological Systems	PBPK	Physiologically-based pharmacokinetic
CF	Conversion factor	ppm	parts per million
CO2	Carbon Dioxide	PrCys	S-propylcysteine
CSF	Cancer slope factor	TNF	Tumor necrosis factor
CTI	California Toxics Inventory	TRI	Toxics Release Inventory
CYP	Cytochrome P450	TWA	Time-weighted average
CYP2E1	Cytochrome P450 2E1 isozyme	US EPA	United States Environmental Protection Agency
DBCP	1,2-dibromo-3-chloropropane	VOC	Volatile organic compound
DNA	Deoxyribonucleic acid	WT	Wild-type
FCM	Flavin-containing monooxygenase		

Preface

This document summarizes the carcinogenicity data and the derivation of an inhalation cancer unit risk factor for 1-bromopropane (1-BP). Cancer unit risk factors are used to estimate lifetime cancer risks associated with inhalation exposure to a carcinogen. The National Toxicology Program (NTP) conducted chronic inhalation toxicity and carcinogenicity bioassays of 1-BP (Morgan *et al.*, 2011; NTP, 2011) and found evidence of carcinogenicity in rats and mice. Consequently, OEHHA has derived a cancer inhalation unit risk factor (IUR) from the NTP animal data for use in the Hot Spots program.

OEHHA is legislatively mandated to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360(b)(2). In implementing this requirement, OEHHA develops IURs for carcinogenic air pollutants listed under the Air Toxics Hot Spots program. The 1-BP IUR was developed using the most recent "Air Toxics Hot Spots Program Technical Support Document for Cancer Potency Factors", finalized by OEHHA in 2009 (OEHHA, 2009). Literature summarized and referenced in this document covers the relevant published reports for 1-BP through winter 2019.

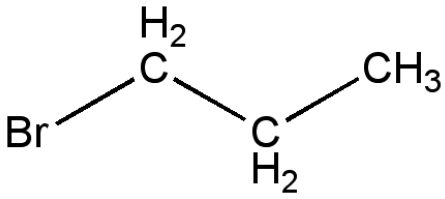
1-BP has been proposed to be added to the list of substances for which emissions must be quantified under the OEHHA Air Toxics Hot Spots Program in 2021, and is a reportable chemical under the US EPA Toxics Reporting Inventory (TRI) program (TRI, 2015). 1-BP is listed as a chemical known to the State to cause cancer by the California Proposition 65 program (OEHHA, 2016). In addition, the National Toxicology Program (NTP) listed 1-BP in the 13th Report on Carcinogens, which identifies substances that either are known to be human carcinogens or are reasonably anticipated to be human carcinogens, and to which a significant number of persons residing in the United States are exposed (NTP, 2013). Finally, 1-BP is listed by the International Agency for Research on Cancer (IARC) as a Group 2B carcinogen, i.e., possibly carcinogenic to humans (IARC, 2018).

1-BP is promoted as an alternative to ozone-depleting chlorofluorocarbons. Exposure to 1-BP may occur from emissions of facilities where 1-BP is used as a solvent vehicle for spray and brush-applied adhesives in laminates and foam products, or as a degreasing/cleaning agent for metals, metal products, plastics, optics, and electronics (TRI, 2015). 1-BP is also listed in California for limited use in dry cleaning technologies, in which it is used as an alternative solvent in modified perchloroethylene dry-cleaning machines (CARB, 2015). Other applications may include use as a chemical intermediate in the production of pharmaceuticals,

pesticides, quaternary ammonium compounds, flavors, and fragrances. In California, reduction in chlorinated hydrocarbon use due to phase-out of these compounds has led to the adoption of alternative solvent formulations, such as those including 1-BP, by end-users. A periodic California survey of businesses that conduct solvent cleaning operations noted no use of 1-BP until 2008 (CARB, 2011). In that year, the Statewide Emission Inventory reported a total of 160.7 tons total organic gases/year of 1-BP emissions due to solvent cleaning operations.

1-BROMOPROPANE

CAS No: 106-94-5



I. PHYSICAL AND CHEMICAL PROPERTIES

(PubChem, 2020)

Molecular formula	C_3H_7Br
Molecular weight	122.99 g/mol
Synonym	n-Propyl bromide
Description	Colorless liquid when fresh
Density/Specific gravity	1.353 @ 20°C/20°C
Boiling point	71°C at 760 mm Hg (torr)
Vapor pressure	110.8 mm Hg (torr) @ 20°C
Solubility	Soluble in acetone, ethanol, ether, benzene, chloroform, carbon tetrachloride; Slightly soluble in water (2,450 mg/L @ 20°C)
Conversion factor	1 ppm = 5.03 mg/m^3

II. HEALTH ASSESSMENT VALUES

Unit Risk Factor:	3.7×10^{-6} (µg/m^3)$^{-1}$
Inhalation Slope Factor:	1.3×10^{-2} (mg/kg-day)$^{-1}$

III. CARCINOGENICITY

Carcinogenicity studies for 1-BP have been conducted in rats and mice. There are no human carcinogenicity data.

NTP Cancer Bioassay

The NTP conducted two-year 1-BP inhalation studies in male and female F344/N rats and B6C3F$_1$/N mice (Morgan *et al.*, 2011; NTP, 2011). 1-BP was chosen for study by NTP due to the potential for increasing widespread use and the lack of carcinogenicity data. Rodents were exposed whole-body in chambers to 0, 62.5 (mice only), 125, 250, or 500 (rats only) ppm (314, 629, 1,258 and 2,515 mg/m^3) 1-BP for 6.17 hrs/day, 5 days/week for 105 weeks. The daily exposures included the 6

hr exposure time at a uniform aerosol concentration plus the ramp-up time of 10 min (0.17 hrs/day) to achieve 90% of the target concentration after the beginning of aerosol generation. The decay time to 10% of the target concentration at the end of the exposures was about 10-11 min.

F344/N rats

Body weights of male and female rats at all exposure levels were similar to controls, remaining within 8% of controls throughout the 2-year study. Survival was significantly reduced in the 500 ppm males compared to controls (p = 0.033, life table pairwise comparison) (NTP, 2011). In this exposure group, 9 of 37 deaths prior to terminal sacrifice were attributed to chronic inflammation in various organs (lung, nose, skin, and bone) that were related to 1-BP exposure, while the remaining early deaths were attributed to various types of neoplasia that were not treatment-related. In females, decreased survival in the 500 ppm group was not significant (p = 0.054) compared to the controls. However, the life table trend test indicated decreased survival of the female rats with increasing dose (p = 0.028).

The statistically significant (p < 0.05) or biologically noteworthy tumor incidences in male and female rats are shown in Table 1. The incidence of adenoma of the large intestine (colon or rectum) was significantly increased in 500 ppm female rats and a significant positive trend (p = 0.004) for this tumor was observed. In 1-BP treated males, the low incidence of these tumors resulted in no significant difference relative to controls, and no significant positive trend was found. This tumor is rare in F344/N rats. The historical incidence in 2-year inhalation studies with male rat chamber controls is: 0/349; all routes 2/1,398 (0.1% ± 0.5%), range 0-2%. The incidence of adenoma of the large intestine was exceeded in 250 ppm males (2/50, 4%) . The NTP (2011) concluded that the presence of these tumors in exposed females and the low historical incidence in controls indicated the tumors in males were exposure related. Although no carcinomas of the large intestine were found in the 1-BP-exposed rats, adenoma of the large intestine can progress to carcinoma (NTP, 2011a).

Skin tumors of epithelial origin were increased in exposed male rats (Table 1). The tumor incidence of keratoacanthoma was significantly increased in the 250 and 500 ppm groups compared to controls, and a significant positive trend was observed. The tumor incidence of keratoacanthoma or squamous cell carcinoma combined was significantly increased in 500 ppm males and a significant positive trend was observed. Keratoacanthoma is a rapidly growing benign neoplasm of squamous epithelial origin that is considered to progress to squamous cell carcinoma. The

historical control range for keratoacanthoma and keratoacanthoma or squamous cell carcinoma (combined) was exceeded in 250 and 500 ppm males.

When combining all neoplasms of epithelial origin, the tumor incidence of keratoacanthoma, basal cell adenoma, basal cell carcinoma, or squamous cell carcinoma in males was significantly increased in all exposed groups, and a positive trend was observed (Table 1). The incidence for all epithelial tumors combined in all exposed groups exceeded the historical control range for inhalation studies. The NTP (2011) concluded that the increased incidences of all tumors of epithelial origin were a result of 1-BP exposure.

Tumors of the skin were not as prevalent in exposed female rats. A positive trend for tumor incidence was found when squamous cell papilloma, keratoacanthoma, basal cell adenoma, or basal cell carcinoma were combined, but pairwise comparison of 1-BP exposed groups with controls did not result in a significant increase in tumors in any group (Table 1). The tumor incidence in the 500 ppm group did exceed the historical incidence for controls for inhalation studies (2/350 – 0.6% ± 1.0%, range 0-2%) and for all routes of exposure (16/1350 – 1.2% ± 1.8%, range 0-6%). The NTP (2011) concluded there was equivocal evidence for these skin tumors in exposed female rats due to the absence of statistically significant pairwise comparisons for keratoacanthoma alone and for all tumors combined, and because there were no observed squamous cell carcinomas.

