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Biological monitoring of occupational exposure to 1-bromopropane by means of urinalysis for 1-bromopropane and bromide ion

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The purposes of the present study are (1) to develop a sensitive analytical method to measure 1-bromopropane (1-BP) in urine, (2) to examine if 1-BP or bromide ion (Br) in urine is a useful biomarker of exposure to 1-BP, and (3) to identify the lowest 1-BP exposure concentration the method thus established can biomonitor. A factory survey was carried out on Friday, and 33 workers (all men) in cleaning and paintng workshops participated; each worker was equipped with a diffusive sampler (carbon cloth KF-1500 as an adsorbent) to monitor 1-BP vapour for an 8-h shift, and offered a urine sample at the end of the shift for measurement of 1-BP and Br in urine. In addition, 10 non-exposed men offered urine samples as controls. The performance of the carbon cloth diffusive sampler was examined to confirm that the sampler is suitable for monitoring time-weighted average 1-BP vapour exposure. A head-space GC technique was employed for analysis of 1-BP in urine, whereas Br in urine was analysed by ECD-GC after derivatization to methyl bromide. The workers were exposed to vapours of seven other solvents (i.e. toluene, xylenes, ethylbenzene, acetone, etc.) in addition to 1-BP vapour; the 1-BP vapour concentration was 1.4 ppm as GM and 28 ppm as the maximum. Multiple regression analysis however showed that 1-BP was the only variable that influenced urinary 1-BP significantly. There was a close correlation between 1-BP in urine and 1-BP in air; the correlation coefficient (r) was >0.9 with a narrow variation range, and the regression line passed very close to the origin so that 2 ppm 1-BP exposure can be readily biomonitored. The correlation of Br in urine with 1-BP in air was also significant, but the r (about 0.7) was smaller than that for 1-BP, and the background Br level was also substantial (about 8 mg l^{-1}). Thus, it was concluded that 1-BP in end-of-shift urine is a reliable biomarker of occupational exposure to 1-BP vapour, and that Br in urine is less reliable.

Keywords: biological monitoring, bromide ion, l-bromopropane, diffusive sampling, occupational exposure, urinalysis.

Introduction

The use of 2-bromopropane (2-BP or isobromopropane) has been phased out sharply in Japan and probably also in other countries, after a mass outbreak of occupational 2-BP poisoning in the neighbouring country of Republic of Korea (Ministry of Labor, Japan 1995, Kim *et al*. 1996, Park *et al*. 1997). Soon after the

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poisoning episode, the toxicity of 2-BP on the haematopoietic, reproductive and peripheral nervous systems was confirmed by animal experiments and through occupational health studies in several laboratories (Ichihara *et al.* 1997, 1999, Kamijima *et al.* 1997, Nakajima *et al.* 1997, Omura *et al.* 1997, Yu *et al.* 1997, 1999). Correspondingly, the use of its isomer, 1-bromopropane (*n*-bromopropane or 1-BP), has been rapidly increasing as a non-flammable surrogate solvent for fine cleaning work in, for example, integrated circuit (IC) industries. Whereas an occupational exposure limit of 1 ppm was set for 2-BP both in Republic of Korea (Ministry of Labor, Republic of Korea 1998) and in Japan (Japan Society for Occupational Health 2000), no limit value has ever been proposed for 1-BP by, for example, the American Conference of Occupational Hygienists (2000), Deutsche Forschungsgemeinschaft (2000) or the Japan Society for Occupational Health (2000) despite its expanding application in various industries.

It is highly probable that 1-BP will penetrate through intact skin, by analogy to 2-PB (Tsuruta *et al.* 1998, Japan Society for Occupational Health 1999) as well as other low molecular weight brominated aliphatics such as methyl bromide, bromoform, ethyl bromide, and ethylene dibromide (Jordi 1953, Longley and Jones 1965, Deutsche Forschungsgemeinschaft 2000, American Conference of Governmental Industrial Hygienists 2000). Accordingly, the biological monotiring for 1-BP would carry more practical importance to protect workers from excessive exposure to this newly introduced solvent.

This report describes the results of successful trials (1) to develop a sensitive analytical method to measure 1-BP in urine, (2) to show that both 1-BP and to a lesser extent bromide ion (Br) excreted in end-of-shift urine sample are useful biomarkers of exposure to this solvent, and (3) to demonstrate that the biomonitoring by means of urinalysis thus established is sensitive enough to detect 1-BP exposure at 2 ppm and 4 ppm when 1-BP and Br are analysed, respectively.

