Dose-Dependent Neurologic Abnormalities in Workers Exposed to 1-Bromopropane

Weihua Li, MD, Eiji Shibata, MD, PhD, Zhijun Zhou, MD, PhD, Sahoko Ichihara, MD, PhD, Hailan Wang, MD, PhD, Qiangyi Wang, MD, Jiefei Li, MD, Lingyi Zhang, MD, Kenji Wakai, MD, PhD, Yasuhiro Takeuchi, MD, PhD, Xuncheng Ding, MD, and Gaku Ichihara, MD, PhD

Objectives: To investigate the health effects of 1-bromopropane (1-BP) and its dose-dependency in 1-BP production factories in China. **Methods:** Data of 60 female and 26 male workers in three 1-BP factories and the same number of age-, sex-, and region-matched controls were interviewed and examined. The time-weighed average exposure levels of individual workers were estimated. **Results:** Regression analysis on exposure level showed dose-dependent increase in the distal latency of tibial nerve, threshold for vibration sense in toes, lactate dehydrogenase, thyroid stimulating hormone, and follicle stimulating hormone in female workers. The analysis also showed dose-dependent decrease in sensory nerve conduction velocity of the sural nerve, red blood cell, and hematocrit in female workers. **Conclusions:** The results indicate that exposure to 1-BP induces dose-dependent neurotoxicity in female workers.

Learning Objectives

- Review the circumstances of the introduction of 1-bromopropane (1-BP) and its current industrial uses.
- Discuss recent evidence for human toxicity of 1-BP, including one common industrial use that has raised special concerns.
- Summarize the new findings regarding dose-dependent toxicity of 1-BP and the implications for occupational and clinical settings.

Bromopropanes were introduced as alternative solvents to chorofluorocarbons (CFCs) or 1,1,1-trichloroethane, along with the Montreal Protocol on banning substances that deplete the ozone layer. 2-bromopropane (2-BP) was first introduced into the workplace in 1995 but was subsequently found to cause severe oligospermia, amenorrhea, and aplastic anemia in the workers and animals.[1–6] Its isomer 1-bromopropane (1-BP, *n*-propylbromide, CAS No. 106-94-5) was soon introduced as a surrogate of 2-BP into the workplace and identified by the Significant New Alternatives Policy program of US Environmental Protection Agency as one of the acceptable alternative compounds to CFCs as a solvent for cleaning.[7] In the United States, 1-BP has been used as a solvent in spray adhesives, degreasing, and precision cleaning.[8] Nevertheless, our initial inhalation studies in rats revealed that exposure to 1-BP caused paralysis, limb muscle weakness, slowing of nerve conduction velocity and distal latency (DL), degeneration of myelin sheath in peripheral nerves, degeneration of preterminal axons in the medulla oblongata, deterioration of epididymal sperm parameters, and spermiation failure in the testes of rats.[9–12] Moreover, human cases with severe toxicity to 1-BP, including disturbance of walking and sensory deficits, were reported recently in the United States,[13–15] suggesting the toxicity of 1-BP on the central nervous system and peripheral nerves. The most recent case was reported by US National Institute for Occupational Safety and Health,[16] raising serious concerns regarding a larger population at risk of 1-BP than previously believed because these case revealed that 1-BP is being commonly used as a solvent in the dry cleaning industry instead of perchloroethylene. Under such situation, investigation of the dose-response relationship is important to prevent new human cases of 1-BP neurotoxicity.

Our previous investigation in China indicated neurological abnormalities in 1-BP workers, although the study did not allow dose-dependent analysis because of the small sample size.[17] This study investigated the dose-dependent effects of 1-BP in a larger number of workers and age-, sex-, and region-matched controls.

SUBJECTS AND METHODS

Factories and Workers

Four-time investigations were conducted in three 1-BP production factories in Yixing city, Jiangsu Province in 2001 and 2004; in Yancheng city, Jiangsu Province in 2003; and in Weifang city, Shandong Province in 2005. The sex-, age- (within 3 years), and region-matched control workers were randomly recruited from a beer factory in 2001, a refrigeration equipment factory in 2003, a knitting workshop in 2004, and a steel operation factory in 2005. In total, 87 female workers and 29 male workers in 1-BP factories were examined, but 1) only the data of 60 female and 26 exposed workers could be used in this analysis because 2) data of six other females examined in 2001 could not be used because the period of exposure was <1 month; 3) data of three other females examined in 2001 and one male worker in Yancheng in 2003 could not be used because the period exposure or exposure level was unknown; and 4) age-matched controls could not be recruited for one male worker in Yixing in 2003, one female worker in Yixing in 2004, and four females and one male in Weifang in 2005.

From the School of Public Health/MOE Key Lab for Public Health Safety (Dr Weihua Li, Dr Zhou, Dr Qiangyi Wang, Dr Jiefei Li) Fudan University, Shanghai, China; Shanghai Institute of Planned Parenthood Research (Dr Weihua Li, Dr Ding), Shanghai, China; Department of Health and Psychosocial Medicine (Dr Shibata), Aichi Medical University, Aichi, Japan; Mie University Graduate School of Regional Innovation Studies (Dr Sahoko Ichihara), Tsu, Mie, Japan; Department of Occupational and Environmental Health (Dr Hailan Wang, Dr Zhang, Dr Gaku Ichihara), Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Preventive Medicine (Dr Wakai), Nagoya University Graduate School of Medicine, Nagoya, Japan; and Emeritus Professor (Dr Takeuchi), Nagoya University, Nagoya, Japan.

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Address correspondence to: G. Ichihara, MD, PhD, Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: gak@med.nagoya-u.ac.jp.

