1-BROMOPROPANE

CAS number: 106-94-5

Synonyms: n-Propylbromide; Propylbromide

Molecular structure: C_3H_7Br

Chemical structure:

TLV–TWA, 0.1 ppm (0.5 mg/m^3)

A3 — Confirmed Animal Carcinogen with Unknown Relevance to Humans

TLV® Recommendation

A TLV–TWA of 0.1 ppm (0.5 mg/m^3) should provide protection against the potential for neurotoxicity, hepatotoxicity, and reproductive and developmental toxicity in 1-bromopropane-exposed workers. 1-Bromopropane (1-BP) is a substitute for solvents used in cleaning, adhesive, and aerosol propellant applications. This document applies to commercial grade bromopropane (99% 1-BP with 0.1%–0.2% 2-bromopropane), not to 2-bromopropane. The recommended TLV–TWA presented here should be applied to 1-BP, not the 2-bromopropane contaminant. 1-BP exhibited low acute toxicity in rats but produced neurotoxicity, (Ichihara et al., 2000b) hepatotoxicity, (ClinTrials, 1997a) and reproductive (WIL, 2001) and developmental (Huntingdon, 2001) toxicity after repeated exposure. Several human case studies have reported polyneuropathy (Sclar, 1999) and neurotoxicity (Ichihara et al., 2002, 2004a, b; Li et al., 2010b; Majersik et al., 2007; Perrone et al., 2008; Samukawa et al., 2012) in 1-BP-exposed workers. Symptoms included headache, nausea, incontinence and subacute spastic paraparesis with distal sensory loss. Diminished vibration sensation and lower scores in memory and mood tests were reported in workers exposed to time-weighted average exposures of 0.34 to 49.19 ppm 1-BP (Ichihara et al., 2004a). A study of 60 female workers in four 1-BP factories demonstrated dose-dependent neurological and hematologic effects of 1-BP exposure with a lowest-observed-adverse-effect level of 1.28 ppm 1-BP for loss of vibration sense in toes and lowered red blood cell count (Li et al., 2010b). A no-observed-adverse-effect level (NOAEL) for 1-BP-induced neurological effects was not identified in this study (Li et al., 2010b). The NOAEL for hepatotoxicity in the chronic rat study was 200 ppm (ClinTrials, 1997a). Inhalation exposure of rats (125, 250, or 500 ppm) or mice (62.5, 125, or 250 ppm) to 1-BP 6 hours/day, 5 days/week for 2 years produced cancer of the large intestine in both sexes of rats and lung tumors in female mice (NTP, 2011), supporting a cancer designation of A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans. There is no basis for a Skin notation because the dermal LD_{50} of 1-BP was > 2 g/kg (Elf AtoChem, 1995b) and no basis for RSEN or DSEN notations (Elf AtoChem, 1995a). There are no data on which to support a TLV–STEL for 1-BP.

TLV® Basis

CNS impairment; peripheral neuropathy; hematologic effects; reproductive (male and female) and developmental toxicity.

Chemical and Physical Properties

Commercial grade 1-BP is a clear, colorless liquid reported to be 99% pure (Fisher Scientific UK, 2000). The U.S. Occupational Safety and Health Administration (U.S. OSHA) analyzed samples of 1-BP and detected 2-bromopropane (2-BP) at 0.1% to 0.2% (U.S. OSHA, 1999). Chemical and physical properties include (Fisher Scientific UK, 2000):

Molecular weight: 122.99
Specific gravity: 1.35
Melting point: -110°C
Boiling point: 71°C
Vapor pressure: 146 torr at 20°C
Saturated vapor concentration: 193,000 ppm
Flash point: 21°C
Explosion limits: lower, 4.60 vol%; upper, 7.8 vol%
Autoignition temperature: 490°C
Solubility: 2.5 g/L water at 20°C
Conversion factors at 25°C and 760 torr: 1 ppm = 5.03 mg/m^3; 1 mg/m^3 = 0.2 ppm

Major Sources of Occupational Exposure

1-BP is used as a solvent to clean metals and electronics, in adhesive and coating applications, and in aerosol propellant applications (U.S. EPA, 2000). Airborne 1-BP has an atmospheric lifetime of 15 days (Nelson et al., 1997), much shorter than that of chlorofluorocarbons. 1-BP is also being used as a replacement for perchloroethylene in dry cleaning operations (Blando et al., 2010). Information on the current production of 1-BP in the United States is not available. U.S. OSHA (1999) estimates that up to 240 million pounds of 1-BP could be produced annually if this substance is used to replace chlorinated solvents in vapor degreasing and cold metal cleaning operations.

Animal Studies

Acute

1-BP exhibits low acute toxicity. The oral LD_{50} in Sprague-Dawley rats was greater than 2000 mg/kg (Elf AtoChem, 1993). The dermal toxicity of 1-BP was investigated in Sprague-Dawley rats at a dose of 2000 mg/kg covered by a semi-occlusive dressing for 24 hours (Elf AtoChem, 1995b). There was no cutaneous reaction to 1-BP and there were no deaths or treatment-related effects, indicating that the dermal LD_{50} for 1-BP was greater than 2000 mg/kg.

