OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Air Toxics Hot Spots Program

1-Bromopropane

Reference Exposure Levels

Technical Support Document for the Derivation of Noncancer Reference Exposure Levels

Appendix D1

Scientific Review Panel Draft

April 2022

Air and Site Assessment and Climate Indicators Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Technical Support Document for the Derivation of Noncancer Reference Exposure Levels Appendix D1

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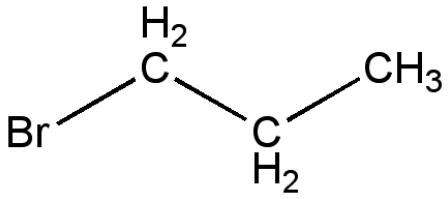
List of Abbreviations

ABT	1-Aminobenzotriazole
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMD	Benchmark dose
BMDF	Brain-derived neurotropic factor
BMDL	95% lower confidence limit of the dose producing a specified response rate (e.g., 5%)
BMR	Benchmark response
1-BP	1-Bromopropane
2-BP	2-Bromopropane
BrdU	5-bromo-2'-deoxyuridine
BW	Body weight
BUN	Blood urea nitrogen
CI	Confidence interval
CNS	Central nervous system
CPK	Creatine phosphokinase
CV	Conduction velocity
CYP	Cytochrome P450
dL	Deciliter
DL	Distal latency
ECG	Electrocardiogram
FSH	Follicle stimulating hormone
GABA	Gamma-aminobutyric acid
GD	Gestation day
GFAP	Glial fibrillary acidic protein
GPT	Glutamate pyruvate transaminase
GR	Glucocorticoid receptor
GSH	Glutathione, reduced
GSSG	Glutathione, oxidized
GST	Glutathione transferase
Hb	Hemoglobin
Ht	Hematocrit
IUR	Inhalation unit risk
IV	Intravenous
Kgst	Rate constant for Glutathione S-transferase pathway
Km	Michaelis constant
LDH	Lactate dehydrogenase
LOAEL	Lowest observed adverse effect level
LC_{50}	Median lethal dose
m/sec	Meters per second
MCH	Mean corpuscular hemoglobin
mRNA	Messenger ribonucleic acid
ms	Millisecond
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
ND	No data
NOAEL	No observed adverse effect level
NTP	National Toxicology Program
ODP	Ozone depletion potential
PBPK	Physiologically-based pharmacokinetic modeling
PLT	Platelet count
POD	Point of departure
POMS	Profile of mood states
PND	Postnatal day
ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cell
REL	Reference exposure level
RGDR	Regional gas dose ratio
ROS	Reactive oxygen species
SD	Standard deviation
SLA	Spontaneous locomotor activity
TAC	Toxic air contaminant
TWA	Time-weighted average
TSH	Thyroid-stimulating hormone
UF	Uncertainty factor
Vmax	maximal velocity for saturable pathway
VOC	Volatile organic compound
WB	Whole body
WBC	White blood cell

1-Bromopropane Reference Exposure Levels

(Propyl bromide ; n-propyl bromide)

CAS Registry Number 106-94-5



1. Summary

The Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidelines for conducting health risk assessments under the Air Toxics Hot Spots Program (Health and Safety Code Section 44360(b) (2)). In response to this statutory requirement, OEHHA has developed acute, 8-hour, and chronic Reference Exposure Levels (RELs) for 1-bromopropane (1-BP).

1.1 1-Bromopropane Acute REL

Reference Exposure Level	**3300 µg/m^3 (700 ppb)**
Critical effect(s)	Skeletal anomalies in rat fetuses
Hazard Index target(s)	Developmental

1.2 1-Bromopropane Chronic REL

Reference Exposure Level	**1.7 µg/m^3 (0.3 ppb)**
Critical effect(s)	Reduction in distal peripheral nerve function in workers
Hazard Index target(s)	Nervous system, respiratory system

1.3 1-Bromopropane 8-Hour REL

Reference Exposure Level	**3.4 µg/m^3 (0.7 ppb)**
Critical effect(s)	Reduction in distal peripheral nerve function in workers
Hazard Index target(s)	Nervous system, respiratory system

Due to the mandated phase-out of perchloroethylene in dry-cleaning in California by 2023, 1-bromopropane (1-BP) is a proposed alternative to perchloroethylene and has been used by some dry-cleaners in California (CARB, 2015). It has also been used as a substitute for methylene chloride in spray adhesives (Adams, 2008). 1-BP is listed as a developmental toxicant and a reproductive toxicant in males and females under the California Proposition 65 Program (OEHHA, 2021a). Subacute exposure during gestation in rodents has resulted in low birth weight and skeletal anomalies in newborns and decreased implantation rates. Decreased reproductive performance in rodent models includes disruption of the ovarian follicular growth process and reduced fertility in females, and decreased reproductive organ weight and inhibition of spermiation in males. Skeletal anomalies in newborn rats following exposure to 1-BP during gestation provided the basis for the acute REL. Benchmark dose (BMD) modeling with individual data for fetuses established the point of departure (POD) for the acute REL.

1-BP is also a known neurotoxicant in humans and animals. Infants and children may be more susceptible to the effects of 1-BP because their nervous systems are still developing. Relatively high subacute/subchronic occupational exposure (>50 to 100 ppm) has resulted in severe symptoms such as dizziness, numbness, ocular disturbances, unsteady gait, weakness, anorexia, dysesthesias (impairment of a person's sense of touch), headache, nausea, pain in limbs, and sleep disturbances.

Repeated low occupational exposure (i.e., roughly <20 ppm) over months to years has been associated with reductions in the peripheral nervous system function in the feet and legs, consisting of decreased nerve conduction velocity, increased "distal latency," and decreased vibration sense (pallesthesia). These neurological effects are likely the most sensitive indicators of toxicity in humans and provided the basis for the chronic REL. A NOAEL/LOAEL approach in a large cohort of 1-BP workers experiencing a reduction in distal peripheral nerve function was used to establish a POD for the chronic REL and 8-hr REL.

OEHHA has derived a draft cancer inhalation unit risk (IUR) factor based on a two-year 1-BP inhalation exposure in rodents which was observed to induce cancer in the exposed animals (NTP, 2011). This draft 1-BP cancer IUR factor is presented in a separate report (OEHHA, 2021b). 1-BP is also included on the Proposition 65 list of chemicals known to the State to cause cancer (OEHHA, 2021a).

This document contains relevant published material and relevant unpublished studies reviewed and supported by authoritative bodies for 1-BP through October 2021. A technical review of those studies specifically applicable to developing non-cancer acute, 8-hour, and chronic inhalation RELs for 1-BP is included.

2. Physical & Chemical Properties (PubChem, 2020)

Description	colorless liquid when fresh
Molecular formula	C_3H_7Br
Molecular weight	122.99
Density	1.353 g/cm^3 at 20°C (water = 1)
Boiling point	71°C at 760 mm Hg (torr)
Melting point	-110°C
Vapor pressure	110.8 mm Hg (torr) at 20 °C (14.772 kPa)
Vapor density	4.25 (air = 1)
Solubility	Soluble in acetone, ethanol, ether, benzene Slightly soluble in water (2,450 mg/L at 20°C)
Odor threshold	Not found. Odor variously described as sweet, strong, or acrid
Log Kow	2.10
Conversion factor	1 ppm = 5.03 mg/m^3

3. Occurrence and Major Uses

1-BP was proposed as an alternative to ozone-depleting chlorofluorocarbons in the 1990s and has an ozone depletion potential (ODP) at latitudes in the United States of 0.013–0.018 (USEPA, 2003). The reference compound CFC-11 (trichlorofluoromethane**)** has an ODP of 1. Exposure to 1-BP may occur from emissions of facilities where 1-BP is used as a solvent vehicle for 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 uses as a chemical intermediate in the production of organic, inorganic, and agricultural chemicals, in the extraction of asphalt, coin and scissors cleaning, and commercial/consumer spot cleaning of fabrics (US EPA, 2017a). 1-BP is a reportable chemical under the US EPA Toxics Release Inventory (TRI) program (TRI, 2015). In California, reductions in chlorinated hydrocarbon use due to the phase-out of these compounds have led end-users to alternative solvent formulations, such as 1-BP. 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 survey reported a total of 160.7 tons of 1-BP emitted due to solvent cleaning operations.

4. Toxicokinetics

The mechanism by which 1-BP causes cellular and organ injury has not been elucidated, although metabolic activation to reactive metabolites is suspected to be involved. The metabolism of inhaled and absorbed 1-BP occurs primarily through oxidative metabolism via P450 enzymes, conjugation with glutathione (GSH), and debromination, although the majority of 1-BP can be excreted unchanged in exhaled air.

4.1 Toxicokinetics in Animal 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 following 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.

Metabolic pathways and urinary metabolites of 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 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 mainly by Garner et al. (2015) for 1-BP metabolism in the rat is shown in Figure 1.

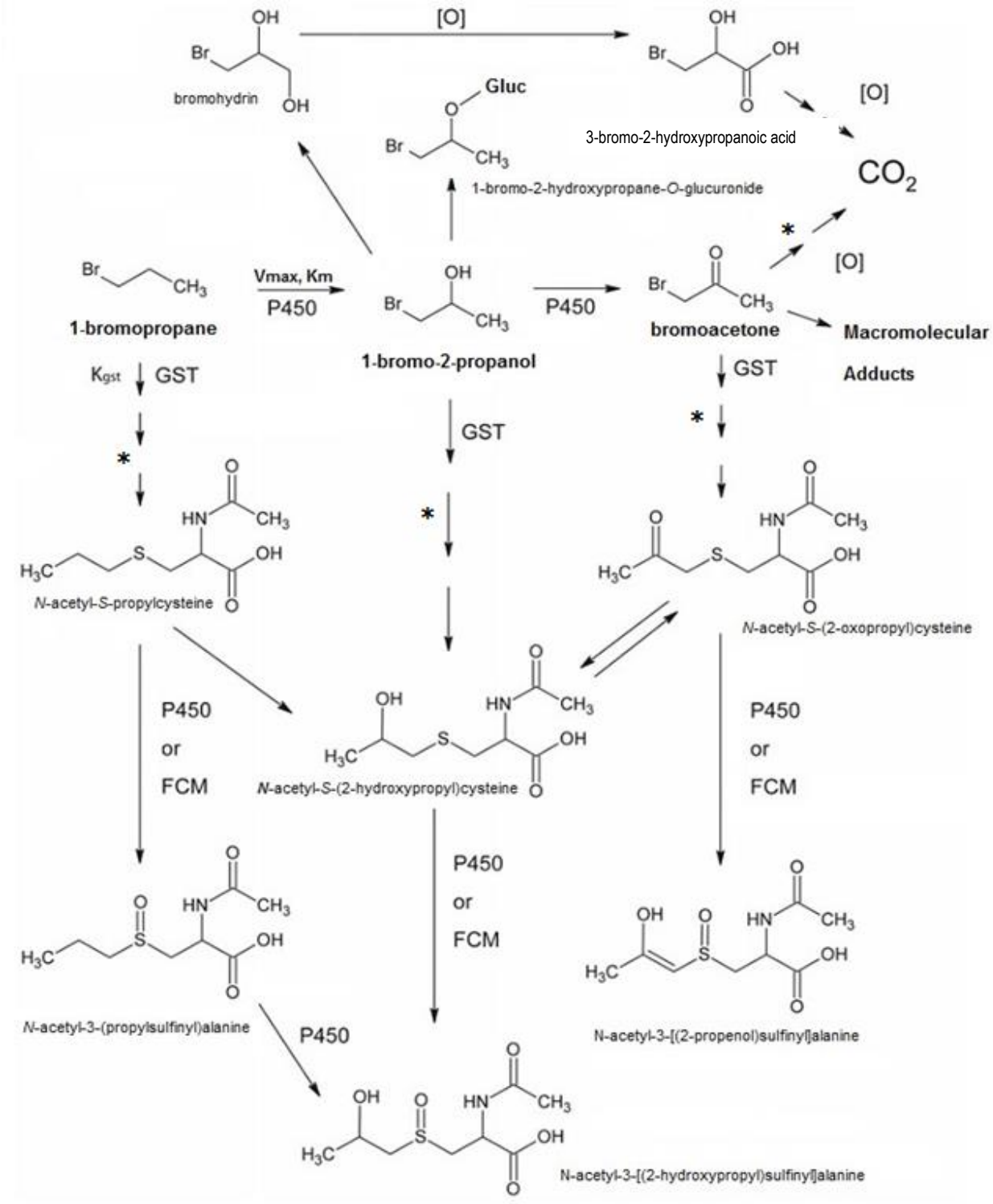


Figure 1. Metabolism of 1-BP in rodents: modified from Figure 2 of Garner *et al*. (2015). * = debromination step; GST = glutathione-S-transferase; FCM = Flavin monooxygenase; Vmax = maximal velocity; Km = Michaelis Constant; Kgst = proportionality constant for linear pathway metabolized by glutathione transferase; →→ multiple steps of reaction; [O] = unspecified oxidation step

When rats were pretreated with 1-aminobenzotriazole (ABT), 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 results confirmed that CYP enzymes contribute significantly to the production of the major oxidative metabolites of 1-BP.

Rate of 1-BP metabolism and sex differences

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 P4502E1 (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 hr). The major urinary metabolite, 1-bromo-2-propanol (*N*-acetyl-*S*-(2-hydroxypropyl)cysteine), derived largely from oxidative metabolism, 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.

Using a closed gas uptake system, rats exposed to increasing levels of 1-BP in a chamber resulted in a decreasing terminal air elimination rate (Garner and Yu, 2014). This finding indicated to the authors that one or more routes of elimination became saturated as chamber concentration increased. 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 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.

Prior to exposure to 1-BP at 800 ppm (4024 mg/m^3) in inhalation chambers, rats were also pretreated with chemical inhibitors of CYP, 1-aminobenzotriazole, and GSH synthesis, D,L-buthionine (S, R)-sulfoximine (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 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 ABT or the GSH synthesis inhibitor d,l-buthionine (S,R)-sulfoximine, prior to inhalation of 800 ppm (4000 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). Among the saturable pathways in the model, the maximal metabolic velocity Vmax (which reflects how fast the enzyme can catalyze the reaction) and Michaelis constant Km (which describes the substrate concentration at which half the enzyme's active sites are occupied by substrate) values 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 the female constant. After adjusting Vmax by the rat's body weight (the male rat body weight was considerably greater than the female rat body weight), the values were 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.

Human PBPK modeling 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 integrating them within 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), 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 would need to be incorporated into the PBPK model to allow the quantitative extrapolation of animal studies to humans for risk assessment purposes.

Role of metabolism in 1-BP toxicity

Garner *et al*. (2007) carried out experiments *in vitro* with sperm from *Cyp2e1*$^{-/-}$ and wild-type (WT) mice to determine if CYP2E1 oxidation of 1-BP is involved in reduced sperm motility. *In vitro*, sperm incubation experiments showed that both 1-BP and its CYP2E1 hydroxylated metabolite, 1-bromo-2-hydroxypropane, caused a time-dependent decrease in motility of sperm isolated from WT mice. However, in the absence of CYP2E1 in the *Cyp2e1*$^{-/-}$ mice, the effect of 1-BP on sperm motility was not observed. When 1-bromo-2-hydroxypropane was introduced into the medium, sperm showed a significant time-dependent decrease in motility. These findings suggested to the authors that conversion of the parent compound to 1-bromo-2-hydroxypropane within the spermatozoa likely plays a role in reduced motility.

In support of the *in vitro* studies, *Cyp2e1-/-* mice exposed to 800 ppm (4000 mg/m^3) 1-BP *in vivo* for 6 hours did not show a decrease in sperm motility (Garner *et al.*, 2007). However, wild-type mice exposed to the same level of 1-BP showed a significant reduction in sperm motility.

The effects of a single oral gavage dose of 1000 mg/kg 1-BP and its conjugation with GSH in the liver were studied in male ICR mice (Lee *et al.*, 2005). 1-BP orally administered in corn oil significantly increased serum levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), an indicator of liver damage. GSH content was dose-dependently lowered in liver homogenates, and S-propyl GSH conjugate was dose-dependently increased. The GSH conjugate was maximally increased in the liver at 6 h after 1-BP dosing at 1000 mg/kg; hepatic GSH content was reciprocally depleted. 1-BP also induced the levels of malondialdehyde in the liver, a marker of lipid peroxidation.

The relationship between reactive oxygen species (ROS) generation by 1-BP and neurotoxicity was explored in oral gavage studies in rodents (Xu *et al.*, 2016). In order to explore if melatonin, a powerful endogenous antioxidant, might reverse 1-BP intoxication, groups of 10-15 male Sprague Dawley rats were treated by gavage daily for 27 days with 0 or 600 mg/kg body weight (BW) 1-BP with or without melatonin (at 2.5, 5, or 10 mg/kg BW given intraperitoneally one hour after 1-BP). All animals were necropsied on day 27. The researchers found that the level of malondialdehyde was significantly increased upon exposure to 1-BP in the hippocampus and significantly attenuated by melatonin. In addition, the GSH/GSSG ratio was decreased, and heme oxygenase 1 (HO-1) was increased in the hippocampus of 1-BP-treated rats. Both are effects of ROS induction. Melatonin reversed both effects. 1-BP also caused a decrease, as measured by staining for NeuN (a neuronal marker), in hippocampal neurons by inducing apoptosis, an effect of some ROS. Melatonin pretreatment

attenuated the apoptosis. Finally, the Morris water maze test was used to evaluate spatial learning and memory ability in 1-BP-exposed rats. In the maze on days 1 through 4 of exposure, 1-BP-treated rats spent more time in the water and swam a longer distance before landing on the hidden platform with a comparable swimming speed to controls. Melatonin lessened the effect in a dose-dependent manner.

4.2 Toxicokinetics in Children and Adults

The urinary mercapturic metabolite N-acetyl-*S*-propylcysteine, found in rodents by Garner and coworkers, has also been identified in urine from 1-BP-exposed workers (Valentine *et al.*, 2007; Hanley *et al.*, 2009) in addition to N-acetyl-S-(3-hydroxy-n-propyl)cysteine(Cheever *et al.*, 2009; Hanley *et al.*, 2009), which was not found in rodents. 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.

Urinary bromide has also been proposed as a biomarker of 1-BP exposure in workers (Hanley *et al.*, 2010). However, bromide analysis in urine may not be ideal for evaluating low-level occupational and non-occupational exposure to 1-BP due to background interference from dietary sources of bromide, such as seafood. Hanley *et al*. (2010) estimated that the lowest 1-BP TWA level above which urinary bromide is a valid biomarker of 1-BP exposure is approximately between 0.5 and 1.0 ppm.

In peer-reviewed reports, NIOSH investigators examined the association between airborne 1-BP exposure and 1-BP urinary metabolites in 30 workers from two factories that manufacture polyurethane foam seat cushions using a spray adhesive containing 1-BP (Hanley *et al.*, 2006; Hanley *et al.*, 2009; Mathias *et al.*, 2012). 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). The urine was collected into composite samples for three daily time intervals over two days starting on Monday: at work, after work but before bedtime, and upon awakening. In addition, seven spot urine samples were collected from persons not employed at the factories. Urinary N-acetyl-S-propylcysteine in urine showed the same trend as TWA exposures to 1-BP (i.e., sprayers had higher levels). Geometric mean 24- and 48-hour total excretion levels for N-acetyl-S-propylcysteine were 36.8 and 43.9 mg/L for sprayers, respectively, and 7.97 and 9.68 mg/L for non-sprayers, respectively. Associations of N-acetyl-S-propylcysteine concentrations with 1-BP TWA exposure were statistically significant for both sprayers ($p<0.05$) and non-sprayers ($p<0.01$). The geometric mean excretion level for controls was 0.035 mg/L, two to three orders of magnitude less than that of the factory workers. 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 were 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).

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 the sources of 1-BP exposure other than to note that dry-cleaning and metal-cleaning solvents are known sources.

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 (2015) also reported that concentrations of 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.

More recently, Louis *et al.* (2021) examined urinary VOC biomarker concentrations among a representative sample of U.S. women (n = 3,278) that participated in NHANES 2015-2016. For the 1-BP metabolite N-acetyl-S-propylcysteine, the detection frequency was 81% in the urine samples, and the geometric mean was 4.04 ng/mL. These values were compared to a cohort of hairdressers (n = 23) working in salons that primarily serve women of color. For the urinary metabolite N-acetyl-S-propylcysteine, the detection frequency was 91%, and the geometric mean was more than 4 times higher (15.1 ng/mL) compared to U.S. women. The source of hairdresser exposure was 1-BP in scissor lubricant.

These surveys suggest potential wide-spread, low-level non-occupational exposure to 1-BP, but no studies could be found that investigated 1-BP exposure and sources of exposure within the general population. Products that contain 1-BP appear to be mostly intended for industrial and commercial uses (US EPA, 2017a; 2020a). However, many products containing 1-BP may be available for consumer use and can be purchased on the internet or off the shelf. These products include aerosol spray adhesives, aerosol spot removers, aerosol cleaners and degreasers, coin and scissors cleaning, adhesive accelerant used in arts, crafts, and hobby materials, automotive care products such as refrigerant flush, cutting oils, and anti-adhesive agents used in mold cleaning and release products. These findings suggest some exposure to 1-BP may occur from consumer products.

The population surveys observed geometric mean concentrations of urinary N-acetyl-S-propylcysteine among the general population of about 2 to 4 ng/ml. Compared to 1-BP worker exposure studies (Hanley *et al.*, 2006; Hanley *et al.*, 2009; Mathias *et al.*, 2012) with urinary N-acetyl-S-propylcysteine levels of about 8 to 44 mg/L (8,000 to 44,000 ng/ml), non-occupational exposure is considerably lower. The TWA geometric mean 1-BP concentration from the 1-BP worker studies was 10.5 to 92.4 ppm, which would suggest mean 1-BP levels among participants in the surveys were in the ppb range.

In theory, exposure to VOCs similar in structure to 1-BP, when absorbed and metabolized, may also generate measurable urinary levels of N-acetyl-S-propylcysteine. As a result, US EPA (2020a) suggested that the use of the urinary metabolite as a biomarker for the general population was uncertain. However, published reviews of mercapturic acid metabolites indicate that N-acetyl-S-propylcysteine is not a common metabolite, at least among more commonly found air pollutants and halogenated and non-halogenated VOCs used in industry (van Welie *et al.*, 1992; Mathias and B'hymer, 2016; Konkle *et al.*, 2020).

In humans, initial reports 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 (messenger ribonucleic acid) for CYP2E1 accumulates, and CYP2E1 protein increases toward adult levels (Table 1) (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 1. Increase of CYP2E1 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 (mean ± SD)
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 (median)
Adult	-	~50 (median)

The low levels of hepatic CYP2E1 may mean reduced oxidative metabolism in infants and potential age-related differences in internal dose of 1-BP.

5. Acute Toxicity of 1-Bromopropane

5.1 Acute Toxicity to Adult Humans

Exposure durations are limited to approximately two weeks or less in this section, which is the duration that has been used to define acute/subacute exposures in toxicology study protocols. Currently, there are no peer-reviewed human studies that examined the toxicological effects of 1-BP with acute exposure of ≤24 hours, even though exposure durations of ≤24 hours are preferred for deriving an acute REL of one hour. The following two case reports suggest that the toxic effects of 1-BP can occur with repeated exposures of a few weeks or less.

In 2008, a dry-cleaner who had switched six weeks earlier from using perchloroethylene to 1-BP filled a dry-cleaning machine with 50 to 60 gallons of solvent without using personal protective equipment and began using 1-BP in the daily operation of the machine. During the next 2 days, he reported unusual fatigue and headaches and developed arthralgia (joint pains), visual disturbances (difficulty focusing), paresthesia (pins and needles sensation), and muscular twitching (MMWR, 2008). The report suggests that high exposure during filling of the dry-cleaning machine precipitated the symptoms of toxicity, but this was not explicitly stated in the report. A site visit by New Jersey government staff to the dry-cleaning facility determined background and high peak concentrations (75 to 250 times background) of 1-BP during the handling of clothes, but the specific background concentration was not stated.

A later workplace investigation found that two dry-cleaning machine operations, including the one in the MMWR article, resulted in an 8-hour time-weighted average of

approximately 50 ppm (250 mg/m^3) 1-BP (Blando *et al.*, 2010). However, this TWA exposure estimate is almost certainly underestimated for the dry-cleaner that experienced symptoms because the dry-cleaning machine had been adjusted to an appropriate lower temperature for 1-BP use prior to the exposure analysis, and room ventilation had been improved. Short-term measurements during filling of the dry-cleaning machine with DrySolv (>90% 1-BP) resulted in brief breathing zone organic vapor concentrations of over 500 ppm. However, since the analyzer (TVA-1000 photoionization detector) was calibrated with isobutylene, the authors stated that the measurement does not reflect actual 1-BP concentrations but rather the relative concentrations.

Four foam furniture gluers in North Carolina, ages 22-41, became ill soon after the introduction of glue containing 70% 1-BP (Raymond and Ford, 2007). Inhalation exposure resulted from both spraying and applying the glue with brushes onto furniture, but dermal exposure was also suspected. Initial symptoms noted by the four workers began at 1, 14, 14, and 26 days following the beginning of the exposure. Three of the workers were employed at the factory 8 to 40 months. The fourth had started work only weeks before the introduction of the glue containing 1-BP. No adverse effects were noted prior to the use of the new glue. In addition to 1-BP, the glue contained resin ester (20% by wt.), styrene-butadiene-styrene copolymer (10% by wt.), and 1,2-epoxy butane (0.3% by wt.).

Symptoms in all or most of the affected workers at the time of hospitalization included dizziness, numbness, ocular symptoms, unsteady gait, weakness, anorexia, dysesthesias (impairment of a person's sense of touch), headache, nausea, pain in limbs, and sleep disturbance (Raymond and Ford, 2007). The glue was also described as having an offensive odor. Signs of toxicity noted at the hospital included ataxic gait and hypoesthesia (partial or total loss of sense of touch) in all four workers, in addition to hyperreflexia and poor tandem gait in two of the workers. Symptoms were still present in all four workers three months after leaving work, and two had milder symptoms eight years after the initial illness. Long-term follow-up was not available for the other two workers.

Raymond and Ford (2007) also observed that the four workers had high concentrations of serum bromide, with levels 50 to 200 times above the normal range (<0.06 mEq/L). In addition, all had elevated urinary arsenic concentrations, but the source of the arsenic could not be determined. Arsenic was 2-3 times above the normal range (<100 mcq/L) but was thought by the authors to be underestimated since urinalysis was not conducted until 8 to 26 days after the last day of work. The authors suspected arsenic contributed to some of the symptoms, particularly the observations of nausea, weakness, and peripheral neuropathy, which were thought more likely related to arsenic exposure.

Breathing zone air samples of 16 workers were collected by NIOSH in a health hazard assessment of the furniture factory nine months after the workers became ill and were no longer employed (Harney *et al.*, 2003). The mean concentration of 1-BP was 81 ppm with a range of 18 to 254 ppm. However, Raymond and Ford (2007) thought the measured concentration underestimated the actual concentration experienced by the original four workers who became ill nine months earlier. Exhaust fans had been installed after the illnesses were reported, which would be expected to lower the 1-BP concentrations in the furniture factory. In the NIOSH report by Harney *et al*. (2003), it was suggested that excessive exposure to bromide (via metabolism of absorbed 1-BP) in the four workers may be the cause of some toxic effects, including ataxia, and that arsenic intoxication was unlikely to be the cause of ataxia and paresthesia.

5.2 Acute Toxicity to Infants and Children

No reports were found.

5.3 Acute Toxicity to Experimental Animals

This section includes studies that used exposure durations of approximately 2 weeks or less. Other than lethality studies, there are few reports that investigated the acute toxicity of 1-BP with exposure durations of ≤24 hours, which is ideally the maximum duration that is used to derive an acute 1-hour REL. Study protocols for 1-BP typically used repeated daily exposures of several weeks or more to achieve toxic responses, particularly to observe neurotoxic endpoints. Other targets of single exposure or short-term repeated exposures in rodents include the liver, respiratory system, reproductive system, and development. Some developmental toxicity studies presented in Section 7.2 examine fetal endpoints (e.g., fetal birth weights, fetal skeletal anomalies) that are considered to be a result of acute exposure at a sensitive time point during gestation. Taking all the acute toxicity data into account, OEHHA found a fetal developmental endpoint to be the most sensitive indicator of acute toxicity. This endpoint was used as the basis of the acute REL. A summary table (Table 2) of the acute and subacute toxicity findings is provided at the end of this Section.