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TABLE 1. Features of the Investigated Factories and Workers

Location	Date of Investigation	Factory Size (Depth × Width × Height)	Work Shift	Number of Exposed Workers		Number of Exposed Workers	
				Female	Male	Female	Male
Yixing	February 15–17, 2001	2 plants, each 9.7 × 24.4 × 7 m	3 shifts of 8 hr	5	0	5	0
Yancheng	November 3–5, 2003	25 × 15 × 7 m	3 shifts of 8 hr	12	0	12	0
Yixing	November 23–25, 2004	2 plants, each 9.7 × 24.4 × 7 m	2 shifts of 12 hr	39	16	39	16
Weifang	November 22–23, 2005	2 floors, each 25 × 10 × 7 m	3 shifts of 8 hr	4	10	4	10

Table 1 summarizes the sample size and features of the investigated factories. Details of the Yixing factory were described in our previous article[17]. These factories used a similar production processes. Basically, 1-BP was synthesized by incubation of n-propanol and hydrogen bromide. In the Yixing and the Weifang factories, concentrated sulfuric acid was used as a catalyst, whereas no catalyst was used in the Yangcheng factory. The product was purified by distillation and subsequently neutralized with hydrogen carbonate. Based on direct observation, exposure of the workers to 1-BP could potentially occur during 1) adding of the chemicals into the reaction pots; 2) sitting close to the reaction pots to observe and record the temperature; 3) taking out the crude product; 4) adding hydrogen carbonate and stirring; or 5) pouring the product into the 1000-L drums. In the final step, the workers added the product with hand scoops to adjust the product volume in the drum. The factory windows and doors were wide open during working hours, and a few exhaust fans were installed in each factory. None of the workers wore masks or gloves during the operation.

Interview

Signed informed consent was obtained from each worker for all examinations and interviews, according to the Helsinki Declaration and laws for personal information protection in Japan. The ethical committee of Nagoya University Medical School approved the design of this study. Questionnaire was filled out by investigators from the local Centers for Disease Control and Prevention (CDC) who could communicate with the workers in their own dialect. The items in the questionnaire included age, sex, habitual smoking or drinking alcohol, education, previous or present illness, and previous exposure to chemicals and period of exposure to 1-BP.

Electrophysiological Studies

Electrophysiological studies were conducted in an air-conditioned room maintained at 24°C. The workers were acclimated to the room temperature for 30 minutes before the electrophysiological studies. The measured parameters were motor nerve conduction velocity (MNCV), DL, F-wave conduction velocity (FCV) in the tibial nerve, sensory nerve conduction velocity (SNCV) in the sural nerve, and amplitude of the electromyogram induced by motor nerve stimulation, F-wave, and potential of sensory nerve. Electric stimulation and recording of evoked potentials were conducted with Neuropack MEB5508 or MEB9102 (Nihon Kohden, Co, Tokyo, Japan) using the motor and sensory nerve conduction, and F-wave programs. Nerve conduction and F-wave studies were performed according to standard techniques using surface electrodes.[18,19] For measurement of the tibial DL and MNCV, the stimulation site was just behind the medial malleolus (distal) and the center of popliteal fossa (proximal), and the recording site was fixed 11 cm distal to the distal stimulation site on the abductor hallucis muscle. For the F-wave, 20 supramaximal percutaneous stimuli were delivered to the ankle, 8 cm proximal to the active recording electrode, at a frequency <0.2 Hz with the cathode proximal to the anode.

Neurological Indexes: Vibration Sense, Reflex, and Muscle Strength

The vibration sense was evaluated by Chinese neurologists using a vibrating tuning fork (128 Hz). The fork was placed on the metatarsal bone of the big toe or pisiform bone of the carpus, and the worker was asked to report the time of vibration cessation. Immediately after reporting, the tuning fork was moved to the same site (big toe or carpus) of the examiner, and the duration of the lasting vibration after worker's report was recorded.[17] Triceps, biceps, patella, and Achillis reflexes in four limbs were scored into four grades (±, +, ++, +++), and strengths of muscles in four limbs were scored into six grades c1 (0, 1, 2, 3, 4, and 5c1) by the neurologists in the investigations except Weifang. The same neurologist examined the aforementioned neurological indices in the individual subjects throughout the same investigation, except Yixing in 2004 investigation. In the investigation of Yixing in 2004, 9 of 39 pairs were examined for vibration sense, reflex, and muscle strength by different neurologists. The right and left measures of vibration sense, reflex, and muscle strength were averaged for the statistical analysis.

Neurobehavioral Tests

Neurobehavioral testing (Santa Ana, simple reaction time, digit symbol, Benton test, digit span, and pursuit aiming tests) was conducted on the basis of the Chinese edition of the World Health Organization Neurobehavioral Core Test Battery (NCTB)[20,21] and Profile of Mood scale (POMS),[22] by trained Chinese researchers.

Blood Tests

The following blood tests were performed in each worker: erythrocyte (RBC) count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte (WBC) count, and platelet count (Plt), as well as fructosamine (FSA; colorimetric method), blood urea nitrogen (BUN; urease ultraviolet [UV] method), creatinine (enzyme method), total protein (biuret method), total cholesterol (enzyme method), creatine kinase (CK; UV N-acetylcysteine method), aspartate aminotransferase (UV method), alanine aminotransferase (UV method), γ-glutamyl transpeptidase (L-γ-glutamyl-3-carboxy-4-nitroanilide substrate method), lactate dehydrogenase (LDH; Wroblewski-LaDue method), alkaline phosphatase (p-nitrophenol substrate method), thyroid-stimulating hormone (TSH; radioimmunoassay [RIA]), luteinizing hormone (RIA), follicle-stimulating hormone (FSH; RIA), and estradiol for females and testosterone for males (RIA). TSH was not measured in Yancheng workers because of insufficient amount of blood collected. Hematocrit, MCV, MCH, and MCHC were not measured in Yancheng workers because the instrument was not available for determination of these indices.