Wistar rats were exposed to 1-BP vapors for 4 hours in nose-only exposure units (Elf AtoChem, 1997). The 4-hour LC_{50} for 1-BP was 7000 ppm (95% confidence limit [CL], 6800–7200 ppm). Mortality was due to respiratory inflammation and pulmonary edema. The 4-hour LC_{50} for 1-BP in SD rats exposed whole body was 14,374 ppm (95% CL, 13,624–15,596 ppm) (Kim et al., 1999b). The lowest lethal concentration (LCL_0) was lower than 11,833 ppm (95% CL, 7829–13,033 ppm), and the 100% lethal concentration (LC_{100}) was greater than 18,186 ppm (95% CL, 16,616–26,632 ppm). These data indicate that the acute toxicity of 1-BP is low. All treated rats exhibited piloerection, decreased activity, ataxia, and lacrimation within 1 hour after 1-BP exposure, but there were no gross pathological findings in any of the rats.

Treatment of female BALB/c mice with 200, 500, or 1000 mg/kg 1-BP by oral gavage in corn oil produced a dose-dependent decrease in hepatic and splenic glutathione content, an increase in serum alanine aminotransferase activity, and decreases in antibody responses, suggesting the potential for hepatotoxicity and immunotoxicity (Lee et al., 2007).

1-BP did not produce cutaneous reactions in guinea pigs attributable to skin sensitization (Elf AtoChem, 1995a). Animals were treated with 1-BP (25% in paraffin oil) for 10 days and challenged with 1-BP after 12 days without treatment. No clinical signs were observed except skin irritation.

Male and female F344/N rats (5 per sex) were exposed to 0, 125, 250, 500, 1000, or 2000 ppm 1-BP for 6 hours and 12 minutes/day, 5 days/week for 16 days (NTP, 2011). Mean body weights of the 2000 ppm exposed rats were decreased. Relative kidney weights were increased in all exposed groups while relative liver weights were increased in groups exposed to 500 ppm and higher concentrations of 1-BP. Nasal inflammation and epithelial cell necrosis were observed following exposures of 500 ppm or greater.

Male and female B6C3F1 mice (5 per sex) were exposed to 0, 125, 250, 500, 1000, or 2000 ppm 1-BP for 6 hours and 12 minutes/day, 5 days/week for 17 days (NTP, 2011). Significant mortality was observed in groups exposed to 500 ppm or greater. Body weight was decreased in the 1000 ppm males. Abnormal breathing, lethargy, and eye discharge were observed in groups exposed to 500 ppm or greater, along with increased liver and kidney weights. Microscopic lesions were seen in the lung, liver, and nose of groups exposed to 500 ppm or greater.

Subchronic

Whole-body inhalation exposure of Sprague-Dawley rats 6 hours/day, 5 days/week over 28 days to 1-BP vapors at 0, 400, 1000, or 1600 ppm produced significant mortality (8/10) at the highest concentration (ClinTrials, 1997b). Significant effects were observed in rats exposed to 1000 and 1600 ppm including clinical signs of deteriorating condition, abnormal gait and decreased body weights and food consumption. Other effects included changes in erythrocyte and blood chemistry parameters, increases in liver and kidney weights, and decreases in brain weight. Histopathological lesions were observed in the central nervous system (CNS), urinary system, nasal cavities, sternal bone marrow, lymphoid tissues, and male reproductive system. Exposure at 400 ppm produced histopathological lesions in the CNS. Thus, a no-effect level could not be identified in this study.

Sprague-Dawley rats exposed 6 hours/day, 5 days/week for 8 weeks at 0, 50, 300, or 1800 ppm 1-BP showed decreased body weights and increased liver weights at the highest concentration (Kim et al., 1999a). No other significant changes in food consumption, urinalysis, hematology, or serum bio-chemistry were observed. All treated rats showed signs of cytoplasmic vacuolization in centrilobular hepatocytes, but these lesions did not exhibit a dose-dependence. Histopathological examinations did not reveal any treatment-related effects in other tissues.

Wistar rats exposed at 1000 and 1500 ppm 1-BP for 4 to 7 weeks exhibited decreases in body weight and motor nerve conduction velocities, increased distal latency of peripheral nerves (Yu et al., 1998), and neuronal dysfunction in the dentate

gyrus of the brain (Fueta et al., 2000). Wistar rats exposed 8 hours/day, 7 days/week for 12 weeks to 200, 400, or 800 ppm 1-BP exhibited dose-dependent decreases in fore limb and hind limb strength, motor nerve conduction velocities, plasma creatine phosphokinase, morphological changes in peripheral nerves and preterminal axons in the gracile nucleus, and increased distal latency of peripheral nerves (Ichihara et al., 2000b). Ovoid or bubble-like debris of myelin sheaths was prominent in the unraveled muscular branch of the posterior tibial nerve observed in the 800-ppm group but not in the 200- or 400-ppm groups. Dose-dependent decreases in neuron-specific γ-enolase and creatine kinase activities in the cerebrum and brain glutathione and nonprotein sulfhydryl levels were also observed (Wang et al., 2003). Wistar rats exposed to 400 ppm 1-BP 6 hours/day, 5 days/week for 12 weeks had reduced function of the hippocampal γ-aminobutyric acid (GABA) receptor system (Ueno et al., 2007). Male F344 rats exposed 8 hours/day, 7 days/week for 4 weeks to 400, 800, or 1000 ppm 1-BP had dose-dependent decreases in mRNA and protein levels of serotonin, dopamine and GABA receptors in brain tissues (Mohideen et al., 2009).