Lethality studies

In an unpublished report, Wistar rats exposed nose-only to 1-BP for 4 hours had a median lethal dose (LC_{50}) of 7000 ppm (35,200 mg/m^3) with a 95% confidence interval (CI) of 6800 to 7200 ppm (34,200 to 36,200 mg/m^3) (Elf Atochem, 1997). Death was due to respiratory inflammation and pulmonary edema. Although this is a non-peer-reviewed study that could not be obtained by OEHHA, the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction Expert Panel (NTP, 2003)

reviewed the study and noted that adequate numbers of animals were used and procedures conformed to current standards and practices.

In another lethality study, adult Sprague-Dawley rats were exposed whole body to 0, 11,000, 13,000, 15,000, and 17,000 ppm 1-BP for 4 hours (Kim *et al.*, 1999a). The 4-hour LC_{50} was 14,374 ppm (72,300 mg/m^3) (95% confidence limit: 13,624-15,596 ppm). The authors reported eye irritation (lacrimation), piloerection, decreased activity, and ataxia in all treated groups within 1 hour after exposure. At necropsy, no gross pathological findings were observed in the lungs or other organs. The only histopathological finding observed among the major organs was cytoplasmic vacuolization around the central veins of the liver of some treated animals but was not considered to be dose-related by the authors. In a subsequent repeated exposure study (6 hours/day, 5 days/week for 6 weeks) in the same strain of rat, Kim *et al*. (1999a) observed decreased activity and mild ataxia after the first hour of exposure to 1800 ppm (9054 mg/m^3). The rats recovered within an hour after the termination of the daily exposures. Repeated exposure to 50 or 300 ppm (252 or 1509 mg/m^3) did not result in ataxia or other neurotoxic effects in rats.

Reproductive, neurotoxicity, and immunotoxicity studies

In a reproductive toxicity study (see Section 7 for more details), exposure of male wild-type (*Cyp2e1+/+)* mice to 800 ppm (4024 mg/m^3) 1-BP for 6 hours resulted in significantly decreased sperm motility (Garner *et al.*, 2007).

The National Toxicology Program (NTP) carried out short-term exposure studies in rats and mice prior to the initiation of two-year exposure studies. Groups of male and female F344/N rats and $B6C3F_1$ mice (5 animals/dose/species/sex) were exposed to 0, 125, 250, 500, 1000 or 2000 ppm (0, 630, 1258, and 2515, 5030, or 10,060 mg/m^3) 1-BP for 6 hours/day, 5 days/week for 16 (rats) or 17 (mice) days (NTP, 2008; Morgan *et al.*, 2011; NTP, 2011). Animals were observed twice daily, and clinical findings were recorded twice daily on exposure days. In rats, the neurological sign of hind limb splaying was observed in some 2000 ppm (10,060 mg/m^3) animals after the first week of exposure, but they had recovered before the beginning of the next scheduled exposure. At the end of exposure, body weights of 2000 ppm (10,060 mg/m^3) rats were significantly lower compared to controls. Microscopic examination revealed nasal lesions in some rats at 500 ppm (2515 mg/m^3) or greater, including suppurative inflammation and necrosis of the respiratory epithelium in males, and respiratory epithelium regeneration in females. The sciatic nerve and spinal cord were examined microscopically. No lesions were found.

In mice, deaths occurred during the first week of exposure in males at 500 ppm and greater, and in females at 1000 ppm (5030 mg/m^3) and greater. The earliest deaths

occurred on day 2 of exposure in 2000 ppm (10,060 mg/m^3) males. Abnormal breathing, lethargy, and eye discharge were observed at 500 ppm (2515 mg/m^3) or greater, mainly during the first week of exposure. Microscopic examination of the lung revealed bronchiolar regeneration and necrosis in males and females of all 1-BP treated groups. Nasal epithelial lesions were seen in males at 500 ppm (2515 mg/m^3) and greater, and in females at 1000 ppm (5030 mg/m^3) and greater. In addition, centrilobular necrosis of the liver was observed in both male and female mice beginning at 500 ppm (2515 mg/m^3), and centrilobular chronic inflammation and cytoplasmic vacuolization were observed at 1000 ppm (5030 mg/m^3) and greater.

In an accompanying immunotoxicity study affiliated with NTP, Anderson *et al*. (2010) exposed groups of F344/N rats and B6C3F$_1$ mice to 0, 125 (mice only), 250, 500, or 1000 ppm (rats only) (0, 630, 1258, 2515, and 5030 mg/m^3) for 6 hours/day, 5 days/week, for 4 or 10 weeks. Similar to the results by NTP (2011), several mice died (3 of 8 mice) in the first week of exposure to 500 ppm (2515 mg/m^3).

In pregnant Sprague-Dawley (female) rats (25 per group) exposed to 0, 500, 2500, or 5000 mg/m^3 (0, 100, 498, or 996 ppm) 1-BP for 6 hours/day on gestation days (GD) 6 through 19, signs of sensory irritation was evident at the highest exposure (Huntingdon Life Sciences, 2001). A higher incidence of lacrimation, excessive salivation, and red stains on the head or snout was observed in the 996 ppm (5000 mg/m^3) group compared to control and other 1-BP treated groups. These signs of toxicity began to occur on days 5-7 of exposure. No apparent signs of neurotoxicity were observed.

Honma and co-workers (2003) studied the effects of acute and subacute 1-BP exposure on the central nervous system of rats by employing a series of neurobehavioral tests. Exposure durations lasted anywhere from a single 8-hour exposure to repeated exposures of 8 hours/day, 7 days/week for 3 weeks. Groups of five male F344 rats per exposure group were used in most tests. Body temperature and spontaneous locomotor activity (SLA) were measured in the rats before and after one day or 3 weeks of exposure to 1-BP at 0, 10, 50, 200, and 1000 ppm (0, 50, 252, 1006, and 5030 mg/m^3). The body temperature was significantly lowered (p<0.05) on days one through seven of exposure at 1000 ppm (5030 mg/m^3) with gradual recovery to normothermia after the first week of exposure. The authors noted that hypothermia frequently develops in animals exposed to organic solvents and appears to be related to the anesthetic action of the solvent. SLA was unaffected by a single 8-hour exposure at the 1-BP concentrations tested, 0, 50, 200, or 1000 ppm (0, 252, 1006, or 5030 mg/m^3). However, a three-week exposure to 0, 10, 50, or 200 ppm 1-BP resulted in increased SLA at 50 and 200 ppm (252 and 1006 mg/m^3).

Open field activity was measured after a single 8-hour exposure. Ambulation and rearing scores increased at 200 and 1000 ppm (1006 and 5030 mg/m^3), but the

differences from control were not statistically significant, and ANOVA did not detect a statistically significant dose-response trend ($p>0.05$). However, ambulation and rearing scores were significantly increased at 200 ppm (1006 mg/m^3) following 3-week exposure to 1-BP. Other open field tests, including preening, urination/defecation, and freezing (latency before leaving the central square after placement in the arena) scores, were not affected by 1-BP exposure durations of up to three weeks.

Honma *et al*. (2003) performed several other neurobehavioral tests, including the traction, rota-rod, passive avoidance, and water maze tests. The traction test, a measure of muscle strength, was conducted on groups of rats exposed to 0, 10, 50, 200, and 1000 ppm (0, 50, 252, 1006, and 5030 mg/m^3) for up to 3 weeks. In the traction test, the time rats hang from a bar by their fore-limbs is measured until they fall. Traction time was unaffected at all 1-BP concentrations after a single 8-hour exposure. After 7 days of exposure, traction time had decreased at 200 and 1000 ppm (1006 and 5030 mg/m^3) but did not reach statistical significance from the control. However, an ANOVA analysis revealed that the dose effects were significant ($p<0.0001$). After two weeks of exposure, the 1000 ppm (5030 mg/m^3) rats had significantly lower traction times ($p<0.05$), and at three weeks of exposure, both the 200 and 1000 ppm (1006 and 5030 mg/m^3) rats had significantly lower traction times.

For the rota-rod test, groups of five rats each also were exposed to 0, 10, 50, and 200 ppm (0, 50, 252, or 1006 mg/m^3) 1-BP for up to 3 weeks (Honma *et al.*, 2003). The amount of time remaining on the rod was unaffected ($p>0.05$) by 1-BP exposure at all concentrations with 1, 3, 7, 14, and 21 days of exposure. For the passive avoidance test, rats were conditioned to avoid electroshock before the 1-BP exposures, and then avoidance tested during and after 1-BP exposures of 0, 10, 50, 200, or 1000 ppm (0, 50, 252, 1006 or 5030 mg/m^3). Latency time to enter a dark “safe” room was unaffected at all exposure concentrations with 1, 3, 7, 14, and 21 days of exposure. In the water maze test, rats were trained to swim to an escape platform prior to exposure to the same 1-BP concentrations. Latency times to reach the platform were recorded during and after exposures to 1-BP. Latency times were unaffected by 1-BP with 1, 3, and 7 days of exposure. At 14 and 21 days, the 1000 ppm (5030 mg/m^3) group had significantly increased latency times ($p<0.05$).

Honma *et al*. (2003) concluded that increased SLA values and open-field activity (e.g., ambulation and rearing) support their view that 1-BP has excitatory effects on the central nervous system (CNS) of male rats. However, repeated daily exposures to 1-BP, not a single 8-hour exposure, were necessary to significantly affect SLA, open field activity, induce muscle weakness (traction test) and affect spatial learning and memory (water maze test).

To investigate the subacute effects of 1-BP on the CNS, Wang *et al*. (2002) exposed groups of male Wistar rats to 0, 200, 400, or 800 ppm (0, 1006, 2012, or 4024 mg/m^3) 1-BP 8 hours/day for one week, followed by morphological and biochemical examinations of the cerebrum, cerebellum, brain stem and lumbar enlargement of the spinal cord. Although body weight was significantly decreased at 800 ppm (4024 mg/m^3), the absolute weights of the various brain regions were not affected by 1-BP exposure. The neuron-specific marker protein γ-enolase was significantly decreased in the cerebrum and cerebellum at 400 and 800 ppm (2012 and 4024 mg/m^3). A reduction of this protein indicates a decrease in the amount of enzyme per cell or a decrease in the number of neurons. A reduction in creatine kinase activity was observed at 400 and 800 ppm (2012 and 4024 mg/m^3) in most brain regions, but glutamic oxaloacetic transaminase and lactate dehydrogenase activity were unchanged. Sulfhydryl base and total GSH were reduced in the brain at 800 ppm, primarily in the cerebrum and cerebellum.

Morphological findings by Wang *et al*. (2002) were observed only in 800 ppm (4024 mg/m^3) rats and included swelling and thinning of myelin sheaths of the preterminal axon of the gracile nucleus. The gracile nucleus is located in the medulla oblongata and is involved in the sensation of fine touch and proprioception (perception or awareness of body position and movement), primarily in the lower body. The only other finding was swelling or a dense mass of myelin sheath of the muscle branch of the posterior tibial nerve. The tibial nerve provides innervation to the muscle of the lower leg and foot. The authors proposed that GSH depletion or modification of functional proteins containing sulfhydryl groups (i.e., creatine kinase) may be involved in 1-BP-induced neurotoxicity. In addition, the study provided evidence that morphological changes can occur within the first week of exposure.

Biochemical and cell proliferation studies

Zhang *et al*. (2013) carried out biochemical and histopathological studies to determine if 1-BP suppresses neurogenesis (i.e., the growth and development of nervous tissue) in the dentate gyrus of the hippocampus in adult rats. It was hypothesized that suppression of neurogenesis in the hippocampus might be related to depression and cognitive and memory deficits observed in workers exposed to 1-BP. Groups of male Wistar rats were exposed to 0, 400, 800, or 1000 ppm (0, 2012, 4024, or 5030 mg/m^3) 1-BP, 8 hours/day for one week. Other groups of rats were exposed to 1-BP for four weeks using the same exposure protocol for the first two weeks, then adjusting the exposures down to 0, 200, 400, and 800 ppm (0, 1006, 2012, or 4024 mg/m^3), respectively, for the last two weeks. Immunostaining techniques did not detect changes in mRNA expression of brain-derived neurotropic factor (BMDF) or glucocorticoid receptor (GR) at any concentration following one week of exposure. BMDF and GR are factors known to affect neurogenesis. With four-week exposure, BMDF mRNA

expression was significantly decreased at 400 and 800 ppm (2012, or 4024 mg/m^3), and GR mRNA expression was reduced at all exposure levels. The neurotransmitter noradrenalin was significantly reduced at 800 and 1000 ppm (4024, or 5030 mg/m^3) in the striatum after one week of exposure. Four-week exposure additionally decreased noradrenalin in the prefrontal cortex and hippocampus at 800/1000 ppm (4024/5030 mg/m^3).

Groups of rats exposed to 1-BP for one week or four weeks were also injected with 5-bromo-2'-deoxyuridine (BrdU) following exposure (Zhang *et al.*, 2013). Sections of the dentate gyrus were then examined for BrdU-positive cells, an indicator of newborn cells. Exposure to 1-BP for one week at all concentrations did not result in changes in BrdU immunostained cells in the dentate gyrus. However, rats exposed to 800/1000 ppm (4024/5030 mg/m^3) for four weeks had significantly fewer BrdU-positive cells. Taken together, the authors concluded that downregulation of BMDF and GR mRNA expression and the low hippocampal NE following 1-BP exposure might be partly responsible for reduced neurogenesis.

Table 2. Summary of Acute and Subacute Effects of 1-BP in Experimental Animals

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Elf Atochem, 1997	Wistar rats Nose-only inhalation exposure for 4 hours	LC_{50} of 7000 ppm (35,000 mg/m^3) (95% CI = 6800 to 7200 ppm)	NOAEL: NA LOAEL: NA: mortality due to respiratory inflammation and edema
Kim *et al.*, 1999	Female Sprague-Dawley rats WB inhalation exposure to 0, 11,000, 13,000, 15,000 or 17,000 ppm for 4 hours.	LC_{50} 14,374 ppm Lacrimation, piloerection, decreased activity, and ataxia in all 1-BP-treated groups	NOAEL: NA LOAEL: 11,000 ppm for sensory irritation and neurotoxicity
	Female Sprague-Dawley rats WB inhalation exposure to 0, 50, 300, or 1800 ppm for 6 weeks (6 hours/day, 5 days/week).	Decreased activity and mild ataxia after the first hour of daily exposures to 1800 ppm	NOAEL: 300 ppm LOAEL: 1800 ppm for neurotoxicity

612 **Table 2. Summary of Acute and Subacute Effects of 1-BP in Experimental Animals**
613 **(continued)**

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Garner *et al*., 2007	Male wild type (*Cyp2e1*+/+) mice WB inhalation exposure to 0 or 800 ppm for 6 hours	↓ sperm motility at 800 ppm	NOAEL: NA LOAEL: 800 ppm
NTP (2011)	Female F344/N rats WB inhalation exposure to 0, 125, 250, 500, 1000 or 2000 ppm for 16 days (6 hours/day, 5 days/week).	Hind limb splaying after the first week of exposure to 2000 ppm ↓ BW at 2000 ppm ↑ nasal lesions at ≥500 ppm	NOAEL: 250 ppm LOAEL: 500 ppm for upper respiratory system toxicity
	Female B6F3N1 mice WB inhalation exposure to 0, 125, 250, 500, 1000 or 2000 ppm for 17 days (6 hours/day, 5 days/week)	Abnormal breathing, lethargy, eye discharge, and mortality at ≥500 ppm during the first week ↑ nasal epithelial lesions at ≥500 ppm in males and ≥1000 ppm in females ↑ liver lesions at ≥500 ppm	NOAEL: 250 ppm LOAEL: 500 ppm for mortality, sensory irritation, neurotoxicity, upper respiratory system lesions, and hepatotoxicity
Anderson et al., 2010	B6C3FN1 mice WB inhalation exposure to 0, 125, 250, or 500 ppm for 4 or 10 weeks (6 hours/day, 5 days/week)	3 of 8 mice in the 500-ppm group died in the first week of exposure	NOAEL:250 ppm LOAEL: 500 ppm for mortality
Huntingdon Life Sciences, 2001	Pregnant female Sprague-Dawley rats WB inhalation exposure to 0, 100, 498, or 996 ppm on GD 6-19 (6 hours/day)	Lacrimation, excessive salivation, and red stains on head or snout at 996 ppm after 5 to 7 days of exposure	NOAEL: 498 LOAEL: 996 ppm for observed signs of sensory irritation and inflammation

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615 **Table 2. Summary of Acute and Subacute Effects of 1-BP in Experimental Animals**
616 **(continued)**

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Honma et al., 2003	Male F344 rats WB inhalation exposure to 0, 10, 50, 200, or 1000 ppm for a single 8-hour exposure, and up to 3 weeks (8 hours/day, 7 days/week)	↓ body temperature after 8 hr exposure at 1000 ppm ↑ SLA after 3-week exposure to 50 and 200 ppm ↑ open field activity after 3-week exposure to ≥200 ppm ↓ hind limb strength at 1000 ppm after 2 weeks, and at ≥200 ppm after 3 weeks ↑ latency time in water maze test after 2- and 3-weeks exposure to 1000 ppm	NOAEL: 200 LOAEL: 1000 ppm for CNS effects ≥2 weeks exposure
Wang et al., 2002	Male Wistar rats WB inhalation exposure to 0, 200, 400, or 800 ppm for 7 days (8 hours/day)	↓ brain γ-enolase and creatine kinase activity at ≥400 ppm, and ↓ total GSH and sulfhydryl base at 800 ppm ↑ lesions of preterminal axon of the gracile nucleus and posterior tibial nerve at 800 ppm	NOAEL: 200 ppm LOAEL: 400 ppm for reduced enzyme levels in the brain

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Table 2. Summary of Acute and Subacute Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Zhang *et al*., 2013	Male Wistar rats WB inhalation exposure to 0, 400, 800, or 1000 ppm for 1 or 4 weeks (8 hours/day)	At 1 week, ↓ noradrenalin in striatum at ≥800 ppm At 4 weeks, ↓ BMDF mRNA at ≥800/400 ppm, and GR mRNA at ≥400/200 ppm in the hippocampus At 4 weeks, ↓ BrdU-positive cells in the hippocampus at 1000/800 ppm	At 1 week NOAEL: 400 ppm LOAEL: 800 ppm for reduced brain noradrenalin

↑ – increase resulting in significant ($p \leq 0.05$) difference; ↓ – decrease resulting in significant ($p \leq 0.05$) difference; BMDF – brain-derived neurotropic factor; BrdU – 5-bromo-2'-deoxyuridine; CI – confidence interval; CNS – central nervous system; GD – gestation day; GR – glucocorticoid receptor; GSH – glutathione (reduced); LC_{50} – median lethal dose; LOAEL – lowest observable adverse effect level; mRNA – messenger ribonucleic acid; NOAEL – no observable adverse effect level; NA – not attained or not applicable; WB – whole body.

6. Chronic Toxicity of 1-Bromopropane

6.1 Chronic Toxicity to Adult Humans

The occupational studies summarized in this section show that neurotoxicity is likely the most sensitive indicator of toxicity in humans, with peripheral nerve damage the most common manifestation of injury. Symptoms include numbness in the lower limbs, decreased pallesthesia (vibratory sensation), unstable gait, and difficulty with walking. Hematological changes also appear to be a frequent finding.

Nerve conduction studies are used primarily for the diagnosis of various neuropathies, especially nerve demyelination diseases in which conduction velocity (CV) of the nerve is reduced. Reference values in adult populations have been determined for the more common peripheral motor and sensory nerves in the upper and lower limbs (Benatar *et al.*, 2009; Chen *et al.*, 2016) and are used in this report to compare with neurotoxicity findings following occupational exposure to 1-BP. Nerve conduction testing can be challenging and is dependent upon the skill of the electrodiagnostic practitioners, instrumentation, and testing circumstances (AAEM, 1999). In addition, increasing age and height (limb length) correlates with decreasing conduction velocity and may need to

be considered in comparing studies. Because of the non-Gaussian distribution of nerve conduction parameters, percentiles are used for cut-off values for normality when available. If not enough subjects were tested, the mean ± 2 SD has been used to describe the normal range.

A summary table (Table 12) of the chronic toxicity findings in the occupational studies is presented at the end of this section.

6.1.1 Case Reports of Chronic Toxicity

A case report from New Jersey described a 19-year-old man who developed complaints including weakness of both legs and of the right hand, numbness, and difficulties in swallowing and urinating following a two-month exposure to an industrial solvent containing 95.5% 1-BP (Sclar, 1999). Vibration sense was also deficient in the right hand and both legs. The patient, who was right-handed, had darkened skin on his right hand, suggesting dermal exposure to 1-BP even though he wore gloves (material unspecified). The solvent also contained butylene oxide, 1,3-dioxolane, nitromethane, and other components. Nerve conduction studies revealed evidence of a primary, symmetric demyelinating polyneuropathy. In the lower limbs, distal latencies (DL) of motor nerves, measured in milliseconds (ms), were above the range of normality (Table 3). Additionally, the sural and superficial peroneal sensory nerve conduction velocities (CV), measured in meters per second (m/sec), were below the range of normality. Evidence of central nervous system (CNS) involvement came from gadolinium-enhanced magnetic resonance imaging scans of the brain. The scans showed patchy areas of increased T2 signal in the periventricular white matter. Similar scans of the spinal cord revealed root enhancement at several lumbar levels. The patient's symptoms had started to resolve following the discontinuation of the exposure, before he was lost to follow-up. Since similar findings follow 1-BP exposure in rats (see below), Sclar (1999) hypothesized that the patient's symptoms may have been due to 1-BP-induced neurotoxicity. No information on the exposure level was available.

Table 3. Results of the nerve conduction tests in lower limbs (Sclar, 1999)

	Motor nerve DLs (ms)[a]	Peroneal nerve motor CV (m/sec)	Sural sensory nerve CV (m/sec)	Peroneal sensory nerve CV (m/sec)
1-BP-exposed patient	Range: 8.0 – 9.6	Left: 39.3	Left: 36.2	Left: 31.2
		Right: 38.3	Right: 31.8	Right: 29.4
Cut-off for normality	6.1, 6.5[b]	37[c]	40[d]	41[e]

[a] Moter nerves not identified but likely both tibial and peroneal nerve DLs were tested
[b] Upper limit - 97th percentile is 6.1 ms for tibial nerve, all ages combined, and upper limit - 97th percentile 6.5 ms for peroneal nerve, all ages combined (Chen *et al*., 2016).
[c] Low limit – 3rd percentile for adults 19-49 yrs of age and >170 cm in height (Chen *et al*., 2016)
[d] Low limit – 3rd percentile for 185 adults (95% CI: 37.7, 42.3 m/sec), (Benatar *et al*., 2009)
[e] Low limit – 4th percentile for 92 adults (95% CI: 38.1, 43.3 m/sec), (Benatar *et al*., 2009)

In 2007, a 50-year-old worker at an electronics plant presented at an emergency room with a history of confusion, dysarthria (poor articulation of sounds), dizziness, paresthesia, and ataxia for 24-48 hours (MMWR, 2008). For three years, he had used 1-BP to clean circuit boards by vapor and immersion degreasing and had done maintenance on the tank. He did not regularly use personal protective equipment and reported that local ventilation was poor. The patient was alert but had slowed mental activity and mild confusion. His gait was wide-based and ataxic, and a Romberg's test was positive (i.e., loss of balance with eyes closed). Mild sensory peripheral neuropathy was found in the upper and lower extremities. At his workplace one week later, the Occupational Safety and Health Administration found a level of 178 ppm (895 mg/m^3) 1-BP by short-term air sampling. The peripheral neuropathy and ataxia persisted one year after the initial visit, so he quit working at the plant.

A 43-year-old male industrial worker, who used 1-BP as a cleaning agent for metal parts at his workplace for 18 months without appropriate protection, developed muscle weakness, pain, numbness, and gait disturbance (Samukawa *et al.*, 2012). With passive samplers, his exposure was estimated to be 553 ppm (2780 mg/m^3) (mean of time-weighted averages, range 353-663 ppm) at his workstation. Neurological examination indicated sensory ataxic neuropathy associated with mild impairment of upper motor neurons. The serum bromide level was elevated (58 µg/mL; normal < 5 µg/mL) at the onset of clinical manifestations. Histopathologic examination of a sural nerve biopsy showed axonal damage. After being kept away from solvent, his symptoms gradually improved, he recovered motor function, and his sensory deficits cleared up.

6.1.2 Occupational studies of chronic toxicity

Japanese and American investigators reported neurological disorders in three women, ages 30, 35, and 50, who sprayed an adhesive mixture containing 55% 1-BP at a facility

manufacturing cushions in North Carolina (Ichihara *et al.*, 2002). Ethyl acetate (8%) and petroleum distillates (2%) were also part of the glue mixture. In 1999, the facility replaced dichloromethane with 1-BP as a solvent. Daily time-weighted average levels of 1-BP in the workplace of the 50-year-old woman were determined over 6 days of work. The TWA concentrations ranged from 60 to 261 ppm (300 to 1300 mg/m^3). However, these measurements were taken after ventilation improvements and may have underestimated exposure. Common symptoms after 1-BP exposure were staggering, numbness, and paresthesia, which were similarly expressed in the feet, legs, thighs, lower back, and hips. All three workers had a definite decrease in vibration sense in the legs and also reported dizziness, light-headedness, headache, and feeling intoxicated. Diarrhea, urinary incontinence, and sweating indicated effects on the autonomic nervous system.

In 1999, Ichihara and co-workers studied 24 female and 13 male workers in a factory in China synthesizing 1-BP from n-propanol and hydrogen bromide using concentrated sulfuric acid (Ichihara *et al.*, 2004a). The investigators had studied the same factory in 1996, when its main product was 2-bromopropane (2-BP). The manufacture of 2-BP at that factory was abandoned due to reports of hematologic, neurotoxic, and reproductive toxicity (Kim *et al.*, 1999b; Yu *et al.*, 2001)). The purity of 1-BP was 96.74%. Impurities included di-n-propyl ether (1.02%), 2-BP (0.83%), 1,2-dibromopropane (0.4%), 1,2-dibromoethane (0.26%) and an unknown peak (0.75%). The authors collected urine and blood samples and measured 1-BP levels in the factory, individual exposure levels, urinary 1-BP, the serum levels of several enzymes including creatine kinase, and the levels of the M subunit of serum creatine kinase. (In an earlier report, rats exposed to 1-BP had decreased creatine kinase activity (Ichihara *et al.*, 2000a)). The 1-BP exposure levels ranged from 0.9 to 170.5 ppm (geometric mean = 52.5 ppm) (4.5 to 880 mg/m^3; geometric mean = 260 mg/m^3)). Symptoms frequently reported by exposed workers were nose, throat, and eye irritation, malaise, and headache. However, the authors found no severe neurological symptoms such as numbness, paresthesia, dysesthesia, urinary or speech difficulties in the exposed workers. Urinary 1-BP levels were significantly correlated with the individual's exposure, but enzymatic activity and creatine kinase-M subunit levels did not correlate. Some of the 1-BP workers had anemia (identified as low hemoglobin (Hb) and hematocrit (Ht) levels) or amenorrhea. But because of the small number of subjects and the lack of appropriate controls, it could not be confirmed if these abnormalities were due to 1-BP exposure.

In 2001, the same investigators surveyed 27 women who had worked 27 ± 31 months in the above 1-BP production factory and compared them to 23 age-matched workers in a beer factory (Ichihara *et al.*, 2004b). The investigation included neurologic, electrophysiologic, hematologic, biochemical, neurobehavioral, and postural sway tests. Individual worker exposure levels were estimated with passive samplers. TWA

exposure levels were 0.34 to 49.19 ppm (median = 1.61 ppm (8 mg/m^3); geometric mean = 2.92 ppm (15 mg/m^3)). These values were much lower than those observed in the 1999 study. Tests with a tuning fork showed diminished vibration sensation of the right and/or left foot in over half the workers exposed to 1-BP; no controls were affected (Table 4).