A positive trend for the incidence of malignant mesothelioma was observed in male rats, and the incidence in the 500 ppm group was near statistical significance (p=0.059). This neoplasm originated in the epididymis but was also found in other tissues, particularly the testis. The NTP (2011) noted that the historical control incidence was surpassed in the 500 ppm group (inhalation studies: 5/349 – 1.4% ± 2.2%, range 0-6%; all routes: 35/1,398 – 2.5% ± 2.3%, range 0-6%). The NTP concluded there was only equivocal evidence for carcinogenicity for this tumor due to its common occurrence in this strain of male rats, lack of a statistically significant increase in exposed groups relative to controls, and because the 500 ppm group tumor incidence was barely above the historical control range.

In male rats, a significant increase in the tumor incidence for pancreatic islet cell adenoma occurred in most 1-BP-exposed groups, and a positive trend near statistical significance (p=0.056) was observed (Table 1). However, the historical control range for this neoplasm in inhalation studies (0% to 12%) was not exceeded in any of the exposed groups and the mean incidence in historical control inhalation studies (5.7% ± 3.9%) was greater than that in chamber controls (0%). Thus, the NTP considered

the increased incidence of this tumor as equivocal evidence for carcinogenicity. No significant difference from control was observed for the incidence of pancreatic islet cell carcinoma, and no positive trend was observed. The incidence of carcinomas in the 125 ppm group (7/50) was above the historical control range (inhalation studies: 17/349 – 4.9% ± 3.3%, range 2-10%; all routes: 29/1,394 – 2.1% ± 2.6%, range 0-10%). The NTP (2011) concluded that pancreatic islet cell carcinoma demonstrated equivocal evidence of carcinogenicity due to the lack of a significant increase over control incidence.

For pancreatic islet cell adenoma or carcinoma (combined), there was a significantly increased tumor incidence in the 125 ppm group, but a significant positive trend was not demonstrated. The historical control range in the 125 ppm group was exceeded (inhalation studies: 37/349 – 10.6% ± 4.8%, range 6-18%; all routes: 119/1,394 – 8.6% ± 4.0%, range 0-18%). Although not specifically addressed by the NTP, the combined tumor incidence data was apparently not strong enough to affect the conclusion of equivocal evidence for carcinogenicity based on the individual adenoma and carcinoma incidence rates.

Table 1. Unadjusted tumor incidence in rats exposed to 1-BP for two years (NTP, 2011a)[a,b]

Tumor Type		Incidence by concentration				Statistical p-values for pairwise comparison with controls			
	ppm	0	125	250	500	Trend[c]	125	250	500
	mg/m^3	0	629	1258	2515		629	1258	2515
Male Rat									
Large Intestine (colon or rectum): Adenoma		0/50	0/50	2/50	1/50	0.140	1.000	0.247	0.500
Skin: Basal Cell Adenoma		0/50	1/50	2/50	1/50	0.247	0.500	0.247	0.500
Skin: Basal Cell Carcinoma		0/50	2/50	1/50	2/50	0.160	0.247	0.500	0.247
Skin: Keratoacanthoma		0/50	3/50	6/50*	6/50*	0.010	0.309	0.013	0.013
Skin: Squamous Cell Carcinoma		1/50	1/50	0/50	2/50	0.247	0.753	1.000	0.500
Skin: Keratoacanthoma or Squamous Cell Carcinoma		1/50	4/50	6/50	8/50*	0.008	0.181	0.056	0.015
Skin: Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma		1/50	7/50*	9/50**	10/50**	0.007	0.030	0.008	0.004
Malignant Mesothelioma†		0/50	2/50	2/50	4/50	0.026	0.247	0.247	0.059
Pancreatic Islets: Adenoma†		0/50	5/50*	4/50	5/50*	0.056	0.028	0.059	0.028
Pancreatic Islets: Carcinoma†		3/50	7/50	5/50	3/50	0.662	0.159	0.357	0.661
Pancreatic Islets: Adenoma or Carcinoma†		3/50	10/50*	9/50	8/50	0.158	0.036	0.061	0.100
Female Rat									
Large Intestine (colon or rectum): Adenoma		0/50	1/50	2/50	5/50*	0.004	0.500	0.247	0.028
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, or Basal Cell Carcinoma†		1/50	1/50	1/50	4/50	0.040	0.753	0.753	0.181

(a) The numerator represents the number of tumor-bearing animals; the denominator represents animals examined. †= Tumor type and incidence data represents equivocal finding for carcinogenicity by NTP (2011a)

(b) * = p<0.05, ** = p<0.01; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA

(c) p-values in the trend column are for the Cochran-Armitage trend test performed by OEHHA.

Nonneoplastic findings included increased incidence of various upper respiratory lesions in the nose, larynx and trachea in some or all exposed groups of rats, including chronic active inflammation, suppurative chronic inflammation, epithelial hyperplasia in the nose and trachea, and respiratory metaplasia of the nasal olfactory epithelium. Chronic suppurative inflammation was significantly increased in the lung of 500 ppm females. Chronic suppurative inflammation was also present in skin and some other tissues of 500 ppm male and females. These lesions are characterized by the presence of Splendore Hoeppli material, which were not seen in controls. The presence of Splendore Hoeppli material has been associated with diseases that compromise the immune system (NTP, 2011a).

B6C3F$_1$/N mice

Body weights of male and female mice at all exposure levels were similar to controls throughout the 2-year studies (NTP, 2011). Survival of the mice was unaffected by 1-BP exposure.

There was no evidence of carcinogenic activity of 1-BP in male mice. However, an increased incidence of lung tumors was observed in 1-BP-exposed female mice (Table 2). Significantly increased tumor incidences of alveolar/bronchiolar adenomas (250 ppm group), alveolar/bronchiolar carcinomas (62.5 and 125 ppm groups), and combined alveolar/bronchiolar adenoma or carcinoma (all exposed groups) were present, including positive trends for the adenoma and combined adenoma or carcinoma. In addition, multiple adenomas were found in two 250 ppm females and multiple carcinomas were found in two 62.5 ppm females, one 125 ppm female, and one 250 ppm female. The inhalation study historical control range for alveolar/bronchiolar adenoma and for the adenoma or carcinoma (combined) was exceeded by the 250 ppm group and by all exposed groups, respectively.

Table 2. Un-adjusted tumor incidence in mice exposed to 1-BP for two years (NTP, 2011a)[a,b]

Tumor Type (Female Mouse)		Incidence by concentration				Statistical p-values for pairwise comparison with controls			
	ppm	0	62.5	125	250	Trend[c]	62.5	125	250
	mg/m^3	0	314	629	1258		314	629	1258
Lung: Alveolar/Bronchiolar Adenoma		1/50	6/50	4/50	10/50**	0.004	0.056	0.181	0.004
Lung: Alveolar/Bronchiolar Carcinoma		0/50	7/50**	5/50*	4/50	0.189	0.006	0.028	0.059
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma		1/50	9/50**	8/50*	14/50**	<0.001	0.008	0.015	<0.001

(a) The numerator represents the number of tumor-bearing animals; the denominator represents animals examined

(b) * = p<0.05, ** = p<0.01; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA;

(c) p-values in the trend column are for the Cochran-Armitage trend test performed by OEHHA.

Increased incidences of nonneoplastic findings were observed in the upper and lower respiratory airways in some or all exposed groups of mice. Bronchiolar regeneration was observed in most exposed male and female mice. This lesion was almost completely absent in control mice. Cytoplasmic vacuolization in the bronchiolar epithelium of the lung, the respiratory epithelium of the nose, and the epithelium of the larynx and trachea was increased in all exposed male groups. Cytoplasmic vacuolization was also increased in upper and lower airways in all exposed female groups, but at lower rates compared to males. In the nose of male and female mice, there was also an increased incidence of hyperplasia of the respiratory epithelium and metaplasia of the olfactory epithelium in some or all exposed groups.

Toxicokinetics

The mechanism by which 1-BP causes cancer has not been elucidated, although metabolic activation to reactive metabolites is suspected to be involved (Morgan *et al.*, 2011). The metabolism of inhaled and absorbed 1 BP occurs primarily through oxidative metabolism via P450 enzymes, conjugation with GSH and debromination, although the majority of 1-BP can be excreted unchanged in exhaled air. Metabolism of 1-BP has been shown to produce effects that other carcinogens are known for, such as oxidative stress via glutathione depletion and immunomodulation (Lee *et al.*, 2007; Guyton *et al.*, 2009; Liu *et al.*, 2009; Miao *et al.*, 2018).

Rodent models

Toxicokinetic studies have been carried out in male F344 rats and $B6C3F_1$ mice (Garner *et al.*, 2006). The disposition of [1-^{14}C]-1-BP radioactivity following relatively low doses (3.4 - 5.9 mg/kg) via intravenous (IV) administration was similar in rats and mice. A majority of the radiolabel was exhaled as volatile organic compounds (VOC; 40–71%) or as $^{14}CO_2$ (10–31%) within four hours. ollowing administration. The radiolabel recovered in urine ranged from 17 to 23%. Roughly 2% and 6% was recovered in feces and carcass, respectively. The radiolabel exhaled as VOC was later identified in Garner et al. (2015) as the parent compound, 1-BP.

