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Urinary Bromide and Breathing Zone Concentrations of 1-Bromopropane from Workers Exposed to Flexible Foam Spray Adhesives

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1-Bromopropane (1-BP) has been marketed as an alternative for ozone depleting solvents and suspect carcinogens and is in aerosol products, adhesives and solvents used for metal, precision and electronics cleaning. Toxicity of 1-BP is poorly understood, but it may be a neurologic, reproductive and hematologic toxin. Sparse exposure information prompted this exposure assessment study using air sampling, and measurement of urinary metabolites. Mercapturic acid conjugates are excreted in urine from 1-BP metabolism involving removal of bromide (Br) from the propyl group. One research objective was to evaluate the utility of urinary Br analysis for assessing 1-BP exposure using a relatively inexpensive, commercially available method. Complete 48 h urine specimens were obtained from 30 workers on two consecutive days at two facilities using 1-BP adhesives to construct polyurethane foam seat cushions and from seven unexposed control subjects. All of the workers' urine was collected into composite samples representing three daily time intervals (at work; after work but before bedtime; and upon wake-up) and analyzed for Br ion by inductively coupled plasma-mass spectrometry. Full-shift breathing zone samples were collected for 1-BP on Anasorb carbon molecular sieve sorbent tubes and analyzed by gas chromatography-flame ionization detection via NIOSH method 1025. Geometric mean (GM) breathing zone concentrations of 1-BP were 92 parts per million (p.p.m.) for adhesive sprayers and 11 p.p.m. for other jobs. For sprayers, urinary Br concentrations ranged from 77 to 542 milligrams per gram of creatinine [mg (g-cr)$^{-1}$] at work; from 58 to 308 mg (g-cr)$^{-1}$ after work; and from 46 to 672 mg (g-cr)$^{-1}$ in wake-up samples. Pre-week urinary Br concentrations for sprayers were substantially higher than for the non-sprayers and controls, with GMs of 102, 31 and 3.8 mg (g-cr)$^{-1}$, respectively. An association of 48 h urinary Br concentration with 1-BP exposure was statistically significant (r^2 = 0.89) for all jobs combined. This study demonstrates that urinary elimination is an important excretion pathway for 1-BP metabolism, and Br may be a useful biomarker of exposure.

Keywords: bromine; 1-bromopropane; CAS No. 106-94-5; furniture cushions; polyurethane foam adhesive; *n*-propyl bromide; urine

INTRODUCTION

In 1998, an industry consortium petitioned the Environmental Protection Agency (EPA) to list 1-bromopropane (1-BP), also named *n*-propyl bromide, as an alternative for ozone-depleting solvents for general metals, precision and electronics cleaning, aerosol products, and adhesives (EPA, 1999, 2000). Prior to 1998, 1-BP was primarily used to manufacture pharmaceuticals, pesticides and other chemicals in well-controlled closed processes. Now, products containing 1-BP have been marketed for emissive applications as a replacement for 1,1,1-trichloroethane, freons®, and suspect carcinogens trichloroethylene and methylene chloride. The principal applications for 1-BP are for vapor degreasing and liquid cleaning agents as well as spray adhesive solvents. However, the need to find alternative solvents in both industrial and commercial products could expand market applications for 1-BP, and could potentially expose thousands of workers and the general public to this chemical.

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The toxicity of 1-BP in humans is poorly understood because there is limited research available in the published literature. There is concern that 1-BP may produce neurotoxic, reproductive and hematopoetic health effects because its chemical structure is similar to that of other brominated-propane compounds with reported health effects, based upon animal studies with 1- and 2-BP (Takeuchi *et al*., 1997, 2001; Ichihara *et al*., 2000a,b; Yu *et al*., 2001). Yu *et al*. (2001) demonstrated peripheral and possibly central neurotoxicity in rats but did not show reproductive or hematologic effects. Several additional rat toxicity reports concluded that 1-BP produced dose-dependent estrous cycle irregularities (Takeuchi *et al*., 2001; Yamada *et al*., 2003), disruption of spermatogenesis [e.g. impaired ovarian follicle maturation at 400 parts per million (p.p.m.)] (Ichihara *et al*., 2000a; Takeuchi *et al*., 2001), reproductive and developmental toxicity (NTP, 2002, 2004), and peripheral and central neurotoxicity (Ichihara *et al*., 2000b; Yu *et al*., 2001). Moreover, two case studies in US workers described peripheral nerve impairment in three foam-cushion workers using spray adhesives containing over 50% 1-BP (Ichihara *et al*. 2002) and in one worker using a degreasing solvent with ~95% 1-BP (Sclar, 1999).