Subjects, materials and methods

Workers with occupational exposure to 1-bromopropane, and their controls

The survey was carried out on a Friday. In total, 33 Japanese workers (all men) agreed to participate in the survey. They worked for 8 h a day to clean and paint metal surfaces with preparations containing 1-BP and other solvents. A walk-through survey showed that the workers used protective gloves when they worked with the solvent preparations, suggesting that the chances of exposure of the skin to liquid solvents should be very remote. At around 08:00, each worker was equipped with a diffusive sampler on the cloth at the chest pocket level. At around 16:00, the worker was invited to a 1-BP free room, and the sampler was removed. The worker collected his urine sample in a disposable paper cup. In addition, 10 non-exposed Japanese men offered urine samples as controls. The exposed and non-exposed subjects were matched by sex (all men), age [39.3 years as an average in a range of 20–59 years for the 33 exposed versus 43.6 years (25–67 years) for the 10 controls], and smoking habits (smoking rates about 50% in both groups). None of them were under medication. Both groups lived in the same region, and were assumed to have similar dietary habits.

Exposure of carbon cloth to 1-bromopropane, and gas chromatographic analysis

Experimental exposure of carbon cloth (KF-1500, a product of Toyobo, Osaka, Japan) (Koizumi and Ikeda 1981) to 1-BP vapours was conducted as previously described for 2-BP (Kawai *et al.* 1997a). The exposure was up to 200 ppm 1-BP for up to 8 h, and each piece of carbon cloth was kept in a holder case (i.e. as a diffusive sampler) during the exposure. After exposure, the carbon cloth was extracted with carbon disulphide (CS_2) (Hirayama and Ikeda 1979, Ikeda *et al.* 1984, Kasahara and Ikeda 1987). A preliminary experiment showed that the rate of extraction for 1-BP was >99%. The extract was analysed for 1-BP under analytical conditions as previously described for 2-BP (Kawai *et al.* 1997a),

with two modifications, (i) that the DB-WAX column (J&W, Scientific, Folsom CA, USA) was 50 m long with a film thickness of 1.00 μm, and (ii) that the programme for column temperature control was slightly changed. When a peak (noise)$^{-1}$ ratio of 2 was taken in the gas chromatogram, the detection limits for the eight measured solvents (including 1-BP) were 0.1 ppm in common.

Gas chromatographic urinalysis for 1-bromopropane and bromide ion

A head-space technique was employed for 1-BP analysis. Immediately after collection of urine and with due caution, to minimize possible loss of 1-BP from urine samples (Ikeda 1999), a 5 ml portion of urine was taken on-site into a 20 ml head-space vial (Hewlett Packard). The vial was sealed with a Teflon-coated septum as soon as possible, and brought to an analytical laboratory. The analytical conditions employed were as previously described (Kawai *et al*. 1997a), with slight modification in column temperature control. A split ratio of 6:1 was employed. The analysis was conducted on the day of the survey in most cases; the sealed vial was kept refrigerated in case the analysis was made the next day.

The ECD-GC analysis for urinary Br after derivatization to methyl bromide was conducted as previously described (Kawai *et al*. 1997a). A split ratio was set at 28:1. It was confirmed that no measurable amount of Br was liberated when 1-BP in water (concentration; 133 mg l^{-1}) was subjected to the analysis under the standard analytical conditions.

When tested at realistic concentrations of 1-BP (13.3 μg l^{-1}) and Br in urine (13.4 mg l^{-1}), both methods gave a small coefficient of variation (<3%) and a high recovery (>90%). The detection limits were 2 μg (l urine)$^{-1}$ for 1-BP and 10 μg (l urine)$^{-1}$ for Br, and were considered to be low enough for practical applications.

Correction for creatinine and specific gravity

Analyte concentrations in urine samples were in some instances corrected for creatinine concentration (Jackson 1966) or a specific gravity of 1.016 (Rainsford and Lloyd Davies 1965).

Statistical analysis

Concentrations in urine were presented in terms of a geometric mean (GM) and a geometric standard deviation (GSD) together with the number of determinations (N). An arithmetic mean (AM) and an arithmetic standard deviation (ASD) were also used when an assumption of normal distrubtion was considered to be more appropriate. Simple and multiple regression analyses (MRA) were employed. In MRA, the step-up procedure was employed with $P < 0.10$ as a criterion for selection of influential variables. Mann-Whitney's U-test was also used. The 95% confidence ranges for means and individual values were calculated using the method of Ichihara (1990).