Table 4. 1-BP workers with reduced vibration sensation in the foot (Table 3 of (Ichihara *et al.*, 2004b))

1991 workers (23 pairs)					**1999 workers (12 pairs)**			
Delay[a] time(sec)	right foot*		left foot*		right foot*		left foot*	
	1BP	control	1BP	control	1BP	control	1BP	Control
<2	8	23	10	23	5	12	5	12
2	0	0	1	0	0	0	1	0
3	3	0	1	0	1	0	1	0
4	2	0	4	0	1	0	1	0
5	2	0	1	0	1	0	0	0
6	4	0	4	0	3	0	2	0
8	3	0	1	0	1	0	1	0
10	0	0	1	0	0	0	1	0
∞[b]	1	0	0	0	0	0	0	0
≥2	**15/23**	**0/23**	**13/23**	**0/23**	**7/12**	**0/12**	**7/12**	**0/12**

[a] Delay time for vibration sensation by tuning fork stimulation; time 0 is the time when the worker reported becoming unaware of the vibration.
[b] One worker felt no vibration sense in the right foot.
* $p < 0.05$ by Wilcoxon test for 1-BP *vs*. control

1-BP workers in the Ichihara *et al*. (2004b) study showed significantly longer DL in the tibial nerve and displayed lower values in sensory nerve CV in the sural nerve compared to matched controls (Table 5). The tibial motor nerve CV and F-wave CV were not significantly different compared to matched controls. For 1-BP workers, both tibial nerve DL and sural sensory nerve CV were outside of the normal range. 1-BP workers also showed lower values for backward recalled digits, Benton visual memory test scores, pursuit aiming test scores, and five items of the Profile of Mood States (POMS) test (tension, depression, anxiety, fatigue, confusion) compared with matched controls. Workers hired after May 1999, who were exposed only to 1-BP, showed similar changes in vibration sense (Table 4), distal latency (Table 5), Benton test scores, and depression and fatigue in the POMS test. One potential confounder was that some workers, who were hired before 1999, were also exposed to 2-BP.

Table 5. Electrophysiologic indices of workers (Ichihara *et al.*, 2004b)

Endpoint	1991 workers (n=23)	Age-matched controls (n=23)	1999 workers (n=12)	Age-matched controls (n=12)	Normal range
Tibial nerve DL (ms)	8.05 ± 2.17*	5.96 ± 1.38	8.36 ± 2.38*	6.06 ± 1.43	6.1[a]
Tibial motor nerve CV (m/sec)	49.8 ±10.3	49.9 ± 8.2	51.3 ± 12.0	51.7 ± 10.7	44[b]
Tibial nerve F-wave CV (m/sec)	52.8 ± 3.5	55.1 ± 3.2	51.8 ± 2.8	55.0 ± 2.9	ND[c]
Sural sensory nerve CV (m/sec)	39.2 ± 3.5*	46.2 ± 6.6	39.2 ± 2.6	47.5 ± 8.5	40[d]

* $p < 0.05$ compared to age-matched controls by paired t-test. Data are mean ± SD.
[a] Upper limit - 97th percentile, all age combined (Chen *et al*., 2016)
[b] Low limit – 3rd percentile for 19-49 yrs old and <160 cm (Chen *et al*., 2016)
[c] No data. F-wave reference values are generally expressed as a latency in ms
[d] Low limit – 3rd percentile (95% CI: 37.7, 42.3 m/sec), range: 35.8 – 62.0 m/sec, for 185 randomly selected healthy adults (Benatar *et al*., 2009)

The report also separated 1-BP exposed workers into those exposed to ≤ 2.64 ppm (13 mg/m^3) (n=17) and those exposed to ≥ 8.84 ppm (44 mg/m^3) (n=7). The worker group, 1991 workers and/or 1999 workers, was not specified. Workers with the higher exposure level showed significantly higher values of motor nerve CV, F-wave CV, POMS (tension), and hematocrit, and lower values of POMS (vigor) and follicle-stimulating hormone (FSH), compared with the lower exposure level group (Table 6). The authors did not specify a control group whereby one could determine if the low exposed group was a NOAEL or a LOAEL. OEHHA staff examined the data from the age and education-matched 1999 control workers in the paper but was unable to make a clear determination that the controls were appropriate. However, based on a comparison of the numbers of workers in Tables 4 and 6, some of the workers with reduced vibration sensation in Table 4 must also be in the low exposure group of Table 6. Thus, 2.64 ppm (13 mg/m^3) is not a NOAEL for reduced vibration sensation in the low exposure group.

Table 6. Comparison of low *vs*. high exposure groups (Ichihara *et al.*, 2004b)

Parameter	**⩽ 2.64 ppm (n=17)**	**⩾ 8.84 ppm (n=7)**
Motor nerve CV (m/sec)*	47.3 ± 8.3 (mean ± SD)	56.4 ± 12.9
F-wave CV (m/sec)*	52.0 ±1.9	54.7 ± 2.8
hematocrit (fraction)*	0.356 ± 0.034	0.393 ± 0.032
POMS tension (score)*	2.73 ± 1.49	5.14 ± 1.77
POMS vigor (score)*	24.3 ± 4.0	18.6 ± 2.5
FSH (mIU/ml)*	27.7 ± 35.3	9.0 ± 6.3

*Each low exposure group test is significantly different from the high group ($p < 0.05$).

Six workers (ages 16-46 years) with neurotoxicity were reported among foam cushion gluers exposed to 1-BP vapors from spray adhesives in Utah (Majersik *et al.*, 2007). Five patients were exposed for 30-40 hours per week over three years; the sixth (age 16) had been employed for only three months. In the previous month, exposure peaked when ventilation fans were turned off. The patients reported the subacute onset of pain/paresthesia in the lower extremities. Five had difficulty walking and had spastic partial paralysis, distal sensory loss, and hyperreflexia. Serum bromide concentrations ranged from 44 to 170 milligrams per deciliter (mg/dL). (All values were greater than the reference range of 0-40 mg/dL determined in healthy individuals.) The patients also had slightly elevated serum chloride. Air samples during gluing operations gave a mean 1-BP level of 130 ppm (range 91-176 ppm) (650 mg/m^3; range 458-885 mg/m^3); the seven-hour TWA was 108 ppm (range 92-127 ppm) (540 mg/m^3; range 463-639 mg/m^3). Two years after exposure, the two most severely affected patients had minimal improvement; they, and one other patient, still experienced chronic neuropathic pain. The authors proposed that 1-BP was the likely cause of the central distal axonopathy syndrome and that there may be major neurotoxic effects at exposures above 100 ppm (503 mg/m^3), some of which may not be reversible.

Wang *et al*. (2007) investigated the changes in the peripheral and central nervous systems of workers at a 1-BP manufacturing plant in Shandong Province, China. Twenty-five 1-BP manufacturing workers (17 males, average age 25.6 yr; 8 females, average age 19.8 yr) formed the exposure group. Twenty-five steel plant workers from the same region comprised the control group (17 males, average age 24.5 yr; 8 females, average age 27.9 yr). The average age for females was significantly lower for the exposure group compared to the control group ($p<0.05$). The average concentration of 1-BP in six areas of the operating environment, measured 12 times at each location, ranged from 13.09 to 38.44 mg/m^3 (2.6 to 7.64 ppm). The average TWA for worker daily individual exposure (apparently measured only once for each worker) was 80.4 mg/m^3

(16.0 ppm) with a range of 2.0~384.9 mg/m^3 (0.4 – 76.5 ppm). Three of these workers had an individual exposure >250 mg/m^3 (49.7 ppm), while the others were below 100 mg/m^3 (19.9 ppm). The employment times of the workers at the plant were not provided in the study.

Nerve CV tests were conducted by Wang *et al*. (2007) at peroneal nerves between the knees and ankles and included motor-nerve CV, sensory-nerve CV, F-wave CV, and DL (Table 7). Compared to the control group, the males in the exposure group had significantly decreased motor CV and prolonged DL ($p<0.05$). However, all peroneal motor nerve CV values were within the range of normality (>37 m/sec). The peroneal nerve DL was above the range of normality in exposed male workers (>6.5 ms), although the control group DL was at the upper limit for normality. Females in the exposure group had no notable differences compared to controls, except one individual in the female exposure group had a much lower motor nerve CV. It was unclear to the authors if the severe reduction in CV was induced by 1-BP exposure or had some other cause. The significantly younger age of female 1-BP workers compared to the control group may be a factor for the lack of significant differences in conduction velocity and latency. Motor CV decreases, and DL increases with age (Stetson *et al.*, 1992).

Among the seven neurobehavioral examinations – POMS, simple reaction time, digit span, dexterity, digit symbol, visual retention, and pursuit aiming — the male exposure group scored significantly higher for tension and anxiety on the POMS scale and scored lower in the visual retention test (i.e., a test for memory) ($p<0.05$). The female exposure group scored significantly lower ($p<0.05$) in the digit symbols test compared to the control group. The authors concluded that low 1-BP exposure may have affected the nerve conduction velocity and neurobehavior of 1-BP-exposed male workers, but the female exposure group was too small to make any conclusions. (The study by Wang *et al*. (2007) was published in Chinese and professionally translated into English for OEHHA.)

Table 7. Results of the peroneal nerve conduction velocity and latency tests (Wang *et al*., 2007)

Exposure Group	N	Motor CV[a] (m/sec)	Sensory nerve CV[b] (m/sec)	F-wave CV[c] (m/sec)	DL[d] (ms)
Control (male)	17	46.26 ± 3.84	44.85 ± 5.66	12.57 ± 0.65	6.54 ± 1.69
1-BP worker (male)	17	43.51 ± 3.25*	44.36 ± 10.76	12.52 ± 1.26	7.63 ± 1.04*
Control (female)	8	48.90 ± 14.11	42.75 ± 3.37	12.51 ± 2.11	7.20 ± 2.10
1-BP worker (female)	8	47.84 ± 3.47	43.21 ± 7.12	12.06 ± 1.61	6.01 ± 2.37

* $p<0.05$ compared to the control group of same gender

[a] 37 m/sec - 3rd percentile (low limit) for adults 19-49 yrs of age and >170 cm in height (Chen *et al*., 2016)

[b] 41 m/sec - 4th percentile (low limit) for adults (95% CI: 38.1, 43.3 m/sec), (Benatar *et al*., 2009)

[c] No normal range data for this nerve conduction parameter

[d] Upper limit, 97th percentile is 6.5 ms for adults all ages combined (Chen *et al*., 2016).

In an extension of previous occupational studies by Ichihara and coworkers, Li *et al*. (2010a) studied 60 female and 26 male workers in three 1-BP production factories in China and compared them to the same number of age-, sex-, and region-matched controls. Exposure estimates were an average of two shifts of 8- or 12-hours in length, although individual exposure was measured three times or only once in some workers. The authors estimated individual time-weighted average (TWA) exposure levels (range = 0.06 - 114.8 ppm (0.3 – 580 mg/m^3)) and divided the females into equal numbers of low (0.07 – 3.35 ppm (0.35 – 17 mg/m^3)), medium (3.39 – 14.13 ppm) (17 – 71 mg/m^3), and high (15.28 – 106.4 ppm) (77 – 540 mg/m^3) exposure. The males were divided into equal numbers of low (0.06 -3.5 ppm (0.3 – 18 mg/m^3)) and high exposure groups (5.7 - 114.8 ppm (29 - 580 mg/m^3)). Individual TWAs of 2-BP exposure were also determined. For females, the TWA ranged from 0.01 to 14.9 ppm with a median of 0.4 ppm. In males, the TWA ranged from 0.004 to 5.4 ppm with a median of 0.15 ppm.

Electrophysiological examination of nerve conduction included motor CV, DL, tibial nerve F-wave CV, sural sensory nerve CV, and amplitudes induced by motor nerve, F-wave, and sensory nerve stimulation. Neurobehavioral testing of the workers used the Chinese edition of the WHO Neurobehavioral Core Test Battery and POMS. The workers were also tested by Chinese physicians for vibration sense (pallesthesia) in the hand and big toe and reflex and muscle strength in the four limbs. Hematological and biochemical exams included routine blood analysis, blood biochemistry, and serum hormone levels.

Table 8 contains data on the female workers exposed to three levels of 1-BP and the unexposed controls. No difference in exposure duration was observed among the three 1-BP exposure groups. After adjusting for alcohol exposure and the effect of pair (one-to-one) matching for age, sex, and region in selecting controls (Analysis of Covariance

(ANCOVA), p<0.05), regression analysis on exposure level showed dose-dependent increases in the DL of the tibial nerve, vibration sense threshold in toes (i.e., vibration perception delay time), lactate dehydrogenase (LDH) activity, and FSH levels. There were also dose-dependent decreases in sural sensory nerve CV, POMS – fatigue, red blood cell counts (RBCs), hemoglobin (Hb), and hematocrit (Ht). The authors estimated that 1.28 ppm (6.4 mg/m^3) (the median of the low dose female exposure group) was the lowest dose that induced adverse effects, mainly due to decreased vibration sense in toes and low red blood cell (RBC) count in female workers.

Table 8. Data[a] on female workers in Li *et al*. (2010a)

Exposure Group	Control	Low	Middle	High	(ANOVA) P
Range (ppm)	-	0.07-3.35	3.39-14.13	15.28-106.4	-
Median (ppm)		1.28	6.60	22.58	
N (all females)	56-60#	19-20	18-20	19-20	-
Exposure duration (months)	39.8	40.2	40.2	38.9	-
Tibial motor DL (ms)	6.7 ± 1.7	7.1 ± 1.7	8.4 ± 2.0*	7.6 ± 1.9	0.0027
Sural nerve CV (m/sec)	49.0 ± 6.2	45.4 ± 4.2	44.6 ± 4.9*	46.5 ± 4.1	0.0075
Toe vibration[b] (sec)	2.9 ± 3.9	5.6 ± 4.4*	6.5 ± 3.7*	6.4 ± 3.4*	0.0001
POMS: Fatigue	8.4 ± 4.6	5.5 ± 4.2*	6.3 ± 4.2	5.9 ± 4.9	0.035
LDH (IU/L)	182 ± 77	276 ± 279	445 ± 526*	333 ± 324	0.0038
FSH (mIU/mL)	7.8 ± 7.6	23 ± 28*	21 ± 25*	18 ± 24	0.0058
RBC (10^6/μL)	4.3 ± 0.4	3.8 ± 0.4*	4.0 ± 0.4*	3.8 ± 0.3*	<0.0001
Hb (g/L)	12.5 ± 1.6	11.5 ± 1.3*	12.4 ± 1.1	11.8 ± 1.0	0.011
Ht (L/L)	0.38 ± 0.04	0.35 ± 0.04	0.38 ± 0.05	0.35 ± 0.03*	0.0063

* p < 0.05 vs the control (unexposed) group using Dunnett's multiple comparison

[a] All measured endpoints are mean ± SD

[b] The vibration sense was evaluated using a vibrating tuning fork (128 Hz) placed on the metatarsal bone of the big toe or pisiform bone of the carpus. The workers were asked to report the time of vibration cessation. The examiner then immediately moved the fork to the same site on his/her foot. The duration of the lasting vibration on the examiner's foot is then recorded as the vibration perception delay time.

Tibial motor nerve DLs in all groups in Table 8 were above the range of normality (>6.1 ms). This discrepancy could be related to differences in the testing circumstances (e.g., colder room temperature during testing), skill level of electrodiagnostic practitioners, and instrumentation. However, sural NCV values in all exposure groups were within the reference range (>41 m/sec). Although mean Hb and FSH levels in 1-BP-exposed women are significantly different from mean control values, these parameters were still within the normal range of reference values (Li *et al*., 2010b). On the other hand, the LDH level was above the normal range (115 – 245 IU/L) in all groups of 1-BP-exposed women. In addition, in the low and high exposure groups, the RBC count (normal range: 3.9 x 10^6/ul – 4.8 x 10^6/ul) and Ht (normal range: 38 – 46%) are below the normal range for adult women. The authors noted that increased serum LDH levels may be an

indicator of cellular damage to liver, kidney, heart, or muscle tissue but did not speculate beyond this why the 1-BP-exposed women had higher levels. The workers were exposed to trace amounts of 2-BP, which is known to cause hematotoxicity. However, the authors only suggested that further tests are needed to determine if the relatively low 2-BP levels in 1-BP manufacturing plants may have contributed, in part, to the low RBC count and Ht.

Compared with female workers, male workers showed significant exposure-associated changes in very few indices. When adjusted by ANCOVA for alcohol exposure and the effect of pair (one-to-one) matching for age, sex, and region in selecting controls, only blood urea nitrogen (BUN) was statistically significantly increased in 1-BP exposed male workers. However, the BUN level in 1-BP-exposed men was within the normal range (6 - 20 mg/dl). A low number of 1-BP-exposed male subjects (n=26), more work duties outside the 1-BP workshop compared to women, and gender differences were suggested by the authors as reasons for the lack of exposure-associated changes in males.

Li *et al*. (2010b) also investigated the effect of 1-BP occupational exposure in 71 female workers and compared them to a control group of female workers from the same region. The 1-BP workers were recruited from four large 1-BP manufacturing plants in China [OEHHA notes that many of the females recruited for this study may have also participated in the study by Li *et al*. (2010a)]. Selection criteria included age between 20~50 years, employment at a 1-BP workshop continuously for more than 12 months (mean length of employment was 38.8 months), and no medical history of diabetes or other chronic diseases that might affect nerve functions. Another 71 female workers from a food factory, a steel plant, and a refrigeration equipment plant were chosen as the control group. The controls were matched for age (average age 36.9±7.3 years) and had no exposure to organic solvents. No statistically significant difference in age, height, medical history, alcohol use, and tobacco use was found between the exposure and control groups ($p>0.05$), although the exposure group did have a significantly lower education level than that of the control group ($p<0.05$).

1-BP concentrations in the breathing zones of the exposure group were monitored at 22 locations within the 1-BP workshops using direct reading 1-BP gas detectors. Samples were collected 3 times daily over 2-3 consecutive days. The average concentrations at various measuring points were between 0 and 108.65 mg/m^3 (21.6 ppm) with a maximum value of 402.40 mg/m^3 (80 ppm) (recorded when pouring the product into the storage tank). The overall average concentration for all the measuring points was 32.19 mg/m^3 (6.4 ppm). Individual exposure was determined for all workers using passive personal 1-BP collection samplers worn throughout their entire 8-hr work shifts. The 8-hr time-weighted average for workers' individual exposure ranged from 0.35 to 535.19 mg/m^3 (0.07 to 106.40 ppm), the median was 20.98 mg/m^3 (4.17 ppm), and the

geometric mean was 14.13 mg/m^3 (2.81 ppm). Geometric mean concentrations for each respective 1-BP plant were 11.92, 5.16, 32.95, and 34.61 mg/m^3 (2.37, 1.03 , 6.55, and 6.88 ppm). The purity of all 1-BP samples was ≥96%. Impurities measured in the work environment by mass spectrometry included di-n-propyl ether, 2-BP, 1,2-BP, and 1,2-dibromoethane (percentage in 1-BP samples not stated).

The neurological examinations included cranial nerves, motor nerves, sensory nerves, physiological/pathological reflexes, pallesthesia (vibratory perception), grip strength, and coordination exams. Hematological and biochemical exams included routine blood analysis, blood biochemistry, and serum hormone levels. Nerve conduction velocity tests included motor nerve and sensory nerve CV, F-wave CV, DL, and F-M latency (not defined by the authors, but likely related to F-wave latency).

Compared to the control group, the exposure group had significantly lower white blood cell count (WBC), RBC, Hb, and creatine kinase levels, and significantly elevated total protein, LDH, thyroid-stimulating hormone (TSH), and FSH levels ($p<0.05$). However, with the exception of LDH, all these values were within the normal range for healthy adults. The average LDH value for the exposure group was 335.2 lU/L, higher than the normal reference values (115–245 IU/L); 21 individuals (29.6%) in the exposure group had LDH readings higher than the upper limit of the normal reference range. No explanation was provided by the authors why the LDH levels were high [OEHHA notes that a significantly elevated LDH level is often used as a general indicator of inflammation and cellular damage in the liver, kidneys, or other organs and tissues]. The authors stated that this was the first report suggesting that 1-BP may cause hematotoxicity. However, some workers may have had previous exposure to 2-BP (prior to 1999, when the factories manufactured 2-BP), which is known to cause decreased RBC, Hb, and mean corpuscular hemoglobin (MCH). 2-BP was also shown to be a minor impurity in the manufacture of 1-BP.

Peripheral nerve conduction was found to be impaired in the 1-BP workers (Table 9). Compared to the control group, the female 1-BP workers had significantly slower tibial motor nerve CV (44.8±8.7 vs. 50.1±10.3 m/s) and sural sensory nerve CV (45.5±4.9 vs. 48.3±5.2 m/s), and significantly prolonged DL (7.5±2.1 vs. 6.7±1.8 ms) ($p<0.05$). Tibial motor nerve CV and sural sensory nerve CV in 1-BP workers were still within the normal range for conduction velocity. However, both control and 1-BP workers had tibial DLs above the normal range, possibly a result of practitioner, instrumentation, and/or testing circumstance differences between studies. F-wave CV and F-M latency differences between the two groups were not statistically significant ($p>0.05$), indicating no measurable effect on spinal cord nerve conduction. One female worker had a motor nerve CV (29 m/sec) far below the reference values, and a notably prolonged DL (13.71 ms). Neurology examination also showed that she had decreased position and vibratory senses. The authors speculated that she might be a case of 1-BP poisoning

since she had a relatively higher TWA exposure level (41.9 mg/m^3) and longer working duration (>24 months).

Table 9. Results of the nerve conduction velocity and latency tests in Li *et al*. 2010b

Exposure Group	N	Tibial nerve DL (ms)	Tibial motor nerve CV (m/s)	Sural sensory nerve CV (m/s)	Tibial F-wave CV (m/s)	F-M latency
Control	71	6.7 ± 1.8	50.1 ± 10.3	48.3 ± 5.2	52.1 ± 4.6	41.7 ± 3.7
1-BP-exposed	71	7.5 ± 2.1*	44.8 ± 8.7*	45.5 ± 4.9*	51.1 ± 5.3	42.5 ± 4.0
Cut-off for normality		6.1[a]	42[b]	40[c]	ND[d]	ND

* 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 for 19-49 yrs old and 160-170 cm in height (Chen *et al*., 2016)
[c] Low limit – 3rd percentile (95% CI: 37.7, 42.3 m/sec), range: 35.8 – 62.0 m/sec, for 185 randomly selected healthy adults (Benatar *et al*., 2009)
[d] ND - No data, no normal range data for this nerve conduction parameter

For the seven neurobehavioral tests (i.e., POMS, simple reaction time, digit span, dexterity, digit symbol, visual retention, and pursuit aiming), the 1-BP-exposed group scored significantly different from the control group in POMS (higher in anger, and lower in tension, fatigue and confusion, p<0.05) and lower compared to the control group in dexterity, digit symbols, and visual retentions (p<0.05). After matching age and educational levels for the two groups, re-examination of the data showed that there was no difference between the two groups in scores for dexterity, digit symbols, and visual retention. However, the 1-BP-exposed group still scored significantly different in tension, anger, anxiety, and confusion in the POMS test.

In the vibratory perception (pallesthesia) test, a vibrometer was used to measure the lowest pallesthesia threshold (dB) in hands and feet. Vibration tuning forks (128 Hz) were used to measure the vibratory perception latency in toes and thumbs; a delay ≤ 2 sec being normal. Compared to the control group, workers in the exposure group had higher pallesthesia thresholds in their left foot, and notably longer right and left toe perception delay times (Table 10). Eighty-one percent of exposed workers had pallesthesia delays in the feet > 2 s vs. only 28.6% in the control group, suggesting that decreased pallesthesia (vibratory perception) may be one of the most sensitive indicators of 1-BP exposure.

Table 10. Results of the pallesthesia (vibratory perception) tests in 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)	Right hand vibration delay (s)	Left hand vibration delay (s)
Control	63	15.9±7.0	15.4±7.2	3.3±4.3	2.9±4.3	0.8±2.3	0.7±2.3
1-BP-exposed	63	16.1±6.8	18.3±7.5*	6.2±4.4*	5.7±4.4*	1.1±3.1	1.0±2.8

* $p<0.05$ compared to the control group

The authors concluded that 1-BP exposure may affect the peripheral and central nervous systems of exposed workers, and cause changes in hematological and biochemical indices. The authors also stated that the workers didn't show obvious clinical symptoms yet, possibly due to long-term, low-dose exposure making these symptoms less noticeable. (This study was published in Chinese and professionally translated into English for OEHHA.)

A third study of the female 1-BP workers was published in the Chinese Journal of Industrial Hygiene and Occupational Disease in the same year (Li *et al.*, 2010c). The same control group and 71 female 1-BP workers as described in Li *et al*. (2010b) were divided into control, low, middle and high exposure groups based on the 2 or 3 consecutive days of TWA 8-hour individual exposure. The exposure groups were 0 mg/m^3 (n=71), ≤10.06 mg/m^3 (n=20), >10.06 mg/m^3 to ≤50.3 mg/m^3 (n=29), and >50.3 mg/m^3 (n=22) (0 ppm, ≤2.00 ppm, >2.00 to ≤10.0 ppm, and >10.0 ppm, respectively). The median of each dose group was used for linear regression analysis because the dose groups did not display a normal distribution. The same neurological, blood and serum, and hormonal endpoints were also examined as those described in Li *et al*. (2010b). Differences between dose groups and the control group were determined (ANOVA, $p<0.05$ Dunnett's t-test), and dose-response correlations were analyzed by linear regression.

Compared to the control group, the tibial nerve DL in the high exposure group and the vibration perception delay in the middle and high exposure groups were significantly greater (Table 11). A significant positive correlation ($p<0.05$) was also found for tibial nerve DL and for vibration perception delay in both feet. In addition, RBC count and creatine phosphokinase decreased significantly with increasing dose. The RBC count was significantly lower in all 1-BP-exposed groups compared to control, and creatine phosphokinase was significantly lower in the high exposure group compared to control. For serum hormone levels, a significant positive correlation was observed for TSH, with a significantly increased level of the hormone in the high exposure group compared to control.

Table 11. Results for female 1-BP workers in Li *et al*. (2010c)[a]

Exposure Group	Control	Low	Middle	High
Range (mg/m^3)	0	0 to ≤10.06	>10.06 to ≤50.3	>50.3
Median[b], mg/m^3 (ppm)	0	6 (1.2)	21 (4)	92 (18)
N	71	20	29	22
Tibial motor DL (ms)	6.6 ± 1.8	7.3 ± 2.2	7.3 ± 2.4	8.0 ± 1.7*
Vibration delay – right foot (sec)	3.3 ± 4.3	5.9 ± 5.5	6.2 ± 4.2*	6.5 ± 3.6*
Vibration delay – left foot (sec)	2.9 ± 4.3	4.5 ± 5.1	5.8 ± 4.4*	6.6 ± 3.7*
RBC count (10^6/μL)	4.2 ± 0.4	4.0 ± 0.5*	3.9 ± 0.4*	3.9 ± 0.5*
Creatine phosphokinase (U/L)	94.8 ± 38.7	86.8 ± 24.4	86.3 ± 29.0	73.7 ± 28.0*
TSH (μU/ml)	2.4 ± 1.5	3.1 ± 1.7	3.2 ± 1.9	4.3 ± 3.0*

[a] p<0.05 by linear regression analysis for all endpoints in the Table
[b] Median determined from Figure 2 in Li *et al*. (2010c)
* $p < 0.05$ vs the control (unexposed) group using Dunnett's t-test

Li *et al*. (2010c) also examined the long-term effects of 1-BP exposure by grouping the female workers according to the product of the 8-hour TWA exposure and exposure duration. The exposure groups were ≤251.50 mg × months/m^3 (n=19), >251.50 to ≤1257.50 mg × months m^3 (n=26), and >1257.50 mg × months/m^3 (n=25). The dose × duration dose-response results were said to agree with the statistically significant 8-hour TWA dose response findings for tibial nerve DL, vibration perception delay, RBC count, serum creatine phosphokinase and TSH levels, although the dose × duration results were not presented. This finding indicates that both concentration and exposure duration are factors in leading to toxic effects. However, the authors did not investigate the health effects of 1-BP by exposure duration alone. The study noted that only 2 or 3 days of individual exposure analysis was a limitation in assessing dose-response effects over time, due to rotation of the workers among the various 1-BP work stations that vary in 1-BP exposure levels. (This study was published in Chinese and professionally translated into English for OEHHA.)

In an occupational study in Taiwan, one man and five women were exposed to high 1-BP levels while employed in a golf club cleaning factory (Wang *et al.*, 2015). The major presenting symptoms were tingling pain, soreness in lower extremities, and paresthesia. 1-BP was identified in the bulk solvent sample used by the workers who had been occupationally exposed for 3–10 months. The work was complicated by recurrent power outages, and by malfunctions of the condenser and the exhaust fans, which may have led to higher exposure levels. Personal protection was deemed inadequate. Although individual exposure measurements were not reported, the mean concentration of samples over the platform of the washing tank was 128.8 ppm (650 mg/m^3) 1-BP (range: 97.3–188.6 ppm (490 – 950 mg/m^3); number of samples not stated). The

metabolite N-acetyl-S-(n-propyl)-L-cysteine was identified in the urine (0.171–1.74 mg/g-Cr) of the six workers 5–26 days following exposure.