Male F344 rats were exposed 8 hours/day, 7 days/week for 3 weeks at 10, 50, 200, or 1000 ppm 1-BP and evaluated for changes in behavior (Honma et al., 2003). Exposure to 1-BP did not affect memory function or motor coordination but muscle strength decreased dose-dependently. Dose-dependent increases in spontaneous locomotor activity and open-field behavior indicated that 1-BP has excitatory effects on the CNS of male F344 rats. F344 rats exposed to 50, 200, or 1000 ppm 1-BP 8 hours/day, 7 days/week exhibited decreased brain concentrations of 5-hydroxyindoleacetic acid, GABA, and taurine, increased brain concentrations of aspartate and glutamine, while acetylcholine concentrations were unchanged (Suda et al., 2008).

Sprague-Dawley rats were exposed 6 hours/day, 5 days/week for 13 weeks at 100, 200, 400, or 600 ppm (ClinTrials, 1997a). No clinical signs related to treatment were observed. Histopathology revealed centrilobular vacuolization of the liver in the two highest dose groups. No other treatment-related effects were observed. The no-effect level for the liver effects was 200 ppm.

Groups of male and female F344/N rats (10 per sex) were exposed to 0, 62.5, 125, 250, 500, or 1000 ppm 1-BP for 6 hours and 10 minutes/day, 5 days/week for 14 weeks (NTP, 2011). Mean body weights of the 1000 ppm males were significantly decreased. Mild hepatotoxicity was observed at 500 and 1000 ppm. Liver weights of males exposed to 250 ppm or greater and of females exposed to 125 ppm or greater were significantly increased. Spleen and kidney weights of 1000 ppm females were significantly increased. Significant decreases in sperm count and motility were observed in the 1000 ppm males. Female rats exposed to 250 ppm or greater exhibited altered estrous cycles.

Groups of male and female B6C3F1 mice (10 per sex) were exposed to 0, 62.5, 125, 250, or 500 ppm 1-BP for 6 hours and 10 minutes/day, 5 days/week for 14 weeks (NTP, 2011). Mortality was observed in the 250 and 500 ppm groups. Increased kidney, liver, and lung weights were observed in the 500 ppm females, while the kidney weights of 500 ppm males were decreased. Sperm counts were decreased in the 500 ppm males. Altered estrous cycles were observed in females exposed to 250 or 500 ppm. Nonneoplastic lesions were observed in the nose, larynx, trachea, lung, and liver of 500 ppm males and in the adrenal cortex of 500 ppm females.

Three strains of male mice (C57BL/6J, DBA/2J, and BALB/cA) were exposed to 0, 50, 110, or 250 ppm 1-BP for 8 hours/day for 28 days (Liu et al., 2009). Liver histology showed significant liver necrosis in BALB/cA > C57BL/6J > DBA/2J. BALB/cA mice had higher cytochrome P450 2E1 levels and lower glutathione content and glutathione S-transferase activity than DBA/2J mice. Comparison with rat studies indicated that mice are more sensitive to the hepatotoxic effects of 1-BP than rats.

Evidence for the involvement of oxidative stress in the hepatotoxicity of 1-BP was obtained from studies with nuclear factor erythroid 2-related factor 2 (Nrf2)-null mice (Liu et al., 2010). Nrf2 is a transcription factor that positively regulates the basal and inducible expression of many cytoprotective genes including glutathione-S-transferases, glucuronosyltransferases and NAD(P)H:quinone oxidoreductase. Nrf2-null mice are more susceptible to oxidative stress-mediated hepatotoxicity than wild-type mice (Klaassen and Reisman, 2010). Groups of 24 male Nrf2-null mice and 24 male wild-type C57BL/6J mice were exposed to 0, 100 or 300 ppm 1-BP for 8 hours/day, 7 days/week for 28 days (Liu et al., 2010). Nrf2-null mice had significantly greater areas of liver necrosis, higher liver malondialdehyde and lower liver glutathione than wild-type mice exposed to 1-BP. Exposure to 300 ppm 1-BP increased mRNA coding for several cytoprotective liver enzymes in wild-type mice but not in the Nrf2-null mice. These results suggest that oxidative stress mechanisms are involved in the hepatotoxicity of 1-BP.

The immunotoxicity of 1-BP was evaluated in B6C3F1 mice and F344/N rats following whole-body inhalation exposure (Anderson et al., 2009). Significant decreases in the spleen immunoglobulin (Ig) M response to sheep red blood cells were observed in both mice (125–500 ppm) and rats (1000 ppm) after exposure to 1-BP for 10 weeks. Total spleen cells and T cells were significantly decreased after approximately 4 weeks of 1-BP exposure in mice (125–500 ppm) and rats (1000 ppm). No change in natural killer cell activity was observed.