Results

Adsorption of 1-bromopropane on carbon cloth

Four pieces each of carbon cloth were exposed to 1-BP vapours at 0, 50, 100, or 200 ppm for 0, 1, 2, 4, 6 or 8 h, and subjected to GC analysis for 1-BP. Plotting of the amounts of 1-BP detected in the exposed cloth against exposure conditions showed that the amount adsorbed was proportional to the exposure durations as well as exposure concentrations.

Carbon cloth was exposed for 15 min at 200 ppm in order to examine the ability of the cloth to absorb 1-BP when exposed for a short-term at a high concentration. Comparison of the amount of 1-BP in the exposed cloth with the amount estimated from the data after 8 h exposure gave 110% as a rate of the measured value over the estimate.

In a separate experiment, possible spontaneous desorption of 1-BP from the exposed cloth was examined. As compared with the amount of 1-BP immediately after the exposure, the succeeding 8 h exposure to fresh air did not induce significant ($P > 0.10$) reduction in the 1-BP in the cloth. In the third experiment, the exposed cloth samples were wrapped air-tight in aluminium foil immediately after exposure to 1-BP, and were kept for up to 2 days at room temperature

Table 1. Exposure of workers of solvent mixture vapour.

Solvent	GM (ppm)	GSD	Maximum (ppm)	<ND[a]
1-Bromopropane	1.42	4.72	27.8	0 (0)
Acetone	0.17	6.10	7.2	22 (15)
Butyl acetate	0.11	3.65	2.9	22 (7)
Ethylbenzene	2.72	2.72	20.2	0 (0)
Ethyl acetate	0.36	4.50	9.9	8 (7)
Isobutyl acetate	0.14	3.27	2.1	16 (9)
Toluene	4.15	4.28	33.5	0 (0)
Xylenes[b]	2.71	2.55	18.4	0 (0)

[a] The number of those with less than detection limit (0.1 ppm) exposure (the number in parentheses shows 0 ppm cases). These exposures were assumed as if it were 0.05 ppm in calculating GM and GSD.

[b] Three xylene isomers in combination.

(about 20°C). There was no loss ($P > 0.10$) in the adsorbed amounts of 1-BP in the 2-day period of storage. Thus it was concluded that the carbon cloth is fit for quantitative measurement of time-weighted average (TWA) 1-BP exposure concentration.

Exposure of workers to 1-BP and other solvents

The intensity of exposure of the 33 workers to mixed solvents is summarized in table 1. It is clear that the workers were exposed to vapours of seven other solvents in addition to 1-BP vapour. Toluene was the solvent with the highest exposure concentration followed by two other aromatics of ethylbenzene and xylenes. Exposures to acetate esters and acetone were also noted. 1-BP was fourth in exposure intensity when GM concentrations were compared, and second highest in the order of the maximum concentrations.

Multiple regression analysis to examine possible effects of co-exposure to other solvents on urinary 1-bromopropane

Multiple regression analysis was carried out with the 33 exposed cases taking the concentrations of the eight solvents as independent variables and either 1-BP in urine as observed, or after correction for creatinine concentration or a specific gravity of 1.016 as a dependent variable (top half in table 2). It should be added that the requirement of independency among the eight solvents as the independent variables were almost met. 1-BP vapour was the only independent variable that significantly ($P < 0.01$) influenced urinary 1-BP; the influence was almost exclusive, explaining 89–91% of total variation. Correlation coefficients (r in the table) obtained by simple regression analysis were identical with the partial correlation coefficients (PCC) after multiple regression analysis, indicating that the effect of the co-exposures to other solvents on urinary 1-BP was essentially nil.

Similar calculation taking urinary Br in place of 1-BP as a dependent variable (the bottom half of table 2) also showed that 1-BP vapour was an exclusive independent variable. The power to explain variation in urinary Br (43–58%) was however weaker ($p < 0.05$ by U-test) than that for urinary 1-BP (89–92%).

Table 2. Multiple regression analysis to show 1-bromopropane as the only solvent with significant influence on 1-bromopropane and bromide ion in urine.

Dependent variable Correction for urine density	R^2 for total[b]	1-Bromopropane[a]		
		R^2	PCC[C]	r[d]
1-Bromopropane				
As observed ($\mu g\,l^{-1}$)	0.919	0.906	0.952	0.952
For creatinine [$\mu g\ (g\,cr)^{-1}$]	0.949	0.886	0.941	0.941
For specific gravity ($\mu g\,l^{-1}$)	0.920	0.893	0.945	0.945
Bromide ion				
As observed ($mg\,l^{-1}$)	0.580	0.544	0.738	0.738
For creatinine [$mg\ (g\,cr)^{-1}$]	0.544	0.432	0.658	0.658
For specific gravity ($mg\,l^{-1}$)	0.560	0.525	0.725	0.725

The values are based on 33 exposed subjects only.