Wang (2015) explored the effect of 1-BP on blood hematological parameters of occupationally exposed workers in a Chinese 1-BP production factory. Interest in 1-BP effects on blood was due to previous production of 2-BP in many of these same factories that resulted in hematological effects in exposed workers. Sixty-three 1-BP production workers (33 males and 30 females, average age 42.6 ± 2.3 yr) from its production line were selected as the exposure group, and another 63 non-1-BP production line workers from the same factory (32 males and 31 females, average age 43.5 ± 2.6 yr) were selected as control group. Workers with pre-existing blood diseases and other chronic diseases were excluded from either group. The two groups were comparable, with no statistically significant difference in general data such as age and gender ($p > 0.05$). The factory's 1-BP production line was fully enclosed, and all the workers in the exposure group had been working continuously at the production line for more than 6 months. The 1-BP concentration in the working environment was monitored at an average of 19.2 ± 1.2 mg/m^3 (3.82 ± 0.2 ppm).

The routine blood indicators of the two groups were examined and compared. The results revealed that the levels of RBC, Hb, MCH, WBC and platelet count (PLT) in the exposure group were all statistically significantly lower ($p<0.05$) than those in the control group. However, all mean levels of blood parameters were still within the normal range. The authors suggested that, since there are few reports on blood toxicity of 1-BP in the literature and no evident hematological toxicity of 1-BP from animal studies, the apparent decrease in blood indicators in exposed workers could be due to low-level contamination of 2-BP in the 1-BP production process. However, the author concluded that 1-BP may cause blood toxicity in exposed workers but might need larger sample investigation studies to confirm. (This study was published in Chinese and professionally translated into English.)

The May 2015 issue of the Chinese Journal of Industrial Hygiene and Occupational Disease (Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi) published several short articles in Chinese on urinary N-acetyl-S-(n-propyl)-L-cysteine as a 1-BP biomarker in urine (Zhang *et al.*, 2015) and on 1-BP toxicity or lack thereof in 54 workers (26 males, 28 females, age 20-50 years, average age 32.6 ± 6.4 years) at three 1-BP factories in Shandong Province (Fang *et al.*, 2015; Fu *et al.*, 2015; Miao *et al.*, 2015a; Miao *et al.*, 2015b; Miao *et al.*, 2015c). The average concentrations of 1-BP in the factories were 12.27, 7.20, and 18.90 mg/m^3 (2.4, 1.4, and 3.6 ppm), based on 40 samples (highest value = 114 mg/m^3 (22 ppm)). The length of service, and presumably of exposure, was <3 years for 27 workers, from 3 to 6 years for 13 workers, and >6 years for 14 workers. Toxicity endpoints were examined in heart, liver and kidney, blood, and nervous system. Controls were 42 workers (23 males, 19 females, average age 34.5 ± 7.9 years) from

manufacturing lines that did not produce 1-BP. These articles are consistent with other reports in showing that the peripheral nervous system effects is likely the most sensitive indicator of 1-BP toxicity in humans. All studies were published in Chinese and professionally translated into English.

Fang *et al*. (2015) studied the effects of 1-BP on liver and kidney function of exposed workers. Both groups were examined for liver and kidney function using an automatic biochemical analyzer with the following criteria for abnormality:

For abnormal liver function,
- bilirubin (T-BIL) > 25.0 µmol / L
- direct bilirubin (D-BIL) > 8.5 µmol / L
- alanine aminotransferase (ALT) > 40.0 U / L

For abnormal kidney function,
- creatinine (Cr) > 120.0 µmol / L
- uric acid (UA) > 420.0 µmol / L
- urea (Urea) > 8.3 mmol / L

The results showed that there was no statistically significant difference in the mean levels of any of the liver and kidney parameters ($p>0.05$) between the control and exposed worker group, and that there was no difference in the number of individuals with abnormal levels for any of the liver and kidney parameters. When the exposed workers were divided into three groups by working duration (i.e., <3 years, 3-6 years, and >6 years) no statistically significant difference in the mean liver and kidney parameters was observed between the exposure groups based on exposure duration (ANOVA, $p > 0.05$). The authors indicated that the present study does not reveal any biochemical changes suggestive of liver or kidney damage under the exposure conditions experienced by the 1-BP workers, but further studies would be needed to verify the findings.

Fu *et al*. (2015) studied the effect of 1-BP exposure on blood glucose levels, which may be elevated as a result of increased neurobehavioral scores in anxiety, anger and confusion observed in other occupational studies of 1-BP workers. In the exposed group, persons with diabetes or other conditions that could affect blood glucose level were excluded. Range of 1-BP concentrations in the working environment at different working posts were 4.32 – 114.46 mg/m^3 for short-term exposure concentrations (duration not specified), and 0.07 – 23.79 mg/m^3 for the 8-hour time-weighted average. Fasting blood glucose testing was conducted for both exposed and control groups, with blood glucose > 6.1 mmol/L as the criterion for abnormality. The results were as follows: 1) no statistically significant difference between the groups in blood glucose levels ($p>0.05$), 2) no difference in the number of individuals with abnormal blood glucose levels ($p>0.05$), 3) no statistically significant differences in blood glucose levels

and rate of abnormality between the control and exposure group when divided into age groups of <30, 30-40, and >40 years old (ANOVA, p>0.05). Within the exposure group, the blood glucose level increased as the working duration increased (i.e., <3, 3-6, and >6 years), but the differences were not statistically significant across different working duration subgroups (p=0.057). The authors suggested that blood glucose levels may increase with increased exposure duration and put workers at increased risk of diabetes. However, due to limited sample size, further investigation with a larger sample size is needed to verify the risk.

Miao *et al*. (2015a) conducted routine blood cell tests on the 1-BP workers and control groups. Compared to the control group, the exposed group had significantly elevated mean platelet volume (MPV), plateletcrit (PCT), and platelet distribution width (PDW) (p<0.05), but it was unclear to the authors what these changes meant. No obvious impacts on other blood test indices were found (e.g., WBC, neutrophil count, lymphocyte count, RBC, Hb, Ht, mean corpuscular volume (MCV), MCH, mean corpuscular hemoglobin concentration (MCHC), coefficient of variation for red blood cell distribution width, and PLT). In addition, all subjects filled out a questionnaire survey for neurological symptoms that they may have experienced. Some 1-BP workers did have neurological complaints, mainly memory loss, dizziness, headache, insomnia, numbness in the limbs and irritability, but there was no apparent differences compared to the control group (14 of 54 1-BP workers, 9 of 42 control workers; no statistical evaluation performed). The authors noted some of the controls worked in other chemical plants or with chemicals that may be neurotoxic (i.e., diphenylethane, bromine, etc.).

To investigate 1-BP's potential impact on the human heart and myocardial enzyme activity, Miao *et al*. (2015b) conducted electrocardiogram (ECG) tests and determined serum aspartate aminotransferase activity (AST) in the 1-BP workers and the control group. Increased AST may be a sign of arrhythmia or myocardial damage. The results showed that there were 11 out of 54 cases of abnormal ECGs within the exposure group and 9 out of 42 within the control group; the difference in the rates of abnormal incidences between the two groups was not significant (p>0.05). Except for one case of mildly elevated AST in each of the exposure and control groups, all other individuals' AST levels were within the normal range.

Effects on the nervous system were tested in the 1-BP-exposed and control workers using neural electrophysiology tests (Miao *et al.*, 2015c). Tests included motor nerve CV, DL, and sensory nerve CV of the ulnar, medial, and tibial nerves, and minimum F-wave latency and H reflex latency. The motor CV of the tibial nerve in exposed men of 46.61 ± 3.96 m/sec was slower than that in control men of 48.70 ± 3.20 m/sec (p = 0.04). The motor CV of the tibial nerve of exposed women was significantly slower than in control women (46.64 ± 6.57 m/s vs. 49.85 ± 4.01 m/s; p = 0.04). However, the tibial

nerve CVs in the 1-BP workers were still within the normal range. No other significant differences were observed between exposed and control workers. The authors concluded that reduced motor CV may be due to damage to the distal peripheral nerves or blockage of chemical transmitters at the neuromuscular junctions, suggesting damage to the phospholipid membrane surrounding the nerve bundles.

Zhong *et al*. (2018) conducted a health survey at an optical instrument manufacturing plant that used pure 1-BP (purity not stated) for stripping and cleaning semi-finished products. Fifteen workers (10 males, 5 females, age 44~54 years) were chosen as study subjects. The short-term detected concentration (presumably 15 min but not explicitly defined) ranged from 1.3 - 318.6 mg/m^3 (0.26 - 63.3 ppm) for a total of 27 samples collected from 4 locations in the operating environment. The time-weighted average concentration ($C_{TWA,}$ presumably 8-hours but not explicitly stated) was 26.8 mg/m^3 (5.33 ppm). The C_{TWA} for individual exposure concentration was 29.7 - 63.4 mg/m^3 (5.90 - 12.6 ppm). The workers were said to prefer using surgical masks and chemical-resistant gloves when working with 1-BP. Occupational health exams were conducted at 3 time intervals: Month 0 (before starting work), and Month 6 and Month 12 (during their work), and the results were compared between the time intervals. Exams included medical interviews, physical examination, and laboratory tests including routine blood and urine tests, electrocardiogram, serum ALT, AST, blood glucose, and neuromyography.

In both men and women over the 12-month period, WBC counts increased significantly, and RBC counts decreased significantly ($p<0.05$, Bonferroni method). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased significantly for men over the 12-month work period ($p<0.05$), but not for women. However, these blood and biochemical parameters were all within the normal range for humans. All other test results were apparently normal, but the results were not presented. The study stated that no evidence of neurotoxicity was observed in the subjects, but the methods used to determine neurotoxicity and the subsequent results were not presented. The authors concluded that the 1-BP workers may have developed some degree of hepatotoxicity, but the study was too small and needs to be verified with a larger group of workers. (This study was published in Chinese and professionally translated into English for OEHHA.)

1218 **Table 12. Summary of Chronic Effects of 1-BP in Adult Humans**

Reference	Subjects & Exposure	Results vs Controls	Point of Departure
Ichihara *et al*. 2004a	Exposed: 37 1-BP manufacture workers (24 female, 13 male) Exposure: 0.9 - 170.5 ppm (geometric mean 52.5 ppm) Duration: <3 yr No control group	Nose, throat, and eye irritation, malaise, and headache No neurological damage	NOAEL: 170 ppm (855 mg/m^3) LOAEL: NA
Ichihara *et al*. 2004b	Exposed: 27 female 1-BP workers Duration: 27 ± 31 months Exposure: TWA 0.34 - 49.19 ppm (median 1.61 ppm) Control: 23 age-matched beer workers	↓ vibration sensation of the right and/or left foot ↑ tibial nerve DL ↓ sural sensory nerve CV ↓ neurobehavioral and POMS test scores	NOAEL: NA LOAEL: ≥ 8.84 ppm
Wang *et al*. 2007	Exposed: 25 (17 males, age 25.6 years; 8 females, age 19.8 years) 1-BP workers Average working environmental 1-BP conc.: 13.09~38.44 mg/m^3 TWA individual exposure: 80.4 mg/m^3 Control: 25 steel plant workers (17 males, age 24.5 years; 8 females, age 27.9 years)	In male exposed workers: ↓ motor nerve CV and ↑ DL neurobehavioral tests: ↑ tension-anxiety of POMS scales ↓ visual retention	NOAEL: NA LOAEL: 16.0 ppm (80.4 mg/m^3) for male workers

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Table 12. Summary of Chronic Effects of 1-BP in Adult Humans (continued)

Reference	Subjects & Exposure	Results vs, Controls	Point of Departure
Li *et al*. 2010a	Exposed: 60 female and 26 male workers in three 1-BP production factories Exposure: TWA 0.06 - 114.8 ppm Female: low (0.07 – 3.35 ppm, medium (3.39 – 14.13 ppm) and high (15.28 – 106.4 ppm) Male: low (0.06 -3.5 ppm) and high (5.7 - 114.8 ppm) Also exposed to 2-BP Controls: 60 female and 26 male age-, gender- and region-matched non-1-BP workers	In females: ↑ tibial nerve DL, ↓ sural sensory nerve CV ↑ vibration perception delay time in toes ↑ LDH activity ↑ FSH levels ↓ POMS – fatigue ↓ RBC counts, Hb and Ht In males: ↑ BUN	NOAEL: NA LOAEL: 1.28 ppm (6.4 mg/m^3)
Li *et al*., 2010b	Exposed: 71 female 1-BP workers from 4 plants (age 36.9±7.0yr), exposure duration: > 12 months Average working environmental 1-BP conc.: 32.19 mg/m^3 8-hr TWA individual exposure: 14.13 mg/m^3 (11.92, 5.16, 32.95, and 34.61 mg/m^3 for each respective 1-BP plant) Control: 71 female workers other industries (age 36.9±7.3yr)	↓ motor and sensory nerve CV ↑ DL neurobehavioral tests: POMS (↑ in anger and ↓ in tension, fatigue and confusion) ↑ foot vibratory perception thresholds and ↑ toe perception delay time	NOAEL: NA LOAEL: 2.81 ppm (14.13 mg/m^3)

Table 12. Summary of Chronic Effects of 1-BP in Adult Humans (continued)

Reference	Subjects & Exposure	Results vs, Controls	Point of Departure
Li *et al*., 2010c	71 female 1-BP workers from 4 plants (age 36.9±7.0 years, exposure duration >12 months), and 71 female control workers other industries (age 36.9±7.3 years) Median 1-BP exposure groups: low (1.2 ppm, n=20), medium (4 ppm, n=29) and high (18 ppm, n=22)	Positive correlations ($p<0.05$) were found for: tibial nerve DL (↑ at 18 ppm) Vibration delay (↑ at 4 ppm and above) TSH (↑ at 18 ppm) Negative correlations ($p<0.05$) were found for: RBC count (↓ at 1.2 ppm and above) Creatine phosphokinase (↓ at 18 ppm)	NOAEL: 1.2 ppm LOAEL: 4 ppm (for nervous system effects - vibration delay) RBC count ↓ at all exposure levels but were still within the normal range
Miao *et al*. 2015a	Exposed: 54 (26 males, 28 females, average age 32.6 ± 6.4 years) 1-BP workers from three 1-BP production plants Exposure duration: >3 months to <3 years for 27 workers, 3 - 6 years for 13 workers and > 6 years for 14 workers Average environmental 1-BP conc.: 12.27, 7.20, and 18.90 mg/m^3 for each plant respectively, TWA 0.07 – 23.79 mg/m^3 Control: 42 non-1-BP workers from the same plants (23 males, 19 females, average age 34.5 ± 7.9 years)	blood cell tests: ↑ in platelet volume, plateletcrit and platelet distribution width	NOAEL: NA LOAEL: 7.20 to 18.90 ppm

1224 **Table 12. Summary of Chronic Effects of 1-BP in Adult Humans (continued)**

Reference	Subjects & Exposure	Results vs, Controls	Point of Departure
Miao *et al*., 2015b	See Miao *et al*., 2015a	No difference in ECG results and serum AST levels compared to control group	NOAEL: 7.20 to 18.90 ppm LOAEL: NA
Miao *et al*., 2015c	See Miao *et al*., 2015a	↓ tibial motor nerve CV in both men and women compared to respective control groups	NOAEL: NA LOAEL: 7.20 to 18.90 ppm
Fang *et al*., 2015	See Miao *et al*., 2015a	No difference in liver function (bilirubin, direct bilirubin, ALT) or kidney function (creatinine, uric acid, urea) compared to controls, or when based on working duration.	NOAEL: 7.20 to 18.90 ppm LOAEL: NA
Fu *et al*., 2015	See Miao *et al*., 2015a	No difference in blood glucose levels compared to control, or when divided into age groups. A non-significant ↑ observed with ↑ working duration	NOAEL: 7.20 to 18.90 ppm LOAEL: NA
Wang *et al*. 2015	Exposed: 63 1-BP workers (33 males and 30 females, average age 42.6 ± 2.3 years) Exposure duration: > 6 months Average environmental 1-BP conc.: 19.2 ± 1.2 mg/m^3 Control: 63 non-1-BP workers (32 males and 31 females, average age 43.5 ± 2.6 years)	blood routine indicators: ↓ RBC, Hb, MCH, WBC and PLT	NOAEL: NA LOAEL: 19.2 ± 1.2 mg/m^3 (3.8 ppm)

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Table 12. Summary of Chronic Effects of 1-BP in Adult Humans (continued)

Reference	Subjects & Exposure	Results vs, Controls	Point of Departure
Zhong *et al*., 2018	Exposed: 15 workers (10 males, 5 females, age 44~54 years) Exposure: time-weighted average concentration 26.8 mg/m^3 Exposure duration: 12 months with exams at 0, 6 and 12 months Each subject acted as their own control	Over 12 months: ↑ WBC and ↓ RBC in both men and women ↑ AST and ALT in men only	NOAEL: NA LOAEL: 26.8 mg/m^3 (5.3 ppm)

↑ – increase resulting in significant ($p \leq 0.05$) difference; ↓ – decrease resulting in significant ($p \leq 0.05$) difference; ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMDF – brain-derived neurotropic factor; BrdU – 5-bromo-2'-deoxyuridine; BUN – blood urea nitrogen; CI – confidence interval; CNS – central nervous system; CV – conduction velocity; DL – distal latency; ECG – electrocardiogram; FSH – follicle-stimulating hormone; Hb – hemoglobin; LDH – lactate dehydrogenase; LOAEL – lowest observable adverse effect level; MCH – mean corpuscular hemoglobin; NA – not attained or not applicable; NOAEL – no observable adverse effect level; PLT – platelet count; POMS – profile of mode states; RBC – red blood cell; TSH – thyroid-stimulating hormone; TWA – time-weighted average; WB – whole body; WBC – white blood cell.

6.2 Chronic Toxicity to Infants and Children

No reports were found. As cited above, the youngest person with 1-BP-related toxic effects was a 16-year-old male exposed for three months in a workplace (Majersik *et al.*, 2007).

6.3 Chronic Toxicity to Experimental Animals

This section includes repeated exposure studies lasting longer than two weeks. Most study protocols used by researchers exposed rodents for three to 12 weeks to achieve neurotoxic endpoints of interest. Consequently, there are fewer rodent studies with exposure durations ≥13 weeks. Animal experiments summarized below show that 1-BP exposure can impact several organ systems other than the nervous system, including the immune system, the liver, respiratory system, and the reproductive/developmental system. A summary table (Table 15) of the subchronic and chronic toxicity findings is at the end of this Section.

The effects of 1-BP on rat brain neurotransmitters were reported by (Suda *et al.*, 2008). The investigators exposed male F344 rats (five per exposure level) to 0, 50, 200, or

1000 ppm (0, 250, 1000, and 5000 mg/m^3) 1-BP 8 hours/day, 7 days/week for 3 weeks and measured the changes in acetylcholine, catecholamine, serotonin, and amino acids and their metabolites or precursors in eight brain regions. Rats were terminated at 2 hours or at 19 hours after the end of exposure. At 2 hours, the level of 5-hydroxyindoleacetic acid, the main metabolite of serotonin, was lowered in some brain regions by the exposure; the decrease in the frontal cortex was statistically significant at 50 ppm (250 mg/m^3) and 1000 ppm (5000 mg/m^3) but not at 200 ppm (1000 mg/m^3) 1-BP ($p<0.05$ by Dunnett's multiple t-test). At 19 hours, gamma-amino butyric acid (GABA) and taurine were decreased in many brain regions of exposed rats, and a significant decrease of taurine in the midbrain occurred at 50 ppm (250 mg/m^3) 1-BP. At both 2 hours and 19 hours aspartate and glutamine were elevated in many brain regions, but acetylcholine did not change in any region. In most cases, the statistically significant differences occurred only at 1000 ppm (5000 mg/m^3).

Four groups of nine F344 rats were exposed at 0, 400, 800, and 1000 ppm (0, 2000, 4000, and 5000 mg/m^3) for 8 hours/day, 7 days/week, for 4 weeks to investigate the effect of 1-BP on neurotransmitter receptor genes in the brain (Mohideen *et al.*, 2009). Total RNA was extracted from various brain regions. "Real-time" polymerase chain reaction (RT-PCR) quantified the mRNA levels of serotonin, dopamine, and GABA receptors. The decreased mRNA expression at 400 ppm (2000 mg/m^3) and above of the dopamine 2 receptor (D2R) in the hippocampus and of two serotonin receptors (5HTr1a and 5HTr3a) in the pons-medulla oblongata were the most sensitive indicators of 1-BP neurotoxicity.

The same group examined the effects of repeated exposure to 1-BP on serotonergic and noradrenergic axons (Mohideen *et al.*, 2011). Four groups of six F344 male rats were exposed to 0, 400, 800, and 1000 ppm (0, 2000, 4000, and 5000 mg/m^3) of 1-BP in inhalation chambers for 8 hours/day, 7 days/week for 4 weeks. The exposure induced dose-dependent decreases in the density of noradrenergic axons in the prefrontal cortex of the brain, but not in the density of serotonergic axons. The authors suggested that the depressive symptoms in exposed workers may be partly due to degeneration of noradrenergic axons.

In a 28 day inhalation study, groups of 10 male and 10 female Sprague-Dawley rats were exposed to 0, 400, 1000, or 1600 ppm (0, 2012, 5030, or 8048 mg/m^3) 1-BP 6 hours/day, 5 days/week ((ClinTrials BioResearch, 1997a; OSHA, 1999) as cited in OSHA (1999)). At 1600 ppm (8048 mg/m^3) there was significant mortality in both sexes (incidence not stated) by the end of the study. Clinical signs of neurotoxicity, including convulsions, incoordination, and hunched posture, were observed at 1000 and 1600 ppm (5030 and 8048 mg/m^3). At these doses, animals were impaired when tested with a modified functional observational battery. Weights of liver, kidney, brain, and lung were slightly increased. Hematologic parameters, such as red blood cells and

hemoglobin, were decreased slightly. Histopathological damage was extensive in testis, bone marrow, brain, spinal cord, kidney, and bladder at 1600 ppm (8048 mg/m^3). Many of the changes were present to a lesser extent at 1000 ppm (5030 mg/m^3). At 400 ppm (2000 mg/m^3), mild vacuolization in the white matter of the brain was observed in 5 of the 10 males and 4 of the 10 females.

Microglial changes and oxidative stress in the CNS were investigated in groups of 12 male Wistar-ST rats exposed to 0, 400, 800 or 1000 ppm (0, 2012, 4024, and 5030 mg/m^3) 1-BP for 8 hours/day on 28 consecutive days (Subramanian *et al.*, 2012). Exposure increased the levels of cellular oxidative stress markers including thiobarbituric acid reactive substances (TBARS; degradation of lipid peroxidation), protein carbonyl, and reactive oxygen species (ROS) in a dose-dependent manner in the cerebellum. TBARS was significantly increased ($p<0.05$) compared to controls at the lowest dose. In addition, the authors reported a dose-dependent increase in nitric oxide (NO) and a dose-dependent decrease in protein concentrations in the cerebellum, both of which were significantly different from control values beginning at 800 ppm (4024 mg/m^3). Immunohistochemical studies showed that 1-BP induced an increase in the CD11b/c-positive microglia area of the white matter of the cerebellar hemispheres at the highest exposure level, another marker of the neurotoxicity of 1-BP.

With the same protocol used by Subramanian and colleagues (2012), the effects of 1-BP on astrocytes and oligodendrocytes in the rat cerebellum and hippocampus were investigated to find sensitive markers of CNS toxicity (Mohideen *et al.*, 2013). Kluver-Barrera staining showed pyknotic shrinkage in the cytoplasm of Purkinje cells and nuclei of granular cells in the cerebellum at 1000 ppm (5030 mg/m^3). Immunohistochemical analysis showed increased length of glial fibrillary acidic protein (GFAP)-positive processes of astrocytes in the cerebellum, hippocampus and dentate gyrus at 800 and 1000 ppm (4024 and 5030 mg/m^3). The myelin basic protein level was lower than controls at 1000 ppm (5030 mg/m^3). The numbers of astrocytes and granular cells per tissue volume increased at 400 ppm (2012 mg/m^3) or higher. The study showed that elongation of processes of astrocytes accompanies degeneration of granular cells and Purkinje cells in the cerebellum of the rats exposed to 1-BP. The decrease in myelin basic protein and number of oligodendrocytes suggest adverse effects on myelination.

Male F344 and Wistar Nagoya rats (7 or 8 per group per test) were exposed to 0 or 1000 ppm (5030 mg/m^3) 1-BP 8 h/day, 7 days/week for 4 weeks (Huang *et al.*, 2017). 1-BP increased systolic blood pressure in both strains ($p < 0.05$) but did not affect heart rate. The increase in blood pressure was associated with a significant decrease in cardiac reduced/oxidized glutathione ratio (GSH/GSSG). The aortas of exposed Wistar Nagoya rats showed a significant increase in nitrotyrosine levels and the activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway

(upregulation of gp91phox, a subunit of NADPH oxidase), and significant decreases in the expressions of antioxidant molecules (Cu/Zn-superoxide dismutase, Mn-superoxide dismutase, catalase, and nuclear factor erythroid 2-related factor 2 (Nfe2l2)).

Liu and coworkers (2009) exposed male mice of three strains (C57BL/6J, DBA/2J, and BALB/cA) to 0, 50, 110, and 250 ppm (0, 252, 553, and 1258 mg/m^3) 1-BP 8 hours/day for 28 days (6 mice/strain/exposure level). At the end of the exposure period, they evaluated the relative susceptibilities of each strain to 1-BP-mediated hepatotoxicity. At 250 ppm (1258 mg/m^3), three mice (two BALB/cA and one C57BL/6J) died between days 3 and 7 of exposure, likely related to liver damage. Liver histopathology showed significantly larger areas of liver necrosis and more degenerative lobules in the order BALB/cA > C57BL/6J > DBA/2J in a dose-dependent fashion from 50 to 250 ppm (252 to 1258 mg/m^3). The percentage area of necrosis and lobule degeneration was significantly increased at 50 ppm (252 mg/m^3) compared to controls in BALB/cA and C57BL/6J mice ($p<0.05$). The authors, who had conducted many of the rat studies, concluded that mice are much more susceptible than rats to 1-BP hepatotoxicity. They also concluded that higher liver CYP2E1 level and a low GST activity or GSH content could contribute to the higher susceptibility of BALB/cA mice to 1-BP-induced liver damage.

In an 8-week study, groups of 10 male and 10 female Sprague-Dawley rats were exposed 6 hours/day, five days/week to 0, 50, 300, or 1800 ppm (0, 252, 1509, and 9154 mg/m^3) 1-BP (Kim *et al.*, 1999a). During the daily exposure to 1800 ppm (9154 mg/m^3), animals showed decreased activity and mild ataxia. The authors reported a definite decrease in body weight and an increase in relative liver weight in males and females ($p<0.001$) after 8 weeks of exposure to 1800 ppm (9154 mg/m^3). Absolute organ weight findings were not provided by the authors, although mean body weight and relative organ weight data presented in the study suggested to OEHHA that mean absolute liver weight was roughly 0.4 g greater in the 1800 ppm (9154 mg/m^3) group compared to the control group. Changes in urinalysis, hematology and serum biochemistry were generally not consistent. For example, in males six hematologic test values were significantly different from controls at 50 ppm (252 mg/m^3) but not at 300 ppm (1509 mg/m^3). However, there was a negative dose-response in the levels of serum alanine aminotransferase and aspartate aminotransferase in both males and females. The significance of this decrease in markers of liver function was not addressed by the authors. Histopathologic examination of the liver revealed cytoplasmic vacuolization in the hepatocytes around the central veins in both males and females at 1800 ppm (9154 mg/m^3). The authors stated that histopathology did not reveal any specific lesions in other organs studied, which included the testis, ovaries and brain.

Fueta and co-workers studied the effects of inhalation of 200, 400, 700, and 1500 ppm (0, 1006, 2012, 3521, and 7545 mg/m^3) 1-BP on the function of the inhibitory neurotransmitter system mediated by gamma-aminobutyric acid (GABA) in the rat hippocampus (Fueta *et al.*, 2002; Fueta *et al.*, 2004; Fueta *et al.*, 2007; Ueno *et al.*, 2007). The hippocampus is in the temporal lobe of the cerebral cortex and is composed of white matter above gray matter. The hippocampus is part of the limbic system, and is involved with emotions, learning, and memory. Exposures were 6 hours/day, 5 days/week for up to 12 weeks. When the inhibitory neurotransmitter system is dis-inhibited, hippocampal excitability increases and convulsive behaviors (seizures) can occur (Fueta *et al.*, 2007). Granule cell disinhibition in the dentate gyrus was observed in hippocampal slices from rats exposed to 400 ppm (2012 mg/m^3) 1-BP for 8 or 12 weeks. The authors concluded that subchronic inhalation exposure to 1-BP reduces the function of the hippocampal GABAergic system.