At present, occupational exposure limits (OELs) for 1-BP are not available from either the National Institute for Occupational Safety and Health (NIOSH, 1992) or the Occupational Safety and Health Administration (OSHA, 2005), and suggested manufacturers' guidelines range from 10 to 100 p.p.m. (Enviro-Tech International, Inc., 2005; Great Lakes Chemicals, 2005). After reviewing industry studies and published literature, Rozman and Doull (2002) concluded that neurotoxicity is the most sensitive adverse health effect, and an OEL for 1-BP, in the range of 60–90 p.p.m. as an 8 h time-weighted average (TWA), should provide an adequate margin of safety. Using a benchmark dose method, Stelljes and Wood (2004) proposed an OEL for 1-BP of 156 p.p.m. In a proposed rulemaking to accept 1-BP as a replacement for ozone depleting solvents, the EPA (2003) recommended an industrial exposure guideline for 1-BP of 25 p.p.m. over an 8 h work shift. Albemarle Corp. (2003), one of the domestic suppliers of 1-BP solvents, concurs with this recommendation. In 2005, the American Conference of Governmental Industrial Hygienists (ACGIH) published a Threshold Limit Value® for 1-BP as a 10 p.p.m., 8 h TWA based on suspected neurological toxicity (ACGIH, 2005).

Based on the uncertainty regarding the toxicity of 1-BP, OSHA and NIOSH requested the National Toxicology Program (NTP) to evaluate the toxicity of this chemical (NTP, 2004). This study was conducted to provide additional information regarding industrial exposures to 1-BP and to evaluate the utility of urinary concentrations of bromide (Br) ion (Br) as a biomarker of exposure to 1-BP.

BACKGROUND

Methods for biological monitoring of occupational exposure to 1- and 2-BP have not been widely reported in the literature. Some absorbed 1-BP is metabolized through conjugation with glutathione, which releases free Br ion (Jones and Walsh, 1979; Stelljes and Wood, 2004). Bromides are not metabolized further and are eliminated mainly in urine (Ryan and Baumann, 1999). Kawai *et al*. (1997) proposed that 1-BP would behave analogously to other low molecular weight brominated-hydrocarbons and suggested that measurement of urinary Br ion would be a useful biomarker of exposure. Kawai *et al*. (2001) also evaluated whether Br ion or 1-BP in urine could be effective biomarkers of 1-BP exposure for 33 men at a cleaning and painting work shop. Urine specimens were collected and head space air was immediately analyzed for 1-BP via gas chromatography-flame ionization detection (GC-FID), whereas Br ion in urine was analyzed by GC with an electron capture detector after it was converted to methyl bromide. Correlations were observed for 1-BP in urine and breathing zone air ($r > 0.9$). Br ion concentration in urine was also statistically correlated with 1-BP in breathing zone air but the association was weaker ($r = 0.7$). Ichihara *et al*. (2004) studied 37 workers synthesizing 1-BP at a chemical manufacturing plant and found significant correlations between 1-BP in urine with measured 1-BP in air; enzyme activity and serum creatine kinase levels were not associated with exposure levels.

Although urinary 1-BP has been proven in these studies to be a useful biomarker of 1-BP exposure, it requires immediate analysis upon collection of the specimen. This greatly diminishes the utility of urinary 1-BP for evaluations of exposure in industrial settings.

METHODS

This study reports worker exposures at two foam fabricating plants manufacturing polyurethane seat cushions. A total of 30 workers were evaluated—13 adhesive sprayers and 17 non-sprayers. Adhesive 'sprayers' constructed polyurethane foam furniture cushions using spray adhesives. The 'non-sprayers' included glue line leads, sewing machine operators, wrappers, pillow stuffers, and foam and cloth cutters. 1-Bromoproane exposure among non-sprayers occurred as a result of over-spray and solvent drift from spraying operations.

Personal breathing zone exposure samples were collected over two consecutive workdays with

Anasorb carbon molecular sieve sorbent tubes. The sorbent was desorbed with 1 ml of carbon disulfide, and analyzed for 1-BP by GC-FID via NIOSH method 1025 (NIOSH, 2003). The limit of detection for this method is 1 μg which equates to a minimum detectable concentration of 0.016 p.p.m. using the maximum recommended air sampling volume of 12 l. Effective quantitative methods are not available to measure skin exposures for compounds, such as 1-BP, that are volatile and readily penetrate the skin. For this reason, qualitative evaluation of skin contact was conducted by visual observation of job tasks.

To obtain data on 1-BP metabolites excreted by humans, all of the workers' urine voids over a 48 h period were collected. The specimens were collected as composite samples over sequential time intervals: (i) at work, (ii) after work but before bedtime and (iii) upon awakening. Each sampling survey occurred over a 48 h period and started at the beginning of the work week (Monday, pre-shift, following nearly 3 days of no exposure) and ended before the work shift began on Wednesday. The urine collection protocol was applied consistently for the high-exposed group (sprayers) and low-exposed group (non-sprayers) to allow for statistical analysis. For additional reference, single 'spot' control samples were collected from seven unexposed office workers who were not employed by this company. Air sampling was not conducted for the control subjects since there was no source of exposure to 1-BP.