The identification of urinary metabolites was carried out following IV administration and inhalation exposure of [1,2,3-^{13}C]-labeled 1-BP in rats (Garner *et al.*, 2006). Similar to the inhalation route, IV administration does not involve hepatic “first pass” metabolism and is more likely to be consistent with metabolism derived from workplace or environment inhalation. As expected, similar results were obtained for both exposure routes. The main urinary metabolites and percent of the total excreted in the urine were: *N*-acetyl-*S*-propylcysteine (37%), *N*-acetyl-3-(propylsulfinyl)alanine

(5%), *N*-acetyl-*S*-(2-hydroxypropyl)cysteine (16%), 1-bromo-2-hydroxypropane-*O*-glucuronide (9%), *N*-acetyl-*S*-(2-oxopropyl)cysteine (12%), and *N*-acetyl-3-[(2-oxopropyl)sulfinyl]alanine (% not stated). The authors indicated that many of these metabolites were likely formed after cytochrome P450 (CYP)-catalyzed oxidation of 1-BP to 1-bromo-2-propanol and bromoacetone, followed by glutathione (GSH) conjugation with either of those metabolites. Other identified 1-BP metabolites formed by CYP-mediated oxidation in rodents include α-bromohydrin and glycidol, both of which have been shown to be mutagenic (Stolzenberg and Hine, 1979; IARC, 2000; Ishidao *et al.*, 2002; Garner *et al.*, 2007). The scheme established in Garner et al. (2015) for 1-BP metabolism in the rat is shown in Figure 1.

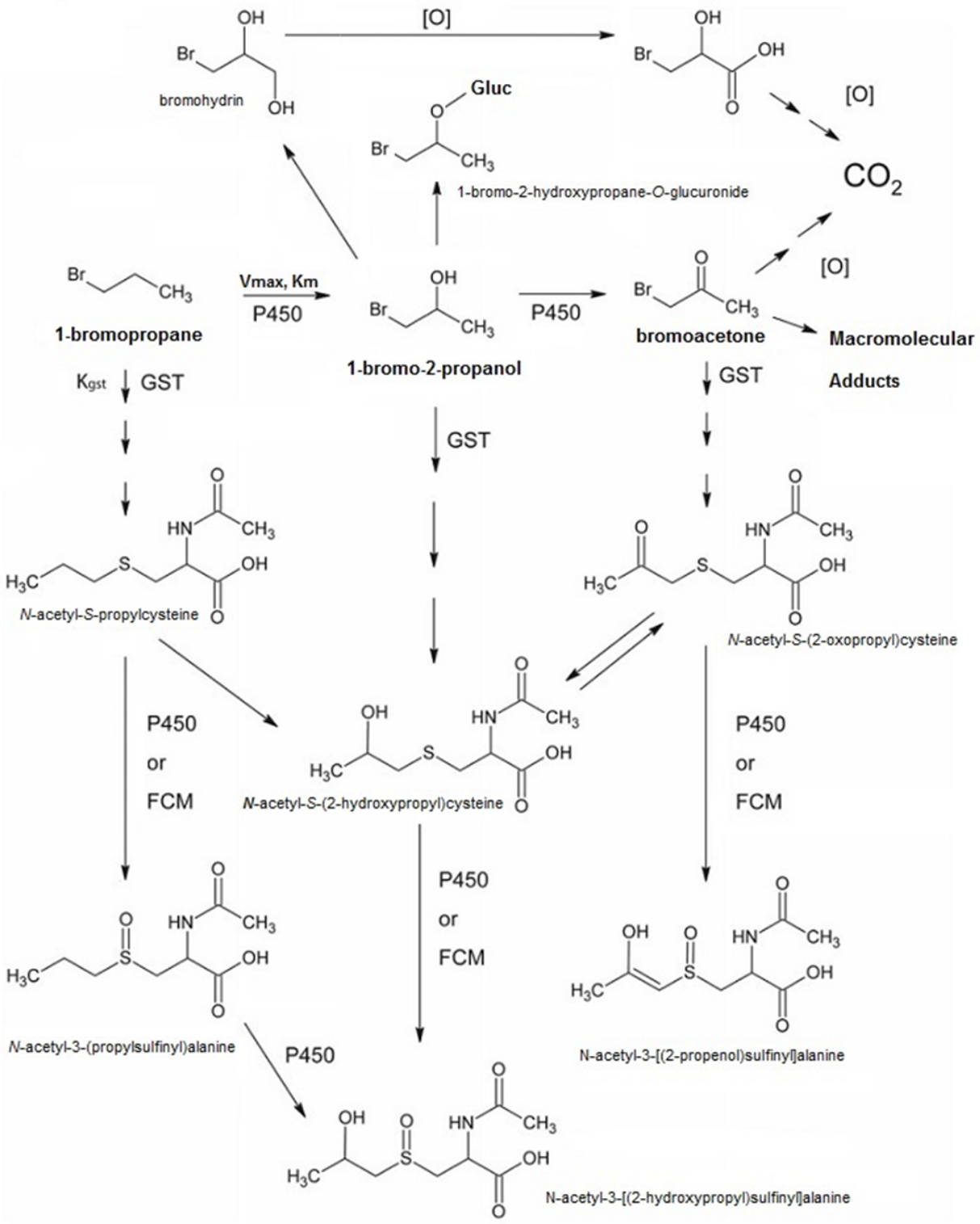


Figure 1. Metabolism of 1-BP in rats: Figure 2 of Garner et al. (2015).
GST = glutathione-S-transferase; FCM = Flavin monooxygenase; Vmax = maximal velocity; Km = Michaelis Constant; Kgst = proportionality constant for linear pathway metabolized by glutathione transferase; →→ multiple steps of reaction

When rats were pretreated with 1-aminobenzotriazole, a potent but nonselective CYP inhibitor/inactivator, the only urinary metabolite found was *N*-acetyl-*S*-propylcysteine, which contributed greater than 90% of the urinary radioactivity (Garner *et al.*, 2006). This metabolite is formed by direct conjugation of 1-BP with GSH. The authors concluded that CYP enzymes contribute significantly to the production of the major oxidative metabolites of 1-BP.

In a follow-up study, Garner et al. (2007) exposed *Cyp2e1*$^{-/-}$ and wild-type (WT) mice to [1,2,3-^{13}C]-1-BP to determine the contribution of cytochrome P450 2E1 (CYP2E1) to the metabolism and elimination of the chemical. In *Cyp2e1*$^{-/-}$ mice, which lack the CYP2E1 isozyme, the elimination half-life in gas uptake studies was longer compared to WT mice (3.2 vs. 1.3 hrs). The major urinary metabolite derived via oxidation to 1-bromo-2-propanol, *N*-acetyl-*S*-(2-hydroxypropyl)cysteine, was reduced about 50% in *Cyp2e1*$^{-/-}$ mice compared to WT mice. In addition, the ratio of products of direct conjugation of 1-BP with GSH to oxidative 2-hydroxylation increased 5-fold in *Cyp2e1*$^{-/-}$ mice relative to WT mice. These data suggested to the authors that CYP2E1 is a major CYP contributor in the oxidative metabolism of 1-BP.

Garner and Yu (2014) evaluated the species and sex-dependent factors influencing 1-BP toxicokinetics in F-344 rats and B6C3F$_1$ mice after intravenous and inhalation exposure. Male F-344 rats were given intravenous (iv) bolus injections of 1-BP at 5 or 20 mg/kg body weight (BW), and blood levels were determined at time intervals up to 4 hours. Male and female F-344 rats and B6C3F1 mice were also exposed to initial inhalation concentrations of 70, 240, 800, and 2,700 ppm (0, 350, 1,200, 4,000, and 14,000 mg/m^3) 1-BP in a closed gas uptake system, and subsequent 1-BP atmospheric loss rates monitored for 6 hours. Systemic clearance of bolus iv-administered 1-BP in the blood of rats was rapid and decreased with increasing dose. Approximately 99% was eliminated from the body by 3 hrs post-exposure. The average elimination half-life was 0.39±0.08 and 0.85±0.09 hr at 5 and 20 mg/kg BW, respectively. However, systemic clearance decreased with increasing iv dose. Plasma bromine levels were measured in the rats after iv administration; bromine is released from 1-BP either by oxidative metabolism or by conjugation with GSH. The bromine levels suggested that approximately 30% of administered 1-BP was metabolized by either route and eliminated in urine. The authors surmised that the remainder was largely lost by exhalation, either as 1-BP or as CO_2.

In the gas uptake portion of the study, as the air concentration of 1-BP increased, the terminal air elimination rate decreased suggesting to the authors that one or more routes of elimination became saturated as chamber concentration increased (Garner and Yu, 2014). At a given starting concentration, male rats tended to eliminate 1-BP

from the chamber more rapidly than females. Plasma bromide levels were also measured in the rats following gas uptake. The results showed that oxidative metabolism in female rats was lower compared to males, indicating that oxidative metabolism in females may be saturated at lower concentrations. In male and female mice, elimination of inhaled 1-BP occurred at similar rates up to 800 ppm. At higher concentrations, the half-life increased, with male mice eliminating 1-BP from the chamber more slowly than female mice. The data also showed that mice tend to have a higher 1-BP oxidative metabolic capacity relative to rats. Regarding urinary metabolites, the authors noted that rats produced both directly GSH-conjugated parent and oxidative metabolites, while mice only produced a single oxidative metabolite (2-hydroxybromopropane) which was then conjugated with GSH.

Rats were also pretreated with chemical inhibitors of CYP (1-aminobenzotriazole) and GSH (D,L-buthionine (S, R)-sulfoximine) synthesis, prior to exposure to 1-BP at 800 ppm (4,024 mg/m^3) in inhalation chambers (Garner and Yu, 2014). The half-life of 1-BP in rats following inhibition of CYP (9.6 hours) or depletion of GSH (4.1 hours) increased relative to controls (2.0 hours), supporting the authors' position that 1-BP elimination is highly dependent on both CYP and GSH-dependent metabolism.