In order to clarify the dose-dependent effects of 1-BP on the nervous system, forty-four Wistar male rats were randomly and evenly divided into four groups (Ichihara *et al.*, 2000a) and were exposed to 0 (fresh air), 200, 400, or 800 ppm (0, 006, 2012, or 4024 mg/m^3) 1-BP eight hours per day for twelve weeks. The study implies that exposures were 7 days/week, although this was not explicitly stated. Grip strength of forelimbs and hind limbs, maximum motor nerve CV in the tail nerve, and DL of the tail nerve were measured in nine rats of each group every four weeks. (The other two rats of each group had morphological examinations at the end of the experiment.)

Rats exposed to 800 ppm (4024 mg/m^3) showed poor kicking activity and poor extension of the limb and were not able to stand still on the testing slope. After twelve weeks, forelimb grip strength decreased significantly at 800 ppm (4024 mg/m^3) and hind limb grip strength decreased significantly at both 400 and 800 ppm (2012 and 4024 mg/m^3) (Table 13). Significantly decreased forelimb strength was first observed after 8 weeks of exposure, and decreased hind limb strength was first observed after 4 weeks of exposure. DL and motor CV of the tail nerve deteriorated significantly ($p<0.05$ or 0.01) at 800 ppm (4024 mg/m^3) beginning at 4 and 8 weeks of exposure, respectively. Ovoid or bubble-like debris of myelin sheaths was prominent in the unraveled muscular branch of the posterior tibial nerve in the 800 ppm (4024 mg/m^3) group. Swelling of preterminal axons in the gracile nucleus increased in a dose-dependent manner. Plasma creatine phosphokinase decreased dose-dependently (Table 13). 1-BP-induced weakness in the muscle strength of rat limbs, and deterioration of motor nerve CV and DL was dose-dependent. Morphological changes in peripheral nerve and preterminal axon were seen in the gracile nucleus.

Table 13. Neurotoxic effects in rats after 12 weeks exposure to 1-BP (Ichihara *et al.*, 2000a)

Exposure (n)	Air control (8)	200 ppm (9)	400 ppm (9)	800 ppm (9)
Body weight (g)	432 ± 21[#]	426 ± 25	403 ± 25*	382 ± 16**
Cerebrum (g)	1.14 ± 0.03	1.13 ± 0.03	1.11 ± 0.03	1.05 ± 0.04**
Forelimb grip strength (mg)	341 ± 136	292 ± 114	210 ± 123	174 ± 94*
Hindlimb grip strength (mg)	353 ± 69	275 ± 67	248 ± 69*	156 ± 74**
Motor CV (m/sec)	29.6 ± 3.1	29.5 ± 4.9	28.5 ± 3.7	22.9 ± 4.1**
DL (m/sec)	2.8 ± 0.3	2.7 ± 0.2	3.0 ± 0.3	4.3 ± 0.8**
CPK (U/l)	339 ± 130	288 ± 93	167 ± 40**	113 ± 25**
GPT (U/l)	40 ± 8	32 ± 4	34 ± 13	25 ± 25

[#] mean ± 1 SD; * $p < 0.05$; ** $p < 0.01$, Dunnett's comparison
DL = distal latency; CPK = creatine phosphokinase;
GPT = glutamate pyruvate transaminase (alanine aminotransferase)

With the same protocol, the research group extended the above study to specific biochemicals and reported biochemical changes in the cerebrum including lower glutathione levels (at 800 ppm (4024 mg/m^3)), decreased activity of the neuron-specific enzyme gamma-enolase (≥ 400 ppm), and dose-dependent decreased creatine kinase (≥ 200 ppm) (Wang *et al.*, 2003). Exposure of male Wistar rats to 1000 ppm (5030 mg/m^3) of 1-BP eight hours/day for five or seven weeks caused a significant decrease in body weight and in motor nerve CV and elongation in DL (Yu *et al.*, 2001). Linearly arranged ovoid- or bubble-like debris of the axons and myelin sheaths in the teased tibial nerves and axonal swelling in the gracilis nucleus were found in this group. This report extends the dose-response relationship seen for neurotoxicity above to 1000 ppm (5030 mg/m^3).

Du *et al*. (2017) studied the electrophysiological and pathological impacts of chronic inhalation exposure to 1-BP on rat peripheral nerves. Forty male SD rats 8 weeks of age and an average weight of 196±8 g were randomly divided into 1 control group and 3 exposure groups, with 10 rats in each group. The exposure was conducted in a dynamic exposure chamber for 6 hours per day, 5 days per week for 12 consecutive weeks, at concentrations of 0, 1000, 2000, or 4000 mg/m^3 1-BP (0, 199, 398, and 795 ppm, respectively).

Body weight reductions, electro-physiological test and electromyography (EMG) changes and adverse pathological changes were observed. Rats in the high exposure group starting from the 4th week of exposure and rats in the medium exposure group starting from the 8th week had significantly lower body weights compared with the control group ($p<0.05$). Food intake also decreased during the exposures, but it was unclear if reduced food consumption was associated with the reduced body weight.

Electrophysiological tests were conducted the day following the last exposure on the rats' right sciatic nerves. Compared with the control group, the high and medium exposure groups both showed significantly decreased motor nerve CV was significantly increased DL ($p<0.05$). Sensory nerve CV was significantly decreased in the high exposure group ($p<0.05$). The compound motor action potential (CMAP), and the sensory nerve active potential (SNAP) of the sciatic nerve was also measured. The amplitudes (in mV) of the CAMP and SNAP were significantly decreased in both the medium and high exposure groups compared to control values. For EMG tests (4 rats per group), all rats examined in the high exposure group exhibited denervation changes (positive sharp waves and fibrillation potentials). Electron microscopic observation of the rats' sciatic nerves (3 rats per group) revealed axonal degeneration and demyelination in all 3 rats examined in the high exposure group, with similar, but less severe, changes in rats of the medium exposure group. The authors concluded that chronic inhalation exposure of rats to 1-BP resulted in peripheral nerve damage, including both axonal degeneration and demyelination. (This study was published in Chinese and professionally translated into English for OEHHA.)

A research group in Korea exposed male and female Sprague-Dawley rats to 0, 200, 500, and 1250 ppm (0, 1006, 2012, and 6288 mg/m^3) 1-BP for 6 hours/day, 5 days/week, for 13 weeks (Sohn *et al.*, 2002). Serial sections of the brain and spinal cord of exposed rats revealed no pathological features in gray or white matter. Nerve fiber teasing and light and electron microscopic studies of the sacral and peroneal nerve fibers showed no significant difference between exposed animals and controls. The authors concluded that the histology of the nervous system was not affected by inhalation of 1-BP up to 1250 ppm (6288 mg/m^3) for 13 weeks. They also did not notice any difference in activity between the control and exposed animals. However, they did not perform any specific functional neurotoxicity tests similar to those done by Ichihara *et al*. (2000a).

In a 13 week non-peer-reviewed study, groups of 15 male and 15 female Sprague Dawley rats were exposed to 0, 100, 200, 400, or 600 ppm (0, 503, 1006, 2012, and 3018 mg/m^3) 1-BP 6 hours/day, 5 days/week (ClinTrials BioResearch, 1997b; OSHA, 1999). No significant treatment-related clinical, functional, or hematological effects were found. The only adverse effect reported was vacuolization of centrilobular liver cells (a reversible effect) at 400 and 600 ppm (2012 and 3018 mg/m^3) in males and at 400 ppm (2012 mg/m^3) in females. No vacuolization of brain tissue was reported at any exposure level in this study, although the same laboratory reported neurotoxicity at 400 ppm (2012 mg/m^3) in the 28-day study described above (ClinTrials BioResearch, 1997a). Based on their findings, the authors reported a NOAEL of 200 ppm (1006 mg/m^3) for liver toxicity. The study did not observe a decrease in hind limb grip strength, which was reported by Ichihara and colleagues (Ichihara *et al.*, 2000a).

The National Toxicology Program (NTP) carried out 14-week exposure studies in rats and mice prior to the initiation of two-year exposure studies. Groups of male and female F344/N rats and $B6C3F_1$ mice (10 dose/species/sex) were exposed to 0, 62.5, 125, 250, 500, or 1000 (rats only) ppm (0, 314, 629, 1258, and 2515, or 5030 mg/m^3) 1-BP for 6 hours/day, 5 days/week for 14 weeks (NTP, 2011). Macroscopic pathology, hematology, and clinical chemistry were carried out at the end of exposure. Complete histopathology was carried out on 0 and 1000 ppm rats, and 0, 250 and 500 ppm mice. Concurrently, reproductive toxicity was investigated in males and females of both species and is presented in Section 7 (Developmental and Reproductive Toxicity).

In rats, body weights of 1000 ppm (5030 mg/m^3) males were significantly lower ($p<0.01$) than controls (NTP, 2011). Hematology endpoints were unaffected in males and females by 1-BP exposure. Early, but transient decreases in albumin and total protein and alanine aminotransferase activities were observed in most rats. NTP suggested this finding was related to 1-BP's effect on hepatic protein metabolism. Sorbitol dehydrogenase activity was increased at the end of the exposures in 1000 ppm (5030 mg/m^3) females, and in 500 and 1000 ppm (2515 and 5030 mg/m^3) males. NTP noted this was consistent with mild hepatotoxicity observed in exposed rats. Treatment-related lesions were limited to the liver of the rats. The incidence of hepatocellular cytoplasmic vacuolization was significantly increased ($p<0.05$) in males at 250 ppm (1258 mg/m^3) and greater, and in females at 500 and 1000 ppm (2515 and 5030 mg/m^3). Hepatocellular degeneration was also observed in females at 1000 ppm (5030 mg/m^3).

In mice, lethargy was observed in 500 ppm (2515 mg/m^3) males and females by day 3 of exposure (NTP, 2011). Abnormal breathing was also observed at this concentration during the first week in moribund mice, some of which died. No changes in hematological endpoints were found in 1-BP-treated mice. At terminal sacrifice, an increased incidence of treatment-related lesions ($p<0.05$, Fisher's exact test) were observed in the liver and respiratory tract of 500 ppm (2515 mg/m^3) males and females, and in the adrenal cortex of 500 ppm (2515 mg/m^3) females. Specifically, cytoplasmic vacuolization was present in the respiratory epithelium of the nose, bronchioles of the lung, and in the trachea. In addition, female mice had a greater incidence of necrosis of bronchiolar epithelium of the lung and respiratory epithelium of the nose. Hepatocyte degeneration, chronic inflammation, necrosis, and mineralization was increased in the liver. NTP concluded that severe centrilobular necrosis was the likely cause of early deaths in mice. In addition, 500 ppm (2515 mg/m^3) female mice had an increased incidence of necrosis of the adrenal cortex.

In a two year study, the National Toxicology Program (NTP) exposed F344 rats to 0, 125, 250, or 500 ppm (0, 629, 1258, and 2515 mg/m^3) 1-BP 6 hours/day, 5 days/week and $B6C3F_1$ mice to 0, 62.5, 125, or 250 ppm (0, 314, 629, and 1258 mg/m^3) 1-BP 6

hours/day, 5 days/week (NTP, 2008; Morgan *et al.*, 2011; NTP, 2011). A primary purpose of an NTP study is to detect carcinogenicity, but incidence rates of non-neoplastic lesions by anatomic site are also reported. In rats, the study indicated some dose-dependent, non-neoplastic effects on the respiratory system in females including inflammation and metaplasia of the larynx and hyperplasia in glands in the nose. Exposure resulted in increased incidences of (non-cancer) adverse effects at and near the portal of entry in: (1) the nose of rats and mice, (2) the larynx of rats and male mice, (3) the trachea of mice and female rats, and (4) the lungs of mice (Table 14) (NTP, 2008). The LOAEL for respiratory tract lesions in mice was 62.5 ppm (314 mg/m^3); a NOAEL was not determined. In rats, the high incidence of respiratory tract lesions in the control group made determination of a LOAEL inconclusive, but 125 ppm (629 mg/m^3) was more likely a LOAEL than a NOAEL. In addition, evidence for immunosuppression was indicated by the presence of suppurative (pus forming) inflammation associated with Splendore Hoeppli material (abscesses) primarily in the nose and skin of exposed rats. The incidence of lesions with Splendore-Hoeppli bodies increased with increasing 1-BP concentration and was considerably higher in males (34%) and females (28%) exposed to 500 ppm (2515 mg/m^3). Lesions with Splendore-Hoeppli bodies were not present in chamber control rats.

Table 14. Incidence of non-cancer lesions from NTP 2-year 1-BP chronic study (NTP, 2011)

Species - Lesion	Sex	0 ppm	62.5 ppm	125 ppm	250 ppm	500 ppm
Mouse – bronchiole regeneration	Male	1/50	44/50**	38/49**	47/49**	-[a]
	Female	0/50	45/50**	43/50**	49/50**	-
Mouse – cytoplasmic vacuolization of the trachea	Male	0/49	15/50**	24/47**	24/50**	-
	Female	0/50	8/49*	7/50**	4/50	-
Mouse – vacuolization of nasal respiratory epithelium	Male	0/50	12/50**	19/50**	20/50**	-
	Female	0/50	3/50	5/50*	8/50*	-
Rat – chronic active inflammation of the larynx	Male	21/50	-	28/50	31/50*	26/50
	Female	18/50	-	25/50	30/50**	32/50**
Rat – chronic active inflammation of the nose	Male	29/50	-	33/48	34/48	35/50
	Female	24/50	-	37/50**	37/50**	36/50**
Rat – chronic suppurative inflammation of the nose	Male	0/50	-	1/48	2/48	7/50**
	Female	0/50	-	1/50	3/49	7/50**

[a] – no exposure group at this concentration

* $p < 0.05$, ** $p < 0.01$, significant difference vs. controls by Poly-3 test

In the NTP study, no lesions were seen in the nervous system in mice. In the female rats there was one animal with a brain hemorrhage at 125 ppm (629 mg/m^3) and one animal with angiectasis (abnormal, and sometimes extreme, dilatation of a blood or lymphatic vessel) at 250 ppm (1258 mg/m^3). In the male rats, brain hemorrhage was seen in one control animal, one animal at 125 ppm (629 mg/m^3), and two animals each

at 250 and 500 ppm (1258 and 2515 mg/m^3). No other lesions were listed for the brain. Functional neurotoxicity tests are usually not done by NTP. The male rat genital system did not show abnormalities and there was no change in testis weight of 1-BP-treated male rats, but the seminal vesicle was not weighed. The non-neoplastic results from mice are also available. The male mouse genital system did not show abnormalities and there was no change in testis weight of 1-BP-treated male mice, but the seminal vesicle was not weighed. In addition, no significant increase in liver lesions were observed in1-BP-treated rats or mice.

In coordination with NTP, Anderson and co-workers used a battery of immunological assays to study the immunotoxicity of 1-BP after whole body inhalation exposure of both mice and rats for either 4 or 10 weeks (Anderson *et al.*, 2010). Groups of rodents were exposed whole-body to 0, 125 (mice only), 250, 500, or 1000 ppm (rats only) (0, 629, 1258, 2515, and 5030 mg/m^3) for 6 hours/day plus T90 (10 minutes)[1], 5 days/week (excluding holidays). Significant decreases in the spleen immunoglobulin M response to sheep red blood cells were observed in mice at 125, 250, and 500 ppm (629, 1258, and 2515 mg/m^3) and in rats at 1000 ppm (5030 mg/m^3) after exposure for 10 weeks. Significant decreases in total spleen cells and in T cells were noted after approximately 4 weeks of exposure in both species at the same levels. Changes in natural killer (NK) cell activity were not observed. The changes in spleen cellularity, phenotypic subsets, and impairment of humoral immune function in these two species may imply adverse immune system effects after human exposure to 1-BP.

[1] T90 is the time following the start of exposure for 1-bromopropane to reach 90% of the final stable concentration in the exposure chamber.

1560 **Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental**
1561 **Animals**

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Suda *et al*., 2008	Male F344 rats WB inhalation exposure to 0, 50, 200, or 1000 ppm for 8 hours/day, 7 days/week for 3 weeks	↓ 5-hydroxyindoleacetic acid in frontal cortex at 50 and 1000 ppm ↓ taurine in midbrain at 50 ppm ↓ GABA and ↑ aspartate and glutamine in several brain regions mainly at 1000 ppm	NOAEL: NA LOAEL: 50 ppm for ↓ neurotransmitter metabolites or precursors in the brain
Huang *et al*., 2017	Male F344 Wistar Nagoya rats WB inhalation exposure to 0 or 1000 ppm for 8 hours/day, 7 days/week for 4 weeks	↑ systolic blood pressure and ↓ GSH/GSSG ratio in the heart ↓ expression of antioxidant levels and ↑ nitrotyrosine and NADPH oxidase pathway in aortas	NOAEL: NA LOAEL: 1000 ppm cardiac toxicity
Mohideen *et al*., 2009	F344 rats WB inhalation exposure to 0, 400, 800, 1000 ppm for 8 hours/day, 7 days/week, for 4 weeks.	↓ mRNA of dopamine 2 receptor in hippocampus and two serotonin receptors in pons-medulla oblongata at 400 ppm	NOAEL: NA LOAEL: 400 ppm for ↓ neurotransmitter receptor mRNA in the brain
Mohideen *et al*., 2011	Male F344 rats WB inhalation exposure to 0, 400, 800, or 1000 ppm for 8 hours/day, 7 days/week for 4 weeks	Dose-dependent ↓ density of noradrenergic axons in the prefrontal cortex at 400 ppm and above	NOAEL: NA LOAEL: 400 ppm for degeneration of noradrenergic axons

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Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
ClinTrials BioResearch (1997a) & OSHA, 1999	Male and female Sprague-Dawley rats inhalation exposure to 0, 400, 1000, or 1600 ppm for 6 hours/day, 5 days/week for 4 weeks	Mortality at 1600 ppm Convulsions and ataxia at 1000 ppm and above. Dose-dependent Histopathologic damage to brain, spinal cord and other organs at ≥1000 ppm Mild vacuolization in brain white matter at 400 ppm	NOAEL: NA LOAEL: 400 ppm for brain lesions
Subramanian *et al*., 2012	inhalation exposure to 0, 400, 800, or 1000 ppm for 8 hours/day, 7 days/week for 4 weeks	Dose-dependent ↑ oxidative stress markers and nitric oxide in cerebellum ↑ cd11b/c-positive microglia at 1000 ppm	NOAEL: NA LOAEL: 400 ppm for oxidative stress in the brain
Mohideen *et al*., 2013	Inhalation exposure to 0, 400, 800, or 1000 ppm for 8 hours/day, 7 days/week for 4 weeks	Elongation of GFAP-positive processes of astrocytes at ≥800 ppm, and ↓ in myelin basic protein and number of oligodendrocytes at ≥400 ppm	NOAEL: NA LOAEL: 400 ppm for adverse effects on granular cells and myelination in the brain
Liu et. al., 2009	Male C57BL/6J, DBA/2J, and BALB/cA mice WB inhalation exposure to 0, 50, 110, or 250 ppm for 28 days (8 hours/day, 7 days/week)	↑ liver necrosis and lobular degeneration at ≥50 ppm in BALB/cA and C57BL/6J mice, and at ≥110 ppm in DBA/2J mice	NOAEL: NA LOAEL: 50 ppm for liver damage

Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Kim *et al*., 1999a	Inhalation exposure to 0, 50, 300, or 1800 ppm for 6 hours/day, 5 days/week for 8 weeks	↓ activity, mild ataxia, and ↓ BW, at 1800 ppm. Dose-dependent ↓ in serum ALT and AST Hepatocyte vacuolization around central veins at 1800 ppm	NOAEL: 300 ppm LOAEL: 1800 ppm for liver, CNS and BW effects
Anderson *et al*., 2010	Male and female F344/N rats 0, 250, 500 and 1000 ppm for 6 hours/day, 5 days/week for 4 or 10 weeks	At 4 weeks: ↓ total spleen cells and T cells at 1000 ppm At 10 weeks: ↓ spleen immunoglobulin M response to sheep RBCs at 1000 ppm	NOAEL: 500 ppm LOAEL: 1000 ppm for immune function changes
	Male and female B6C3F_1 mice 0, 125, 250, and 500 ppm for 6 hours/day, 5 days/week for 4 or 10 weeks	At 4 weeks: ↓ total spleen cells and T cells at ≥125 ppm At 10 weeks: ↓ spleen immunoglobulin M response to sheep RBCs at ≥125 ppm	NOAEL: NA LOAEL: 125 ppm for immune function changes
Fueta *et al*., 2002, 2004, 2007; Ueno *et al*., 2007	Inhalation exposure to 0, 200, 400, 700 or 1500 ppm for 6 hours/day, 5 days/week for up to 12 weeks	↓ function of hippocampal GABAergic system at ≥400 ppm	NOAEL: 200 ppm LOAEL: 400 ppm for CNS effects

Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Ichihara *et al*., 2000a	Inhalation exposure to 0, 200, 400, or 800 ppm for 8 hours/day, 7 days/week for up to 12 weeks	After 12 weeks exposure: ↓ forelimb and hindlimb grip strength at 800 and ≥400 ppm, respectively ↓ BW and cerebrum wt at ≥400 and 800 ppm, respectively ↓ Motor CV and ↑ DL at 800 ppm Myelin lesions in the peripheral nerve, preterminal swelling in the gracile nucleus, and irregular muscle fiber banding in soleus muscle at 800 ppm	NOAEL 200 ppm LOAEL 400 ppm for neurotoxicity
Wang *et al*., 2003	Male Wistar rats Inhalation exposure to 0, 200, 400, or 800 ppm for 8 hours/day, 7 days/week for up to 12 weeks, and 1000 ppm for 5-7 weeks	↓ creatine kinase at ≥200 ppm, ↓ gamma-kinase at ≥400 ppm, and ↓ GSH at 800 ppm in cerebrum. At 1000 ppm, ↓ BW, ↓ motor CV and elongation in DL, lesions in axons and myelin sheaths of tibial nerves, and axonal swelling in gracilis nucleus	NOAEL: NA LOAEL: 200 ppm for biochemical changes in the brain

Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Du *et al*., 2017	Male SD rats Inhalation exposure to 0, 1000, 2000, or 4000 mg/m3 (0, 199, 398, or 795 ppm) for 6 hours/day, 5 days/week for 12 weeks	↓ BW ≥398 ppm ↓ MCV, compound motor action potential, sensory nerve action potential and ↑ DL of sciatic nerve ≥398 ppm ↑ denervation changes of sciatic nerve at 795 ppm Axonal degeneration and demyelination by electron microscopy at ≥398 ppm	NOAEL 199 ppm LOAEL 398 ppm for sciatic nerve damage and weight loss
Sohn *et al*., 2002	Sprague-Dawley rats Inhalation exposure to 0, 200, 500, or 1250 ppm for 6 hours/day, 5 days/week for 13 weeks	No effect on BW, observed behavior or urinalysis findings No effect on morphologic features of brain grey or white matter, spinal cord, and peripheral nerve fibers	NOAEL: 1250 ppm LOAEL: NA
(ClinTrials BioResearch, 1997b; OSHA, 1999)	Male and female Sprague-Dawley rats Inhalation exposure to 0, 100, 200, 400, or 600 ppm for 6 hours/day, 5 days/week for 13 weeks	Vacuolization pf centrilobular hepatocytes in 400 ppm males and females, and 600 ppm males	NOAEL: 200 ppm LOAEL: 400 ppm for liver effects

Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
NTP, 2011	Male and female F344/N rats 0, 62.5, 125, 250, 500 and 1000 ppm for 6 hours/day, 5 days/week for 14 weeks	↓ BW. in 1000 ppm, males, and ↓ sorbitol dehydrogenase activity in ≥500 ppm males and 1000 ppm females ↑ liver hepatocyte vacuolization in ≥250 ppm males and ≥500 ppm females ↑ hepatocyte degeneration in 1000 ppm females	F344/N rats NOAEL: 125 ppm LOAEL: 250 ppm for liver effects
	Male and female B6C3F_1 mice 0, 62.5, 125, 250, and 500 ppm for 6 hours/day, 5 days/week for 14 weeks	↑ lethargy, abnormal breathing, mortality, liver and respiratory tract damage at 500 ppm, ↑ adrenal cortex necrosis in females at 500 ppm	NOAEL: 250 ppm LOAEL: 500 ppm for liver, respiratory tract, and adrenal cortex lesions
NTP, 2011	Male and female F344/N rats 0, 125, 250, and 500 ppm for 6 hours/day, 5 days/week for 2 years	↑ incidence of nasal, larynx, and trachea lesions at nearly all dose levels ↑ incidence of nasal suppurative inflammation with Splendore-Hoeppli bodies at 500 ppm	NOAEL: 125 ppm LOAEL: 250 ppm for nasal and larynx lesions

Table 15. Summary of Subchronic and Chronic Effects of 1-BP in Experimental Animals (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
NTP, 2011 (continued)	Male and female B6C3F$_1$ mice 0, 62.5, 125, and 250 ppm for 6 hours/day, 5 days/week for 2 years	↑ incidence of nasal, larynx, and trachea lesions in rats and mice at nearly all dose levels, and in the lungs of mice ↑ incidence of nasal suppurative inflammation with Splendore-Hoeppli bodies in rats at 500 ppm	NOAEL: NA LOAEL: 62.5 ppm upper and lower respiratory tract lesions

↑ – increase resulting in significant ($p \leq 0.05$) difference; ↓ – decrease resulting in significant ($p \leq 0.05$) difference; ABT – 1-aminobenzotriazole; BW – body weight; ALT – alanine aminotransferase; AST – aspartate aminotransferase; CNS – central nervous system; CV – conduction velocity; DL – distal latency; GABA – gamma aminobutyric acid; GD – gestation day; GFAP – glial fibrillary acidic protein; GSH – glutathione, reduced; GSSG – glutathione, oxidized; LOAEL – lowest observed adverse effect level; mRNA – messenger ribonucleic acid; NA – not attained or not applicable; NADPH – nicotinamide adenine dinucleotide phosphate; NOAEL – no observed adverse effect level; PND – postnatal day; RBC – red blood cell; WB – whole body; wt – weight.

7. Developmental and Reproductive Toxicity

7.1 Human Reproductive Toxicity

In exposed humans, there have been limited occupational and case studies of developmental and reproductive toxicity.

NIOSH conducted an investigation in North Carolina of a cushion factory in which neurologic symptoms were reported in male workers who used a spray gun to apply an adhesive that contained 1-BP (Harney *et al.*, 2003). Forty-three of 60 male workers participated in the questionnaire portion of the survey, including 13 adhesive sprayers and 30 workers not directly exposed to 1-BP. The questionnaire included questions about male reproductive function. In addition, three sperm indices (shape, motility, and number) were evaluated in nine men, three of which were 1-BP sprayers. At the time of the survey, 16 full-shift personal breathing zone samples for 1-BP were collected from sprayers. The geometric mean 1-BP concentration was 81.2 ppm with a range of 18 - 254 ppm) (408 mg/m^3, range: 90.5 – 1278 mg/m^3). Among unexposed workers (conducted during a second assessment 15 months later), the geometric mean

concentration was 1.1 ppm with a range of 0.1 - 4.9 ppm (5.5 mg/m^3, range: 0.5 – 24.7 mg/m^3). None of the workers completing the questionnaire responded that they had a doctor-diagnosed reproductive or infertility problem. Five of the nine men in the laboratory analysis had an abnormal semen analysis, only one of which was a 1-BP sprayer. No statistically significant correlation was found between measures of exposure (including 1-BP personal breathing zone concentration and end-of-week urine Br concentration) and the three sperm indices.

In case reports from what was likely the same North Carolina cushion factory, two of three female workers experienced temporary menstrual cycle disruption following exposure to 1-BP for several months (Ichihara *et al.*, 2002). All three workers were using a glue spray gun that contained 55% 1-BP with little or no dermal and respiratory protection. All three had been admitted to a hospital due to severe neurological symptoms. Exposure levels during six 8-hour work days was determined with a passive sampler attached to the body of one of the women. The average of the daily values was estimated at 133 ppm with a range of 60 – 261 ppm (669 mg/m^3, range: 302 – 1313 mg/m^3). However, ventilation had been improved prior to conducting the exposure test, which suggested to the authors that the earlier 1-BP exposures were higher than this.