Assessment of Ambient Concentrations of Bromopropanes by Using Detection Tubes

The ambient concentrations of bromopropanes in factories were measured with a detection tube (Kitagawa type, Komyo Rikagaku Kogyo KK, Kanagawa, Japan). For each sampling spot, the ambient concentration was measured 2 to 30 times within the breathing zone of the workers. The value indicates the total amounts of 1-BP and 2-BP, assuming that other brominated hydrocarbons in the local environment are negligible.

Assessment of Individual Exposure to 1-BP and 2-BP

Individual exposure levels during work shift were evaluated with passive samplers (Sibata Kagaku Co, Saitama, Japan) by using the method described previously by Ichihara et al.[23] A passive sampler was attached to each worker during one 8- or 12-hour shift and was collected immediately after the shift and kept in separate sealed bags at 4°C until analysis. For analysis, the activated charcoal particles were taken from the samplers and then immersed in 2 mL of carbon disulfide (Wako Pure Chemicals, Osaka, Japan) in a glass tube with a screw cap. The tube was vigorously shaken for 5 minutes, left to stand for 1 hour, and the supernatant was then injected into a gas chromatography-mass spectrometry (GC-MS) (GCD system G1800A or Agilent Network GC system 6890N combined with mass spectrometer 5973 Network; Agilent, Santa Clara, CA). The concentrations of 1-BP and 2-BP were quantified by the selected ion mode for all samples except those from Yixing in 2001 where only 1-BP concentration was determined at that time. The time weighted average (TWA) was calculated on the basis of the following formula: TWA = [absorbed solvent (μg)/sampling rate (μg/ppm · min) × sampling time (min)]. In our calculations, the values of 0.134 and 0.117 were used as the sampling rate of 1-BP and 2-BP, respectively. Those values were determined by the diffusing cell method.[23,24] Assessment of individual exposure was conducted twice for two shifts, except that it was conducted only once for each five female workers in Yixing in 2001 and two female workers in Yancheng in 2003 and three times for one female worker in Yancheng in 2003. When the exposure assessment was conducted two to three times, the average of exposure levels measured was used as the representative exposure level.

For the dose-dependent analysis, exposed female workers were classified into low-, medium-, and high-exposure groups of equal numbers, whereas male workers were classified into low- and high-exposure groups of equal numbers on the basis of the tertiles or median TWA levels assessed with passive diffusion samplers.

Statistical Analysis

Data of health effect parameters are expressed as mean ± SD. Analysis of variance (ANOVA) followed by Dunnett's multiple comparison was applied to compare continuous variables between the exposure groups and the control. Education level and scores of reflex and muscle strength were compared between groups by nonparametric Wilcoxon test. Linear regression analysis was performed to confirm the trend with the exposure level or the product of exposure level and period of exposure. The median value of each exposure group was used for regression analysis or analysis of covariance (ANCOVA) on the exposure level. ANCOVA with covariants of 1-BP exposure level (or 1-BP cumulative exposure level) and alcohol exposure and "a factor of pair" was also conducted to confirm the result of regression analysis as mentioned earlier to adjust alcohol exposure and the effect of pair (one-to-one) matching for age, sex, and region in selecting controls. The data of vibration sense were further analyzed by ANCOVA with a covariant of 1-BP exposure level (or 1-BP cumulative exposure level), age, height, and body weight and examining neurologist. P value <0.05 was defined as significant. Statistical analysis was performed using the JMP software version 8.0 (SAS Institute, Cary, NC).

RESULTS

Assessment of 1-BP Concentration in the Factories

The GC-MS results showed >96% purity of 1-BP product manufactured at Yixing factory during 2001 investigation. The impurities were di-n-propyl ether, 2-BP, 1,2-dibromopropane, and 1,2-dibromoethane, and an unknown peak in GC-MS analysis. The purities at Yancheng factory and Weifang factory were ≥99% (gas chromatograph flame ionization detector, data provided by the factories).

The ambient concentrations of 1-BP at different locations inside the factories are listed in the Supplemental Table (http://links.lww.com/JOM/A36). Assessment of 1-BP exposure levels in the factories revealed that the ambient 1-BP concentrations at reaction pots were 3.3 ± 1.3, not detected, 4.4 ± 4.4, and 5.5 ± 5.8 (median ± interquartile range) ppm in Yixing in 2001, Yancheng in 2003, Yixing in 2004, and Weifang in 2005, respectively. On the other hand, 1-BP concentrations at raw product collection were 16.5 ± 9.9 and 58.3 ± 44 ppm in Yixing in 2001 and Yancheng in 2003, respectively. 1-BP concentrations at the raw product collection sites tended to be higher than those at reaction pot sites.

Assessment of Individual Exposure to 1-BP

The individual TWA of 1-BP exposure levels during 8- or 12-hour work shift ranged from 0.07 to 106.4 (median ± interquartile range, 6.6 ± 16.3) ppm for female workers (n = 60) and from 0.06 to 114.8 (median ± interquartile range, 4.6 ± 11.6) ppm for male workers (n = 26). The individual TWAs for 2-BP were 0.01 to 14.9 (median ± interquartile range, 0.4 ± 1.2) ppm for females (n = 55) and 0.004 to 5.4 (median ± interquartile range, 0.15 ± 0.26) ppm for males (n = 26).

Characteristics of Workers Exposed to 1-BP

None of the workers investigated had a history of diabetes mellitus; and thus, none had diabetic polyneuropathy. The FSA level, an indicator of averaged 2-week blood glucose level, was within the reference range (upper limit, 285), except in three control females (FSA levels = 288, 289, 317 μmol/L) and one female of high-exposure group (FSA level = 306μmol/L). None of the workers had history of neurological diseases. At the time of the study, one female and one male of the control group were being treated with thiamazole and thyroxine for hyperthyroidism. Two control female workers, one female worker, and one male worker of the low-exposure group had chronic hepatitis B infection. Two female workers of the control group and one female of the low-exposure group were taking Chinese medicine.