Participants were instructed to collect urine specimens in nitric acid rinsed Nalgene® bottles [high density polyethylene (HDPE)] and immediately chilled in with gel ice. At the end of the collection period, a 25 ml aliquot was dispensed into nitric acid rinsed HDPE bottles and immediately frozen on dry ice. The total urine volume for this collection period was also measured with a graduated cylinder. The specimens were analyzed for Br and creatinine. Br ion was measured using inductively coupled plasma/mass spectrometry (Varion Ultra-mass 700) operated at radiofrequency power of 1300 W yielding a limit of detection of 100 μg l^{-1} (Allain *et al*., 1990). Ion optics included a stack of six metal lenses with applied DC voltage to alter ion paths. Recoveries for Br using this method were reported to be near 100%, the coefficient of variation was 3%, and between-day reproducibility ≈5%. One ml of each sample was diluted to 10 ml using 1% nitric acid and mixed prior to analysis. Analytical standards and quality control samples were prepared using Uri-sub, a synthetic urine solution and yttrium was used as an internal standard. This was necessary since background concentrations of Br may be present in pooled urine from the general population. Calibration graphs were linear over a range of 0–40 mg l^{-1}; additional 2- or 5-fold dilutions were prepared for samples exceeding the standard calibration range. Five replicates, with 20 scans per replicate, were analyzed for each sample.

The data were analyzed for all jobs grouped together and by sprayers and non-sprayers separately. However, after examining residuals from models regressing urinary Br on 1-BP TWA, day, and the TWA by day interaction, it was decided to only do statistical testing for sprayers and non-sprayers separately. The non-sprayers' urinary Br residuals were approximately log-normally distributed, and the sprayers' urinary Br residuals were approximately normally distributed. For consistency, however, geometric means (GMs) are presented for both groups. Because of the distribution types, however, hypothesis testing was based on logged values for the non-sprayers and on untransformed values for the sprayers. Simple relationships between urinary Br and 1-BP TWA are presented in terms of the proportion of variability of urinary Br explained by 1-BP TWA (denoted as r^2). For most models, the distributional assumptions were more closely met when logarithms of the 1-BP TWA were used as the independent variable. Thus, these were used for all models for which urine Br was regressed on 1-BP TWA, and hypotheses were tested. These models, regressing 24 h Br on the logarithm of 1-BP TWA, also included terms for day, the interaction of day and the logarithm of 1-BP TWA, which were removed when not significant. Employee was treated as a random effect, and restricted maximum likelihood was used to estimate the covariance parameters using PROC MIXED in SAS (SAS Institute, Cary, NC).

RESULTS

Table 1 presents the demographic data for the workers in this study. The work force was predominately female; 12 out of 13 (92.3%) of the sprayers, and 13 out of 17 (76.5%) of the non-sprayers. Ages were also similar between job categories and the average age for both groups was ∼36. Nearly half (46.2%) of the sprayers were black while the non-sprayers were mostly white (82.4%). However, there are no reports in the literature that suggest different Br excretion rates between races. Based on this demographic information, it is unlikely that the results would be confounded by the characteristics of the study population.

The full-shift TWA personal breathing zone concentrations for 1-BP exposure measured for both sprayers and non-sprayers are provided in Table 2. It is evident from this table along with workplace observations, that the sprayers' exposures were substantially greater than those for non-spraying jobs due to their immediate proximity to the contaminant emission. The sprayers' exposures to 1-BP ranged from 45 to 200 p.p.m. with a GM of 92 p.p.m.,

Table 1. Demographic information for sprayers and non-sprayers

Parameter[a]	Job	
	Sprayers (n = 13)	Non-sprayers (n = 17)
Gender		
Male	1 (7.7)	4 (23.5)
Female	12 (92.3)	13 (76.5)
Age		
Minimum	18	24
Maximum	57	54
Average (SD)[b]	35.5 (11.9)	36.1 (8.8)
Race		
White	5 (38.5)	14 (82.4)
Black	6 (46.2)	3 (17.6)
Hispanic	2 (15.4)	0 (0.0)

[a]For gender and race data is presented as number and (percentage). Percentage refers to job stratified data, not overall study subjects.
[b]SD = Standard deviation.

Table 2. Full-shift time-weighted average breathing zone concentrations for 1-bromopropane (p.p.m.)

Job	Day	Minimum	Maximum	Average ± SD	GM (GSD)
Sprayers (n = 13)	First	45	106	76 ± 19	73 (1.32)
	Second	85	200	121 ± 37	116 (1.32)
	Overall	45	200	98 ± 37	92 (1.43)
Non-sprayers (n = 17)	First	0.6	32	13 ± 10	8.4 (3.43)
	Second	1.6	60	19 ± 15	13 (2.66)
	Overall	0.6	60	16 ± 13	11 (3.07)

while the non-sprayers' exposures ranged from 0.6 to 60 p.p.m. with a GM of 11 p.p.m. Higher exposures occurred on the second day of monitoring as shown by the GMs for both job classes, which increased by more than 50%. Overall, the sprayers' GM exposure for both days combined was more than 8 times greater than the GM for non-sprayers. Moreover, 20 out of 26 TWA measurements for sprayers exceeded 75 p.p.m. while all of the non-sprayers' exposures were <75 p.p.m. (not shown). Greater variability was observed for non-spraying jobs as demonstrated by the geometric standard deviations (GSDs) of 3.07 and 1.43, respectively, for non-sprayers and sprayers (Table 2).