The same researchers investigated neurologic, electrophysiologic, neurobehavioral and other effects in women working at a 1-BP production factory in China (Ichihara *et al.*, 2004b). Twenty-three women at the factory were compared to 23 age-matched controls. The exposed workers exhibited a number of neurologic symptoms related to 1-BP exposure, including reduced vibration sensation in the feet (See Section 6.1 for details). The women were also asked about the frequency of menstrual abnormalities. No difference in frequency was found between exposed workers and controls. However, the authors noted that the workers were exposed to lower levels of 1-BP (0.34 – 49.19 ppm) compared to the women in their earlier case study by Ichihara *et al*. (2002) in which menstrual abnormalities were reported.

7.2 Reproductive and Developmental Studies in Animal Models

A summary table (Table 25) of the reproductive and developmental findings in animal models is presented at the end of this Section.

7.2.1 Reproductive toxicity in female animals

To study the effects of 1-BP on female reproductive function, groups of ten female Wistar rats were exposed daily for eight hours to 0, 200, 400, or 800 ppm (0, 1006, 2012, and 4024 mg/m^3) 1-BP (Yamada *et al.*, 2003). After 7 weeks, all rats at the highest dose became ill. They were necropsied during the 8th week. The other groups

were exposed for 12 weeks. In the 800 ppm (4024 mg/m^3) group only, body weights were significantly less than the controls at each time point from weeks 2 through 7. Vaginal smears showed a significant increase in the number of irregular estrous cycles; extended diestrus ($p<0.01$) was noted at 400 and 800 ppm (2012 and 4024 mg/m^3). Histopathological examination of the ovary after 12 weeks of exposure showed a significant reduction of the number of normal antral follicles at 200 and 400 ppm (1006 and 2012 mg/m^3) and a decrease in the number of normal growing follicles at 400 ppm (2012 mg/m^3) ($p<0.05$) (Table 16). No significant change was found in plasma concentrations of luteinizing hormone or FSH in any group as compared with the control. The authors concluded that 1-BP induces a dose-dependent ovarian dysfunction in non-pregnant female rats, which is associated with disruption in follicular growth process.

Table 16. 1-Bromopropane decreases ovarian follicles in rats (from Table 4 of (Yamada *et al.*, 2003))**.**

Exposure (no. of rats)	**0 ppm (8)**	**200 ppm (9)**	**400 ppm (9)**	**800 ppm (9)**
Exposure duration	**12 weeks**	**12 weeks**	**12 weeks**	**7 weeks**
Primordial follicles[#]	176.8 ± 48.8	157.8 ± 49.4	206.0 ± 66.6	423.1 ± 140
Antral follicles[#]	30.1 ± 22.4	12.6 ± 4.82*	7.44 ± 6.52**	3.8 ± 3.9
Growing follicles[#]	70.0 ± 20.3	53.4 ± 17.9	47.2 ± 17.3*	30.1 ± 15.1

[#] mean ± SD; * $p < 0.05$; ** $p < 0.01$ by Dunnett's multiple comparison method.

Sekiguchi and colleagues studied the toxic effects in female F344 rats of inhalation to 1-BP on the estrous cycle and spontaneous ovulation (and also to 2-BP and 1,2-dichloropropane) (Sekiguchi *et al.*, 2002). Rats (5-8 rats per exposure level) were exposed daily for 8 h for 20 days to 0, 50, 200, and 1000 ppm (0, 252, 1006, and 5030 mg/m^3) of 1-BP. During exposure to 1-BP, the ratio of estrous cycles of 6 days or longer to all estrous cycles in the 1000 ppm (5030 mg/m^3) group was about twice the control group (7/34 vs. 3/31), but the difference was not statistically significant ($p>0.05$). The absolute and relative weights of the ovaries and uterus in rats exposed to 1-BP were not significantly different from the controls. In addition, no significant change in the number of ovulated ova was observed following exposure to 1-BP.

NTP carried out 14-week 1-BP toxicity studies that included an investigation of female reproductive toxicity (NTP, 2011). Groups of 10 female F344/N rats and 10 female B6C3F$_1$ mice were exposed to 0, 125 (mice only), 250, 500, or 1000 (rats only) ppm (0, 629 (mice only), 1258, 2515, 5030 (rats only) mg/m^3) 1-BP for 6 hours/day, 5 days/week for 14 weeks. In female rodents, vaginal fluid and cells were collected for 12 consecutive days prior to terminal sacrifice. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous cells were counted for cytology evaluation and to determine estrous cycle stage. Histopathological examination of the ovary, uterus and mammary glands was conducted on 0 and 1000 ppm (0 and 5030 mg/m^3) rats and 0, 250, and 500 ppm (0, 1258, and 2515 mg/m^3) mice.

In rats, all treated female groups spent significantly more time in extended estrus (p<0.001), and significantly less time in extended diestrus (p<0.005) compared to the control group (NTP, 2011). The relative time spent in the estrous stage was significantly greater (p<0.05) in all treated female groups compared to control. No apparent histopathological changes were observed in the female rat reproductive organs examined. In mice, the 250 ppm (1258 mg/m^3) females spent significantly more time in extended estrus (p<0.001) compared to control, and the 500 ppm (1258 mg/m^3) females spent significantly more time in extended diestrus (p<0.05) compared to control. In addition, the length of the estrous cycle was slightly increased (p<0.05) in 500 ppm (2515 mg/m^3) mice. No apparent histopathological changes were found in the female mouse reproductive organs examined. The NTP concluded that 1-BP has the potential to cause adverse effects on the fertility and reproductive performance in rats and mice at similar exposures.

7.2.2 Reproductive toxicity in male animals

In a study of male reproductive function, 36 Wistar male rats were divided into four groups of nine and exposed to 0, 200, 400, or 800 ppm (0, 1006, 2012, and 4024 mg/m^3) 1-BP, eight hours per day for 12 weeks (Ichihara *et al.*, 2000b). The testes, epididymides, seminal vesicle, prostate, and six other glands or organs were weighed and examined for histopathology. Spermatogenic cells (in stage VII seminiferous tubules) and retained spermatids (at the basal region of stages IX-XI seminiferous epithelium) were counted. The weight of the testicles did not significantly change, but the weight of the prostate gland, epididymides, and seminal vesicles decreased dose-dependently (Table 17). The weight of seminal vesicle decreased significantly at the lowest concentration of 200 ppm (1006 mg/m^3) and above. 1-BP induced a significant decrease in the epididymal sperm count (Table 17) and in sperm motility beginning at 400 ppm (2012 mg/m^3) and was dose-related. A significant increase in tailless sperm and sperm with immature head shape occurred at ≥400 ppm (≥2012 mg/m^3) and 800 ppm (4024 mg/m^3), respectively. The spermatogonia, preleptotene spermatocytes, pachytene spermatocytes, and round spermatids (meiotic stages in sperm development) did not decrease significantly at stage VII. Retained, elongated spermatids near the basement membrane at the post-spermiation stages IX-XI increased significantly beginning at 400 ppm (2012 mg/m^3) and was dose-dependent. Plasma testosterone, measured by radioimmunoassay, decreased significantly at 800 ppm (4024 mg/m^3). The authors concluded that the solvent may have serious reproductive toxic effects in men (e.g., failure of spermiation), and should be used very cautiously in the workplace.

Table 17. Male rat reproductive toxicity data (from Ichihara *et al*. (2000b), Tables 1 and 3)

1-BP group (n)	**0 ppm (8)**	**200 ppm (9)**	**400 ppm (9)**	**800 ppm (9)**
Body weight[#] (g)	432 ± 21	426 ± 25	403 ± 25*	382 ± 16**
Seminal vesicle weight[#] (g)	1.88 ± 0.27	1.38 ± 0.26**	1.27 ± 0.25**	1.00 ± 0.36**
Seminal vesicle relative weight[#] (mg/g BW)	4.35 ± 0.62	3.23 ± 0.55**	3.17 ± 0.67**	2.62 ± 0.87**
Sperm count[#] ($\times 10^6$/g cauda)	792 ± 199	772 ± 221	588 ± 132*	240 ± 240**

[#] mean ± standard deviation; * $p<0.05$; ** $p<0.01$ (ANOVA followed by Dunnett's method)

In order to determine if reproductive effects were reversible, male Wistar rats were divided into three groups of 24 and exposed to 0, 400, or 1000 ppm (0, 2012, or 5030 mg/m^3) of 1-BP for 6 weeks (8 hours/day, 7 days/week) (Banu *et al.*, 2007). Eight from each group were necropsied at the end of the exposure, and at 4 and 14 weeks post-exposure. At the end of exposure to 1000 ppm (5030 mg/m^3) (no recovery), testicular weight, epididymal weight, sperm count, and motility were low; morphologically abnormal sperm were increased; and spermatogenic cells showed diffuse degeneration. Most changes did not show full recovery at 14 weeks post-exposure. However, prostate and seminal vesicular weights recovered to control values. At 400 ppm (2012 mg/m^3), retained spermatids were increased at 0 week recovery but returned to normal levels at 4 weeks recovery. The authors concluded that the effect of 1-BP on spermatogenesis is dose-dependent. The low exposure of 400 ppm (2012 mg/m^3) inhibits spermiation and causes hormone-dependent organ weight reduction (but the changes are transient), while 1000 ppm (5030 mg/m^3) causes persistent depletion of spermatogenic cells.

Liu and coworkers (2009) exposed male mice of three strains (C57BL/6J, DBA/2J, and BALB/cA) to 0, 50, 110, and 250 ppm (0, 252, 553, and 1258 mg/m^3) 1-BP 8 hours/day for 28 days (6 mice/strain/exposure level). At the end of the exposure period, they evaluated the relative susceptibilities of each strain to 1-BP-mediated male reproductive toxicity and hepatotoxicity. The hepatotoxicity results are presented in Section 6.3. Exposure to 50 or 110 ppm (252 or 553 mg/m^3) 1-BP significantly decreased sperm counts (Table 18) and sperm motility and significantly increased abnormal sperm heads in all three strains of mice. These changes were all dose-related, with the exception of sperm count in DBA/2J mice. The authors, who had conducted many of the rat studies, concluded that mice are much more susceptible than rats to 1-BP reproductive toxicity. No strain difference in sperm count or percentage abnormal sperm was found, although sperm motility tended to be lower in BALB/cA mice compared to the other two strains.

Table 18. Effect of 28-day 1-BP exposure on sperm counts (Liu *et al.*, 2009)

	1-BP exposure group			
Mouse strain	**0 ppm**	**50 ppm**	**110 ppm**	**250 ppm**
C57BL/6J[#]	73.18±42.4	45.84±30.15*	25.24±18.56*	17.21±9.11*
DBA/2J[#]	43.17±19.9	22.26±14.95*	16.83±8.12*	21.62±14.3*
BALB/cA[#]	58.57±26.03	36.63±10.89*	23.54±3.35*	12.85±4.66*

[#] Mean sperm count ($\times 10^7$/g tissue) ± SD; * $p < 0.05$ *vs*. 0 ppm (ANOVA followed by Dunnett's multiple comparison)

When male wild type (*Cyp2e1+/+)* and CYP2E1 knockout mice (*Cyp2e1-/-*) were exposed to 0 or 800 ppm (0 or 4024 mg/m^3) 1-BP for 6 hours, a significant decrease in sperm motility was seen in the wild type mice but not the knockout mice ($p<0.05$). This finding indicated that metabolism of 1-BP by CYP2E1 was involved in the male reproductive toxicity (Garner *et al.*, 2007).

NTP carried out 14-week 1-BP toxicity studies that included an investigation of male reproductive toxicity (NTP, 2011). For assessment of sperm count and motility, groups of 10 male F344/N rats and 10 male B6C3F$_1$ mice were exposed to 0, 125 (mice only), 250, 500, and 1000 (rats only) ppm (0, 629 (mice only), 1258, 2515, 5030 (rats only) mg/m^3) 1-BP for 6 hours/day, 5 days/week for 14 weeks. Histopathological examination of the testis with epididymis and seminal vesicle, and the prostate gland was conducted. In male rats, significant decreases in body weight, and absolute weight of the left cauda epididymis and left epididymis occurred at 1000 ppm (5030 mg/m^3) ($p<0.05$). Sperm motility was significantly reduced ($p<0.01$) at 250 (7%), 500 (10%), and 1000 (28%) ppm and was dose-related. In 1000 ppm (5030 mg/m^3) rats, the number of sperm per cauda epididymis and the total sperm per cauda epididymis was significantly decreased ($p<0.01$). Histopathological examination revealed a dose-related trend of minimal suppurative inflammation of the prostate. However, the increased incidence of this lesion at 1000 ppm (5030 mg/m^3) did not reach statistical significance. The NTP noted the lesion is a common background finding in rats, so the biological significance of the increased incidence was unclear.

In the male mice, significantly decreased ($p<0.05$) sperm motility of 4% at both 250 and 500 ppm (1258 and 2515 mg/m^3) was observed (NTP, 2011). Slight increases of cauda epididymis weight were observed in 250 (9%) and 500 (17%) ppm mice but was not statistically significant. The number of sperm per gram cauda epididymis was reduced by 28% in 500 ppm (2515 mg/m^3) mice ($p<0.01$). No apparent histopathological changes were observed in the male reproductive organs examined. The NTP concluded that 1-BP has the potential to cause adverse effects on the fertility and reproductive performance in rats and mice at similar exposures.

To investigate the role of P450 enzymes in 1-BP male reproductive toxicity, Zong *et al*., (2016) treated groups of adult male C57BL/6J mice (6 per group) to the non-selective

P450 inhibitor ABT twice per day during exposure to 0, 50, 250, or 1200 ppm (0, 252, 1258, or 6036 mg/m^3) 1-BP 8 hours/day, 7 days/week, for four weeks. Concurrent groups of male mice were treated with saline and exposed to 0, 50, or 250 ppm (0, 252, or 1258 mg/m^3) 1-BP under the same exposure protocol. Body weight, epididymides, and testis weights were significantly reduced in the ABT-treated 1200 ppm group (p<0.05). Prostate plus seminal vesicle weight was significantly decreased at 250 ppm in both saline control and ABT-treated mice, and at 1200 ppm in ABT-treated mice. Sperm count and motility were significantly decreased in the 250 ppm (1258 mg/m^3) saline control group, whereas ABT-treatment prevented these decreases at the same concentration. However, ABT treatment did not prevent a significant decrease in sperm count and motility at 1200 ppm (6036 mg/m^3). A significant increase in morphologically abnormal sperm was observed only in the ABT-treated 1200 ppm (6036 mg/m^3) group.

Exposure to 50 and 250 ppm (252 and 1258 mg/m^3) 1-BP also resulted in a significant increase in the numbers of elongated spermatids retained at the basal region of stage IX, X, and XI seminiferous tubules, whereas ABT treatment prevented this increase (Zong *et al.*, 2016). However, the number of retained spermatids was significantly greater in ABT-treated 1200 ppm (6036 mg/m^3) mice. Exposure to 250 ppm (1258 mg/m^3) 1-BP in both saline and ABT-treated mice increased the number of round structures in stage IX, X, and XI tubules, although this increase was reduced by ABT treatment compared to saline control (p<0.05). It was not known to the authors what these round structures represent. The authors concluded that reduction in P450 activity with ABT treatment resulted in reduced male reproductive toxicity caused by 1-BP.

7.2.3 Developmental toxicity in animals

In a non-peer reviewed developmental toxicity study sponsored by the Brominated Solvents Consortium, 25 pregnant Sprague-Dawley (female) rats per group were exposed to 0, 500, 2500, or 5000 mg/m^3 (0, 100, 498, or 996 ppm) 1-BP for 6 hours/day on gestation days (GD) 6 through 19 (Huntingdon Life Sciences, 2001). The fetuses were delivered by cesarean section on GD 20. Although this is a non-peer reviewed study, the NTP-CERHR Expert Panel (NTP, 2003) noted that this bioassay was well-conducted with Good Laboratory Practices in accord with current regulatory guidelines and standard practices using appropriate numbers of animals.

The 996 ppm dams exhibited an increased incidence of lacrimation, excessive salivation and red stains on head or snout compared to control and other 1-BP treated groups. These signs of toxicity began to occur on days 5-7 of exposure. At sacrifice, significantly decreased maternal body weight, weight gain, and net weight change (body weight minus uterine weight) was observed in the 498 and 996 ppm groups (Table 19). The authors noted that the decrease in body weight paralleled the observed decreases in food consumption in the 498 and 996 ppm groups.

1-BP treatment had no effect on mortality, pregnancy rates, implantation data, sex distribution, or fetal malformations. Among the offspring, a statistically significant ($p<0.01$) decrease in fetal body weight was observed at 100 ppm and above (Table 19). The authors stated that implementation of a new procedure resulted in delay of cesarean section of one or two control dams each day of sacrifice, resulting in heavier control fetal body weights of about 0.2 g. Adjustment for this artifact was said to result in no difference in control and 100 ppm fetal body weights, a marginal reduction in fetal weight at 498 ppm and a significant reduction in fetal body weight at 996 ppm. Details such as the total number of control dams held back on sacrifice days and presentation of statistical analyses with the revised body weight data were not included in the report.

Table 19. Rat maternal BW gain and fetal BW data (mean ± SD)

Exposure	0 ppm	100 ppm	498 ppm	996 ppm
Net maternal BW change[a] (g)	40 ± 9.9	37 ± 10.2	27 ± 8.4**	15 ± 11.5**
N (litters)	23	23	25	24
Fetal BW (g)	4.1 ± 0.29	3.9 ± 0.23[b]**	3.9 ± 0.18**	3.8 ± 0.21**
Male fetuses (g)	4.2 ± 0.33	4.1 ± 0.26	4.0 ± 0.18*	3.9 ± 0.20**
Female fetuses (g)	4.0 ± 0.27	3.8 ± 0.23**	3.8 ± 0.20**	3.7 ± 0.21**

[a] Net body weight change minus uterine weight

[b] One dam in this group had fetuses with unusually low body weights (mean 3.2 g, more than 3 SD lower than group mean of 3.9 g). Removal of fetuses in this litter results in an adjusted mean of 4.0 ± 0.17 g for the 100-ppm group.

* $p < 0.05$; ** $p < 0.01$; data from Table 8 and 9 of (Huntingdon Life Sciences, 2001)

Approximately half of the fetuses were examined for soft tissue malformations, and the other half were prepared and examined for skeletal malformations. Significant increases in litters with bent ribs or reduced skull ossification ($p<0.01$) were observed beginning at 996 ppm and 498 ppm, respectively (Table 20). Both skeletal variations were considered to be exposure-related. The authors indicated that bent ribs is a reversible condition, while the reduced ossification is associated with reduction in maternal weight gain and fetal body weights.

Table 20. Skeletal abnormalities in fetuses of 1-BP exposed rats

Exposure	0 ppm	100 ppm	498 ppm	996 ppm
Litters examined viscerally	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*

* $p < 0.01$; data from Table 11 of (Huntingdon Life Sciences, 2001)

7.2.4 Two-generation reproductive/developmental toxicity studies

In a two-generation reproductive study sponsored by the Brominated Solvents Consortium, F_0 and F_1 parental animals were exposed to 1-BP to investigate the effects on reproductive performance in F_0 and F_1 generations, and the effects on F_1 and F_2 neonatal survival, growth and development (WIL Research Laboratories Inc, 2001). Although this study has not been published in a peer-reviewed journal, the NTP-CERHR Expert panel determined that this was a comprehensive study conducted under GLP, and that it meets specifications of EPA's harmonized reproductive test guidelines (NTP, 2003).

Beginning at seven weeks of age, male and female Crl:CD®(SD)IGS BR rats (25/sex/group) of the F_0 generation were exposed to 0, 100, 250, 500, or 750 ppm (0, 503, 1258, 2515, or 3773 mg/m^3) 1-BP 6 hours/day, 7 days/week, for at least 70 days prior to mating (WIL Research Laboratories, 2001). Daily exposures were continued through the maximum 14-day mating period for males and females, and then through GD 20 for females. Exposure of males continued through the day prior to euthanasia (week 19 of exposure). In females, exposure ceased at parturition, but was reinstated for the dams on lactation day 5. During lactation, the dams were removed from their litters during each daily six-hour exposure period. Pups were examined for gross malformations at PND 0. Litter sizes were randomly reduced to eight per litter on PND 4; the remaining pups were euthanized and discarded without further examination. With the exception of lactation days 0 to 4, F_0 females were exposed for 19 weeks. Whole body exposure of the F_1 pups began on PND 22 (50 weanlings per sex per group, when possible) and ended the day prior to euthanasia (approximately 19-20 weeks of exposure). Twenty-five per sex per group were selected on PND 28 to constitute the F_1 generation. Unselected F_1 pups were terminated and necropsied on PND 21 or 28. Groups of F_1 males and females were exposed using the same exposure protocol as that used for F_0 rats (i.e., exposure for 70 days prior to 14-day mating period, and then

exposed up to a total of 19 -20 weeks, except lactation days 1-4 for nursing females). F_2 pups were terminated and necropsied on PND 21.

No treatment-related deaths occurred in F_0 rats. No clinical findings were observed in 1-BP-exposed F_0 rats during weekly examinations or at one hour post-exposure. Specifically, the authors reported no signs suggestive of peripheral or central nervous system dysfunction. However, complete infertility occurred in the F_0 rats exposed to 750 ppm (3773 mg/m^3), resulting in no F_1 generation at this concentration.

Mean weekly body weights were significantly reduced (p<0.05) in F_0 generation males and females at 750 ppm (3773 mg/m^3) compared to control, with modest, transient reductions occurring in 500 ppm (2515 mg/m^3) F_0 males that did not reach statistical significance. Mean maternal body weights and body weight gains were significantly lower (p<0.05) in the 500 ppm (2515 mg/m^3) group F_0 and F_1 females during GD 14–20 and remained reduced into the lactation period. Decreased mean body weights late in the gestation in these females were attributed to the reduced mean litter sizes in the 500 ppm (2515 mg/m^3) group females of both generations. Slight reductions in mean gestational body weights and body weight gains were observed in 250 ppm (1258 mg/m^3) F_0 and F_1 females, primarily during the latter portion of gestation, but did not reach statistical significance.

Mean body weights of 500 ppm (2515 mg/m^3) F_1 males and females on PND 1 were significantly greater (p<0.05) than controls, which was attributed to the smaller litter sizes at this concentration. Mean body weights in the 500 ppm (2515 mg/m^3) group F_1 males starting at PND 28 (following beginning of whole body 1-BP exposure at PND 22) were 9.3 -18.5% lower than the control group values and remained significantly lower throughout the remainder of the 19-week exposure period. The differences were statistically significant (p<0.01). Mean body weights in 500 ppm (2515 mg/m^3) F_1 females were 9.7% lower than those in the control group on PND 28 after the first week of whole body 1-BP exposure but did not reach statistical significance (p>0.05). Following weaning, mean body weights of the 500 ppm (2515 mg/m^3) F_1 females were comparable to that of the control group. Mean F_1 pup body weights in the 250 ppm (1258 mg/m^3) F_1 males were reduced significantly (p<0.01) on PND 28, but were not significantly different from control values for the remainder of exposure.

A statistically significant reduction in fertility indices (p<0.01) were observed in the 500 ppm (2515 mg/m^3) F_0 males and females (Table 21). The female fertility index is the number of females with confirmed pregnancy divided into the total number of females used for mating. The male fertility index is the number of males siring a litter divided into the total number of males used for mating. Fertility indices were reduced at 250 ppm (1258 mg/m^3) in the F_0 generation, and at 100 and 250 ppm (503 and 1258 mg/m^3) in F_1 generation rats but did not reach statistical significance compared to the control

group. However, these fertility indices were below the historical control value of about 90%. The authors noted that the higher fertility index in the F_1 500 ppm (2515 mg/m^3) group, relative to the 100 and 250 ppm (503 and 1258 mg/m^3) groups, may have been biased because the F_0 animals most sensitive to the effects of 1-BP were not represented in the F_1 generation.

Extended mean estrous cycle lengths were observed in the 250 (F_1), 500 (F_0 and F_1) and 750 (F_0) ppm group females when compared to the control group (Table 21), with the 500 and 750 ppm F_0 groups above the range of the WIL Research Laboratories, Inc. historical control data of 4.1 – 5.1 days. Estrous cycle length could not be determined in two and three females in the 500 and 750 ppm F_0 groups, respectively, because no complete cycles occurred, In addition, estrous cycle length could not be determined in three and four females in the 250 and 500 ppm F_1 groups, respectively, because no complete cycles occurred, Although no statistical analysis was performed (likely due to no complete cycles in some rats in the 500 and 750 ppm groups), the authors concluded that the effects on estrous cycle length was related to 1-BP exposure in the 250 (F_1), 500 (F_0, and F_1) and 750 ppm (F_0) groups.

The mean number of pups born, and pups born alive per litter were significantly decreased (p<0.01) in the 500 ppm F_1 and F_2 generations compared to the controls (Table 21). The number of litters were also reduced in the 500 ppm F_1 group. Reductions in mean number of pups born and live litter size were observed in the 250 ppm F_1 and F_2 groups, but the differences were not statistically significant. Postnatal survival in the F_1 and F_2 litters was not affected by parental exposure to 1-BP.

A statistically significant reduction (p<0.01) in the mean number of implantation sites was observed in the 500 ppm F_0 and F_1 females (Table 19). The mean number of implantation sites was reduced in 250 ppm F_0 and F_1 females but was not statistically significant. There was also a decrease in mean numbers of former implantation sites in the 250 (not statistically significant) and 500 (p<0.05) ppm F_0 and F_1 females.

Table 21. Major developmental/reproductive endpoints affected by 1-BP exposure (WIL Research Laboratories, 2001)

Endpoint	0 ppm	100 ppm	250 ppm	500 ppm	750 ppm
Fertility index (%)[a]					
F_0 (M & F)	92.0	100.0	88.0	52.0**	0**
F_1 (M)	87.5	68.0	64.0	70.8	NA
F_1 (F)	88.0	68.0	64.0	72.0	NA
Estrous cycle length (days)[b]					
F_0	4.2 ± 0.49	4.5 ± 1.05	4.7 ± 0.49	5.5 ± 2.17†	5.6 ± 1.79†
F_1	4.5 ± 1.25	4.5 ± 0.91	4.9 ± 1.43	5.1 ± 1.68	NA
Live litter size (mean no.)[c]					
F_1	14.4 ± 2.2	13.3 ± 3.7	12.3 ± 4.5	8.3 ± 4.1*	NA
F_2	14.5 ± 2.0	14.9 ± 3.3	12.5 ± 4.3	8.6 ± 4.5**	NA
Implantation sites (mean no.)[c]					
F_0	15.3 ± 2.53	14.3 ± 3.09	13.8 ± 4.23	9.0 ± 4.54**	NA
F_1	15.5 ± 2.11	15.8 ± 3.29	13.5 ± 4.34	9.8 ± 4.93**	NA

[a] Fertility index - ** p<0.01 by Chi-square test with Yates' correction factor
[b] † = estrous cycle length outside WIL historical control range of 4.1 to 5.1 days. No statistical analysis performed likely due to incomplete cycles occurring in some 250 (F_1), 500 (F_0 and F_1) and 750 ppm (F_0) females
[c] Live litter size and number of implantation sites - * p<0.05, ** p<0.01 by one-way ANOVA with Dunnett's test.
M – male; F - female
NA – Not applicable

Several male rat reproductive endpoints were affected by 1-BP exposure (Table 22). Significantly decreased sperm motility (p<0.01) and significantly increased sperm abnormalities (p<0.01) occurred in the 750 (F_0) and 500 ppm (F_0 and F_1) groups. Normal sperm morphology was reduced (p<0.05) in 250 ppm F_0 males, but was slightly higher than WIL Research Laboratories, Inc., historical controls (99.0%) and not considered exposure-related by the authors. Sperm motility was significantly lower (p<0.05) compared to controls in 250 ppm F_1 males but was slightly above WIL Research Laboratories, Inc., historical controls (83.2%). Therefore, the authors also did not consider this change to be exposure-related. Reduced normal sperm morphology (p<0.01) in the 100 ppm F_1 males was not considered exposure-related due to lack of a dose-response trend (i.e., no significant effect on sperm morphology in 250 ppm F_1 males). Low incidences in the number of F_0 males with small epididymides (left and/or right) and small and/or soft testes were observed in the 500 and 750 ppm groups. Although the incidence was not significantly lower than in controls, these findings were considered by the authors to be potentially related to 1-BP exposure.

The mean day of balanopreputial separation in the 500 ppm F_1 males was delayed due to the reductions in body weight. Mean body weight on the day of balanopreputial separation was similar to the control group value; however, the pups were approximately four days older.