The education level of the control subjects was similar to that of the two exposure groups for female and male workers (Wilcoxon test, data not shown). Other characteristics of the control and exposure workers are listed in Table 2. There were no significant differences in age and height between the exposure groups and the control (ANOVA), except in age in male workers (Table 2).

We reported previously that Yixing factory produced 2-BP in 1996,[24] but the main product was switched from 2-BP to 1-BP before May 1999, although the exact time of this shift was not available.[23] The analyzed data from Yixing factory did not include any workers who had started work before May 1999, except for one female worker who started work in December 1998. This worker reported handling 2-BP, but the influence of this exposure on hematological parameters was considered negligible, although the hematological data could not be obtained from this worker. No other female workers from the exposure group and the control reported any exposure to chemicals other than 1-BP. For the control male workers, one worker handled polyurethane and another worker handled CFC. Three male workers in the exposure group

TABLE 2. Characteristics of Workers Exposed to 1-BP and the Controls

	Control	Exposed Workers (Total)	Low-Exposure Group	Middle-Exposure Group	High-Exposure Group
Females					
Exposure level (ppm)		0.07–106.4	0.07–3.35	3.39–14.13	15.28–106.4
Median (ppm)		6.6	1.28	6.60	22.58
Number of workers	60	60	20	20	20
Age (yr)	38.0 ± 6.9	38.2 ± 7.6	38.4 ± 8.2	37.9 ± 7.8	37.9 ± 7.0
Height (cm)	160.0 ± 3.9	159.7 ± 4.6	160.3 ± 5.4	159.5 ± 4.0	159.1 ± 3.6
Exposure period (mo)	0	39.8 ± 18.8	40.2 ± 17.8	40.2 ± 19.9	38.9 ± 19.5
Habitual drinking	2	1	1	0	0
Habitual smoking	3	0	0	0	0
Males					
Exposure level (ppm)		0.06–114.8	0.06–3.5		5.7–114.8
Median (ppm)		4.6	1.05		12.5
Number of workers	26	26	13		13
Age (yr)	28.9 ± 6.9	28.5 ± 7.1	31.8 ± 8.0		25.2 ± 4.1
Height (cm)	171.5 ± 4.5	173.1 ± 4.7	172.7 ± 5.1		173.6 ± 4.3
Exposure period (mo)	0	41.5 ± 20.7	47.0 ± 17.0		35.9 ± 23.2
Habitual drinking	12	10	4		6
Habitual smoking	16	13	6		0

Data are mean ± SD or number of workers. There were no significant differences in age, height, and exposure period between the control and exposure groups (ANOVA), except in age of male workers ($P < 0.0487$). Significant level: $P < 0.05$.

handled 2-BP and one of them also handled ethanol. Two other males of the exposure group reported having used organic solvent, but its chemical name was not available. Because no accurate information was available regarding the exact time of handling 1-BP by 4 female workers and 11 male workers in Yancheng in 2003 and 1 female worker in Yixing in 2004 (who started working in the factory before January 1999), the exposure period was calculated for these individuals on the assumption that January 1999 was the commencement date, which was deduced from the fact of shift from 2-BP to 1-BP production.

ANOVA did not show any significant difference in the period of exposure between the low-, middle-, and high-exposure groups for female workers and between low- and high- exposure groups for male workers (Table 2).

There were significant differences between the control, low-, middle-, and high-exposure groups for female workers in tibial DL, sural SNCV, vibration sense in toes, Fatigue of POMS, LDH, TSH, FSH, estradiol, WBC, RBC, Hb, and Ht (ANOVA; Table 3). ANOVA did not show significant differences between the same groups in tibial MNCV or FCV, amplitudes of evoked response in tibial MNCV or FCV, sural SNCV, vibration sense in hands, all NCTB tests (simple reaction time, digit span, Santa Ana, digit symbol, and Benton test), tension, depression, anxiety, vigor and confusion of POMS, total protein, FSA, total cholesterol, BUN, creatinine, CK, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, luteinizing hormone, MCV, MCH, MCHC, and Plt. In male workers, there were no significant differences between the exposure groups and the control, except for Santa Ana nonpreferred in NCTB, BUN and testosterone (Table 3). In female workers, regression analysis of exposure level showed significant trend in tibial DL, vibration sense in toes, Benton test, BUN, LDH, TSH, RBC count, Ht, and Plt (Table 4). In male workers, Santa Ana nonpreferred hand and BUN showed significant trend (Table 4).

Considering that the period of exposure to 1-BP is also a potentially important factor in the long-term health effects, we conducted ANOVA and regression analysis on the product of exposure level and duration. ANOVA showed significant difference among the groups in tibial DL, sural SCV, vibration sense in both feet, Vigor, Fatigue and Confusion of POMS, TSH, FSH, estradiol, WBC, RBC, and Ht in female workers and Santa Ana nonpreferred hand and BUN in male workers (Tables 5 and 6). Regression analysis showed significant increase with cumulative exposure level in tibial DL, threshold for vibration sense, BUN, LDH, TSH, FSH, MCV and MCH in female workers and BUN in male workers (Table 7). Regression analysis also showed significant decreases in CK, RBC, Ht, and Plt in female workers and Santa Ana nonpreferred hand in male workers with cumulative exposure level (Table 7).