All breathing zone concentrations of 1-BP measured for adhesive sprayers in this study exceeded the proposed EPA industrial exposure guideline of 25 p.p.m. The highest exposure guideline recommended by some solvent distributors (100 p.p.m.) was exceeded in 10 out of 26 measurements of workers spraying 1-BP adhesives; their overall GM (92 p.p.m.) also approached this criterion. Exposure to 1-BP among employees performing non-spraying jobs was due to ineffective general exhaust ventilation and solvent drift from spraying stations. None of the non-sprayers' exposure concentrations were observed to exceed the highest exposure guideline of 100 p.p.m., but 8 out of 34 non-sprayers' exposures to 1-BP exceeded 25 p.p.m., the exposure criterion proposed by the EPA (2003). The most heavily exposed non-spraying jobs (e.g. lead glue operators, wrappers, and pillow stuffers) were found to be at work locations closest to the glue lines where 1-BP vapors and mists were generated.

GM concentrations calculated from the composite urine specimens collected over the seven sequential time periods are plotted in Fig. 1, for the creatinine-adjusted urinary Br ($Br_{adj\text{-}cr}$) concentrations. The excretion pattern is quite similar for both sprayers and non-sprayers, although the sprayers' levels were ~4 times higher for most time intervals. The data show an increase in the excreted concentration on the second exposure day. However, the significance of this is unclear since breathing zone exposures were also ~50% higher on the second day.

In Table 3, descriptive statistics were tabulated for U-$Br_{adj\text{-}cr}$ from both days combined, grouped according to collection period. Again, the sprayers' GM and arithmetic mean values were substantially greater than those for non-sprayers, ranging from 3.3 to 5.5 times higher, depending on the collection period. For both job categories, the highest mean excretion concentrations were observed while at work, and the second highest occurred after the work shift. Urinary Br concentrations for seven control subjects, without exposure to 1-BP, are also included in Table 3. The control's $Br_{adj\text{-}cr}$ ranged from 2.6 to 5.9 mg $(g\text{-}cr)^{-1}$, with a GM of 3.8 (GSD = 1.32). The GMs of pre-week $Br_{adj\text{-}cr}$ for sprayers and non-sprayers were ~27 and 8 times higher than that for the control subjects, respectively.

Composite urinary Br excretion rates of 24 and 48 h were calculated to reduce the impact that individual variability of excretion rates and urination patterns may have on the time specified data (Table 4). Consistent with previous data, sprayers' GM $Br_{adj\text{-}cr}$ concentrations were ~4 times higher than those for non-sprayers, and the non-sprayers' $Br_{adj\text{-}cr}$ were more variable [e.g. GM concentrations for both days were 195 (GSD = 1.23) versus 43 mg $(g\text{-}cr)^{-1}$ (GSD = 2.19), respectively, for sprayers and non-sprayers]. Table 5 lists the descriptive statistics for the total Br excreted by each worker as determined by summing the product of the $Br_{unadj\text{-}cr}$ concentrations by the total urine volume from each composite sample collected over the specified time periods. Again, for nearly every time interval, the mean values for total Br excreted by sprayers' was ~3–4 times higher than that of the non-sprayers. The pre-week GM value of total Br

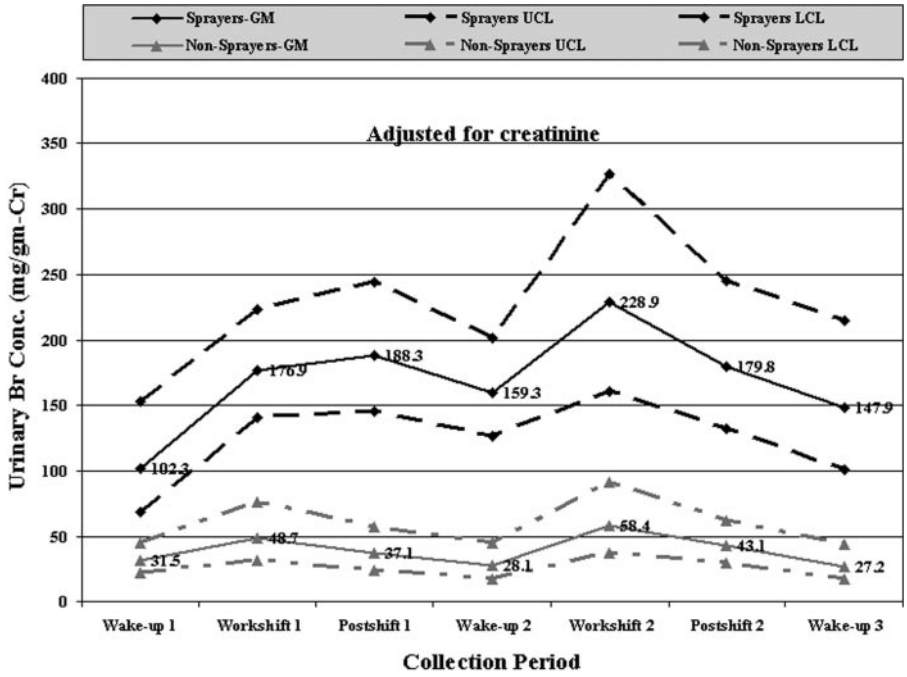

Fig. 1. Composite urinary Br GM concentration over time.