Mean absolute and relative epididymal weights (right and left cauda) in males were reduced in a dose-dependent manner and were statistically significant reduced at 750 ppm (F_0, absolute and relative weight) and 500 ppm (F_0 and F_1 absolute weight) (Table 22). Mean absolute and relative prostate weights were reduced in F_0 males in a dose-dependent manner, and the absolute weight was statistically significantly lower at ≥250 ppm. Although there were no macroscopic or microscopic observations that correlated with the changes in prostate and epididymal weights, the authors concluded that the reductions were considered to be related to 1-BP exposure because of the reductions in fertility and/or litter size observed in the 250, 500 and 750 ppm groups. In the histomorphological incidence tables, OEHHA noted that an increased incidence of testis degeneration of the seminiferous tubules (p=0.049, one-tailed Fisher's exact test) occurred in 750 ppm F_0 males (Table 22).

Table 22. Main male reproductive endpoints affected by 1-BP exposure (WIL Research Laboratories, 2001)

Endpoint	0 ppm	100 ppm	250 ppm	500 ppm	750 ppm
Sperm motility (% motile)[a]					
F_0	86.8 ± 11.9	88.8 ± 7.2	83.4 ± 10.4	71.9 ± 9.3**	53.2±19.59**
F_1	88.9 ± 4.5	86.4 ± 5.0	84.8 ± 6.0*	74.4 ± 14.1**	NA
Sperm morphology (% normal)[a]					
F_0	99.7 ± 0.6	99.7 ± 0.5	99.3 ± 0.8*	98.2 ± 2.6**	90.6±8.74**
F_1	99.5 ± 0.79	98.9 ± 0.95**	99.1 ± 1.13	95.3 ± 6.51**	NA
Right cauda epididymis absolute wt (g)[b]					
F_0	0.3327 ±0.03631	0.3311 ±0.04453	0.3953 ±0.04188	0.2912 ±0.05206**	0.2405 ±0.04804**
F_1	0.3178 ±0.03778	0.3129 ±0.03862	0.3029 ±0.03885	0.2720 ±0.03787**	NA
Right cauda epididymis relative wt (g/100 g)[b]					
F_0	0.061 ±0.0096	0.064 ±0.0121	0.059 ±0.0098	0.057 ±0.0320	0.050 ±0.0097**
F_1	0.055 ±0.0075	0.058 ±0.0104	0.054 ±0.0083	0.052 ±0.0073	NA
Testis – seminiferous tubule degeneration incidence[c]					
F_0	1/25	2/25	0/25	3/25	6/25*
F_1	3/24	NE	NE	2/24	NA

[a] Sperm motility and morphology - ** p<0.01, * p<0.05 by Kruskal-Wallace test with Mann-Whitney U-test;

[b] Absolute and relative organ weight changes - ** p<0.01 by one-way ANOVA with Dunnett's test;

[c] Testis incidence findings – p=0.049 by one-tailed Fisher's exact test calculated by OEHHA.

NA – Not applicable; NE – Not evaluated

Regarding female rat reproductive organ changes, mean absolute and relative ovary weights in the F_0 generation were reduced in a dose-dependent manner, and both absolute and relative ovary weight was statistically significantly reduced (p<0.01) in 750

ppm females (Table 23). In addition, increased ovarian histopathology (decreased corpora lutea, and increased follicular cysts, follicular luteinized cysts and interstitial hyperplasia) in the 500 (F_0 and F_1) and 750 ppm (F_0) females correlated with the reduced ovary weights in these groups. However, the authors did not believe the decreased corpora lutea in the 750 ppm females fully accounted for the complete absence of litters in this group.

Table 23. Main female reproductive endpoints affected by 1-BP exposure (WIL Research Laboratories, 2001)[a]

Endpoint	0 ppm	100 ppm	250 ppm	500 ppm	750 ppm
Ovary absolute wt (g)[a]					
F_0	0.1227 ±0.02592	0.1265 ±0.02404	0.1152 ±0.02360	0.1119 ±0.01514	0.0975 ±0.02798**
F_1	0.1131 ±0.01554	0.1077 ±0.03170	0.1056 ±0.02791	0.1062 ±0.02302	NA
Ovary relative wt (g/100 g)[a]					
F_0	0.037 ±0.0078	0.038 ±0.0068	0.035 ±0.0072	0.034 ±0.0056	0.031 ±0.0079**
F_0	0.035 ±0.0055	0.033 ±0.0093	0.033 ±0.0087	0.035 ±0.0076	NA
Ovaries – decreased corpora lutea incidence[b]					
F_0	3/25	0/25	3/26	6/24	11/25*
F_1	3/25	3/25	7/25	4/24	NA
Ovaries – increased luteinized follicular cyst incidence[b]					
F_0	2/25	4/25	3/25	5/24	9/25*
F_1	2/25	3/25	2/25	3/25	NA
Ovaries - Increased follicular cyst incidence[b]					
F_0	7/25	1/25	3/25	8/24	12/25
F_0	5/25	5/25	7/25	10/25	NA

[a] Absolute and relative organ weight changes - ** $p<0.01$ by one-way ANOVA with Dunnett's test;
[b] Ovarian histomorphological incidence findings – * $p<0.05$ by two-tailed Fisher's exact test.
NA – Not applicable

Overall, the adverse effects on litter size and reproduction parameters at 500 and 750 ppm were consistent across generations, suggesting a lack of a transgeneration effect or increased susceptibility during perinatal or pubertal stages.

Mean absolute brain weights were reduced ($p<0.05$) compared to the control group values in the 250 (F_0 and F_1), 500 (F_0) and 750 ppm (F_0) group males and in the 500 (F_0) and 750 (F_0) ppm group females. Mean absolute brain weights were also reduced ($p<0.05$) in 100 ppm F_1 males and females. However, brain weights relative to final body weights were similar to the control group values, and the reductions in absolute brain weights compared to controls were only 5% or less. The authors suggested that the brain weight difference in the F_1 generation may be related to the smaller birth

weight of these animals. The areas of the brain histomorphologically examined in control and 750 ppm animals included the cerebral cortex, hippocampus, basal ganglia, cerebral peduncles, pons, tectum, central gray matter, thalamus, hypothalamus, cerebellum and nucleus gracilis. These are the regions that are typically examined in a neurotoxicity screen and are representative of each of the developmental regions of the brain (telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon). Additionally, the nucleus gracilis was examined because morphologic findings in this area have been reported following 1-BP exposure. No corresponding macroscopic or microscopic findings were found in any region of the brain of 1-BP-exposed rats.

Mean relative liver weights were increased in 750 ppm animals, and in 500 ppm F_0 males and F_1 males and females. The increased weight correlated with increased microscopic findings of vacuolation and glycogen (Table 24). The severity of these liver effects also appeared to increase with increasing dose. However, the authors considered the liver findings reversible and not an adverse effect. In other organs, mean absolute pituitary gland weights were reduced in 500 ppm F_1 males and in 750 ppm F_0 males without correlating microscopic findings. Due to infertility observed in 750 ppm F_0 males, the authors considered the reduction in pituitary weight related to 1-BP exposure. Mean absolute thymus gland weights were increased without correlating microscopic findings in the F_1 males at 250 ppm and above. During microscopic examination of the kidneys, the incidence of combined minimal and mild pelvic mineralization was increased in 500 and 750 ppm F_0 females ($p<0.05$) (Table 24). OEHHA also noted an increase in this lesion in 750 ppm F_0 males ($p=0.049$, one-tailed Fisher's exact test). An increased incidence of minimal and mild secondary transitional epithelial hyperplasia was observed in 500 ppm F_0 females ($p<0.05$). This lesion was also increased in 750 ppm F_0 females but did not reach statistical significance ($0.05<p<0.10$). The authors commented that these kidney effects are a common finding in rats of this strain and age, and the increase was considered to be incidental.

Table 24. Incidence of liver and kidney lesions in F_0 and F_1 rats after 19 week exposure to 1-BP (WIL Research Laboratories, 2001)[a]

Endpoint	0 ppm	100 ppm	250 ppm	500 ppm	750 ppm
Liver: vacuolation					
F_0(m)[b]	0/25	0/25	7/25*	22/25*	24/25*
F_1(m)	0/24	0/25	15/25*	23/24*	NA
F_0(f)[c]	0/25	0/25	0/25	6/24*	16/25*
F_1(f)	0/25	0/25	2/25	6/25*	NA
Liver: increased glycogen					
F_0(m)	14/25	14/25	20/25	21/25	24/25*
F_1(m)	19/24	18/25	17/25	24/24*	NA
F_0(f)	15/25	18/25	22/25*	23/24*	23/25*
F_1(f)	16/25	24/25*	23/25*	23/25*	NA
Kidney: pelvic mineralization					
F_0(m)	1/25	0/25	1/25	2/25	6/25*
F_1(m)	0/24	1/25	0/25	3/24	NA
F_0(f)	2/25	3/25	5/25	12/24*	14/25*
F_1(f)	4/25	5/25	7/25	8/25	NA
Kidney: transitional epithelial hyperplasia					
F_0(f)	1/25	0/25	2/25	6/24*	5/25
F_1(f)	2/25	3/25	2/25	2/25	NA

[a] Liver and kidney histomorphological incidence findings – * $p<0.05$ by two-tailed Fisher's exact test, except for F_0 male 750 ppm kidney pelvic mineralization findings (* $p<0.05$ by one-tailed Fisher's exact test calculated by OEHHA)
[b] m – male
[c] f – female
NA – Not applicable

Mean body weights of 500 ppm F_2 pups were not different from controls on PND 1-7. However, mean pup body weights were reduced ($p<0.01$) in both 500 ppm males and females at PND 14-21. F_2 pups were euthanized on PND 21 and organ weight and macroscopic examination of organs were conducted. Mean absolute and relative spleen weights were reduced ($p<0.01$) in the F_2 males and females in the 500-ppm group. The authors considered the spleen effects related to 1-BP exposure. Mean absolute brain weights (both sexes) and the thymus gland weights of F_2 males were reduced in the 500-ppm group. However, the relative brain and thymus weights in these animals were similar to those in the control group and not considered exposure-related. No other macroscopic organ findings were observed in F_2 generation rats.

Furuhashi *et al.*, 2006

Groups of 10 Wistar-Imamichi rats were exposed to 0, 100, 400, and 800 ppm (0, 500, 2000, and 4000 mg/m^3) 1-BP during pregnancy (GD 0 - 20) and lactation (PND 0 - 20) for 8 hours/day (Furuhashi *et al.*, 2006). During the lactation period, mothers were exposed to 1-BP without their young for four hours followed by a 2.5 hr rest for nursing

their young, then another four hours of 1-BP exposure without their young. A separate control group of nursing mothers were not separated from their litters to observe for possible effects of separating rat dams and offspring. On PND 21, the offspring were weaned and followed for up to day 50 (male adulthood) or day 63 (female adulthood) to investigate the early-in-life exposure effects on reproductive organs and other organ systems in growing rats.

Body weights of mothers during gestation and of offspring on PND 1 (8-10 per group) were unaffected by 1-BP exposure. The number of dead offspring per litter was also not significantly different from control at PND 1. However, only about one in 10 pups in the 800-ppm group survived to the end of lactation (day 21), and body weight of 800 ppm mothers became significantly reduced ($p<0.05$) during the lactation phase. Body weights of remaining groups of offspring were not significantly different from control at 7, 14 and 21 days of age, but there was a dose-dependent reduction in survival rate by PND 21. Body weights of control and treated offspring groups were lower during lactation compared to the control offspring group not separated from their mothers, but this difference did not reach statistical significance. Body weight of mothers not separated from their offspring was significantly greater than the 0 ppm mothers at PND 21. After weaning, body weights of the 800-ppm offspring remained significantly lower compared to control until 7-8 weeks of age. The authors suggested that the more adverse effects of 1-BP during lactation may be related to poor maternal nursing behavior, or that maternal behavior was a secondary reaction to the weak offspring.

In male offspring at 50 days of age, epididymal sperm count and percentage motile sperm were unaffected by 1-BP exposure. However, the rate of sperm arrival at the cauda epididymis was significantly lower in the 400 and 800 ppm groups at 50 days [OEHHA notes that only one 800 ppm male survived to this part of the study]. Histopathological examination of the testis of male offspring showed fewer cells in seminiferous tubules and fewer cell layers in the 400 and 800 ppm groups at PND 21, and a delay in thickening and differentiation of seminiferous tubules in the 400-ppm group at PND 33. In female offspring at 50 days of age, the estrous cycle was unaffected by 1-BP exposure. Histopathological examination of the ovary showed more primitive follicles in the 800 ppm of 21 day olds compared to the 0 ppm group. The authors suggested that the histopathological changes in the testes and ovaries in young rats may be due to the delay in growth, since the changes were not observed later at 50 (males) and 63 (females) days of age.

No significant histopathological changes were observed in the muscle branch of the posterior tibial nerve of the offspring at adulthood. However, swelling of preterminal axons in the medulla oblongata was observed at 800 ppm in PND 50 male and PND 63 female offspring. In the liver, vacuolization in the cytoplasm of hepatocytes was observed in 800 ppm male offspring at PND 21, and in the 800 ppm female offspring at

PND 63. The kidneys of female offspring showed dilation of the proximal tubules in the 400 and 800 ppm groups at 63 days of age.

Furuhashi *et al*. (2006) undertook a subsequent fostering experiment to investigate whether the decrease in survival rate and body weight gain of offspring resulted from exposure to 1-BP during pregnancy or during lactation. Four groups of pregnant rats (10 rats/group) were exposed to fresh air (three groups) or 800 ppm 1-BP (one group) following the same exposure protocol as the previous study (GD 0-20 and PND 0-20). At birth, the offspring of the exposed and non-exposed dam rats were exchanged. The offspring of the remaining two non-exposed dams were also exchanged. The number of live offspring per litter was significantly less in the 1-BP treated group compared to control at day 0 (p<0.05). At PND 21, the survival rate and body weight of offspring nursed by dams exposed during nursing (Group A) and those of exposed dams exposed during gestation (Group B) were significantly lower than non-exposed groups (Groups C+D). The body weight of Group A offspring was lower than that of Group B offspring, although the two groups showed a significant equal decrease in survival rate. After weaning, the Group B offspring had body weights similar to Groups C+D by 8 weeks of age, while Group A offspring had significantly reduced body weights compared to the control groups until the end of the experiment at 12 weeks.

To examine the effects of 1-BP on F_2 generation rats, Furuhashi *et al*. (2006) housed male and female F_1 offspring of each group (A, B, C, and D) in one cage to determine whether they could produce their own offspring (F2 rats). The age of F_1 females at the time they give birth to F_2 pups and the body weights of the pups on PND 0 were not different among the groups. However, the number of dead F_2 rats and the ratio of dead to live + dead F_2 rats per litter of Group A were significantly higher (p<0.05) than those of Groups B or C + D. The authors concluded that exposure to 1-BP during lactation adversely affected growth of offspring more than exposure during pregnancy, resulting in reduction of early survival of F_2 rats.

7.2.5 Developmental neurotoxicity

Kainate (kainic acid), an excitotoxin, is 100-fold more potent than the neurotransmitter glutamate and can induce seizures. Kainate receptors are ionotropic receptors that respond to glutamate. In animals kainate induces behaviors such as scratching and "wet dog shakes." Fueta *et al*. (2015) exposed pregnant Wistar rats to 0 or 700 ppm (3500 mg/m^3) 1-BP by inhalation 6 hours/day from GD 1 to GD 20. Kainate (0.1, 0.5, and 2.0 mg/kg) was intraperitoneally injected into air-exposed controls and 1-BP-exposed rat pups on PND 14. There was no significant difference in scratching between the control and the 1-BP-exposed groups (11/11 vs 7/7 at 0.1 mg/kg kainic acid). However, suppression of the occurrence ratio of "wet dog shakes" was observed at 0.1 mg/kg kainate in the 1-BP-exposed rat pups (11/11 control pups had the shakes vs.

only 4/7 of the 1-BP exposed pups) but not at higher concentrations of kainite. This finding indicated to the authors that the effects of prenatal 1-BP exposure can be observed only at the subclinical doses of KA.

Using a similar exposure protocol, Fueta *et al*. (2018) exposed pregnant Wistar rats (12-15/group) to 0 or 700 ppm 1-BP for 6 hours/day on GD 1 to 20 to investigate effects of 1-BP on neuronal excitability in the offspring. Hippocampal slices were collected from male offspring at 2, 5, 8 and 13 weeks of age to examine stimulation-dependent responses in the CA1 subfield, stimulation/response (S/R) relationships, and the ratio of responses to double-pulse stimulations. At 2 weeks of age, S/R relationships of the population spike amplitude was significantly greater in 1-BP-exposed rats compared to the S/R relationships in control rats ($p<0.001$ by repeated-measure ANOVA). However, the enhancement of the S/R relationship due to 1-BP exposure had disappeared by 5 weeks of age, suggesting the increased excitability of CA1 subfield pyramidal neurons was a transient effect. With double stimulation of 5 and 10 ms interpulse intervals, the paired-pulse ratios decreased significantly in 1-BP-exposed rats at 2 weeks of age ($p<0.05$, Welch's t-test). At 8 and 13 weeks of age, the paired-pulse ratio of the 5 ms interpulse interval was greater in 1-BP-exposed rats compared to control ($p<0.05$), but the paired-pulse ratio of the 10 ms interpulse interval in 1-BP-exposed rats was similar to that of control. The effects of 1-BP to the paired pulse ratio at 8- and 13-week exposure was a disinhibitory effect (i.e., interpreted as an increase in an inhibition). The authors concluded that prenatal 1-BP exposure may make CA1 neurons hyperexcitable at the developmental stage, and that disinhibition in later stages of development can be characterized as a disturbance of the excitation/inhibition balance in the hippocampal CA1 area. Such changes in the brain may be related to epileptic or anxiety disorders.

2163 **Table 25. Summary of Developmental and Reproductive Effects of 1-BP**

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Female Reproductive System Effects			
Sekiguchi *et al*., 2002	Female F344 rats WB inhalation exposure to 0, 50, 200, or 1000 ppm for 20 days (8 hours/day, 7 days/week)	At 1000 ppm, increased ratio of estrous cycles of ≥6 days or longer, but did not reach statistical significance	NOAEL: 1000 ppm LOAEL: NA for evidence of reproductive toxicity
Yamada *et al*., 2003	Female Wistar rats WB inhalation exposure to 0, 200, 400, or 800 ppm for 12 weeks (8 hours/day, 7 days/week).	800 ppm rats became moribund at week 7 and were sacrificed at week 8 Extended diestrous at 400 and 800 ppm ↓ in normal antral follicles at 200 and 400 ppm, and ↓ no. of normal growing follicles at 400 ppm	NOAEL: NA LOAEL 200 ppm, for disruption of ovarian follicular growth process
NTP (2011)	Female F344/N rats WB inhalation exposure to 0, 250, 500 or 1000 ppm for 14 weeks (6 hours/day, 5 days/week).	↑ time in extended estrous and ↓ time in extended diestrous at ≥250 ppm ↑ relative time spent in estrous stage at ≥250 ppm	NOAEL: NA LOAEL: 250 ppm for adverse effects on fertility and reproductive performance
	Female B6F3N1 mice WB inhalation exposure to 0, 125, 250, or 500 ppm for 14 weeks (6 hours/day, 5 days/week)	WB inhalation exposure to 0, 125, 250, or 500 ppm for 14 weeks (6 hours/day, 5 days/week)	NOAEL: 125 ppm LOAEL: 250 ppm for adverse effects on fertility and reproductive performance

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Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Male Reproductive System Effects			
Ichihara *et al*., 2000b	Male Wistar rats WB inhalation exposure to 0, 200, 400, or 800 ppm for 12 weeks (8 hours/day, 7 days/week)	↓ absolute and relative seminal vesical wt at ≥200 ppm; ↓ BW and absolute wt of epididymis at ≥400 ppm; ↓ absolute wt of prostate at 800 ppm ↓ epididymal sperm count and motility at ≥400 ppm ↑ tailless sperm and sperm with abnormal heads at ≥400 ppm and 800 ppm, respectively ↑ retained spermatids in seminiferous tubules at ≥400 ppm ↓ testosterone at 800 ppm	NOAEL: NA LOAEL: 200 ppm for ↓ reproductive organ weight, and inhibition of spermiation activity at ≥400 ppm
Banu *et al*., 2007	Male Wistar rats WB inhalation exposure to 0, 400, or 1000 ppm for 6 weeks (8 hours/day, 7 days/week) Necropsies at 0, 4, and 14 weeks post-exposure	↓ testicular and epididymal weight, sperm count and motility, ↑ abnormal sperm and spermatogenic degeneration at 1000 ppm. Only limited recovery at 14 weeks post-exposure ↑ retained spermatids at 400 ppm, but recovered by 4 weeks post-exposure	NOAEL: NA LOAEL: 400 ppm for transient inhibition of spermiation, but persistently inhibited spermiation at 1000 ppm

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Male Reproductive System Effects			
Garner et. al., 2007	Male wild type (*Cyp2e1*+/+) mice, and male CYP2E1 knockout mice (*Cyp2e1-/-)* WB inhalation exposure to 0 or 800 ppm for 6 hours	↓ sperm motility at 800 ppm in wild type (*Cyp2e1*+/+) mice, but not in CYP2E1 knockout mice (*Cyp2e1-/-)*	Wild type mice NOAEL: NA LOAEL: 800 ppm for ↓ sperm motility Knockout mice: NOAEL: 800 ppm LOAEL: NA
Liu et. al., 2009	Male C57BL/6J, DBA/2J, and BALB/cA mice WB inhalation exposure to 0, 50, 110, or 250 ppm for 28 days (8 hours/day, 7 days/week)	↓ sperm count at ≥50 ppm in all strains; ↓ sperm motility at ≥50 or 110 ppm, and ↑ abnormal sperm heads at ≥50 or 110 ppm	NOAEL: NA LOAEL: 50 ppm for inhibition of spermiation
NTP, 2011	Male F344/N rats WB inhalation exposure to 0, 250, 500, and 1000 ppm for 14 weeks (6 hours/day, 5 days/week)	↓ BW, left cauda, and left epididymis at 1000 ppm ↓ sperm motility at ≥250 and sperm count at 1000 ppm	NOAEL: NA LOAEL: 250 ppm for inhibition of spermiation
	Male F6C3F1 mice WB inhalation exposure to 0, 125, 250, or 500 ppm for 14 weeks (6 hours/day, 5 days/week)	↓ sperm motility at ≥250 and sperm count at 500 ppm	NOAEL: 125 ppm LOAEL: 250 ppm for inhibition of spermiation

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Male Reproductive System Effects			
Zong *et al*., 2016	Male C57BL/6J mice WB inhalation exposure to 0, 50, or 250 ppm (saline control), and 0, 50, 250, or 1200 ppm (ABT-treated) for 4 weeks (8 hours/day, 7 days/week)	↓ sperm count and motility at 250 ppm, which was prevented in ABT-treated mice ↑ retained spermatids in seminiferous tubules at 50 and 250 ppm, which was prevented in ABT-treated mice ↓ prostate plus seminal vesicle wt at 250 ppm in saline and ABT-treated mice At 1200 ppm: ↓ BW, epididymis, testis, and prostate plus seminal vesicle wt ↓ sperm count and motility; ↑ retained spermatids and morphologically abnormal sperm	NOAEL: NA LOAEL: 50 ppm for inhibition of spermiation With ABT treatment: 250 ppm for ↓ prostate plus seminal vesicle wt
Huntingdon Life Sciences, 2001	Female Sprague-Dawley rats WB inhalation exposure to 0, 100, 498, or 996 ppm for 6 hr/day on GD 6-19	↓ maternal BW at ≥498 ppm ↓ fetal BW at ≥498 ppm ↑ litter incidence of reduced skull ossification and bent ribs at ≥498 and 996 ppm, respectively	NOAEL: 100 ppm LOAEL: 498 ppm for skeletal abnormalities and reduced BW in fetuses, and reduced maternal BW

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Developmental Effects			
WIL Research Laboratories, 2001	Male and Female Sprague-Dawley rats WB inhalation exposure to 0, 100, 250, or 750 ppm for 6 hr/day, 7 days/week for 19-20 weeks in F_0 and F_1 males and females (70-day exposure prior to 14-day mating period, followed by exposure out to 19-20 weeks. No exposure in nursing females on lactation days 1-4)	↓ fertility index F_0 males and females at ≥500 ppm ↑ estrous cycle length in F_0 and F_1 females at ≥500 ppm, and possibly 250 ppm ↓ live litter size in F_1 and F2 rats at 500 ppm ↓ implantation sites in F_0 and F_1 females at 500 ppm ↓ sperm motility and ↑ abnormal sperm morphology in F_0 and F_1 males at ≥500 ppm ↓ absolute cauda epididymis wt. in F_0 (500 and 750 ppm) and F_1 (500 ppm), and ↓ relative wt in 750 ppm F_0 males ↑ testis seminiferous tubule degeneration in 750 ppm F_0 male rats ↓ absolute and relative ovary wt in 750 ppm F_0 females	NOAEL: 100 ppm LOAEL: 250 ppm for liver hepatocyte lesions; 500 ppm for inhibited spermiation and decrease fertility in F_0 and F_1 males, and disruption of ovarian follicular growth process and decreased fertility in F_0 and F_1 females

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Developmental Effects			
WIL Research Laboratories, 2001 (continued)	Male and Female Sprague-Dawley rats WB inhalation exposure to 0, 100, 250, or 750 ppm for 6 hr/day, 7 days/week for 19-20 weeks in F_0 and F_1 males and females (70-day exposure prior to 14-day mating period, followed by exposure out to 19-20 weeks. No exposure in nursing females on lactation days 1-4)	↓ corpora lutea and ↑ luteinized follicular cysts in ovaries of 750 ppm F_0 females ↑ vacuolation of hepatocytes ≥250 ppm in F_0 and F_1 males, and ≥500 ppm in F_0 and F_1 females ↑ liver glycogen at 750 ppm (F_0 males), 500 ppm F_1 males and F_0 females, and ≥100 ppm in F_1 females ↑ kidney pelvic mineralization 750 ppm F_0 males, ≥500 ppm F_0 females; ↑ transitional epithelial hyperplasia in 500 ppm F_0 females ↓ absolute and relative spleen wt in 500 ppm F_2 males and females	NOAEL: 100 ppm LOAEL: 250 ppm for liver hepatocyte lesions; 500 ppm for inhibited spermiation and decrease fertility in F0 and F1 males, and disruption of ovarian follicular growth process and decreased fertility in F0 and F1 females

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Developmental Effects			
Furuhashi *et al*., 2006	Female Wistar-Imamichi rats WB inhalation exposure to 0, 100, 400, or 800 ppm for 8 hr/day on GD 0-20 and PND 0-20	During lactation, ↓ survival of pups and ↓ BW of dams at 800 ppm. At weaning, ↓ pup weights until 8 weeks of age at 800 ppm ↓ rate of epididymis sperm arrival at ≥400 ppm in male pups Delayed testicular maturation at 400 and 800 ppm and delayed ovary maturation at 800 ppm ↑ swelling of preterminal axons of medulla oblongata at 800 ppm, ↑ hepatocyte vacuolization in females at 800 ppm, and ↑ dilation of proximal tubules at 400 and 800 ppm in females	NOAEL: 100 ppm LOAEL: 400 ppm for delayed testicular maturation and inhibited spermiation in male offspring, and kidney lesions in female offspring

Table 25. Summary of Developmental and Reproductive Effects of 1-BP (continued)

Reference	Animal Model & Exposure	Results Relative to Controls	Point of Departure
Developmental Effects			
Furuhashi *et al*., 2006 (Continued)	Female Wistar-Imamichi rats, fostering study WB inhalation exposure to 0 or 800 ppm for 8 hr/day on GD 0-20 and PND 0-20	↓ postnatal BW and survival at 800 ppm in fostering study ↓ BW at 8 weeks of age in offspring nursed by exposed dams ↑ number of dead F_2 pups per litter born to F_1 rats nursed by exposed dams	NOAEL: NA LOAEL: 800 ppm for ↓ BW and survival of both F_1 foster groups, and ↑ number of dead F_2 pups
Fueta *et al*., 2015	Female Wistar rats WB inhalation exposure to 0 or 700 ppm for 6 hr/day on GD 1-20	↓ occurrence ratio of "wet dog shakes" in rat pups treated with 0.1 mg/kg kainite on PND 14	NOAEL: NA LOAEL: 700 ppm for suppression of excitatory neurotransmission in the brain
Fueta *et al*., 2018	Female Wistar rats WB inhalation exposure to 0 or 700 ppm for 6 hr/day on GD 1-20	↑ transient population spike amplitude in stimulation/response relationship at 2 weeks of age ↓ paired-pulse ratio at 2 weeks of age, followed by ↑ in 5 ms interpulse interval of paired-pulse ratio at 8 and 13 weeks of age	NOAEL: NA LOAEL: 700 ppm for disturbance of excitation/inhibition balance in hippocampal CA1 area

↑ – increase resulting in significant ($p \leq 0.05$) difference; ↓ – decrease resulting in significant ($p \leq 0.05$) difference; ABT – 1-aminobenzotriazole; BW – body weight; GD – gestation day; LOAEL – lowest observed adverse effect level; NA – not attained or not applicable; NOAEL – no observed adverse effect level; PND – postnatal day; WB – whole body; wt – weight.