The level of daily alcohol exposure was assessed on the basis of the assumption that the alcohol percentages are 4%, 12%, 15%, 38%, and 45% in beer, red wine, Chinese yellow wine, light Chinese white liquor and strong Chinese white liquor, respectively. ANCOVA for 1-BP exposure level (or 1-BP cumulative exposure level), alcohol exposure, and a factor of pair matching for age, sex, and region in selecting controls was conducted for health parameters that showed significant trend in regression analysis on 1-BP exposure level (or 1-BP cumulative exposure level) or significant difference among groups in ANOVA (Tables 4 and 7). The analysis confirmed significant effect of 1-BP exposure on tibial DL ($P = 0.0014$), sural SNCV ($P = 0.023$), vibration sense in toes ($P < 0.0001$), Benton test ($P = 0.046$), LDH ($P = 0.015$), TSH ($P = 0.034$), FSH ($P = 0.026$), RBC ($P = 0.0005$), Hb ($P = 0.042$), and Ht ($P = 0.012$), but not BUN ($P = 0.075$), estradiol ($P = 0.40$), WBC ($P = 0.32$), or Plt ($P = 0.15$) in female workers (Table 4). In male workers, the analysis confirmed the significant effect of 1-BP exposure level on BUN ($P = 0.015$), but did not confirm any significant effect of 1-BP exposure on Santa Ana nonpreferred hand ($P = 0.23$) or testosterone ($P = 0.65$) (Table 4). ANCOVA on cumulative exposure to 1-BP, alcohol exposure, and a factor of pair matching confirmed significant effect of cumulative 1-BP exposure on tibial DL ($P = 0.0035$), vibration sense in toes ($P = 0.0002$), LDH ($P = 0.0086$), TSH ($P = 0.0002$), FSH ($P = 0.011$), RBC ($P < 0.0001$), Ht ($P = 0.012$), MCV ($P = 0.0039$), and MCH ($P = 0.010$) but not on sural SNCV ($P = 0.057$), BUN

TABLE 3. Health Parameters in Control and Exposure Groups in Female and Male Workers

	Control		Low-Exposure Group			Middle-Exposure Group			High-Exposure Group			ANOVA
	n	Mean ± SD	*n*	Mean ± SD	*P**	*n*	Mean ± SD	*P**	n	Mean ± SD	*P**	*P*†
Females												
Electrophysiology												
Tibial motor DL (ms)	60	6.7 ± 1.7	20	7.1 ± 1.7	0.64	20	8.4 ± 2.0	0.0010	20	7.6 ± 1.9	0.12	0.0027
Sural NCV (m/s)	57	49.0 ± 6.2	17	45.4 ± 4.2	0.063	20	44.6 ± 4.9	0.0077	20	46.5 ± 4.1	0.22	0.0075
Vibration sense												
Toe (s)	60	2.9 ± 3.9	20	5.6 ± 4.4	0.022	20	6.5 ± 3.7	0.0014	20	6.4 ± 3.4	0.0021	0.0001
POMS												
Fatigue	56	8.4 ± 4.6	19	5.5 ± 4.2	0.047	18	6.3 ± 4.2	0.23	19	5.9 ± 4.9	0.12	0.035
Biochemistry												
LDH (IU/L)	58	182 ± 77	20	276 ± 279	0.47	19	445 ± 526	0.0016	19	333 ± 324	0.12	0.0038
Endocrinology												
TSH (μIU/mL)	45	2.3 ± 1.3	11	2.9 ± 1.9	0.70	16	4.2 ± 2.8	0.0035	18	3.8 ± 2.3	0.017	0.0028
FSH (mIU/mL)	57	7.8 ± 7.6	19	23 ± 28	0.010	19	21 ± 25	0.035	19	18 ± 24	0.15	0.0058
Estradiol (pg/mL)	56	112 ± 98	19	52 ± 39	0.017	18	71 ± 54	0.17	19	83 ± 69	0.43	0.026
Hematology												
WBC ($10^3/\mu$L)	59	6.0 ± 1.7	20	4.8 ± 1.1	0.012	19	195.8 ± 2.1	0.92	20	5.4 ± 1.5	0.40	0.031
RBC ($10^6/\mu$L)	59	4.3 ± 0.4	20	3.8 ± 0.4	<0.0001	19	4.0 ± 0.4	0.015	20	3.8 ± 0.3	<0.0001	<0.0001
Hb (g/L)	57	12.5 ± 1.6	19	11.5 ± 1.3	0.010	18	12.4 ± 1.1	0.97	20	11.8 ± 1.0	0.083	0.011
Ht	42	0.38 ± 0.04	11	0.35 ± 0.04	0.085	14	0.38 ± 0.05	1.00	17	0.35 ± 0.03	0.0069	0.0063
Males												
Neurobehavioral test												
Santa Ana (nonpreferred hand)	26	33.0 ± 4.1	13	34.6 ± 3.3	0.44				13	30.4 ± 4.8	0.12	0.036
Endocrinology												
Testosterone (pg/mL)	17	273 ± 248	10	353 ± 164	0.57				7	75 ± 186	0.092	0.041
Biochemistry												
BUN (mg/dL)	24	13.3 ± 2.5	13	13.6 ± 3.0	0.94				11	16.2 ± 2.3	0.0078	0.012

Dunnett's multiple comparison was applied for comparison with the control following ANOVA. Delay time in vibration sense is the mean of right and left toes. Only the health parameters that showed significance in ANOVA are presented.

DL, distal latency; NCV, nerve conduction velocity; POMS, profile of mood status.

**P* value for comparison with the control.

†*P* value for ANOVA.

($P = 0.15$), CK ($P = 0.13$), estradiol ($P = 0.34$), WBC ($P = 0.15$), Hb ($P = 0.055$), or Plt ($P = 0.14$) (Table 7). The analysis could not confirm significant effect on Santa Ana nonpreferred hand in male workers ($P = 0.17$) (Table 7).