[a] 1-Bromopropane is the only significantly ($P < 0.10$) influential independent variable among the eight variables in all cases studied.

[b] R^2 for all eight parameters in combination.

[c] Partial correlation coefficient by multiple regression analysis ($P < 0.01$ for all cases).

[d] Correlation coefficient by simple regression analysis ($P < 0.01$ for all cases).

Table 3. 1-Bromopropane and bromide ion concentrations in urine of 10 men with no occupational exposure to 1-bromopropane.

Analyte in urine Correction for urine density	GM	GSD[a]	Maximum	95% upper limit[a]
1-Bromopropane				
As observed ($\mu g\,l^{-1}$)	0	—	0	0
Bromide ion				
As observed ($mg\,l^{-1}$)	8.22	1.25	11.1	12.8
For creatinine [$mg\ (g\,cr)^{-1}$]	6.39	1.33	10.0	11.3
For specific gravity ($mg\,l^{-1}$)	5.58	1.20	8.6	8.0

The value was based on determinations of urine from 10 non-exposed controls.

No *n*-propyl alcohol was detected in urine samples.

[a] GSD (geometric standard deviation) is dimensionless.

Background levels of 1-BP and bromide ion in urine from non-exposed subjects

The levels of 1-BP and Br in the urine samples obtained from 10 non-exposed men are summarized in table 3. No 1-BP was detected in any urine sample. In contrast, Br was measureable in all of the 10 urine samples; the maximum levels observed were $11\,mg\,l^{-1}$. When the 95% upper limit for urinary Br was calculated with an assumption of log-normal distribution by the equation of $GM \times GSD^2$, the limit was $12.8\,mg\,l^{-1}$ when the non-corrected observed value was taken.

Excretion of 1-bromopropane and bromide ion in urine of workers exposed to 1-bromopropane

In examining the exposure – excretion relationship (table 4), simple regression analysis was applied, because the effects of co-exposures to other solvents were essentially negligible (table 2). It is clear from the top half of the table that there was a very close correlation between 1-BP in urine and 1-BP in air. The correlation coefficient was as large as >0.9 irrespective of the combination of the non-exposed with the exposed, and regardless of correction for urine density; correction for

Table 4. Correlation of 1-bromopropane and bromide ion in end-of-shift urine with time-weighted average intensity of exposure to 1-bromopropane.

Analyte in urine Correction for ueine density	Parameters		
	α	β	r
1-Bromopropane			
As observed ($\mu g\,l^{-1}$)	0.20 (0.29)	0.66 (0.66)	0.956 (0.952)
For creatinine [$\mu g\,(g\,cr)^{-1}$]	0.07 (0.11)	0.46 (0.46)	0.947 (0.941)
For specific gravity ($\mu g\,l^{-1}$)	0.11 (0.16)	0.41 (0.41)	0.950 (0.945)
Bromide ion			
As observed ($mg\,l^{-1}$)	11.6 (13.0)	1.27 (1.17)	0.763 (0.738)
For creatinine [$mg\,(g\,cr)^{-1}$]	8.9 (9.9)	0.82 (0.75)	0.690 (0.658)
For specific gravity ($mg\,l^{-1}$)	8.0 (9.0)	0.74 (0.66)	0.750 (0.725)

The values are based on calculation with 33 exposed and 10 non-exposed in combination. The values in parentheses are with 33 exposed subjects only. α and β are parameters of a calculated regression line so that $y = \alpha + \beta x$, in which x is time-weighted average intnsity of exposure to 1-bromopropane (1-BP) vapour and y is either 1-BP or bromide ion in the end-of-shift urine. r is a correlation coefficient (dimensionless); all coefficients are statistically significant ($P < 0.01$).

creatinine concentration or urine specifc gravity did not improve the correlation. Further perusal of urinary 1-BP data on an individual basis disclosed that the lowest 1-BP concentration in air among the 15 exposed with measurable urinary 1-BP was 0.9 ppm, whereas the highest 1-BP in air was 2.2 ppm for the 18 subjects who had no measurable 1-BP in urine despite exposure to 1-BP vapour.