Chronic/Carcinogenicity

Groups of male and female F344/N rats (50 per sex) were exposed to 0, 125, 250, or 500 ppm 1-BP for 6 hours and 10 minutes/day, 5 days/week for 105 weeks (Morgan et al., 2011; NTP, 2011). Mortality was observed in all groups, including the unexposed controls. Nodules were observed in the nose and skin of exposed rats that were due to inflammation. The incidence of adenoma of the large intestine was significantly increased in the 500 ppm females. The incidences of combined keratoacanthoma, basal cell adenoma, basal cell carcinoma, and squamous cell carcinoma were significantly greater in all exposed groups of males than in controls. Observations of malignant mesothelioma and pancreatic islet adenoma in exposed males were considered equivocal. NTP concluded that there was some evidence of carcinogenicity of 1-BP in male rats and clear evidence of carcinogenicity in female rats (Morgan et al., 2011; NTP, 2011).

Groups of male and female B6C3F1 mice (50 per sex) were exposed to 0, 62.5, 125, or 250 ppm 1-BP for 6 hours and 10 minutes/day, 5 days/week for 105 weeks (Morgan et al., 2011; NTP, 2011). Mortality was observed in all groups, including the unexposed controls. There were increased incidences of cytoplasmic vacuolization and regeneration of the bronchiolar epithelium in all exposed groups. There were significantly increased incidences of cytoplasmic vacuolization of nasal respiratory epithelium in all exposed males and in 125 and 250 ppm females. Incidences of alveolar/bronchiolar adenoma and carcinoma were significantly increased in all exposed females. Neoplastic lesions were not observed in exposed males. NTP concluded that there was no evidence of carcinogenicity of 1-BP in male mice and clear evidence of carcinogenicity in female mice (NTP, 2011).

Genotoxicity

Mutagenicity studies with 1-BP gave mixed results. 1-BP was mutagenic with or without metabolic activation toward *Salmonella typhimurium* tester strains TA1535 and TA100 when tested in a closed system, but it was not mutagenic toward strains TA1537, TA1538, or TA98 (Barber et al., 1981). In NTP studies, 1-BP was not mutagenic with or without metabolic activation toward *Salmonella typhimurium* tester strains TA97, TA98, TA100, or TA1535, or toward *Escherichia coli* WP2 *uvrA*/pKM101 (NTP, 2011). An increase in micronuclei was not observed in Swiss mice given intraperitoneal injections of 600 mg 1-BP/kg (males) or 800 mg 1-BP/kg (females) (Elf AtoChem, 1995c). 1-BP did not induce dominant lethal mutations in Sprague-Dawley rats given 400 mg/kg by oral gavage for 5 days (Saito-Suzuki et al., 1982). 1-BP did not induce dominant lethal mutations in mice given 300 or 600 mg/kg by oral gavage for 10 days (Yu et al., 2008). 1-BP did not increase the frequency of micronucleated normochromatic erythrocytes in male or female B6C3F1 mice exposed to 62.5, 125, 250 or 500 ppm 1-BP for 3 months (NTP, 2011).

Reproductive/Developmental Toxicity

Repeated chronic inhalation exposure of female Sprague-Dawley rats to 1-BP at concentrations of 250 ppm and higher resulted in reproductive toxicity (WIL, 2001). In this two-generation study, 7-week-old rats were exposed 6 hours/day, 7 days/week for 70 days prior to mating at 0, 100, 250, 500, or 750 ppm 1-BP. Females were not exposed on postnatal days 0 to 4 and only they, not their litters, were exposed during postnatal days 5 to 21. F_1 rats began direct exposure at weaning. Dose-related increases in estrous cycle length at $\geq$ 250 ppm, and follicular cysts and interstitial hyperplasia of ovaries at $\geq$ 500 ppm were observed in F_0 and F_1 females. Reduced fertility and litter size were observed in the F_0 and F_1 generations at $\geq$ 250 ppm. The no-effect level in this study was 100 ppm 1-BP.

Female Wistar rat dams were exposed to 0, 100, 400, or 800 ppm 1-BP during pregnancy and lactation for 8 hours/day (Furuhashi et al., 2006). The survival rate and body weight of the offspring of exposed dams decreased in a dose-dependent manner. Offspring of nonexposed dams that were nursed by exposed dams also had significantly lower body weights. A no-effect level was not identified in this study.

A dose-dependent disruption of ovarian function was observed in nonpregnant female Wistar rats exposed to 0, 200, 400, or 800 ppm 1-BP 8 hours/day for 12 weeks (Yamada et al., 2003). All rats in the 800 ppm group had to be killed at 7 weeks. Vaginal smears showed a significant increase in irregular estrous cycles with extended diestrus at 400 and 800 ppm exposures. Histological examination of the ovaries showed a dose-dependent decrease in the number of normal antral follicles but no changes in plasma LH or FSH were observed.