Because estimation of vibration loss is influenced by the examining neurologist and also its estimation is affected by age, height, and body weight,[25] ANCOVA on 1-BP exposure level (or 1-BP cumulative exposure level), neurologist, age, height, body weight and alcohol consumption was conducted in female workers. Because data of body weight were not available for five pairs in Yixing in 2001, missed data of body weight in five controls and five exposed workers in Yixing in 2001 were substituted by the average of body weights in the remaining data of exposure group and control group in female workers. The result showed that the effect of 1-BP exposure was significant ($P = 0.0002$) with estimated coefficient ± standard error of 0.14 ± 0.04 s/ppm, and the effect of neurologist was also significant ($P < 0.0001$), but the effect of age, height, or weight was not significant ($P = 0.079$, 0.16, 0.28, respectively). Similarly, the effect of 1-BP cumulative exposure level was significant ($P = 0.0001$) with estimated coefficient ± standard error of 0.0031 ± 0.0008 s/(ppm.month), and the effect of neurologist was significant ($P < 0.0001$) but the effect of age, height, or weight was not ($P = 0.11$, 0.17, and 0.27, respectively). These results of significant effects of 1-BP exposure and 1-BP cumulative exposure on the vibration sense was confirmed by a model that removed the data of five pairs, the body weight data of which were missed in Yixing in 2001.

The aforementioned results of significant effect of 1-BP exposure level or 1-BP cumulative exposure level for the average of both toes were also confirmed by separate analyses of the right and left toes.

DISCUSSION

This study provided strong evidence for dose-dependent toxicity of 1-BP, manifested by prolongation of the DL of the tibial nerve, decrease in SNCV of sural nerve and vibration sense in toes, reduced score of Benton cognitive test, increase in LDH, TSH, and FSH and decrease in RBC count and Ht in female workers and increase in BUN in male workers. Furthermore, analysis based on the product of exposure levels by exposure period showed cumulative dose-dependent changes in tibial DL, vibration sense in toes, LDH, TSH, FSH, RBC count, Ht, MCV, and MCHC in female workers. To the best of our knowledge, this study is the first to document the dose-dependency of 1-BP toxicity in humans. The results also suggest that the lowest adverse effect

TABLE 4. Regression Analysis of Health Parameters on Exposure Level in the Exposed Female and Male Workers and Controls

	Single Regression Model			
	n	Regression Coefficient	*P*	95% CI
Females				
Electrophysiological tests				
Tibial motor DL (ms/ppm)	120	0.042	0.040*	0.002 to 0.083
Sural NCV [m/(s · ppm)]	114	−0.091	0.15*	−0.22 to 0.03
Neurobehavioral test				
Benton	120	−0.043	0.032*	−0.082 to −0.004
Vibration sense				
Toes (s/ppm)	120	0.14	0.0023*	0.05 to 0.23
Biochemistry				
BUN [IU/(L · ppm)]	116	0.082	0.048	0.0009 to 0.16
LDH [IU/(L · ppm)]	116	6.7	0.044*	0.2 to 13.2
Endocrinology				
TSH [μIU/(mL · ppm)]	90	0.024	0.0075*	0.02 to 0.11
FSH [mIU/(mL · ppm)]	114	0.34	0.14*	−0.11 to 0.78
Estradiol [pg/(mL · ppm)]	112	−0.82	0.39	−1.1 to 2.7
Hematology				
WBC [10^3/(μL · ppm)]	118	−0.015	0.43	−0.052 to 0.022
RBC [10^6/(μL · ppm)]	118	−0.017	0.0004*	−0.026 to −0.008
Hb [g/(L · ppm)]	114	−0.25	0.12*	−0.57 to 0.07
Ht (ppm^{-1})	84	−0.0014	0.0088*	−0.0024 to 0.0004
Plt [10^3/(μL · ppm · mo)]	118	−3.7	0.023	−16.9 to −0.5
Male				
Neurobehavioral test				
Santa Ana (nonpreferred hand) (ppm^{-1})	52	−0.25	0.026	−0.47 to −0.03
Biochemistry				
BUN [mg/(dL · ppm)]	48	0.23	0.0028*	0.08 to 0.38
Endocrinology				
Testosterone [pg/(mL · ppm)]	40	−14	0.053	−29 to 0.2

*ANCOVA adjusting alcohol exposure and the effect of pair (one-to-one) matching for age, sex, and region in selecting controls showed significant effect ($P < 0.05$). Delay time in vibration sense is the mean of right and left toes. All health parameters with significant trend with exposure level are presented. Parameters that did not show significant trend with exposure level are presented if ANOVA (Table 3) showed significant difference between groups.

DL, distal latency; NCV, nerve conduction velocity; POMS, profile of mood status; CI, confidence interval.

level is 1.28 ppm for vibration sense in toes and RBC count in female workers.

This study showed that tibial MNCV is less affected than tibial DL following 1-BP exposure. This is in agreement with the New Jersey case reported by Dr Sclar, which showed marked prolongation (range, 8.0 to 9.6 ms) of DL in the lower extremity, whereas motor conduction velocity mildly decreased only for the peroneal segment under the knee (left 39.3 m/s; right 38.3 m/s).[15] The present results are also in agreement with our previous animal study, which showed earlier change in DL than MNCV in tail nerve[9,11]. The discrepancy of changes between DL and MNCV can be caused by distal-dominant degeneration of peripheral motor nerve, or derangement of chemical transduction in neuromuscular junction by 1-BP exposure. Nevertheless, the latter is unlikely, given that the workers lacked symptomatology of neuromuscular junction disorder. This study also showed that SNCV is more sensitive than MNCV to 1-BP exposure, consistent with the New Jersey case, which showed marked decrease of SNCVs in the lower extremities.[15]

In contrast to the changes in tibial DL and sural SNCV, the amplitudes of corresponding evoked response did not show any significant change. This finding is in agreement with the New Jersey case, which showed normal amplitudes of the corresponding motor-evoked response and all sensory-evoked responses in lower extremities except for mild attenuation of the left sural response (3.1 μV).[15] This suggests that the primary target of 1-BP could be the myelin sheath rather than axons, as shown by the degeneration of the myelin in rat in our experiments.[9,11]

Scores of the reflex test did not show any significant effect for 1-BP (Wilcoxon test), although the Achilles reflex showed marginal increase in the high-exposure group ($P = 0.0516$). In contrast to human cases reported in the United States, this study did not show clear enhancement of reflexes in lower extremities. This difference might be due to differences in the exposure levels between the US cases and the Chinese workers. The 1-BP exposure levels in the investigated Chinese factories were obviously lower than those found in US cases (60 to 261 ppm [average, 133 ppm][13] and 91 to 176 ppm [average, 130 ppm]).[14]