Applying the above gas-uptake experiments in the Fischer 344 rat, a physiologically based pharmacokinetic (PBPK) model was developed by simulating the 1-BP level in a closed chamber (Garner *et al.*, 2015). They tested the hypothesis that metabolism includes both P450 CYP2E1 activity and glutathione (GSH) conjugation. The results showed that two metabolic pathways adequately simulated 1-BP levels in the closed chamber. Furthermore, the model was tested by simulating the gas-uptake data of the female rats pretreated with the P450 inhibitor 1-aminobenzotriazole, or the GSH synthesis inhibitor d,l-buthionine (S,R)-sulfoximine, prior to inhalation of 800 ppm (4,000 mg/m^3) 1-BP. As in their previous study, pretreatment with either of these inhibitors dramatically prolonged the half-life of 1-BP elimination, and suggested CYP 450 and GSH had major roles for 1-BP metabolism.

Based on the closed chamber and gas-uptake data in the female rat, sex-specific metabolic parameters were also estimated and extrapolated into different exposure levels in the PBPK model (Garner et al., 2015). In the model, the metabolic rate Vmax and Km were about 1.5 and 2 times larger in the male rat than those in the female. The GSH-related constant (Kgst) in the male rat was estimated to be about 2 times that of the female constant. After adjusting Vmax by the rat's body weight (male rat body weight was considerably greater than the female rat body weight), the values were improved and shown to be similar between male and female rats, which

indicates body weight as a possible contributor to the sex-specific differences in the toxicokinetics of 1-BP.

A human PBPK model for 1-BP was developed by extrapolating the metabolic parameters obtained from the gas-uptake studies in rats, and applying them to a general human PBPK model for volatile compounds (Garner et al., 2015). In a repeated exposure scenario (20 or 200 ppm per day), modeling showed that rats do not accumulate 1-BP in blood, whereas humans show a 20% increase over 5 days of exposure. While 1-BP has a moderate fat:blood partition coefficient (20.2), a higher fat tissue content in humans (21.4%) compared to rats (7%) may explain this increase. However, additional experimental data for specific organ dosimetry and for the metabolites of 1-BP will need to be incorporated into the PBPK model to allow the quantitative extrapolation of animal studies to humans for risk assessment purposes.

Toxicokinetics in children and adults

The urinary mercapturic metabolite, N-acetyl-*S*-propylcysteine, found in rodents by Garner and associates has also been identified in the urine of 1-BP-exposed workers (Valentine *et al.*, 2007; Hanley *et al.*, 2009). In addition, a urinary metabolite not identified in rodents, N-acetyl-S-(3-hydroxy-n-propyl)cysteine, has been found in workers exposed to 1-BP (Cheever *et al.*, 2009; Hanley *et al.*, 2009) . As in rodents, N-acetyl-*S*-propylcysteine was identified as the predominant urinary metabolite in exposed workers and was proposed as a biomarker of exposure. Although less specific for 1-BP exposure, urinary bromide has also been proposed as a biomarker of 1-BP exposure in workers (Hanley *et al.*, 2010) .

In a peer-reviewed report, NIOSH investigators obtained 48-hour urine specimens from 30 workers at two factories making polyurethane foam seat cushions and from 21 unexposed control subjects (Hanley *et al.*, 2009). The urine was collected into composite samples for three time intervals: at work, after work but before bedtime, and upon awakening. Time-weighted average (TWA) geometric mean breathing zone concentrations of 1-BP were 92.4 ppm (460 mg/m^3) for sprayers (n=13) and 10.5 ppm (53 mg/m^3) for non-spraying jobs (n=17). Urinary N-acetyl-S-propylcysteine in urine showed the same trend as TWA exposures to 1-BP (i.e., sprayers had higher levels). Associations of N-acetyl-S-propylcysteine concentrations, adjusted for creatinine, with 1-BP TWA exposure were statistically significant for both sprayers ($p < 0.05$) and non-sprayers ($p < 0.01$). The study confirmed that urinary N-acetyl-S-propylcysteine is an important 1-BP metabolite and an effective biomarker for highly exposed foam cushion workers.

The unmetabolized parent compound has also been identified in end-of-shift urine samples from 1-BP-exposed production workers, and was significantly correlated to the concentration of 1-BP in air (Kawai *et al.*, 2001; Ichihara *et al.*, 2004a). Measurable levels of 1-BP in end-of-shift urine was found when the TWA exposure was >2 ppm (Kawai *et al.*, 2001). Unmetabolized 1-BP has not been detected in the urine of rats and mice (Garner *et al.*, 2006). Due to potential evaporative loss of 1-BP from urine, the samples need to be immediately placed in sealed head-space vials with analysis often conducted the next day (Ikeda, 1999; Kawai *et al.*, 2001).

CYP2E1 is known to be a major CYP isozyme that metabolizes 1-BP in rodents. Initial reports in humans did not detect CYP2E1 in fetal liver samples, but CYP2E1 increased rapidly within hours of birth (Vieira *et al.*, 1996; Cresteil, 1998). A more recent report with 73 fetal samples and 165 postnatal samples found that CYP2E1 is detectable by immunological techniques at low levels in some (37%) fetuses beginning in the second trimester, and in the third trimester it is present in most (80%) fetuses at 10-20% of adult levels (Johnsrud *et al.*, 2003; Hines, 2007). In the neonatal period (0-29 days) the mean level was about 25% that of adults but the variability among samples was nearly 80-fold (Johnsrud *et al.*, 2003). From 1 month to 1 year, the mRNA for CYP2E1 accumulates and CYP2E1 protein increases toward adult levels (Table 3) (Vieira *et al.*, 1996; Hines, 2007) (Vieira *et al.*, 1996; Hines, 2007). However, considerable interindividual variability is observed in the immediate postnatal (1–6 months) onset or increase in expression of CYP2EI and other CYP enzymes (Johnsrud *et al.*, 2003; Hines, 2007).

Table 3. Increase of CYP2E1 (mean ± SD) with age in human liver (Hines, 2007)

Age	n	pmol CYP2E1/mg protein
1st trimester fetus: 8-13.4 weeks	14	- (not detectable)
2nd trimester fetus: 13.6-25 weeks	45	0.3 ± 0.6
3rd trimester fetus: 27-40 weeks	14	5.8 ± 4.6
Neonate: 0-29 days	42	13.4 ± 16.0
Infant: 1.1-11.3 months	64	36.2 ± 20.3
Prepubertal: 1.1-10.0 years	41	43.1 ± 20.6
Adolescent: 11.0-17.7 years	20	~68[a]
Adult	-	~50[a]

[a] Median, in pmol CYP2E1/mg protein

OEHHA noted that low levels of CYP2E1 in infants may reduce metabolism of 1-BP in the infant, resulting in increased elimination of unchanged 1-BP via exhalation. Presuming that the parent compound has little or no toxicity, this could decrease, rather than increase, the sensitivity of the very young to the toxicity of 1-BP. However, there is currently no evidence to support this concept.

In non-occupational settings, surveys of children and pregnant women have found the 1-BP metabolite, N-acetyl-S-propylcysteine in most urine samples examined. From 2009 to 2010 the National Children's Vanguard Study collected urine samples from 488 third trimester pregnant women at in-person study visits (Boyle *et al.*, 2016). Urinary metabolites of 28 VOCs were quantified simultaneously using ultra-high performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry (UPLC-ESI/MSMS). N-acetyl-S-propylcysteine was present in 99% of the urine samples. The levels reported were 2.61 ng/mL for the 50th percentile, 9.44 ng/mL for the 75th percentile, and 4,260 ng/mL for the maximum person. The authors did not identify sources of the metabolite, other than to note that dry cleaning and metal cleaning solvents are known sources of 1-BP.

Data from the National Health and Nutrition Examination Survey (NHANES) for 2011-2012 were used to evaluate variability in the levels of 20 urinary metabolites of VOCs (including 1-BP) by age, gender, and race/ethnicity (Jain, 2015) Among 417 children ages 6 through 11, the mean levels of N-acetyl-S-propylcysteine were 2.6 (2–3.3) ng/mL in boys and 3.3 (2.5–4.3) ng/mL in girls (adjusted geometric means with 95% confidence intervals). Jain also reported that concentrations of the urinary 1-BP metabolite decreased with the increase in the number of rooms in the child's home (p=0.03). The number of rooms in a child's home is an indicator of socioeconomic status. However, the reason for this correlation was not known. No correlation of the 1-BP metabolite was observed with age, poverty income ratio, body mass index, or number of smokers in the house.

Genotoxicity

The genotoxicity and mutagenicity database for 1-BP is not extensive, and the overall results have been mixed. Genotoxicity studies are summarized below, followed by a table summary (Table 4 at the end of the section).

DNA strand-break tests

The comet assay is a commonly used method to identify DNA lesions (*e.g.*, breaks or alkali-labile sites) following exposure of an isolated cell culture with a genotoxin. This assay measures premutagenic lesions, which, in intact cells, can be removed by DNA repair processes, if the repair occurs prior to DNA replication. Thus, positive assay data for a given compound do not necessarily indicate that the compound will induce mutations.

Toraason and coworkers used the comet assay to assess DNA damage in human leukocytes exposed *in vitro* to 1-BP, and in peripheral leukocytes *in vivo* from 53

workers occupationally exposed at two facilities to 1-BP (Toraason *et al.*, 2006). In the *in vitro* portion of the study, leukocytes were collected from a single non-1-BP-exposed human volunteer and cultured with 1- or 2-BP (0, 0.01, 0.1 or 1 mM). The cells were cultured without metabolic activation. Both 1- and 2-BP induced a significant increase ($p < 0.05$, ANOVA) in comet tail moment at the highest concentration (1 mM). However, 1-BP induced apoptosis at a lower concentration (0.1 mM), which the authors suggested could mean cells with excessive DNA damage may be eliminated and reduce the potential for mutation.