Repeated chronic inhalation exposure of male Sprague-Dawley rats (WIL, 2001) or Wistar rats (Ichihara et al., 2000a) to 1-BP at concentrations of $\geq$ 500 ppm resulted in reproductive toxicity. Dose-related decreases were observed in normal sperm and sperm motility at $\geq$ 500 ppm and in sperm count at 750 ppm in both F_0 and F_1 males (WIL, 2001). Histopathological changes in epididymides, prostate, and seminal vesicles and decreased plasma testosterone levels were observed at 800 ppm 1-BP, while reductions in sperm count and motility were observed at $\geq$ 400 ppm (Ichihara et al., 2000a).

Male Wistar rats were exposed to 0, 400, or 1000 ppm 1-BP 8 hours/day, 7 days/week for 6 weeks (Banu et al., 2007). Groups of exposed rats were allowed to recover for 4 and 14 weeks.

Exposure to 1-BP produced decreased testicular and epididymal weights, decreased sperm counts and motility, and increased abnormal sperm. The changes following exposure to 400 ppm 1-BP returned to normal by 4 weeks of recovery, while the changes following 1000 ppm 1-BP exposure did not show full recovery.

Exposure of male F344/NSlc rats to 1000 ppm 1-BP for 8 hours decreased the expression of several testicular sex hormone-related and cytoprotective genes including cytochrome P450 aromatase and glutathione-S-transferase (Li et al., 2010a). Alterations in the expression of these genes may be involved in the male reproductive toxicity of 1-BP.

Three strains of male mice (C57BL/6J, DBA/2J, and BALB/cA) were exposed to 0, 50, 110, or 250 ppm 1-BP for 8 hours/day for 28 days (Liu et al. 2009). Decreased sperm count and motility and increased abnormal sperm were observed following all exposures in a dose-dependent manner. Comparison with rat studies indicated that mice are more sensitive to the reproductive effects of 1-BP than rats.

Both 1-BP and its metabolite 1-bromo-2-hydroxypropane inhibited the motility of sperm from wild type mice *in vitro* while only 1-bromo-2-hydroxypropane inhibited the motility of sperm from cytochrome P450 2E1 knock-out mice (Garner et al., 2007). These results suggest that cytochrome P450 2E1 oxidation of 1-BP to 1-bromo-2-hydroxypropane may contribute to male reproductive toxicity.

Inhalation exposure of rats to 1-BP produced developmental toxicity (Huntingdon, 2001). Pregnant Sprague-Dawley rats were exposed 6 hours/day from gestational days 6 to 19 at 0, 100, 498, or 996 ppm 1-BP, and fetuses were removed at gestational day 20. Maternal weight gain and food intake decreased at ≥ 498 ppm. Decreased fetal weight was observed at all doses. Embryotoxicity was not observed. A dose-related decrease in ossification in the litters was observed at ≥ 498 ppm, with a significant increase in bent ribs at 996 ppm. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was 100 ppm, but decreased fetal weights were observed at this dose.

Absorption, Distribution, Metabolism, and Excretion

Several studies of the metabolism of 1-BP in rats demonstrated that glutathione conjugation was the major metabolic pathway (Barnsley et al., 1966; Jones and Walsh, 1979), resulting in the urinary excretion of the metabolites n-propylmercapturic acid, 2-hydroxypropylmercapturic acid, and n-propylmercapturic acid sulfoxide. Oxidation of the propyl group also occurred prior to glutathione conjugation (Jones and Walsh, 1979). Studies with isolated rat hepatocytes showed that 1-BP depleted cellular glutathione (Khan and O'Brien, 1991). Liver enzymes oxidized both 1-BP and 2-BP to their respective alcohols at slow rates (Kaneko et al., 1997).

Jones and Walsh (1979) injected Sprague-Dawley rats intraperitoneally with 200 mg/kg 1-BP and observed a rapid excretion of greater than half of the administered dose in expired air. By hour 100, 25% of the 1-BP dose was excreted in the urine.

Male F344 rats and B6C3F1 mice treated with 1-BP by intravenous administration (5, 20, or 100 mg/kg) exhaled most of the dose as volatile organic chemicals (40–72%) and CO_2 (10–30%) (Garner et al., 2006). The formation of 1-BP metabolites derived from oxidation relative to metabolites derived from glutathione conjugation decreased as the 1-BP dose increased. Approximately 13–23% of the dose was excreted in urine, < 2% in feces, and < 6% retained in tissues. Treatment of rats with the irreversible cytochrome P450 inhibitor aminobenzotriazole significantly decreased 1-BP-derived metabolites in urine, exhaled CO_2, and material retained in tissues while exhalation of volatile organic chemicals was significantly increased (Garner et al., 2006). Similarly, cytochrome P450 2E1 knock-out mice metabolized 1-BP through glutathione conjugation 5-fold more than wild type mice (Garner et al., 2007). The mercapturic acid of 1-bromo-2-hydroxypropane was the major urinary metabolite in wild type mice.

Kim et al. (1999b) exposed 7-week-old male and female Sprague-Dawley rats 6 hours/day, 5 days/week for 8 weeks at 50, 300, or 1800 ppm 1-BP. At the highest dose, increases in cytochrome P-450 2E1, glutathione S-transferase, and glutathione peroxidase activity, as well as in protein and lipid peroxides were observed. These results indicate the potential of 1-BP to induce its own metabolism at high exposure concentrations.