Table 3. Composite urinary bromide concentrations by job for both days combined, adjusted for creatinine [mg (g-cr)$^{-1}$]

Job	Period	Minimum	Maximum	Average ± SD	GM (GSD)
Sprayers (n = 13)	Pre-week	43	382	125 ± 95	102 (1.89)
	Work-shift	77	542	226 ± 110	201 (1.66)
	After work	58	308	199 ± 71	184 (1.56)
	Wake-up	46	672	176 ± 118	154 (1.67)
	All samples	43	672	190 ± 105	165 (1.73)
Non-sprayers (n = 17)	Pre-week	5.2	90	39 ± 25	31 (2.03)
	Work-shift	5.8	231	72 ± 55	53 (2.38)
	After work	6.3	135	51 ± 34	40 (2.17)
	Wake-up	3.1	123	39 ± 31	28 (2.43)
	All samples	3.1	231	52 ± 41	38 (2.33)
Controls (n = 7)	n.a.	2.6	5.9	3.9 ± 1.1	3.8 (1.32)

Table 4. Twenty-four and forty-eight hour composite urinary bromide concentrations by job, adjusted for creatinine [mg (g-cr)$^{-1}$]

Job	Day[a]	Minimum	Maximum	Average ± SD	GM (GSD)
Sprayers (n = 12)	First	108	242	183 ± 40	179 (1.27)
	Second	74	309	215 ± 74	198 (1.60)
	Overall[b]	119	250	199 ± 37	195 (1.23)
Non-sprayers (n = 17)	First	5.1	149	51.8 ± 36.3	39.8 (2.27)
	Second	5.8	150	58.3 ± 38.8	46.2 (2.16)
	Overall	5.5	149	54.7 ± 37.5	42.9 (2.19)

[a]'First' and 'second' day results represent 24 h composite results separately for each day starting after the beginning of the workshift.
[b]'Overall' results represent 48 h composite results for both days combined starting after the beginning of the workshift on the first day.

excreted (after an extended weekend) by non-sprayers was nearly twice that of control subjects, while that of sprayers was more than four times that of controls (data not shown).

Figure 2 presents the linear regressions for the 24 h urinary Br concentrations versus the 1-BP TWA concentrations for 'all jobs combined' using the unadjusted and creatinine adjusted concentrations.

Table 5. Urinary bromide mass[a] by job, unadjusted for creatinine (mg)

Job	Period[b]	Minimum	Maximum	Average ± SD	GM (GSD)
Sprayers (n = 13)	Pre-week	1.8	78	29 ± 23	18 (3.25)
	First day	92	348	195 ± 84	179 (1.52)
	Second day	30	340	216 ± 96	184 (2.05)
	Overall[c]	121	658	411 ± 156	378 (1.58)
Non-sprayers (n = 17)	Pre-week	1.5	32	10.0 ± 9.4	6.5 (2.68)
	First day	6.5	190	60 ± 42	48 (2.10)
	Second day	9.0	173	59 ± 41	49 (1.92)
	Overall	15	363	120 ± 81	98 (1.98)

[a]Bromide mass excreted was calculated by summing the product of each composite sample concentration by the specimen volume for that time period.
[b]'First' and 'second' represent 24 h Br mass excreted separately for each day starting after the beginning of the workshift.
[c]'Overall' represents 48 h Br mass excreted for both days combined starting after the beginning of the workshift on the first day.

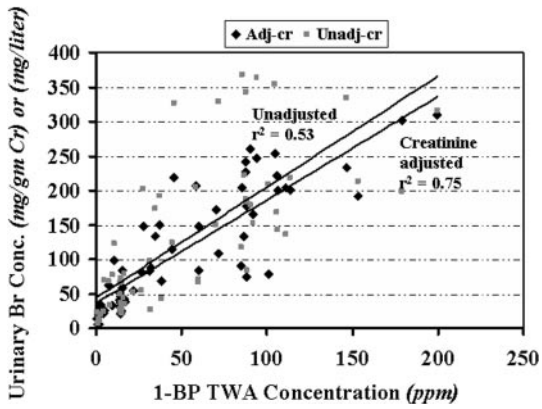

Fig. 2. Twenty-four hour urinary Br concentration versus full-shift 1-bromopropane TWA concentration for all jobs.