TABLE 5. Classification of Female and Male Workers by Cumulative Exposure Level

	Control	Exposed Workers (Total)	Low-Cumulative Exposure Group	Middle-Cumulative Exposure Group	High-Cumulative Exposure Group
Female					
Cumulative exposure (ppm · mo)		2.0–3617.5	2.0–120.7	125–426	446–3618
Median of group (ppm · mo)		255.6	23.2	256	1056
Number of workers	60	60	20	20	20
Age (yr)	38.0 ± 6.9	38.2 ± 7.6	35.8 ± 8.2	40.0 ± 7.8	38.7 ± 6.3
Height (cm)	160.0 ± 3.9	159.7 ± 4.6	160.5 ± 6.1	159.0 ± 4.0	159.6 ± 3.2
Habitual drinking	2	1	1	0	0
Habitual smoking	3	0	0	0	0
Male					
Cumulative exposure (ppm · mo)		0.8–3787.9	0.8–140.4		151–3788
Median of group (ppm · mo)		145.7	54.3		414.4
Number of workers	26	26	13		13
Age (yr)	28.9 ± 6.9	28.5 ± 7.1	31.2 ± 8.4		25.7 ± 4.2
Height (cm)	171.5 ± 4.5	173.1 ± 4.7	172.4 ± 4.1		173.8 ± 5.3
Habitual drinking	12	10	6		4
Habitual smoking	16	13	8		5

Data are mean ± SD or number of workers. There were no significant differences in age and height between the control and exposure groups (ANOVA). Data of height were not available for each one pair of low- and high-cumulative exposure groups in male workers.

TABLE 6. Health Parameters in Control and Exposure Groups Classified by Cumulative Exposure Level

	Control		Low-Cumulative Exposure Group			Middle-Cumulative Exposure Group			High-Cumulative Exposure Group			ANOVA
	n	Mean ± SD	*n*	Mean ± SD	*P**	*n*	Mean ± SD	*P**	*n*	Mean ± SD	*P**	*P*†
Females												
Electrophysiology												
Tibial motor DL (ms)	60	6.7 ± 1.7	20	7.7 ± 1.6	0.068	20	7.6 ± 2.4	0.16	20	7.8 ± 1.7	0.045	0.022
Sural NCV (m/s)	57	49.0 ± 6.2	18	43.8 ± 4.5	0.0017	19	46.1 ± 4.7	0.14	20	46.5 ± 3.7	0.22	0.0036
Vibration sense												
Toe (s)	60	2.9 ± 3.9	20	5.6 ± 4.3	0.025	20	6.4 ± 3.8	0.0019	20	6.5 ± 3.4	0.0013	0.0001
POMS												
Vigor	58	18.2 ± 6.2	20	22.0 ± 4.2	0.048	19	19.5 ± 6.3	0.77	20	21.7 ± 6.2	0.070	0.035
Fatigue	56	8.4 ± 4.6	20	5.5 ± 4.3	0.044	18	6.1 ± 3.8	0.17	18	6.1 ± 5.2	0.17	0.036
Confusion	56	7.8 ± 3.9	19	5.0 ± 4.0	0.031	19	5.8 ± 3.7	0.20	18	7.1 ± 4.5	0.90	0.046
Endocrinology												
TSH (μIU/mL)	45	2.3 ± 1.3	11	3.4 ± 1.6	0.22	16	3.0 ± 2.0	0.51	18	4.6 ± 2.9	0.0001	0.0005
FSH (mIU/mL)	57	7.8 ± 7.6	19	17 ± 24	0.21	19	24 ± 28	0.0062	19	21 ± 25	0.033	0.0045
Estradiol (pg/mL)	56	112 ± 98	19	50 ± 30	0.012	18	72 ± 56	0.19	19	85 ± 72	0.47	0.022
Hematology												
WBC ($10^3/\mu L$)	59	6.0 ± 1.7	20	4.8 ± 1.3	0.015	19	5.8 ± 2.1	0.95	20	5.3 ± 1.4	0.30	0.031
RBC ($10^6/\mu L$)	59	4.3 ± 0.4	20	3.9 ± 0.4	0.0035	19	3.9 ± 0.4	0.0008	20	3.7 ± 0.3	<0.0001	<0.0001
Ht	42	0.38 ± 0.04	11	0.35 ± 0.04	0.085	14	0.38 ± 0.05	1.00	17	0.35 ± 0.03	0.0069	0.0063
Males												
Neurobehavioral test												
Santa Ana (nonpreferred)	26	33.0 ± 4.1	13	34.5 ± 3.4	0.48				13	30.5 ± 4.8	0.13	0.046
Biochemistry												
BUN (mg/dL)	24	13.3 ± 2.5	13	13.6 ± 3.1	0.93				11	16.2 ± 2.0	0.0081	0.013

Dunnett's multiple comparison was applied for comparison with the control following ANOVA. Delay time in vibration sense is the mean of right and left toes. Only health parameters that showed significance in ANOVA are presented.

DL, distal latency; NCV, nerve conduction velocity; POMS, profile of mood status.

*P value for comparison with the control.

†P value for ANOVA.