Human Studies

Case Reports

Sclar (1999) reported a case study of a 19-year-old male who experienced weakness of the lower extremities and the right hand, numbness, and difficulty swallowing and urinating after 2 months of occupational exposure to a degreasing solvent. The solvent contained primarily 1-BP (95.5%) as well as butylene oxide (< 0.5%), 1,3-dioxolane (< 2.5%), and nitromethane (< 0.25%). The levels and routes of exposure were unclear. Although the patient wore gloves (material unspecified), the skin on his right hand darkened. Nerve conduction tests revealed prolonged distal motor and F response latencies with slower extremity sensory nerve conduction velocities but preserved amplitude response. Magnetic resonance imaging revealed patchy areas of increased T_2 signal in the periventricular white matter and root enhancement in the lumbar region of

the spinal cord. Antibodies to infectious agents were not detected in spinal fluid. The author (Sclar, 1999) concluded that the patient was suffering from a symmetric demyelinating polyneuropathy with CNS involvement. Since similar findings have been reported in 1-BP-exposed rats (Yu et al., 1998; Fueta et al., 2000; Ichihara et al., 2000b), Sclar (1999) concluded that the human neuropathy may have resulted from 1-BP exposure.

Ichihara et al. (2002) reported neurological disorders in three workers exposed to 1-BP from solvent adhesive spraying operations. The three workers developed a staggering gait, numbness with paresthesia/dyesthesia, decreased vibration sense in the legs, and other symptoms including incontinence, diarrhea, headaches and abnormal sweating. The daily time-weighted average exposure concentrations ranged from 60 to 261 ppm 1-BP after the workplace ventilation was improved. The authors concluded that 1-BP induced neurological disorders in the peripheral nerves and central nervous system, and possibly in the autonomic nervous system (Ichihara et al., 2002).

In addition to urinary 1-BP levels (Ichihara et al., 2004b), urinary bromide levels have been suggested as useful biomarkers of 1-BP exposure (Hanley et al., 2006). Urinary N-acetyl-S-(n-propyl)-L-cysteine has been shown to be a major urinary metabolite of 1-BP in exposed workers (Valentine et al., 2007; Hanley et al., 2009, 2010) and an effective biomarker of 1-BP exposure.

Six cases of 1-BP neurotoxicity were reported in foam cushion gluers exposed to 1-BP from spray adhesives (Majersik et al., 2007). Patients complained of lower extremity pain, difficulty walking, nausea, and headache. Serum bromide concentrations were 44–170 mg/dl (reference 0–40 mg/dl) and hyperchloremia was present with serum chloride concentrations of 105–139 mmol/dl (reference 98–107 mmol/dl). Air samples taken during gluing operations indicated 1-BP concentrations ranging from 91 to 176 ppm. Two of the patients had minimal improvement two years after the exposures. Majersik et al. (2007) concluded that 1-BP neurotoxicity involved headache, nausea, and subacute spastic paraparesis with distal sensory loss.

Raymond and Ford (2007) reported four workers hospitalized with high serum bromide concentrations after exposure to glue containing 1-BP. The workers also had elevated urinary arsenic concentrations from unknown sources, confounding interpretation of the clinical findings. The 1-BP exposure concentrations were not reported.

Perrone et al. (2008) reported two cases of neurological illness associated with occupational exposure to the solvent 1-BP in New Jersey and Pennsylvania. In one case, an electronics worker using 1-BP as a cleaning solvent developed confusion, dysarthria, dizziness, paresthesias, and ataxia upon hospitalization. Air sampling of the workplace showed a 1-BP concentration of 178 ppm. The patient's peripheral neuropathy and ataxia persisted beyond a year after the initial hospitalization. The second case involved use of 1-BP as a dry cleaning solvent with the operator complaining of headache, dizziness, nausea, and malaise. The operator manually charged the dry cleaning machine with 50–60 gallons of 1-BP and did not use personal protective equipment.

Samukawa et al. (2012) reported neurotoxicity in a male industrial worker using 1-BP as a cleaning agent without appropriate personal protective equipment. The exposed worker developed muscle weakness, pain, numbness, and gait disturbance. Neurological examination indicated sensory ataxic neuropathy associated with mild impairment of upper motor neurons. Histopathologic examination of sural nerve biopsy showed axonal damage. The worker was kept away from exposure to 1-BP and his symptoms gradually improved.

Epidemiology Studies

Twenty-four female and 13 male workers from a 1-BP factory were assessed for 1-BP exposure levels and health status (Ichihara et al., 2004b). The exposed workers reported eye, nose, and throat irritation with headache and malaise. There were no severe chronic symptoms of neurological damage in workers exposed to < 170 ppm 1-BP. Urinary levels of 1-BP correlated significantly with individual exposure levels, suggesting that urinary 1-BP may be a good indicator of exposure.