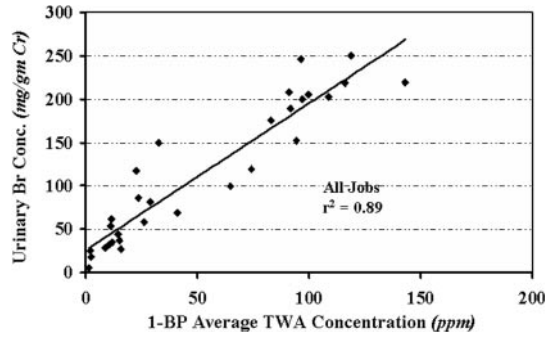

Fig. 3. Forty-eight hour urinary Br concentration versus average full-shift 1-bromopropane TWA concentration for all jobs, adjusted for creatinine.

The strength of the linear relationships were not as strong for the unadjusted data ($r^2 = 0.53$) than for the adjusted data ($r^2 = 0.75$). In Fig. 3, the 48 h $Br_{adj\text{-}cr}$ excretion concentrations are compared with the 2-day average TWA exposure to 1-BP, and the strength of the association is much stronger than those for the 24 h data ($r^2 = 0.89$).

The relationship between 24 h urinary Br (for both $Br_{adj\text{-}cr}$ concentration and total Br mass excreted) with 1-BP TWA and the effect of day on either the slope or the intercept was examined for all models. Neither the slope nor the intercept was modified by day for any model. There was a strong positive relationship between urinary Br and 1-BP TWA for non-sprayers for both creatinine adjusted Br concentration and 24 h Br excretion ($P \leqslant 0.01$). For sprayers, there was a relationship for creatinine adjusted Br concentration ($P \leqslant 0.05$) but not for Br excreted over 24 h periods ($P > 0.05$).

Differences in 1-BP TWA and urinary Br levels between the two plants were examined in models containing effects for plant, employee within plant and day. Based on examining residuals, the natural logarithm of TWA was used for both sprayers and non-sprayers. There were no significant differences between the plants.

DISCUSSION

One objective of this field study was to investigate the utility of urinary Br analysis for evaluating worker exposure to 1-BP. Br ion analysis in urine is appealing because it is based on well-established methodology, is relatively non-invasive and is commercially available at ~$60 per sample. Urinary Br levels in the general population are typically <10 mg l^{-1}, well above the limit of quantification provided by the contract laboratory (0.3 mg l^{-1}). Urinary Br excretion, however, may be variable in the general population because it can be influenced by diet, pharmaceuticals, including over-the-counter medications, or exposure to other bromine containing compounds. Because of scant reports in the published literature, it was difficult to predict whether urinary Br analysis would be useful for evaluating occupational exposure to 1-BP. This study demonstrates that urinary Br can be an effective index to evaluate workers' exposures to 1-BP, providing care is exercised to identify non-occupational exposure to brominated compounds.

The main pathway for elimination of Br is first-order urinary excretion, primarily as the mercapturic acid conjugate and Br (Jones and Walsh, 1979; Ryan and Baumann, 1999). The elimination half-life of Br (in blood) is reported to range between 10.5 and 14 days (Woody, 1990). Elevated urinary Br concentrations significantly above normal reflect an accumulated exposure over 1–2 weeks because Br ion is excreted at a relatively slow rate (Jones and Walsh, 1979; Rauws, 1983). In our study, elevated urinary Br levels were observed in 'pre-week' urine specimens collected from workers after an extended weekend. This indicates that exposed workers were still excreting substantial quantities of Br after nearly 3 days absence from 1-BP exposure.

The urine specimens collected during the work week showed the same pattern as the pre-week specimens: sprayers' mean urinary Br concentrations were ~4 times greater than those for non-sprayers. For both sprayers and non-sprayers, the highest observed mean Br concentrations were excreted while at work. Even though the elimination half-life for Br is >10 days, this should not be surprising because these workers were constantly exposed to high concentrations of 1-BP throughout the entire work shift.

Jobs remote or up-wind from the glue lines (e.g. foam and cloth cutters) experienced the lowest exposures to 1-BP. There were three workers in these low exposure jobs, and all six TWA daily measurements were <5 p.p.m.; four were <2 p.p.m. Some of the lowest daily $Br_{adj\text{-}cr}$ concentrations were also from these same jobs. The minimum excretion concentration detected from one of these workers [3.1 mg $(g\text{-}cr)^{-1}$] was comparable to those from controls [2.6–5.9 mg $(g\text{-}cr)^{-1}$]. Interestingly, the pre-week $Br_{adj\text{-}cr}$ concentration for another one of these non-sprayers was 50 mg $(g\text{-}cr)^{-1}$. We presume this value is most likely due to non-occupational factors such as 'as needed' medication or diet because the 48 h composite Br concentration during work days [24.8 mg $(g\text{-}cr)^{-1}$] for this worker was approximately half of her pre-week value.