In the *in vivo* worker study, 1-BP was used at the facilities as a solvent for spray adhesives in foam cushion fabrication (Toraason *et al.*, 2006). Breathing zone samples, collected with personal air monitors, was assessed in sprayers and non-sprayers for 1 to 3 days. The exposure concentrations ranged from 0.2 to 271 ppm (1-1,363 mg/m^3). The mean 1-BP time-weighted average (TWA) at Facility A for sprayers (n=3 and 10 for men and women, respectively) and non-sprayers (n=15 and 14 for men and women, respectively) was 83 ± 85 ppm and 2 ± 2 ppm, respectively. The mean 1-BP TWA at Facility B for sprayers (n=6, women only) and non-sprayers (n=3 and 13 for men and women, respectively) was 21 ± 5 ppm and 5 ± 1 ppm, respectively. The study lacked a control group with no 1-BP exposure. Internal biomarkers of exposure (serum and urine Br levels) were highly correlated with 1-BP environmental exposure levels.

At both facilities, comet tail moments of leukocytes from sprayers were greater than comet tail moments of leukocytes from non-sprayers, but the difference did not reach statistical significance at $p < 0.05$ (Toraason *et al.*, 2006). An increased dispersion coefficient ($p < 0.05$) in sprayers from Facility A was observed at the end-of-week relative to start-of-week. The dispersion coefficient is the tail moment variance divided by the mean, and variance was determined from 100 leukocytes from each sample. The increased dispersion coefficient during the work week occurred in the subgroup with the highest exposure (i.e., sprayers at Facility A), which suggested to the authors that comets in a sub-population of cells were affected by 1-BP. However, confirming this conclusion would require data indicating that dispersion coefficients were not increased during the week in an unexposed control group, which was not included in this study.

Using multiple linear regression models, Toraason *et al.*, found that start-of-week tail moment was significantly associated with serum Br quartiles ($p<0.05$). End-of-week comet tail moment was also significantly associated with 1-BP TWA quartiles and serum Br quartiles ($p<0.05$). For quartile analysis, all workers were placed into four exposure groups of equal number, (low, medium low, medium high and high

exposure). Other positive associations were observed with tail moment (e.g., 1-BP TWA log ppm, serum Br log mg/dl), but did not reach statistical significance. No statistically significant positive associations were found with the dispersion coefficient and exposure. Overall, the authors found the comet assay results inconsistent, providing only limited evidence that 1-BP increased DNA damage in the workers. Possible confounders cited included temporal variation in the comet assay, lack of breathing zone data from some workers, breathing zone concentrations of 1-BP too low to show definitive *in vivo* evidence of DNA damage in leukocytes, and small sample size.

The human hepatoma cell line, HepG2, was used to determine if 1-BP can induce DNA single strand breaks in these cells *in vitro* (Hasspieler *et al.*, 2006). In addition, cell viability and altered enzyme activity were measured using the neutral red uptake assay and the ethoxyresorufin *O*-deethylase assay, respectively. The tests were performed at seven dose levels, from 25 to 500 ppm. 1-BP did not induce an increase in single strand breaks at the concentrations tested. Cell viability was reduced at the highest concentration (500 ppm), and no effect on enzyme activity was observed.

DNA Adduct formation *in vitro* and *in vivo*

Thapa et al., (2016) observed the formation of N-propyl guanine adduct when 1-BP was incubated with 2'-deoxyguanosine. Subsequently, 1-BP was incubated with calf thymus DNA *in vitro* under physiological conditions for 18 hr, following which unreacted 1-BP was removed and the reactant subjected to thermal hydrolysis to look for the presence of N-propyl guanine. The adduct was found to be generated in a dose-dependent manner without enzymatic support, suggesting that 1-BP could be a direct-alkylating agent.

Adult male Sprague-Dawley rats were injected intraperitoneally with 500 or 1000 mg/kg 1-BP once or daily for three days and then necropsied six hours following the last injection to determine the extent of N-propyl guanine adduct formation in DNA of several organs (Nepal *et al.*, 2019). The highest levels of adduct formation (in pmole/g DNA) was found in the liver, followed by spleen and kidney. Smaller amounts were observed in testis and lung, and none was detected in heart tissue. DNA adduct formation in tissues increased in both a time- and dose-dependent manner.

In a subsequent study by Nepal et al. (2019), 1-BP was incubated *in vitro* with calf thymus DNA, both with and without liver homogenate. Formation of N-propyl

guanine was not affected by the addition of liver homogenate, suggesting to the authors that 1-BP can act as a direct alkylating agent.

Induction of DNA repair

In addition to the DNA single strand break test conducted by Hasspieler et al. (2006), the ability of 1-BP to induce DNA repair in human HepG2 hepatoma cells was investigated over the same concentration range of 25 to 500 ppm. Repair of DNA was measured by incorporation of labelled healthy nucleotides ([^{3}H]-thymidine) at previously damaged DNA sites. 1-BP did not induce an increase in DNA repair over the range of concentrations tested.

Bacterial mutation tests

Barber and coworkers were able to show mutagenic activity of 1-BP in the Ames Salmonella test when evaporation of 1-BP was prevented by using a closed system (Barber *et al.*, 1981). Bacterial strains tested included *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100. 1-BP (1.1 to 20.3 µmoles/plate, or 135 to 2497 µg/plate) was mutagenic only in *S. typhimurium* TA1535 and TA100 strains, showing similar activity in the presence and the absence of S9. This finding indicated it is a direct acting mutagen.

The mutagenicity of 1-BP was also tested in the same five *S. typhimurium* strains (i.e., TA98, TA100, TA1535, TA1537 and TA1538) with and without S9 mix by Elf Atochem (1994). Concentrations ranged from 100 to 10,000 µg/plate, with the highest concentration resulting in cytotoxicity. A closed system for incubation of culture plates was used to prevent volatilization of 1-BP. Unlike the results of Barber et al. (1981), no evidence of mutagenicity was observed in any strain, with or without S9 mix. This study has not been published in a peer-reviewed publication, but was summarized by the NTP-CERHR expert panel (NTP, 2003). The panel found this study to be well conducted and without any perceived weaknesses.

1-BP was not mutagenic in either of two independent bacterial mutagenicity assays, each conducted with and without induced-rat liver activation enzymes (S9) (NTP, 2011). Bacterial strains tested included *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, and *Escherichia coli* strain WP2 *uvrA*/pKM101. Exposure levels tested ranged from 33 to 10,000 µg 1-BP per plate. The NTP (2011) did not use a closed system to prevent potential 1-BP loss due to volatilization, as Barber *et al.* had

used. NTP suggested volatility as a possible cause of the negative results in the study.

Mammalian cell gene mutation tests

1-BP was investigated for the ability to induce mutations *in vitro* at the thymidine kinase (TK) locus in L5178Y mouse lymphoma cells (Elf Atochem, 1996). The test determines if a substance can induce forward mutation from the parental type ($TK^{+/-}$) to the mutant form ($TK^{-/-}$), which in a specific medium only allows mutant cells to grow and form colonies. The top dose level of 1-BP used was based on cytotoxicity, identified as giving ≥10-20% relative survival assessed by relative cloning efficiency. Two independent tests were run, each in the presence or absence of S9 mix, resulting in a total of four tests. A positive response was considered to be a dose-related increase in mutant frequency and/or a reproducible increase in the mutant frequency (at least a doubling compared to control) for at least one dose level.

Over a dose range of 125 to 1500 µg/ml 1-BP, without S9 mix, a reproducible and significant increase in the mutation frequency occurred between 1000 and 1500 µg/ml. The relative cloning efficiency at 1500 µg/ml was 21-33%, indicating acceptable viability for the tests. A significant increase in the mutation frequency of both large and small colonies was observed. Small, slow growing colonies are mainly produced by chromosome rearrangements and large colonies are mainly produced by point mutations. With S9, over a similar dose range, no increase in mutation frequency was observed in the first test. However, a significant increase in the mutation frequency together with an increase in the number of small colonies was observed at 1500 to 2000 µg/ml in the second test. The relative cloning efficiency at 1500 and 2000 µg/ml was 36 and 9%, respectively.

Under the experimental conditions, the authors concluded that 1-BP showed mutagenic activity in their mouse lymphoma assay, especially without S9 mix. Although this study has not been published in a peer-reviewed publication, the NTP-CERHR expert panel (NTP, 2003) found that this study was well conducted and without any perceived weaknesses.

Chromosomal damage

The frequency of micronucleated cells in mouse bone marrow cells was examined following intraperitoneal (i.p.) injection of Swiss OFI/ICO:OF1 mice (at least 5 animals/group) to 600 mg/kg (males) or 800 mg/kg (females) 1-BP (Elf Atochem, 1995). Micronuclei are biomarkers of induced structural or numerical chromosomal alterations and are formed when acentric fragments or whole chromosomes fail to

incorporate into either of two daughter nuclei during cell division. Initial studies found that exposure of male mice to 800 mg/kg 1-BP by i.p injection resulted in mortality, so the dose was reduced to 600 mg/kg for male mice. No increase in micronucleated erythrocytes in bone marrow was observed in either male or female mice. A positive control group treated with cyclophosphamide did show a significant increase in micronucleated erythrocytes. This study has not been published in a peer-reviewed publication, but was summarized by the NTP-CERHR expert panel (NTP, 2003). The panel found the study to be well conducted and without any perceived weaknesses.