The correlation of Br in urine with 1-BP in air was also statistically significant, with the largest value of r being obtained when Br concentrations were not corrected (i.e. as observed). Compared with the cases of 1-BP in urine, the r values for Br tended to be smaller (although with $P > 0.10$ by U-test) than the counterpart values for 1-BP. The intercepts were relatively large, in the sense that the intercepts were as great as the increments after 10 ppm 1-BP exposure. Such was not the case for 1-BP in urine; 10 ppm 1-BP exposure would induce increments in urinary 1-BP more than 30 times greater than the intercepts.

For visual understanding of the correlation, scatter diagrams of 1-BP and Br in the end-of-shift urine samples of the 43 subjects in total against the TWA intensity of 1-BP vapour exposure are depicted in figure 1, in which non-corrected values for analytes in urine are taken as examples.

Discussion

The present study demonstrates that 1-BP in end-of-shift urine samples is a good biomarker of exposure to 1-BP vapour. The observation gives another example that organic solvent itself in urine rather than its metabolite is recommended as a biomarker of occupational exposure to the solvent (e.g. Ghittori *et al.* 1987, Mizunuma *et al.* 1995, Kawai *et al.* 1996). Urinary Br is also a biomarker of exosure to 1-BP, although its sensitivity may be lower than that of urinary 1-BP.

When overall sensitivity of urinary 1-BP and Br is evaluated by the method previously proposed (LSC-2; Kawai *et al.* 1992), those exposed to 1-BP vapour at 1.3 ppm can be distinguished from the non-exposed (with $P < 0.05$) when biomonitored in terms of urinary 1-BP, whereas it was about 4 ppm with urinary Br. The former evaluation is apparently on line with the observation on an

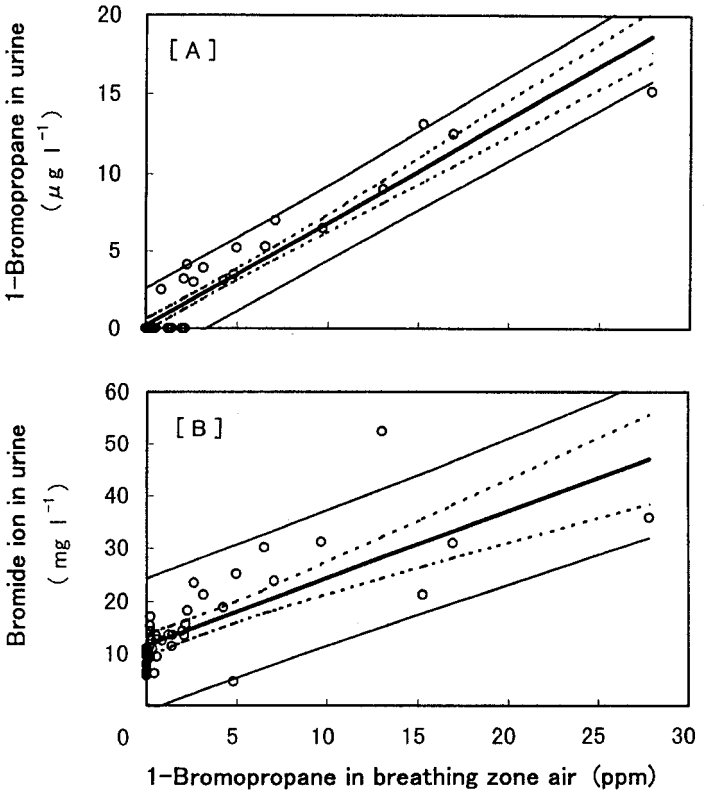

Figure 1. Correlation between 1-bromopropane (1-BP) vapour exposure, and 1-BP and Br in urine. The scatter diagrams show correlation of the intensity to 1-BP vapour during 8-h work shift and [A] 1-BP and [B] Br in end-of-shift urine (both non-corrected observed values). Each dot represents one case (33 exposed cases; open circles), except the dot at the origin which represents 10 non-exposed cases (a solid circle). The solid line in the middle is a calculated regression line (for the equation parameters, see table 4), two dotted curves on both side of the line show the 95% range of the group means, and two solid outermost curves show the 95% range of the individual values.

individual basis that a worker exposed to >2 ppm 1-BP vapour will have 1-BP in urine at a measurable level. Comparison with the background level (LSC-1; Kawai *et al.* 1992) shows that urinary Br can separate those with 2.3 ppm 1-BP exposure from the non-exposed.