Female workers (n = 23) in a Chinese 1-BP production factory were surveyed and compared to age-matched controls from a beer factory (Ichihara et al., 2004a). Tests with a tuning fork showed diminished vibration sensation of the foot in 15 workers exposed to 1-BP but none in the controls. One worker showed complete loss of vibration sense on her right toe. The time-weighted average exposure to 1-BP for this worker was 1.10 ppm. Workers showed significantly longer distal latency in the tibial nerve than controls but no changes in motor nerve conduction velocity. Workers displayed lower sensory nerve conduction velocity and lower scores in memory and mood tests than controls matched for age and education. The time-weighted average exposures to 1-BP measured by passive samplers were 0.34 to 49.19 ppm (median 1.61 ppm; geometric mean 2.92 ppm). From analysis of 1-BP exposure levels, workers could be classified into groups of lower and higher exposure (≤ 2.64 ppm and ≥ 8.84 ppm) and shorter or longer duration of exposure (≤ 9.31 months and ≥ 16.33 months). The workers and controls were also examined for disease states (especially diabetes) and nutritional status. The only significant differences between the exposed workers and the controls were lower levels of vitamin B_1 and lower white blood cell count. Despite these differences, the levels of vitamin B_1 were in the normal range for all subjects. No

differences were observed between exposed workers and controls in the frequency of menstrual abnormalities. Ichihara et al. (2004a) concluded that 1-BP exposure could adversely affect the peripheral sensory and motor nerves and central nervous system in humans.

Li et al. (2010b) investigated 60 female workers and 26 male workers in four 1-BP factories in China, including the factory investigated in a previous study (Ichihara et al., 2004a). Age-, sex-, and region-matched controls were randomly selected from a beer factory, a refrigeration equipment factory, a knitting workshop, and a steel operation factory. The workers and controls were examined by questionnaire and by electrophysiological, neurological, neurobehavioral and blood tests. The ambient concentration of 1-BP in the factories was measured by a Kitagawa-type detection tube while individual worker exposure was assessed using passive samplers and gas chromatographic-mass spectral analysis. The purity of the 1-BP product produced in the factories ranged from > 96% to ≥ 99% 1-BP. The ambient concentrations of 1-BP ranged from 3.3 to 5.5 ppm at reaction pot sites and from 16.5 to 58.3 ppm at raw product collection sites. Individual time-weighted average exposures to 1-BP ranged from 0.07 to 106.4 ppm (median 6.6 ppm) for female workers (n = 60) and from 0.06 to 114.8 ppm (median 4.6 ppm) for male workers. The female workers could be classified into three 1-BP exposure groups: low (0.07–3.35 ppm), middle (3.39–14.13 ppm), and high (15.28–106.4 ppm), while the male workers could be classified into low (0.06–3.5 ppm) and high (5.7–114.8 ppm) 1-BP exposure groups. The duration of 1-BP exposure (39.8 ± 18.8 months for females and 41.5 ± 20.7 months for males) was not significantly different among the 1-BP exposure groups. None of the workers investigated had diabetes mellitus or a history of neurological diseases. Dose-dependent adverse effects of 1-BP were observed in the exposed workers. 1-BP exposure produced prolongation of the distal latency of the tibial nerve, decreased sensory nerve conduction velocity and vibration sense in toes, and decreased scores in the Benton cognitive test. Exposed female workers had increased LDH, TSH and FSH and decreased red blood cell count and hematocrit, while exposed male workers had increased blood urea nitrogen. The results suggest a lowest-observed-adverse-effect level (LOAEL) of 1.28 ppm 1-BP for loss of vibration sense in toes and lowered red blood cell count in exposed female workers (Li et al., 2010b). Although the use of a tuning fork to detect loss of vibration sense can be criticized as subjective methodology, the decreased nerve conduction velocity and distal latency of the tibial nerve in exposed female workers were measured by objective methods. Analysis based on the product of 1-BP exposure level and exposure duration showed cumulative dose-dependent changes in the neurological, endocrinological, hematological and biochemical endpoints given above in female workers.

Toraason et al. (2006) examined the peripheral leukocytes of 63 workers using 1-BP as a solvent for spray adhesives in foam cushion fabrication. Exposure to 1-BP ranged from 0.2 to 271 ppm with the highest exposures from spraying operations. DNA damage in leukocytes was assessed using the comet assay. Multivariate analysis revealed an association between 1-BP exposure and DNA damage but interpretation was complicated by other variables such as gender, age, smoking, and glutathione-S-transferase polymorphisms.

Toxicity of the Contaminant 2-Bromopropane

2-BP (CASRN 75-26-3) is present as a contaminant in commercial grade bromopropane at 0.1% to 0.2% (U.S. OSHA, 1999). 2-BP is also known as isopropylbromide; 2-propylbromide; and *sec*-propylbromide. Use of 2-BP as a solvent in the Asian electronics industry was minimized and controlled to an occupational exposure level of 1 ppm (Yu et al., 1999a) after South Korean workers experienced hematopoietic and reproductive toxicity (Park et al., 1997).

Animal Studies

Acute/Subacute/Chronic

2-BP exhibits low acute toxicity. The oral LD_{50} in rats was greater than 2000 mg/kg (Yu et al., 1999a). The 4-hour LC_{50} for ICR mice was 31,171 ppm (Kim et al., 1996b).