Mouse peripheral blood was examined for the frequency of micronucleated erythrocytes following 3-month inhalation exposure of male or female $B6C3F_1$ mice to 62.5 to 500 ppm (314 to 2,515 mg/m^3) 1-BP (NTP, 2011). No increases in the frequencies of micronucleated normochromatic erythrocytes were observed in the 1-BP-exposed mice.

Transgenic rodent mutation assay

A gene mutation study was conducted with 1-BP in Big Blue® transgenic female B6C3F1 mice to investigate the mutagenic mode of action (Stelljes *et al.*, 2019). The assay measures the mutation frequency in the *cII* gene in any tissue in the body. Female transgenic mice (7 per group) were exposed to 1-BP 6 hrs/day, 5 days/week, for 28 days at the concentrations used in the NTP (2011) mouse carcinogenicity study – 0, 62.5, 125, and 250 ppm. Another group of female transgenic mice were exposed to N-ethyl-N-nitrosourea, a known mutagen, which acted as a positive control group. At the end of the exposures, the lungs, colon and liver of the mice were collected and analyzed for increased *cII* mutant frequency. 1-BP did not induce *cII* mutations different from negative control values in any of the three organs examined, while *cII* mutations were increased in all three tissues of the positive control. The authors indicated this was evidence that 1-BP is not a direct acting genotoxic carcinogen, and should be considered a threshold carcinogen.

Table 4. Genotoxicity and mutagenicity study summaries for 1-BP

Cell type or species/strain	Description	Metabolic Activation		Reference
		without	with	
DNA strand-break tests (comet assay or other DNA damage assay)				
Human leukocytes (*in vitro*)	Comet assay	+/-	NA	Toraason *et al.,* (2006)
Human leukocytes of exposed workers (*in vivo*)	Comet assay	+/-	NA	Toraason *et al.,* (2006)
Human HepG2 cells	Hydroxylapatite DNA chromotography	-	NA	Hasspieler *et al*., (2006)
DNA adduct formation				
Calf thymus DNA	N-propyl guanine adduct formation	+	NA	Thapa et al., 2016
Calf thymus DNA	N-propyl guanine adduct formation	+	+	Nepal et al., 2019
Male rats (*in vivo*)	N-propyl guanine adducts in tissues	+	NA	Nepal et al., 2019
Induction of DNA repair (Unscheduled DNA synthesis)				
Human HepG2 cells	[^{3}H]-thymidine incorporation	-	NA	Hasspieler *et al*., (2006)
Bacterial mutation tests				
S. typhimurium	TA98 TA100 TA1535 TA1537 TA1538	- + + - -	+ + - -	Barber *et al.,* (1981)
S. typhimurium	TA98, TA100, TA1535, TA1537, TA1538	-	-	Elf Atochem, (1994)
S. typhimurium	TA97, TA98, TA100 and TA1535	-	-	NTP (2011a)
E. coli	WP2 uvrA/pKM101	-	-	NTP (2011a)
Mammalian cell gene mutation test				
L5178Y mouse lymphoma cells	parental type TK+/- to mutant form TK$^{-/-}$ forward mutation	+	+	Elf Atochem (1996)
Chromosomal damage				
Mouse bone marrow cells (*in vivo*)	Micronuclei after i.p injection	-	NA	Elf Atochem (1995)
Mouse peripheral erythrocytes (*in vivo*)	Micronuclei after 3-month inhalation exposure	-	NA	NTP (2011a)
Transgenic rodent mutation assay				
Big Blue® transgenic female B6C3F1 mice (*in vivo*)	*cII* gene mutation frequency in lung, colon, and liver	-	NA	Stelljes *et al.,* 2019

+/-: equivocal; NA: not applicable

Dominant lethal mutations in rodents

The dominant lethal test identifies germ-cell mutagens by measuring embryonic death of the progeny of treated males caused by an absorbed chemical penetrating gonadal tissue and producing chromosomal breakage in parent germ cells. This test does not detect somatic mutations, so it is not included in Table 4. It also has a low sensitivity for detecting small increases in induced mutation frequency due to a high rate of spontaneous mutations.

Dominant lethal studies were conducted in male Sprague Dawley rats (15/chemical) with 5 halogenated 3-carbon compounds (including 1-BP) that were similar in structure to 1,2-dibromo-3-chloropropane (DBCP), a compound that is known to cause dominant lethal mutations (Saito-Suzuki *et al.*, 1982). Treated males were exposed by gastric intubation to 400 mg/kg 1-BP for 5 consecutive days. Males were then mated with untreated females during ten sequential mating periods of a week each. 1,2,3-Tribromopropane (50 mg/kg daily) acted similarly to DBCP (50 mg/kg) in causing dominant lethal mutations based on dead embryonic implants, especially in the early spermatid stage. 1,2-Dibromopropane (200 mg/kg) gave a minimal response. 1-BP (400 mg/kg), 1,2,3-trichloropropane (80 mg/kg) and 1-chloropropane (1,000 mg/kg) were inactive.

1-BP was administered orally to ICR male mice (20/group) at 300 or 600 mg/kg for 10 days before mating to investigate the potential of 1-BP to induce dominant lethality (Yu *et al.*, 2008). Males were mated with untreated females during six sequential mating periods of a week each. Males were necropsied at the end of mating and the pregnant females on days 15-17 of gestation. A positive control group (40 mg/kg cyclophosphamide administered intraperitoneally) was included and followed the same mating schedule. There were no treatment-related changes in clinical signs, gross findings, mating index, gestation index, number of corpora lutea and implantations, pre-implantation loss, live fetuses, resorptions, dead fetuses, and post-implantation loss at either 1-BP dose that would indicate dominant lethality. An increase in pre-implantation loss during the fifth week was attributed to treatment-related low sperm quality. In the positive control group mating and gestation indices were normal, but a decrease in the number of implantations and an increase in pre-implantation loss and fetal deaths were observed during the first 2 or 3 weeks, resulting in a markedly increased dominant lethal mutation rate for the first 3 weeks.

Other Supporting Data

Cancer Bioassays with Structurally Related Compounds

Previous long-term rodent toxicology and carcinogenesis studies with brominated hydrocarbons have been conducted by the NTP, which have resulted in tumors in the same organs and tissues as those following 1-BP exposure (see below).

Chronic inhalation exposure of F344 rats and B6C3F$_1$ mice to 1,2-dibromoethane resulted in significantly increased incidences of alveolar/bronchiolar adenomas and carcinomas in male and female mice and female rats (NTP, 1982a). 1,2-Dibromoethane exposure also led to an increased incidence of mesotheliomas of the tunica vaginalis (epididymis) in male rats. Similarly, long-term inhalation exposure of F344 rats and B6C3F$_1$ mice to 1,2-dibromo-3-chloropropane led to increased incidences of alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas in male and female mice (NTP, 1982b).

In separate two-year oral gavage studies in F344/N rats and B6C3F$_1$ mice treated with bromodichloromethane (NTP, 1987) and tribromomethane (NTP, 1989), significantly increased incidences of adenomatous polyp and adenocarcinoma, and adenomatous polyps or adenocarcinomas (combined), respectively, were observed in the large intestine of male and female rats. The occurrence of this rare tumor following exposure to brominated compounds structurally related to 1-BP strengthened NTPs conclusion for “some evidence” for adenoma of the large intestine in male rats resulting from 1-BP exposure (NTP, 2011).

Genotoxicity of 1-BP metabolites

1-BP metabolites formed by CYP-mediated oxidation in rodents include α-bromohydrin and glycidol (Ishidao *et al.*, 2002; Garner *et al.*, 2007). Both are direct-acting mutagens that induce DNA damage in bacteria (Stolzenberg and Hine, 1979; IARC, 2000). In addition, glycidol has been shown to be mutagenic in mammalian cells, and induce DNA damage and chromosomal damage *in vitro* in rodent and human cells. *In vivo* studies in mice indicate that glycidol induces micronucleus formation but not chromosomal aberrations (IARC, 2000).

Immune System and Cancer

Inflammation is a precursor of many diseases including several types of cancer (Coussens and Werb, 2002; Colotta *et al.*, 2009; Korniluk *et al.*, 2017). In the NTP (2011) carcinogenicity study, 1-BP produced an inflammatory reaction in the respiratory system of rats and mice, but only female mice developed tumors in the

lung. Chronic suppurative inflammation was significantly increased in rats in the highest 1-BP exposure group. These lesions were characterized by the presence of Splendore Hoeppli (S-H) material, which were primarily found in the nose and skin of affected animals and typically surrounds or is adjacent to the agent causing S-H bodies (i.e., fungi, helminthes or bacteria). Immunosuppression has been suggested as a cause for the development of these lesions(Morgan *et al.*, 2011). S-H bodies following 1-BP exposure in rats and mice have only occurred in rats, although immunotoxicity tests have shown that both rodent species were immunosuppressed after 1-BP exposure (Anderson *et al.*, 2010). Species differences in the presence of opportunistic bacteria, or differences in innate resistance to infection, have been postulated as possible causes.

Han *et al.* (2008) investigated the proinflammatory effects of 1-BP *in vitro* in mouse macrophages. 1-BP induced the production of nitric oxide (NO) and proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α in the macrophages. The expression levels of these genes increased in a dose-dependent manner (from 0.5 to 10 micromolar in cell culture). Nuclear transcription factor-κB (NF-κB) sites were identified in the promoter of the inducible nitric oxide synthase (iNOS) and proinflammatory cytokine genes. The authors noted that NO synthesized by iNOS is considered an important mediator of carcinogenesis that may elevate cancer progression, and that overexpressed iNOS has been found in human breast and colorectal tumors (Thomsen *et al.*, 1995; Hao *et al.*, 2001).