Although this study does not fully test the sensitivity of urinary Br to adequately measure 1-BP exposure among workers with low level exposures, it clearly shows that substantial quantities of Br are excreted in urine of the most highly exposed workers. Furthermore, the 1- and 2-day Br concentrations were statistically associated with 1-BP in breathing zones. The highest correlation ($r^2 = 0.89$) occurred for the 48 h composite Br and the 2-day average 1-BP TWA for 'all jobs combined' because this represents exposure levels ranging over two orders of magnitude and is probably a better sample of the workers' true body burden.

Dermal exposure to 1-BP can potentially add to a worker's absorbed dose of this compound.

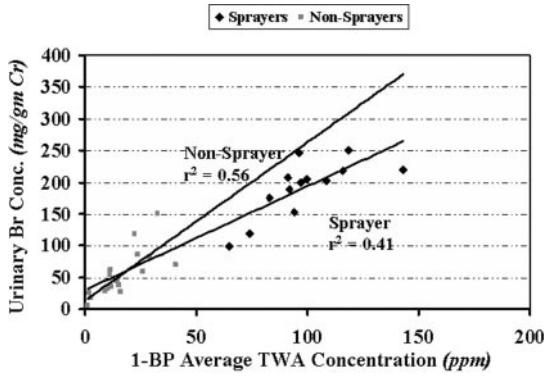

Fig. 4. Forty-eight hour urinary Br concentration versus average full-shift 1-bromopropane TWA concentration by job, adjusted for creatinine.

In our study, sprayers constructed furniture cushions by using compressed air spray guns to moisten precut materials and assemble polyurethane foam pieces, springs and protective cloth. In some cases, sprayers were observed to use their bare hands to smooth edges and pinch corners of the foam pieces. Non-spraying jobs, including sewing machine operators, cutters, glue line leads, pillow stuffers and product wrappers, were not observed to have skin contact with the wet adhesive. When stratified by job, the lower observed correlation of Br with 1-BP TWA for sprayers (Fig. 4) may be due, in part, to the greater potential skin contact with wet adhesive.

The purpose of the biological monitoring conducted in this study was to evaluate occupational exposure to and excretion of 1-BP. It was not intended to determine health and toxicological indices, and as such, serum Br levels were not measured. However, it is well known that Br is removed from the blood through the renal system and excreted into urine. Therefore, it is conceivable that workers spraying adhesives in this industry experiencing high urinary Br levels may also be at risk for elevated serum Br from metabolism of 1-BP. Adverse effects of excessive Br absorption can potentially be life threatening and cause skin lesions, gastrointestinal effects and central nervous system dysfunction (e.g. drowsiness, headache, irritability, cognitive impairment, delirium, dementia/hallucinations, loss of pupil and gag reflexes, and diminished deep tendon reflexes) (Ryan and Baumann, 1999). Furthermore, the case study of foam cushion workers' neurological impairment described by Ichihara *et al*. (2002) presents symptoms consistent with excessive Br absorption.

CONCLUSIONS

Workers at polyurethane foam fabricating plants manufacturing furniture seat cushions using 1-BP spray adhesives with poor ventilation are exposed to excessive concentrations of 1-BP. Adhesive sprayers'

breathing zone concentrations were much higher than those for non-spraying jobs because they were at the point of contaminant emission. Many workers' TWA breathing zone concentrations exceeded proposed OELs.

Urinary Br concentrations were substantially higher for sprayers than for non-sprayers with GM values for the daily Br excretion ~4 times higher. GM Br concentrations were an order of magnitude greater and forty times greater for the non-sprayers and sprayers, respectively, than for non-exposed control subjects. For non-sprayers, daily levels of urinary Br, as well as total excreted Br, were significantly correlated with the breathing zone concentration of 1-BP. For sprayers, the 1- and 2-day Br concentrations were also significantly correlated with 1-BP breathing zone concentrations. The potential for dermal contact of sprayers with wet adhesives containing 1-BP was also noted.

This study demonstrates that urinary elimination of Br is an important excretion pathway for 1-BP metabolism. Moreover, urinary Br appears to be a useful index of 1-BP exposure, particularly in the foam fabricating industry where exposures are high. Thus, urinary Br should be considered as a useful supplement to air monitoring of 1-BP.

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REFERENCES

ACGIH. (2004) 2004 TLVs® and BEIs®: Threshold limit values for chemical substances and physical agents. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Albemarle Corp. (2003) Albemarle workplace exposure guideline for Abzol™ cleaners. Baton Rouge, LA: Albemarle Corporation.

Allain P, Mauras Y, Douge C *et al*. (1990) Determination of iodine and bromine in plasma and urine by inductively coupled plasma spectrometry. Analyst 115:813–15.

Enviro Tech International, Inc. (2005) Material Safety Data Sheet for Ensolv®. Melrose Park, IL: Enviro Tech International, Inc. Available from: www.Ensolv.com. (Accessed on 17 February 2005).

EPA. (1999) Protection of stratospheric ozone: listing of substitutes for ozone depleting substances. Request for data and advanced notice of proposed rulemaking. 40 CFR Part 82. Fed Regist; 64: 8043–8.