Male Sprague-Dawley rats were given daily intraperitoneal injections of 125, 250, or 500 mg/kg 2-BP in olive oil for 28 days. The rats exhibited dose-dependent decreases in body weight and testicular weight, with histopathological evidence of testicular necrosis (Yu et al., 1997). The no-observed-effect-level (NOEL) was 125 mg/kg body weight.

Male Wistar rats were exposed 8 hours/day, 7 days/week for 9 weeks at 300 or 1000 ppm 2-BP. Exposures at 3000 ppm were terminated after 9 to 11 days due to morbidity. The rats exhibited decreased testicular and epididymal weights, decreased sperm count and motility, and decreased erythrocytes and platelets, indicating testicular and hematopoietic toxicity from 2-BP (Ichihara et al., 1997). Hypoplasia of bone marrow was observed at exposures of 1000 ppm 2-BP (Nakajima et al., 1997). Female Wistar rats exposed at 100, 300, or 1000 ppm 2-BP for 9 weeks developed irregular estrous cycling due to the destruction of primordial follicles and their oocytes (Kamijima et al., 1997; Yu et al., 1999c).

Inhalation exposure of Wistar rats 8 hours/day, 7 days/week for 12 weeks at 100 or 1000 ppm 2-BP produced a decrease in motor nerve conduction velocity and prolonged distal latency at the high

exposure along with decreases in body and brain weight (Yu et al., 1999b).

Genotoxicity

2-BP was mutagenic toward *Salmonella typhimurium* strain TA1535 with or without metabolic activation, but it required metabolic activation to exert mutagenicity toward TA100 (Maeng and Yu, 1997). 2-BP did not induce chromosomal aberrations in Chinese hamster lung cells *in vitro* and did not increase the frequency of micronuclei in the bone marrow of rats treated with intraperitoneal injections of 125, 250, or 500 mg/kg 2-BP daily for 28 days (Maeng and Yu, 1997).

Reproductive/Developmental Toxicity

2-BP induces alterations in the neuro-endocrine axis and reproductive tract. Sprague-Dawley rats were exposed to 0, 125, 250, 500, or 1000 ppm 2-BP for 6 hours/day, 7 days/week during 2 weeks of pre-mating, during mating until copulation, and during gestation days 0 to 19 (Takeuchi et al., 2004). After parturition, dams were allowed to breast feed their pups until postnatal day 4. Maternal toxicity was not observed but exposure to 1000 ppm induced fetal lethality and decreased the litter size.

Treatment of female Sprague-Dawley rats by intraperitoneal injection of 300, 600, or 900 mg/kg 2-BP for 21 days produced delayed estrous cycle and decreased the number of pups born in the high-dose group (Lim et al., 1997). Male Sprague-Dawley rats treated with subcutaneous injections of 200, 600, or 1800 mg/kg 2-BP 5 days/week for 5 to 7 weeks exhibited decreased testis weight, decreased sperm concentration and viability, increased sperm abnormalities, decreased serum testosterone concentrations, atrophied seminiferous tubules, and reduced pregnancy and fertility indices when mated with females (Wu et al., 1999).

Pregnant Sprague-Dawley rats were subcutaneously administered 0, 250, 500, or 1000 mg/kg/day 2-BP on gestational days 6 through 19, then subjected to caesarean section on gestation day 20 (Kim et al., 2004). Maternal toxicity was observed at 1000 mg/kg/day. Skeletal abnormalities and decreased fetal weights were observed at 500 and 1000 mg/kg/day. The no-effect level for embryotoxicity was 250 mg/kg/day. In contrast, significant fetal malformations were not observed after single intraperitoneal injections of 300, 600, 900 or 1800 mg/kg 2-BP to pregnant Jcl:ICR mice on gestation day 10 (Ishikawa and Yamauchi, 2003).

Human Studies

An outbreak of reproductive and hematopoietic toxicities occurred in Korean electronics workers in 1995 exposed to solvents containing 2-BP that were used as alternatives to chlorofluorocarbons for cleaning tactile switches (Park et al., 1997; Kim et al., 1996a; Takeuchi et al., 1997). Seventeen of 25 female workers showed ovarian dysfunction accompanied by amenorrhea and severe anemia, and 6 of 8 male workers had oligospermia or azospermia (Park et al., 1997). The mean ambient 2-BP concentration in the work area was 12.4 ppm, and the 2-BP concentration inside the hood of the cleaning baths was 4141 ppm (Kim et al., 1996a). Some workers had skin contact with 2-BP. Two of the affected female workers regained normal ovarian function within 2 years following exposure (Koh et al., 1998). A study of 25 workers in a Chinese 2-BP manufacturing plant found amenorrhea or polymenorrhea in 4 female workers exposed at >10 ppm (TWA) 2-BP (Ichihara et al., 1999).

TLV® Chronology

2003: *proposed*: TLV–TWA, 10 ppm (50 mg/m^3)
2004: Adopted: TLV–TWA, 10 ppm (50 mg/m^3)
2011: *proposed:* TLV–TWA, 0.1 ppm (0.5 mg/m^3), A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans
2014: Adopted: TLV–TWA, 0.1 ppm (0.5 mg/m^3); A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans

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