The regression equation parameters in table 4 indicate that the increment in urinary 1-BP after 10 ppm (or 50 mg m^{-3}) 1-BP vapour will be 6.6 μg l^{-1}. Assuming that a worker inspires 15 l (or 0.015 m^3) air min^{-1} and excretes urine at a rate at 1 ml min^{-1} (Inoe *et al.* 1995), and that the absorption of 1-BP through the lungs is 50% by analogy to other solvent such as benzene, toluene and ethylbenzene (Inoue *et al.* 1995), a hypothetical exposure to 1-BP vapour at 10 ppm will result in 1-BP absorption through the lungs at a rate of 0.375 mg min^{-1} (=50 mg m^{-3} × 0.015 m^3 min^{-1} × 50%), and excretion into urine of 6.6×10^{-6} mg min^{-1} (= 6.6×10^{-3} mg l^{-1} × 10^{-3} l min^{-1}). The ratio of 1-BP excreted in urine over 1-BP absorbed through the lungs gives 0.002% [= $6.6 \times 10^{-6} \times 0.375^{-1} \times 100$(%)]. A similar calculation in the case of urinary toluene (Kawai *et al.* 1996) after 10 ppm toluene vapour exposure gives 0.006%

as the ratio for urinary toluene to estimated respiratory uptake of toluene, and it is 0.03% for urinary methylchloroform after methylchloroform vapour exposure at 10 ppm (Mizunuma *et al.* 1995). Thus, the low ratio is not unique to 1-BP but may probably be common to lipophilic solvents in general.

A further calculation with urinary Br (in place of urinary 1-BP) taking two molecular weights of 122.98 for 1-BP and 79.90 for Br into consideration suggests that uptake of 0.375 mg min^{-1} 1-BP after 10 ppm 1-BP exposure is associated with that of 0.244 mg min^{-1} Br, whereas 12.7×10^{-3} mg min^{-1} Br will be excreted into urine. The ratio will be 5.2%. Simple assumption that removal of Br from 1-BP molecule will result in the formation of *n*-propanol (followed by urinary excretion either in a free form or as conjugated) suggests that 5.2% of the 0.375 mg min^{-1} 1-BP absorbed (or 0.183 mg min^{-1} as *n*-propanol when the molecular weight of *n*-propanol of 60.09 is taken into account) should appear in urine as *n*-propanol. The calculation gives 9.5×10^{-3} mg min^{-1} or 9.5×10^{-3} mg $(10^{-3}\,l)^{-1}$ and therefore 9.5 mg l^{-1}. A preliminary analysis of the urine samples for *n*-propanol [either as free or after acid hydrolysis by analogy to analysis for *n*-butanol analysis (Kawai *et al.* 1997b; the detection limit for *n*-propanol being 0.01 mg l^{-1}) was however unsuccessful to detected possible urinary excretion of *n*-propanol.

Quantitative exposure – excretion analysis in relation to exposure intensity was not possible in the 2-BP-exposed case which this study group had experienced (Kawai *et al.* 1997a), because no personal 2-BP exposure data were available. It was observed however that a foreman with expectedly highest exposure to 2-BP excreted 1.95 mg l^{-1} acetone and 15.9 mg l^{-1} Br in his late Friday afternoon urine, indicating increases of 0.96 mg (or 17×10^{-6} mole) l^{-1} acetone and 5.4 mg (or 68×10^{-6} mole) l^{-1} Br over geometric mean background levels of 0.99 mg l^{-1} acetone and 10.5 mg l^{-1} Br (Kawai *et al.* 1997a). Thus, the amounts of the two debromination metabolities of 2-BP in urine showed a ratio of 1:4 for acetone:Br. This makes rather a contrast to the present observation on 1-BP metabolites that the urinary excretion of *n*-propanol should be much less than one-hundredth of that of Br [i.e. <0.01 mg (= 0.17 mmole) *n*-butanol versus 9.5 mg (= 119 mmole) Br]. It remains possible however that other debrominated metabolites may be excreted in urine.

The background level of Br-U (about 8 mg l^{-1}; table 3) is in general agreement with the total dietary intake of 8.5 to 11.8 mg Br day^{-1} (Matsuda *et al.* 1994) when daily urine volume of 1 to 1.5 l is assumed. This study group found that background Br-U is associated at least in part with dietary habits of Japanese people such as high consumption of sea food (Ministry of Health and Welfare, Japan 2000), which is known to be rich in Br. This observation will be published in a separate paper (Zhang *et al.* 2000).

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