EPA. (2000) Protection of stratospheric ozone: notice 14 for significant new alternatives policy program. 40 CFR Part 82. Fed Regist; 65: 78977–89.

EPA. (2003) Protection of stratospheric ozone: listing of substitutes for ozone depleting substances. *n*-Propyl bromide. Proposed rule. 40 CFR Part 82. Fed Regist; 68: 33284–316.

Great Lakes Chemicals. (2005) Material safety data sheet for *n*-propyl bromide. In: West Lafayette, ed., *Great Lakes Chemicals*. Available from: www.e1.greatlakes.com/common/msdspdf/00164/pdf (Accessed 7 March 2005).

Ichihara G, Yu X, Kitoh J *et al*. (2000a) Reproductive toxicity of 1-bromopropane, a newly introduced alternative to ozone layer depleting solvents, in male rats. Toxicol Sci; 54: 416–23.

Ichihara G, Kitoh J, Yu X *et al*. (2000b) 1-Bromopropane, an alternative to ozone layer depleting solvents, is dose-dependently neurotoxic to rats in long-term inhalation exposure. Toxicol Sci; 55: 116–23.

Ichihara G, Miller JK, Ziolkowska A *et al*. (2002) Neurological disorders in three workers exposed to 1-bromopropane. J Occup Health; 44: 1–7.

Ichihara G, Li W, Ding X *et al*. (2004) A survey on exposure level, health status, and biomarkers in workers exposed to 1-bromopropane. Am J Ind Med; 45: 63–75.

Jones AR, Walsh DA. (1979) The oxidative metabolism of 1-bromopropane in the rat. Xenobiotica; 9: 763–72.

Kawai T, Okada Y, Odachi T *et al*. (1997) Diffusive sampling and biological monitoring of 2-bromopropane. Arch Environ Contam Toxicol; 33: 23–8.

Kawai T, Takeuchi A, Miyama Y *et al*. (2001) Biological monitoring of occupational exposure to 1-bromopropane by means of urinalysis for 1-bromopropane and bromide ion. Biomarkers; 6: 303–12.

NIOSH. (1992) Recommendations for occupational safety and health: compendium of policy documents and statements. DHHS (NIOSH) Publication No. 92-100. Cincinnati, OH: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH. (2003) 1- and 2-Bromopropane. NIOSH analytical method no. 1025. In: Eller PM, Cassinelli ME, editors. NIOSH manual of analytical methods. 4th edn. DHHS (NIOSH) Publication No. 94-113. Cincinnati, OH: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NTP. (2002) NTP-CERHR expert panel report on the reproductive and developmental toxcity of 1-bromopropane. DHHS (NTP) Publication No. NTP-CERHR-1-BP-02. Washington, DC: US Department of Health and Human Services, National Institutes of Health, National Institute of Environmental Health Sciences, National Toxicology Program.

NTP Center for the Evaluation of Risks to Human Reproduction Bromopropanes Expert Panel. (2004) NTP-CERHR expert panel report on the reproductive and developmental toxicity of 1-bromopropane. Reprod Toxicol; 18: 157–88.

OSHA. (2005) Permissible exposure limits. 29 CFR 1910.1000. Code of Federal Regulations. Washington, DC: US Government Printing Office, Office of Federal Register.

Rauws AR. (1983) Pharmocokinetics of bromide ion—an overview. Food Chem Toxicol; 21: 379–82.

Rozman KK, Doull J. (2002) Derivation of an occupational exposure limit (OEL) for n-propyl bromide using an improved methodology. Appl Occup Environ Hyg; 17: 711–16.

Ryan M, Baumann RJ. (1999) Use and monitoring of bromides in epiliepsy treatment. Pediatric Neurol; 21: 523–8.

Sclar G. (1999) Encephalomyelo-radiculoneuropathy following exposure to an industrial solvent. Clin Neurol Neurosurg; 101: 199–202.

Stelljes ME, Wood RR. (2004) Development of an occupational exposure limit for n-propyl bromide using benchmark dose methods. Regul Toxicol Pharmacol; 40: 136–50.

Takeuchi T, Okuda H, Nagano K *et al*. (2001) Reproductive and developmental toxicity of 1-bromopropane in rats. J Toxicol Sci; 26: 222.

Takeuchi Y, Ichihara G, Kamijima M. (1997) A review on toxicity of 2-bromopropane: mainly on its reproductive toxicity. J Occup Health; 39: 179–91.

Woody RC. (1990) Bromide therapy for pediatric seizure disorder intractable to other antiepileptic drugs. J Child Neurol; 5: 65–7.

Yamada T, Ichihara G, Wang H *et al*. (2003) Exposure to 1-bromopropane causes ovarian dysfunction in rats. Toxicol Sci; 71: 96–103.

Yu X, Ichihara G, Kitoh J *et al*. (2001) Neurotoxicity of 2-bromopropane and 1-bromopropane, alternative solvents for chlorofluorocarbons. Environ Res; 85: 48–52.