8. Derivation of Reference Exposure Levels

8.1 1-Bromopropane Acute Reference Exposure Level

Study	Huntingdon Life Sciences, 2001
Study population	Pregnant Sprague Dawley female rats
Exposure method	Inhalation
Exposure continuity	Exposure to 0, 500, 2500, or 5000 mg/m^3 (0, 100, 498, or 996 ppm)
Exposure duration	6 h/day on gestation days 6 through 19
Critical effects	Reduced skull ossification in offspring
LOAEL	2500 mg/m^3 (498 ppm)
NOAEL	500 mg/m^3 (100 ppm)
Benchmark concentration	659 mg/m^3 (131 ppm)
Time-adjusted exposure	659 mg/m^3 (131 ppm)
Human Equivalent Concentration	659 mg/m^3 (131 ppm) (RGDR = 1) (systemic effect)
LOAEL uncertainty factor (UF_L)	1
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (default
Toxicodynamic (UF_{A-d})	√10 (default)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10 (default)
Toxicodynamic (UF_{H-d})	√10 (sensitive endpoint as POD)
Database uncertainty factor	1
Cumulative uncertainty factor	200
Acute Reference Exposure Level	3300 µg/m^3 (0.7 ppm; 3.3 mg/m^3)

The acute Reference Exposure Level (REL) is a level at which infrequent one-hour exposures to 1-BP are not expected to result in adverse health effects (see Section 5 of the Technical Support Document (OEHHA, 2008)).

Single exposure 1-BP studies resulting in acute effects are lacking in humans, and are few in rodent studies. In rat lethality studies, relatively high acute exposures in the range of 11,000 ppm result in observed signs of CNS depression. However, several daily repeated exposures are needed to produce signs of neurotoxicity at much lower concentrations (1800 to 2000 ppm). Histopathological and biochemical changes in rat nerve cells and tissue employed repeated daily exposures of one week or more, possibly due to difficulty in finding measurable changes with shorter exposures. In mice, acute or subacute exposure to 1-BP in the range of 500-800 ppm has resulted in hepatotoxicity and male reproductive toxicity. Mice are sensitive to these particular effects, relative to rats. However, limited human occupational studies have not observed clear evidence of effects in these organs, whereas clear evidence of neurotoxicity has been observed.

For developmental toxicity studies that employ daily exposures during gestation, no time adjustment is used in deriving acute RELs. A one-hour exposure at a sensitive time point during gestation may be sufficient to result in a developmental effect (OEHHA, 2008). Consequently, the fetal effects of 1-BP exposure in rats during gestation were identified as a sensitive indicator of acute toxicity and selected as the POD for the acute REL.

Three multi-dose reproduction/developmental studies in rodents have been performed with 1-BP: Huntingdon Life Sciences (2001), WIL Research Laboratories (2001), and Furuhashi *et al*. (2006). The developmental study by Huntingdon Life Sciences (2001) was chosen as the key study for REL derivation. Reduced skull ossification in rat fetuses was the most sensitive developmental endpoint. The study by WIL Research Laboratories investigated the effects of 1-BP on reproductive performance in F_0 and F_1 generations, and the effects on F_1 and F_2 neonatal survival, growth and development. Only a limited number of developmental endpoints (litter size, fetal BW, number of implantation sites) were investigated in this multi-generation study. In the study by Furuhashi *et al*. (2006), dams were exposed during gestation and lactation, but again provided only limited information on developmental endpoints of fetuses at birth.

In the Huntingdon Life Sciences (2001) study, individual data for fetuses from each litter was available to perform a benchmark dose (BMD) analysis. Nested dichotomous models are used for developmental toxicity studies when such data is available. They account for any intra-litter correlation, or the tendency of littermates to respond more similarly to one another relative to the other litters in a dose group. Although litter size was not shown in the study to be affected with increasing exposure level, a litter-specific covariate is also included in the model. A potential limitation of this study is that only half the fetuses in each litter were examined for skeletal abnormalities; the other half were examined for soft tissue abnormalities.

The nested logistic model provided by U.S. EPA, version 3.1.2, was used to determine the Point of Departure (POD) for the acute REL (U.S. EPA, 2019). The model output in Table 26 shows that the best “viable” fit to the data (i.e., lowest AIC value, a reflection of fewer parameters in the model, combined with acceptable p-value and visual model fit to the data) resulted when intra-litter correlations are incorporated (ilc+), but not the litter-specific covariate (lsc-). The BMDL (and the POD) was 131 ppm. Thus, intra-litter correlations are important for describing the observed variability in this dataset, but litter size was not an important factor. The benchmark response (BMR) of 5% extra risk was used to derive the BMD and BMDL. The BMD is the dose at the 5% response rate, and the BMDL represents the 95% lower confidence limit of the dose producing a 5% response rate.

Table 26. Nested logistic BMD model results for reduced skull ossification in rat fetuses exposed to 1-BP during gestation (Huntingdon Life Sciences, 2001)

Model	BMD (ppm)	BMDL (ppm)	P Value	AIC
Nested Logistic (lsc+ilc+)	186.120	130.992	0.498	426.650
Nested Logistic (lsc+ilc-)	161.03	122.644	0.002	444.091
Nested Logistic (lsc-ilc+)[a]	**187.406**	**130.786**	**0.447**	**423.324**
Nested Logistic (lsc-ilc-)	162.952	124.272	0.0007	441.050

[a] - Bold type indicates best viable fit to the data

The nested logistic model demonstrated an adequate visual fit to the skull ossification data (Figure 2).

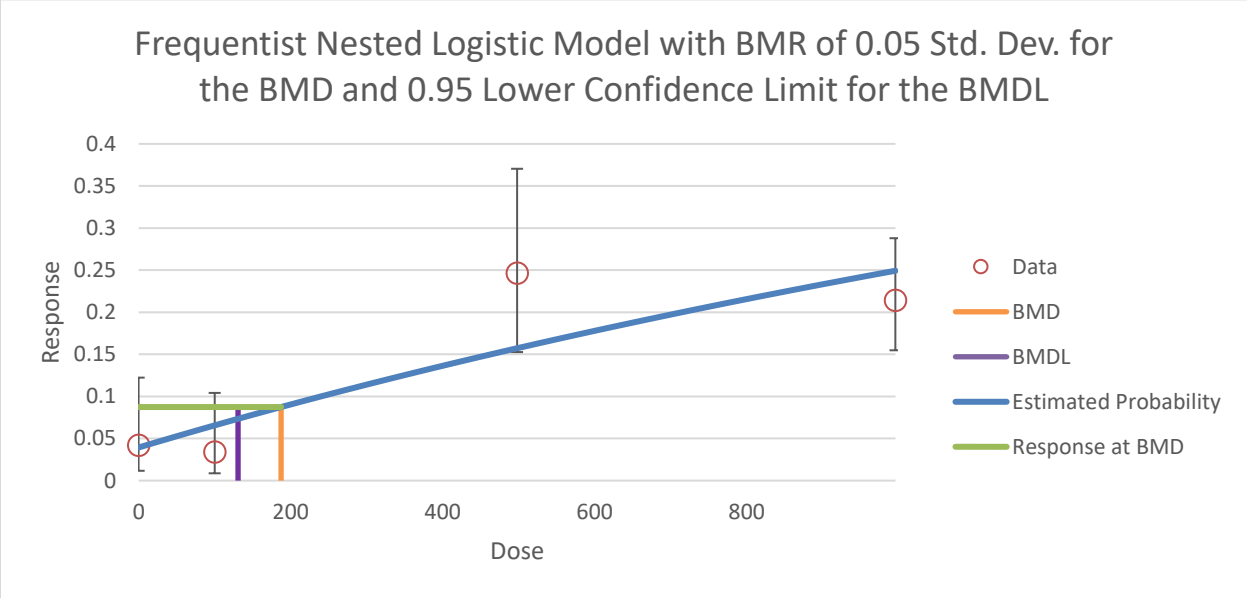

Figure 2. Nested logistic model fit to the skull ossification data in rat fetuses exposed to 1-BP during gestation (Huntingdon Life Sciences, 2001)

As noted above, no time adjustment is used to modify the POD if a developmental toxicity study is the basis of the acute REL.

The RGDR (Regional Gas Dose Ratio) is the ratio of the regional gas dose calculated for a given exposure for the respiratory region affected by a toxicant in the animal species to the regional gas dose of the same exposure in humans. For a systemic effect, the default value is 1 (OEHHA, 2008). This value assumes the blood:air

coefficient is the same across species where chemical-specific data were unavailable. The rat and human 1-BP blood:air coefficients are 11.7 and 7.08, respectively (Gargas *et al.*, 1989; Meulenberg and Vijverberg, 2000). The rat blood:air partition coefficient for rats is greater than that for humans, so a default ratio of 1 was applied.

The interspecies $UF_{A\text{-}k}$ of 2 is the default value used when there are no pharmacokinetic data available for interspecies extrapolation. The default interspecies $UF_{A\text{-}d}$ of $\sqrt{10}$ is applied to compensate for the absence of data for pharmacodynamic differences between species. The default intraspecies $UF_{H\text{-}k}$ of 10 is used when there is no information on pharmacokinetic differences for 1-BP among adults, infants, and children (OEHHA, 2008). An intraspecies $UF_{H\text{-}d}$ (toxicodynamics) of $\sqrt{10}$ is used when the key study is based on a sensitive endpoint (development), and there is low relative potency for neurotoxicity with acute exposure.

US EPA BMD software (BMDS Version 3.2) was also used to determine BMDs and BMDLs for the fetal body weight data in the Huntingdon Life Sciences study (See Section 7). Fetal body weights were used as presented in the study, but without the BW data from a 100-ppm litter with abnormally low body weights. BMDLs (95% lower confidence limit on the BMD) were calculated in one run with a BMR of 5% relative deviation from the control BW mean, and in a second run with 1 SD from the control BW mean. Continuous models with acceptable fits to the data (and BMD/BMDL ratio <3) had similar BMD and BMDL values. The BMDLs with a 5% relative deviation from the control BW ranged from 557 to 570 ppm. BMDLs with 1 SD from the control BW ranged from 600 to 613 ppm. The BMDL for reduced skull ossification was lower (131 ppm), so this endpoint was used as the POD for the acute REL.

BMD modeling was also conducted with summary means of the most sensitive developmental endpoints in the two-generation WIL (2001) study: post-implantation loss in F_0 females and reduced live litter size of F_1 offspring (See Table 21). Both endpoints are considered to be acute developmental effects. BMDLs (95% lower confidence limit on the BMD) were calculated with a BMR of 1 SD from the control mean. Continuous models with the lowest AIC and acceptable fits to the data (BMD/BMDL ratio <3, p > 0.10 for Test 4) were chosen for the POD. The BMDL for post-implantation loss was 188 ppm (Linear model, non-constant variance), and the BMDL for live litter size was 158 ppm (Exponential 2 model, non-constant variance). Application of the same time adjustment and uncertainty factors as that used for reduced skull ossification results in "comparison RELs" of 0.9 and 0.8 ppm (5 and 4 $\mu g/m^3$), respectively.

8.2 1-Bromopropane Chronic Reference Exposure Level

Study (key study)	Li *et al*., 2010b
Study population	71 female workers from four 1-BP manufacturing plants
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	Average of 38.8 months
Critical effects	Reduction in distal peripheral nerve function
LOAEL	14.13 mg/m^3 (2.81 ppm) geometric mean
NOAEL	Not determined
Time-adjusted exposure	5.05 mg/m^3 (14.13 mg/m^3 × 10 m^3/20 m^3 × 5 days/7 days)
LOAEL uncertainty factor (UF)	√10 (subclinical findings)
Subchronic UF	10 (duration <8% of estimated lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (human study)
Toxicodynamic (UF_{A-d})	1 (human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10 (default to protect infants and children)
Toxicodynamic (UF_{H-d})	10 (neurotoxicity)
Cumulative uncertainty factor	3000
Chronic Reference Exposure Level	1.7 µg/m^3 (0.3 ppb; 0.0017 mg/m^3)

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from continuous chronic exposure to 1-BP (see Section 7 in the Technical Support Document (OEHHA, 2008)). Numerous case reports and occupational studies show that neurotoxicity, primarily affecting the peripheral nervous system in the legs and feet, is the most sensitive effect of repeated exposure in humans (Sclar, 1999; Samukawa *et al*., 2012; Wang *et al*., 2015; Ichihara 2004b; Majersik *et al*., 2007; Wang *et al*., 2007; Li *et al*., 2010a, b; Miao *et al*., 2015c). Early occupational studies observed severe neurological symptoms in workers at exposures >50-100 ppm (>250-500 mg/m^3) that occurred over exposure durations of weeks to months (Harney *et al*., 2003). Improved working conditions and lower exposure in more recent studies resulted in few or no severe neurotoxic effects, but subclinical findings of neurotoxicity were still present.

The key study by Li *et al*. (2010b) examined the largest cohort of 1-BP manufacturing workers (71 females) studied thus far, comparing them to an age-matched control group. Two other studies by Li *et al*. (2010a, c) separated the 1-BP workers (it is likely many of the same workers participated in all three studies) into three exposure groups to look for dose-response relationships for many of these same health effects. Exposures in the three studies were estimated mostly by individual passive monitoring over one or two days of work. However, Chinese workers in the regions investigated were said to rotate among the various jobs within the 1-BP workshops, which suggested

that over time the long-term average exposure among the workers would be more similar (Miao *et al*., 2015c; Li *et al*., 2010c). This might explain why most parameters in the Li *et al*. (2010a) and (2010c) studies lacked a clear linear dose-response among the three 1-BP-exposed groups. Thus, the Li *et al*. (2010b) study that compared all 1-BP exposed workers to an age-matched control group was chosen as the key study.

Work shifts for the female employees were 8-hours/day. Although not explicitly stated, work shifts of 5 days/week were implied and used to calculate exposure continuity. A time- and breathing-rate-adjusted exposure of 5 days/7 days x 20 m^3/10 m^3 was used to extrapolate from discontinuous occupational exposure to an annualized average continuous exposure. The adjustment includes the assumption that half the daily volume of air intake in humans (i.e., 10 m^3) occurs during an active 8-hour period, in accordance with OEHHA guidelines.

Since a NOAEL was not reported, the LOAEL was used as the POD. Due to a lack of obvious clinical symptoms in the 1-BP workers, a LOAEL UF of $\sqrt{10}$ (square root of 10) was used, rather than a LOAEL UF = 10. Examination by physicians did not observe physiological/pathological changes in limb reflexes, grip strength, or coordination. No effects were observed in the neurological battery, following adjustment for level of education. The neurological effects observed were statistically significant, including increases in tibial nerve DL and reductions in tibial motor nerve and sural sensory nerve CVs. However, the CVs were still within the normal range for healthy workers. Decreased vibratory perception (pallesthesia) was also observed by the authors in the feet (but not the hands) of the 1-BP workers. However, the pallesthesia effects were not apparent to the affected workers themselves (i.e., subclinical).

A weakness of the key study is that the exposure level appears to be based on a single, or perhaps two, eight-hour personal sample(s) from each worker. In addition, although workers were acclimatized in a room at 24ºC for 30 min prior to the nerve tests, skin temperature measurement was not performed. Skin temperature is a known factor that can affect nerve conduction. Pallesthesia can be affected by differences in the Body Mass Index (BMI). BMI data were missing for five pairs of workers and controls, so the average body weight of the remaining female workers and controls were substituted. Additionally, it was noted in Li *et al*. (2010a) that vibration sense can also be affected due to sensitivity differences between the subjects and the examiner. The effect of the examining neurologist was found to be a significant factor ($p<0.0001$) for vibration loss in 1-BP workers. However, the same neurologist conducted the vibration loss tests in all pairs of workers, except for nine pairs. Regardless of these limitations, the weight of evidence indicates that a subtle loss of peripheral nerve function occurs with repeated exposure to low ppm levels of 1-BP.

A default subchronic UF of 10 was applied since the average workplace exposure of 28.8 months (2.4 years) is less than 8% of a 70-year (lifetime) exposure. The default intraspecies UF_{H-k} of 10 is used when there is no specific information on pharmacokinetic differences among adults, infants, and children. An intraspecies UF_{H-d} of 10 is used when the critical effect for a chemical is neurotoxicity, as is the case for 1-BP. Neurotoxic chemicals are more likely to adversely affect the developing nervous system in infants and children.

Several Chinese occupational studies show a statistically significant reduction in RBC count in 1-BP-exposed workers compared to a control group (Ichihara *et al*., 2004a,b; Li *et al*., 2010a, b; Wang *et al*., 2015; Zhong *et al*., 2018). Other factors that were not examined could have caused the low RBC count (iron deficiency, vitamin deficiency, menstruation), and the mean values for most blood test results in exposed workers were still within the normal range for healthy adults. 2-BP has been shown to cause severe anemia in human occupational studies and in rodent studies. However, 1-BP has not produced anemia in rodent studies (Yu *et al.*, 2001; NTP, 2011). Some researchers have suggested that 2-BP as an impurity may be the cause of lower hematological indices in 1-BP workers (Li *et al*., 2010b; Ichihara *et al*., 2004a, b), although when tested, the levels of 2-BP is low in 1-BP formulations (0.83%) and in the air of 1-BP manufacturing factories (median 0.15 to 0.4 ppm) (Ichihara *et al*., 2004a, Li *et al*., 2010a). Subsequently, OEHHA staff consider the blood test findings too uncertain to support hematotoxicity as an additional critical endpoint for chronic 1-BP exposure.

Comparison RELs were derived for endpoints from the two rodent studies in which exposures were chronic in duration (>14 weeks), the 2-year NTP (2011) bioassay in rats and mice, and the two-generation reproductive/developmental study by WIL (2001) in rats. BMD modeling was conducted for several respiratory tract lesions observed following two-year 1-BP exposure in rats and mice (See Tables 14 and 27). The incidence data suggest that bronchiole regeneration in mice could be the most sensitive endpoint. However, an acceptable model fit to the data was not attainable with BMD software due to high incidence of the lesion (>77%) in all 1-BP exposure groups. A NOAEL/LOAEL approach would necessitate the use of a 10-fold Uncertainty Factor (UF) due to the lack of a NOAEL. This would result in an unacceptably high cumulative UF ≥3000 when combined with intraspecies and interspecies UFs.

Acceptable BMD model runs were attained for two other sensitive endpoints, cytoplasmic vacuolization of the trachea and vacuolization of nasal respiratory epithelium in male mice. BMDLs (95% lower confidence limit on the BMD) were calculated with a BMR of 5% (extra risk). Dichotomous models with the lowest AIC and acceptable fits to the data (BMD/BMDL ratio <3, $p > 0.10$) were chosen for the POD for both lesions. The BMDL for cytoplasmic vacuolization of the trachea was 6.76 ppm

(log-logistic model), and the BMDL for vacuolization of the nasal respiratory epithelium was 10.06 ppm (log-logistic model). A limitation for both modeling runs was that the BMD and BMDL were both 3-fold lower than the lowest non-zero dose.

A time adjustment factor (6.2 hours/24 hours x 5 days/7days) to obtain an annual average concentration was applied to both PODs. RGDRs of 0.27 and 3.73 were calculated for the extrathoracic (nasal) and tracheobronchial (trachea) regions, respectively, using the US EPA default approach for estimating the HEC (OEHHA, 2008). Inputs included the male mouse minute volume calculated with the specified linear regression equation, and a body weight of 47.5 g averaged over the two years of the study. A human minute volume of 13,889 ml/min was calculated from the default daily air intake of 20 m^3/day.

An interspecies toxicokinetic factor (UFA-k) of 2 (with use of an RGDR) and an interspecies toxicodynamic (UFH-d) of √10 (default) was applied. Toxicokinetic and toxicodynamic intraspecies UFs of 10 each were applied for human diversity in the absence of human kinetic data and increased susceptibility of children to neurotoxicants, respectively. The total UF is 600. The calculated comparison RELs are 39 and 4.2 µg/m^3 for tracheal cytoplasmic vacuolization and nasal respiratory epithelial vacuolization, respectively.

Comparison RELs were also determined with summary means of the most sensitive liver and male reproductive endpoints in the two-generation WIL (2001) study, including increased liver vacuolation in F_1 male mice, decreased sperm motility, and decreased percent normal sperm morphology in both F_0 and F_1 generations (see Tables 22, 24 and 27). BMDLs (95% lower confidence limit on the BMD) were calculated with a BMR of 5% for the dichotomous liver data and 1 SD from the control mean for the reproductive endpoints. Models with the lowest AIC and acceptable fits to the data (BMD/BMDL ratio <3, $p > 0.10$) were chosen for the POD.

A $BMDL_{1SD}$ of 327 ppm (polynomial degree 2 model, constant variance) was attained for decreased sperm motility in F_0 rats, but the model was regarded as “questionable” primarily due to high variance in the high exposure group. Removal of this exposure group and re-running the program resulted in a “viable” model with a POD of 300 ppm (polynomial degree 2 model, constant variance). The two POD values are not substantially different, so the $BMDL_{SD1}$ of 327 ppm was chosen as the POD for this endpoint. For F_1 rats, a $BMDL_{SD1}$ of 161 ppm (polynomial 3 model, non-constant variance) was obtained for decreased sperm motility.

For decreased percent normal sperm morphology, a $BMDL_{SD1}$ of 193 ppm (polynomial 2 model, non-constant variance) was obtained for F_0 rats. Similar to the data for sperm motility, the model was regarded as “questionable” primarily due to high variance in the

high exposure group. Re-running the data without the high exposure group resulted in a viable model fit of 216 ppm (polynomial 2 model, non-constant variance). The two POD values are not substantially different, so the $BMDL_{SD1}$ of 193 ppm was chosen as the POD for this endpoint. For F_1 rats, a $BMDL_{SD1}$ of 201 ppm (polynomial 3 model, non-constant variance) was obtained for decreased percent normal sperm morphology, although the model was "questionable" due to a goodness of fit p-value <0.10. No "viable" models could be achieved with either non-constant or constant variance modeling.

For the liver vacuolation data, a $BMDL_{05}$ (95% lower confidence limit on the BMD) of 90 ppm was calculated (log-logistic model). Applying the same time adjustment, RGDR and UFs as that used for the reproductive endpoints resulted in a comparison REL of 37.5 ppb (189 $\mu g/m^3$).

The comparison chronic RELs in Table 27 are greater than the chronic REL of 1.7 $\mu g/m^3$ derived from the occupational study by Li *et al*. (2010b). However, the comparison REL for nasal respiratory epithelial vacuolization in male mice is close to the REL based on the key occupational study. Therefore, the respiratory system is also considered to be a critical endpoint for 1-BP chronic toxicity.

Table 27. Comparison chronic RELs for 1-BP

Species/sex Target Organ Effect	BMR POD	Exposure duration	RGDR	Compari-son REL[a]	Reference
Male mice Respiratory system Nasal respiratory epithelial vacuolization	$BMDL_{05}$ 10.06 ppm	6.2 hrs/day, 5 days/week for 2 years	0.27	0.84 ppb 4.2 µg/m^3	NTP, 2011
Male mice Respiratory system Tracheal cytoplasmic vacuolization	$BMDL_{05}$ 6.76 ppm	6.2 hrs, 5 days/week for 2 years	3.73	7.77 ppb 39 µg/m^3	NTP, 2011
Male F_1 rats Liver Increased vacuolation	$BMDL_{05}$ 90 ppm (V)	6 hrs/day, 7 days/week for 19-20 weeks	1	37.5 ppb 189 µg/m^3	WIL, 2001
Male F_1 rats Reproductive system Decreased sperm motility	$BMDL_{SD1}$ 161 ppm (V)	6 hrs/day, 7 days/week for 19-20 weeks	1	67 ppb 337 µg/m^3	WIL, 2001
Male F_0 rats Reproductive system Decreased % normal sperm morphology	$BMDL_{SD1}$ 5 dose groups 194 ppm (Q)	6 hrs/day, 7 days/week for 19 weeks	1	81 ppb 407 µg/m^3	WIL, 2001
Male F_0 rats Reproductive system Decreased % normal sperm morphology	$BMDL_{SD1}$ 4 dose groups 216 ppm (V)	6 hrs/day, 7 days/week for 19 weeks	1	90 ppb 453 µg/m^3	WIL, 2001
Male F_1 rats Reproductive system Decreased % normal sperm morphology	$BMDL_{SD1}$ 4 dose groups 201 ppm (Q)	6 hrs/day, 7 days/week for 19-20 weeks	1	84 ppb 421 µg/m^3	WIL, 2001
Male F_0 rats Reproductive system Decreased sperm motility	$BMDL_{SD1}$ 4 dose groups 300 ppm (V)	6 hrs/day, 7 days/week for 19 weeks	1	125 ppb 629 µg/m^3	WIL, 2001
Male F_0 rats Reproductive system Decreased sperm motility	$BMDL_{SD1}$ 5 dose groups 327ppm (Q)	6 hrs/day, 7 days/week for 19 weeks	1	136 ppb 685 µg/m^3	WIL, 2001

[a] Applied UFs are the same for all endpoints: UF_{A-k}=2, UF_{A-d}=√10, UF_{H-k}=10, and UF_{H-d}=10

Q – Questionable model fit to the data, as determined by US EPA BMD software (Version 3.2)

V – Viable model fit to the data, as determined by US EPA BMD software (Version 3.2)

8.3 1-Bromopropane 8-Hour Reference Exposure Level

Study (key study)	Li *et al*., 2010b
Study population	71 female workers from four 1-BP manufacturing plants
Exposure continuity	8 hours/day, 5 days/week
Exposure duration	Average of 38.8 months
Critical effects	Reduction in distal peripheral nerve function
LOAEL	14.13 mg/m^3 (2.81 ppm) geometric mean
NOAEL	Not determined
Time-adjusted exposure	10.09 mg/m^3 (14.13 mg/m^3 x 5 d/7 d)
LOAEL uncertainty factor (UF)	√10 (subclinical findings)
Subchronic UF	10 (duration <8% of estimated lifetime)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	1 (human study)
Toxicodynamic (UF_{A-d})	1 (human study)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10 (default to protect infants and children)
Toxicodynamic (UF_{H-d})	10 (neurotoxic)
Cumulative uncertainty factor	3000
Chronic Reference Exposure Level	3.4 µg/m^3 (0.7 ppb, 0.0034 mg/m^3)

The 8-hour Reference Exposure Level is a concentration at or below which adverse non-cancer health effects would not be anticipated for repeated 8-hour exposures seven days a week (see Section 6 in the TSD (OEHHA, 2008)).

The key study is the same one selected for the chronic REL. The selection of uncertainty factors is discussed in the chronic REL derivation. Following OEHHA guidelines, time adjustment based on an occupational exposure study is 8 hours work exposure / 8 hours/day x 5 days worked per week (i.e., per 7 days)

8.4 1-Bromopropane as a Toxic Air Contaminant Especially Affecting Infants and Children

Under Health and Safety Code Section 39669.5, OEHHA establishes and maintains a list of Toxic Air Contaminants (TACs) that may disproportionately impact infants and children. OEHHA evaluates TACs for addition to this list and develops Reference Exposure Levels for TACs. The CARB anticipates identifying 1-BP as a TAC in 2022, in accordance with section 39657(b) of the California Health and Safety Code (Title 17, California Code of Regulations, section 93001) (CCR, 2007).

OEHHA considers substances that cause neurotoxicity to disproportionally impact children (OEHHA, 2001). It has been demonstrated in this report that 1-BP is neurotoxic in animal models and human occupational studies. In addition, evidence of

developmental and reproductive toxicity has been demonstrated in animal models. 1-BP is listed under Proposition 65 as a chemical known to the State of California to cause developmental toxicity and male and female reproductive toxicity and is a chemical subject to the Air Toxics Hot Spots Information and Assessment Act of 1987.

Taking these findings into consideration, OEHHA recommends that 1-BP be identified as a Toxic Air Contaminant which may disproportionally impact infants and children pursuant to Health and Safety Code, section 39669.5(c).

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