Induction of cancer stem cells in colorectal cancer

Colorectal cancer has a high relapse rate, attributed to the high proportion of cancer stem cells, or self-renewing cells within tumors. Cho *et al*. (2017) investigated the effects of 1-BP and similar brominated compounds on the “stemness” in human colorectal cancer cell lines [although not explicitly defined by the authors, OEHHA notes that “stemness” generally refers to a state of a cell characterized by a high degree of plasticity, where plasticity is the property of being transmutable into either a less committed or a more committed state]. 1-BP was observed to increase the spheroid formation in colorectal cancer cells (CSC221, DLD1, Caco2, and HT29 cells) *in vitro*, which is a measure of the ability to induce cancer cell stemness. 1-BP also induced the expression of cancer stemness markers, including ALDH-1, CD133, Lgr-5, and Msi-1, at both the mRNA and protein levels. Finally, 1-BP was found to increase the transcriptional activity of the Hedgehog, Notch, and Wnt signaling pathways, which supports the hypothesis that induction of cancer cell stemness by 1-BP occurs via these signaling pathways. The authors concluded that 1-BP and other related compounds have the potential to promote cancer stemness.

IV. CANCER HAZARD EVALUATION

The chronic toxicity/carcinogenicity studies by NTP in rats and mice (Morgan *et al.*, 2011; NTP, 2011) are the only source of carcinogenicity data for 1-BP. Although there is human exposure to 1-BP (Ichihara *et al.*, 2004a; Hanley *et al.*, 2006; Hanley *et al.*, 2009; 2010), widespread exposure has occurred relatively recently so no long term epidemiology studies have been identified. The initial reports of high occupational exposure were based on workers studied in the 1990s (Ichihara *et al.*, 2004a). Human cancer generally has a long latency period, so occupational exposure data of sufficient exposure duration may not yet exist.

Lifetime exposure to 1-BP in rodents resulted in tumors in male and female rats, and female mice (Morgan *et al.*, 2011; NTP, 2011). Tumors that the NTP concluded were a result of 1-BP exposure included adenomas of the large intestine in male and female rats, skin tumors of the epithelium in male rats, and alveolar/bronchiolar adenoma or carcinoma of the lungs in female mice. However, the low incidence of adenoma in the large intestine of male rats resulted in no significant difference relative to controls, and no significant positive trend. The low tumor incidence will not contribute to the overall cancer potency, so OEHHA did not use this particular tumor data to derive a cancer potency. The tumors OEHHA identified as being suitable for cancer potency determination were adenomas of the large intestine in female rats, the combined skin neoplasms of epithelial origin in male rats (keratoacanthoma, basal cell adenoma or carcinoma, and squamous cell papilloma or carcinoma), and lung tumors in female mice (alveolar/bronchiolar adenomas or carcinomas combined).

Supporting data for the carcinogenicity of 1-BP included some evidence for genotoxicity and mutagenicity in cell culture studies, although most genotoxicity studies conducted were negative. *In vitro* exposure of cultured human leukocytes to 1-BP resulted in equivocal evidence of increased DNA damage by the comet assay (Toraason *et al.*, 2006). 1-BP was mutagenic in a closed system bacterial Ames assay with and without S9, suggesting 1-BP is a direct acting mutagen (Barber *et al.*, 1981). 1-BP also induced mutations *in vitro* at the thymidine kinase (TK) locus in L5178Y mouse lymphoma cells (Elf Atochem, 1996).

In addition, long-term rodent exposure studies with structurally-related brominated compounds, including 1,2-dibromoethane, 1,2-dibromo-3-chloropropane, bromodichloromethane and tribromomethane, have resulted in similar tumors as that caused by 1-BP. *In vivo* metabolism of 1-BP produced protein adducts both in rats and humans (Valentine *et al.*, 2007), and resulted in the production of direct acting

mutagens such as α-bromohydrin and glycidol in rodents (Ishidao *et al.*, 2002; Garner *et al.*, 2007). Finally, 1-BP increased the "stemness" in human colorectal cancer cell lines.

V. QUANTITATIVE CANCER RISK ASSESSMENT

Effective Tumor Incidences

The effective tumor incidences in rats and mice (Table 5) were determined from individual animal survival data of the NTP study located in the Chemical Effects in Biological Systems (CEBS) database for rats (NTP-CEBS, 2011a) and mice (NTP-CEBS, 2011b). The effective tumor incidence is the number of tumor-bearing animals (numerator) over the number of animals alive at the time of first occurrence of the tumor (denominator). In most cases, the effective tumor incidences were used to calculate the cancer slope factor for 1-BP. This method of tallying tumor incidence removes animals from the assessment that died before they are considered at risk for tumor development. Table 5 does not include treatment-related tumors that were of very low incidence (large intestine tumors in male rats) or tumors that were of equivocal significance (malignant mesothelioma and pancreatic islet tumors in male rats, and skin tumors in female rats).

Table 5. Adjusted tumor incidence in rats and mice exposed to 1-BP for two years (NTP, 2011b)[a,b]

Tumor Type		Incidence by concentration				Statistical p-values for pairwise comparison with controls			
	ppm	0	125	250	500	Trend[c]	125	250	500
	mg/m^3	0	629	1258	2515		629	1258	2515
Male Rat									
Skin: Basal Cell Adenoma		0/46	1/42	2/39	1/36	0.191	0.477	0.208	0.439
Skin: Basal Cell Carcinoma		0/28	2/31	1/26	2/21	0.089	0.272	0.481	0.179
Skin: Keratoacanthoma		0/49	3/49	6/49*	6/44**	0.006	0.121	0.013	0.009
Skin: Squamous Cell Carcinoma		1/37	1/34	0/29	2/29	0.881	0.732	1.000	0.408
Skin: Keratoacanthoma or Squamous Cell Carcinoma		1/49	4/49	6/49	8/44*	0.004	0.181	0.056	0.010
Skin: Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma		1/49	7/49*	9/49**	10/44**	0.003	0.030	0.008	0.002
Female Rat									
Large Intestine (Colon or Rectum): Adenoma		0/45	1/43	2/41	5/36*	0.001	0.489	0.224	0.015
Female Mouse	ppm	0	62.5	125	250	0	62.5	125	250
	mg/m^3	0	314	629	1258	0	314	629	1258
Lung: Alveolar/Bronchiolar Adenoma		1/41	6/46	4/42	10/47**	0.006	0.075	0.187	0.007
Lung: Alveolar/Bronchiolar Carcinoma		0/36	7/42*	5/38*	4/43	0.250	0.010	0.031	0.082
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma		1/41	9/46*	8/42*	14/47**	0.001	0.012	0.016	<0.001

(a) Incidence ratio after adjusting for intercurrent mortality using the effective number adjustment method (i.e., number alive on day of first tumor).

(b) * = p<0.05, ** = p<0.01; p-value indicators are from pairwise comparisons with controls using Fisher exact tests performed by OEHHA;

(c) p-values in the trend column are for the Cochran-Armitage trend test performed by OEHHA.

Cancer Slope Factor Derivation

For the derivation of the CSF, 1-BP chamber concentrations of 0, 62.5 (mice only), 125, 250 and 500 (rats only) ppm were time-adjusted and converted to mg/m^3 (6.17 hrs/24 hrs × 5 days/7 days × 5.03 mg/m^3 / ppm) to extrapolate from the intermittent chamber exposure conditions to a continuous exposure over the life span of the animals (*i.e.*, to simulate an annualized average air concentration). The time-adjusted concentrations were 0, 57.73, 115.46, 230.92, and 461.83 mg/m^3.

The average daily dose, in mg/kg BW-day, is used for calculating the cancer potencies. To calculate the daily dose, the average body weight of the rats and mice over the duration of the study is used to determine the inhalation rate (IR). The weighted average lifetime body weights for control rats of both sexes and female mice were calculated from the NTP (2011) study based on the regular reporting of group mean body weights every 1 to 4 weeks during the 2-year exposure. Body weights and daily dose for male mice were not calculated since no 1-BP-related carcinogenicity was observed in male mice. The average body weights were 440.6, 284.9, and 47.4 g for the control male rats, female rats, and female mice, respectively.

A comprehensive analysis of rat minute volume data was undertaken by OEHHA (2018) to update the IR equation by Anderson (1983) and is shown below (Eq. 6-1a). The analysis incorporates studies published since 1988 that more accurately reflect true resting IRs of rats. For mice, the IRs were determined using the equation (Eq. 6-1b) by Anderson (1983). These formulas reflect proportional differences of body weight (BW$^{2/3}$) on the respiratory rate within a species.

Rats: $IR\ (m^3/day) = 0.702\ m^3/day\text{-}kg \times (BW)^{2/3}$ Eq. 6-1a

Mice: $IR\ (m^3/day) = 0.0345\ m^3/day \times (BW / 0.025\ kg)^{2/3}$ Eq. 6-1b

The calculated average daily IRs during the 1-BP exposures are 0.406, 0.304, and 0.0528 m^3/day for male and female rats and female mice, respectively. The average daily doses (shown in Table 6) could then be calculated with the following equation:

$$Dose\ (mg/kg\ BW\text{-}day) = IR \times C / BW \quad \text{Eq. 6-2}$$

Where:

C = time-adjusted 1-BP concentration (mg/m^3)

Table 6. Calculated average daily exposed dose of 1-BP in rats and mice

Species sex	**1-BP Chamber Concentration (mg/m^3)**				
	0	**314**	**629**	**1,258**	**2,515**
	Daily Exposed Dose (mg/kg-day)				
Rats					
Males	0	-	106.39	212.78	425.56
Females	0	-	123.20	246.40	492.79
Mice					
Females	0	64.31	128.61	257.22	-

The United States Environmental Protection Agency's (US EPA's) Benchmark dose (BMD) methodology and Benchmark Dose Modeling Software (BMDS, version 3.2) were used to perform dose-response extrapolation (US EPA, 2020). BMD analyses were run for the tumor data that were identified as treatment-related and showed a statistically significant increase above control values and a statistically significant positive trend (See Table 7). Where tumors of the same histological cell type or tissue type (*e.g.*, skin tumors of epithelial origin; pulmonary alveolar/bronchiolar adenomas and carcinomas) are observed, the combined incidence is used for dose-response assessment.