TABLE 7. Regression Analysis of Health Parameters on Cumulative Exposure Level in Exposed Female and Male Workers and Controls

	Single Regression Model			
	n	Regression Coefficient	*P*	95% CI
Females				
Electrophysiological tests				
Tibial motor DL [ms/(ppm · mo)]	120	0.0009	0.048*	0.0001 to 0.017
Sural NCV [m/(s · ppm · mo)]	114	−0.0013	0.35	−0.0039 to 0.0013
Vibration sense				
Toes [s/(ppm · mo)]	120	0.0029	0.0026*	0.0010 to 0.0048
Biochemistry				
BUN [IU/(L · ppm · mo)]	116	0.0018	0.041	0.00001 to 0.00036
LDH [IU/(L · ppm · mo)]	116	0.16	0.021*	0.030 to 0.296
CK [IU/(L · ppm · mo)]	116	−0.024	0.013	0.042 to 0.0050
Endocrinology				
TSH [μIU/(mL · ppm · mo)]	90	0.0020	0.0001*	0.0010 to 0.0030
FSH [mIU/(mL · ppm · mo)]	114	0.011	0.025*	0.0008 to 0.0206
Estradiol [pg/(mL · ppm · mo)]	112	−0.013	0.52	−0.027 to 0.053
Hematology				
WBC [10^3/(μL · ppm · mo)]	118	−0.0004	0.36	−0.0012 to 0.0004
RBC [10^6/(μL · ppm · mo)]	118	−0.0004	<0.0001*	−0.0006 to −0.0002
Hb [g/(L · ppm · mo)]	114	−0.0036	0.30	−0.0103 to 0.0031
Ht [10^{-5}/(ppm · mo)]	84	−2.7	0.018*	−0.000048 to −0.5
MCV [fL/(ppm.mo)]	94	0.0037	0.031*	0.0003 to 0.0071
MCH [pg/(ppm.mo)]	94	0.0019	0.0046*	0.0005 to 0.0033
Plt [10^3/(μL · ppm · mo)]	118	−0.089	0.011	0.021 to 0.157
Males				
Neurobehavior test				
Santa Ana [nonpreferred hand (ppm · mo)$^{-1}$]	52	−0.0072	0.0033	0.00047 to 0.014

DL, distal latency; NCV, nerve conduction velocity; POMS, profile of mood status; CI, confidence interval.

*ANCOVA adjusting alcohol exposure and the effect of pair (one-to-one) matching for age, sex, and region in selecting controls showed significant effect ($P < 0.05$). Delay time in vibration sense is the mean of right and left toes. All health parameters that showed significant trend with cumulative exposure level are presented. Parameters that did not show significant trend with cumulative exposure level are also presented when ANOVA (Table 6) showed significant difference between groups.

A decrease in vibration sensation in the lower extremities was also described in a case intoxicated with 1-BP in New Jersey,[15] 3 of 3 cases in North Carolina,[13] and 4 of 4 cases (none reported in two other patients) in Utah.[14] Considered together with the finding of this study, the results suggest that vibration sense is one of the most sensitive indicators of 1-BP neurotoxicity.

This study indicates that 1-BP induces dose-dependent falls in RBC count and Ht. Animal studies showed possible hematotoxicity for 1-BP at relatively high exposure levels. In a 4-week study, female rats exposed to 1590 ppm of 1-BP showed erythropenia, anemia, and a fall in Ht.[14] In our previous study, 9 of 24 females and 4 of 13 males in Yixing factory in 1999 showed lower Hb or Ht than the lower limit of reference values, although possible effects of previous exposure to 2-BP could not be ruled out. The hematological data of this study did not include those of the Yixing workers who started work before the switch from 2-BP to 1-BP. Nevertheless, it should be noted also that the workers in this study were also coexposed to a trace of 2-BP as shown by the data of passive diffusion samplers. In this regard, the US National Institute for Occupational Safety and Health investigation revealed that a trace of 2-BP could be present even in the commercially available 1-BP product.[26,27] The hematological effect of possible contamination of 2-BP should be explored in future studies.

The dose-dependent increases in BUN and LDH suggest possible adverse effects on the liver,[28] kidney,[29] heart, or muscle or hemolysis in mice. The 3-month 1-BP inhalation study in the recent National Toxicological Program also showed dose-dependent increase in BUN in male and female rats on days 3 and 23, respectively, but not week 14,[30] and the lowest exposure level that significantly increased BUN was lower in male rats than in female rats. Further study is needed to clarify the mechanism of the 1-BP-induced increase in BUN and LDH.

The mechanism of the dose-dependent increase in serum TSH and FSH levels remains elusive. Nevertheless, one of our 12-week inhalation studies showed a decrease in T4 level (unpublished results), which could, at least theoretically, result in a secondary increase of TSH.

Compared with female workers, male workers showed significant exposure-associated changes in fewer indices. The difference in results between females and males might be explained by 1) the lower statistical power for male data; 2) difficulty in assessment of exposure for male workers because male workers tended to play multiple roles such as carrying heavy load, whereas female workers tended to remain at the same site in the factory; or 3) possible sex difference in susceptibility. With regard to item 3, our previous studies showed the female Wistar rats became seriously ill after

7-week exposure at 800 ppm, 8 hr/d, and 7 d/wk,[29] whereas male Wistar rats did not after 12-week exposure under the same condition.[9–10] The National Toxicology Program also reported a higher susceptibility of female mice and rats to 1-BP-induced carcinogenicity.[30]

This study has several limitations. First, acclimating workers to room temperature is not sufficient for controlling the skin temperature in the legs. Such uncontrolled leg skin temperature might cause potential errors in the collected data. Second, clinical vibration assessment using tuning fork is inherently inaccurate, particularly in tall, obese, and elderly people. Although multiple regression analysis that included age, height, and weight still showed significant effect of 1-BP exposure level on vibration sense, quantitative assessment of vibration sensation would improve the accuracy of this measurement.[25] Third, the cumulative exposure levels were limited by 1 to 3 day measurements of individual exposure levels, presumed to be at the same level when averaged more than the number of exposed months.

CONCLUSION

In conclusion, this study documented important adverse effects for 1-BP in workers handling 1-BP production and that the neuro-, endocrine-, and hemotoxicities were dose dependent and worse in female workers. The lowest 1-BP exposure level to induce these adverse effects was estimated to be 1.28 ppm.

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