The multistage-cancer polynomial model was fit to the female rat and female mouse data. Survival was unaffected by 1-BP exposure in these groups, so the effective tumor incidences were used to derive the cancer potencies. The multistage Weibull model was used for the male rat tumor data due to decreased survival in the 500 ppm group relative to the control group (US EPA, 2017). OEHHA applies this adjustment in lifetime rodent exposure studies when 1) survival is reduced by about 15% or greater compared to controls before week 85, and 2) less than 85% of these early deaths occur in animals that have treatment-related tumors. The 500 ppm group displayed reduced survival of 10-11% between week 70 and week 80. The difference in survival increased to 22% at week 83, and then varied mostly between 16-22% to the end of the study at week 104. Nine of 37 early deaths were due to chronic inflammation in various organs (lung, nose, skin, and bone) that was treatment-related; the remaining early deaths were due to various types of neoplasia that were not treatment-related. Only seven of the male rats that died early had a treatment-related tumor (i.e., large intestine or skin tumor), none of which were the cause of death.

For large datasets such as those by the NTP, a Benchmark Dose Response (BMR) of 5% is recommended by OEHHA (2008) for the BMD, and 95% lower confidence bound (BMDL). First and 2nd degree polynomial multistage models were run for all

tumor data sets, and the most appropriate model fit was chosen based on BMD technical guidance (US EPA, 2012). The degree of polynomial chosen was 1 in all cases.[1] The resulting BMD and BMDL values for each tumor type are shown in Table 7. The rodent CSFs, in units of $(mg/kg\text{-}day)^{-1}$, are calculated as 0.05/BMDL, where 0.05 represents the 5% tumor response, or BMR. The rodent CSFs (CSF(a)) were then converted to human equivalents (CSF(h)) using body weight ($BW^{3/4}$) scaling:

$$CSF(h) = CSF(a) \times (BW(h) / BW(a))^{1/4} \qquad \text{Eq. 6-3}$$

Lifetime body weights for rodents (BW(a)) were calculated from the NTP (2011) study as described above. The default body weight for humans (BW(h)) is 70 kg. The body weight scaling factor assumes that mg/surface area/day is an equivalent dose between species (OEHHA, 2009). Using this interspecies scaling factor is preferred by OEHHA because it is assumed to account not only for pharmacokinetic differences (*e.g.*, breathing rate, metabolism), but also for pharmacodynamic considerations, *i.e.*, tissue responses to chemical exposure (US EPA, 2005).

When extrapolating to the human equivalent dose using the body weight scaling factor, pulmonary alveolar/bronchiolar adenoma and/or carcinoma combined in female mice provided the highest CSF(h) value of 0.013 $(mg/kg\text{-}day)^{-1}$ (CSFs rounded to two significant figures in the final assessment), establishing this tumor in female mice as the most sensitive endpoint for 1-BP-induced carcinogenicity. The multistage model fit to the female mouse tumor data is shown in Figure 2.

[1] For female mice alveolar/bronchiolar tumors (See Table 7 below), BMD guidance suggested a 2nd degree multistage model provided the best fit to the data. However, this choice was based on an Akaike Information Criterion value that was only 0.0000001 lower than the 1st degree multistage model. Due to nearly identical model fits, OEHHA chose the simpler 1st degree model to calculate the BMDL.

Table 7. BMDS Modeling Results

Tumor type	Akaike Information Criterion	*p*-value	BMD (mg/kg-day)[a]	BMDL (mg/kg-day)	CSF - Rodent (mg/kg-day)$^{-1}$	CSF - Human (mg/kg-day)$^{-1}$
Rats						
Skin tumors						
Males	151.75	NA[a]	57.57	33.43	0.001496	0.0053
Large Intestine						
Females	56.84	0.95	202.43	119.07	0.000420	0.0017
Mice						
Alveolar/bronchiolar						
Females	159.53	0.26	36.34	24.54	0.00204	0.013

[a] Not applicable for the multistage Weibull model

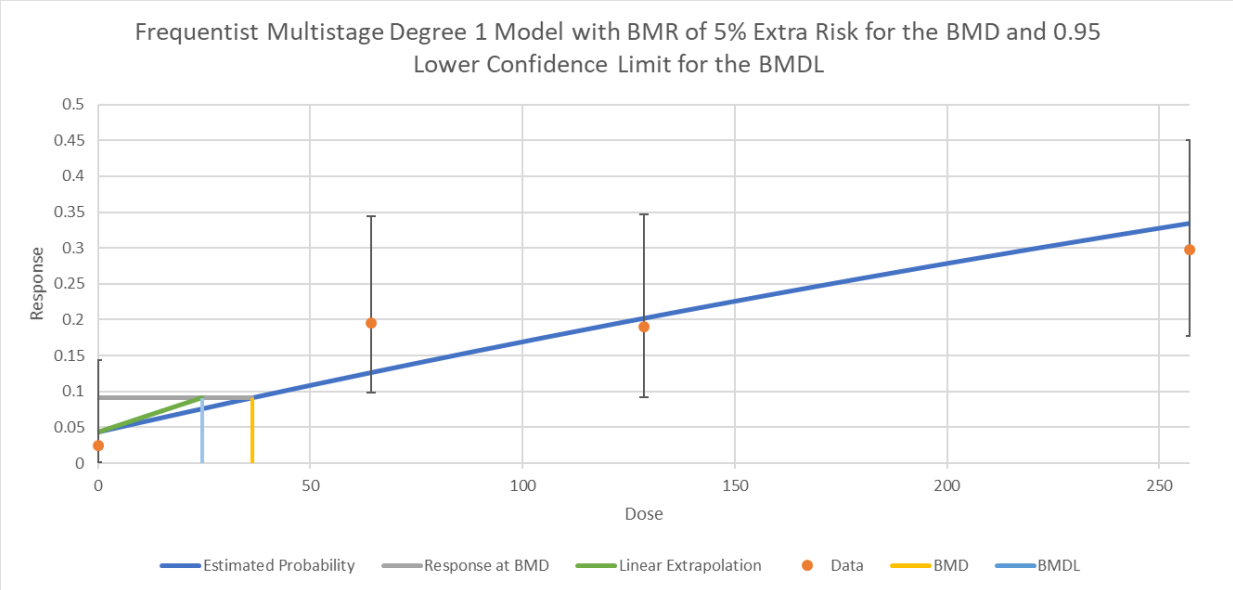


Figure 2. Multistage model plot fit to the female mouse lung tumor data for 1-BP. The Multistage polynomial degree 1 model with BMR of 5% extra risk for the BMD and 95% lower confidence bound (BMDL).

Inhalation Unit Risk Factor

The Inhalation Unit Risk (IUR) describes the excess cancer risk associated with inhalation exposure to a concentration of 1 µg/m^3 and is derived from the human CSF(h):

$$IUR = (CSF(h) \times BR) / (BW \times CF) \quad \text{Eq. 6-4}$$

Where:

BR = mean human breathing rate (20 m^3/day)
BW = mean human body weight (70 kg)
CF = mg to µg conversion factor of 1,000

Use of the equation above with the 1-BP CSF of 0.013 $(mg/kg\text{-}day)^{-1}$ results in a calculated IUR of 0.0000037 $(\mu g/m^3)^{-1}$, which can also be expressed as 3.7×10^{-6} $(\mu g/m^3)^{-1}$. Thus, the extra cancer risk associated with continuous lifetime exposure to 1 µg/m^3 1-BP is 3.7 in a million.

VI. CONCLUSIONS

Two-year 1-BP inhalation studies conducted by the NTP established evidence of carcinogenicity in male and female rats, and female mice. Supporting evidence for the carcinogenicity of 1-BP include some positive genotoxic results from *in vitro* studies, a positive *in vivo* study for DNA adduct formation, development of similar tumors in long-term rodent exposure studies by structurally related brominated compounds, and CYP-mediated oxidation of 1-BP to known mutagenic compounds. Rodent CSFs were calculated from the NTP tumor incidence data for each tumor type in each affected species and sex. This was performed by calculating the lower 95% confidence limit on the inhalation concentration associated with a 5% tumor response (BMDL) using the multistage cancer model in Benchmark Dose Software (BMDS) version 3.1 (US EPA, 2020). Linear extrapolation from the BMDL to the origin was used to determine the slope of the dose-response curve for low level exposure, the inhalation CSF. The rodent CSFs were then converted to human equivalent exposure levels using body weight scaling to the ¾ power. The CSF used for 1-BP, based on the most sensitive species and sex, is 0.013 (mg/kg-day)-1) for pulmonary alveolar/bronchiolar adenomas or carcinomas combined in female mice. An IUR of 3.7×10^{-6} $(\mu g/m^3)^{-1}$ was calculated from the CSF using the assumption of a human breathing rate of 20 m^3/day and an average human body weight of 70 kg.

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