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Brief Report

Comparison of the exposure-excretion relationship between men and women exposed to organic solvents

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Abstract: Comparison of the exposure-excretion relationship between men and women exposed to organic solvents: Toshio KAWAI, *et al*. Osaka Occupational Health Service Center—Objectives: The present study was initiated to examine if application of the same biological occupational exposure limits (BOELs) for organic solvents is applicable across the sexes. **Methods:** A survey was conducted in 69 micro-scale enterprises in a furniture-producing industrial park. In practice, 211 men and 52 women participated in the survey. They worked in a series of production process, and were exposed to solvent vapor mixtures. The exposure intensities were monitored with two types of diffusive samplers, one with carbon cloth (for solvents in general) and the other with water (for methyl alcohol) as adsorbents. Solvents in the adsorbents and headspace air from urine samples were analyzed with capillary FID-GC. The measured values were subjected to linear regression analysis followed by statistical evaluation for possible sex-related differences in slopes. **Results:** Essentially no significant difference was detected between men and women in regression line parameters including slopes. Possible differences in the cases of acetone and toluene were discussed and excluded. **Conclusions:** With the exceptions for acetone and toluene, the present study did not detect any clear differences between men and women. In examinations of past reports, no support for the observed differences was found. The present findings deserve further study so that a solid conclusion can be formed.
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Key words: Biological exposure limit, Organic solvents, Sex-related difference, Toluene, Un-metabolized solvents in urine, Urinalysis

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Biological monitoring of occupational exposure to organic solvents (solvents in short) in terms of urinalysis for un-metabolized solvents per se has been gaining attention[1)]. For several solvents, biological occupational exposure limits (BOELs) are set not based on the direct exposure-effect relationship, but instead are derived indirectly as the level of a biological exposure indicator that corresponds to the effect-based occupational exposure limit[2)]. Usually only one value is set to be applied to both men and women, despite the empirical understanding that body compositions are different between men and women. The setting of a single value is probably due to the fact that historically work in hazardous environments (including workplaces using solvents) has been limited to men. Opportunities are therefore limited to compare the exposure-excretion relationship between the two sexes.

This study group had a unique opportunity to study cases in which men and women were working together under conditions of exposure to solvent mixtures. The findings are reported in this communication.

Materials and Methods

The survey was conducted in 1998–9 in a furniture-producing industrial park in southern Japan. Enterprises were mostly of micro-scale with less than 10 workers. Solvents were employed as mixtures in paints, thinner or adhesives, and both men and women were engaged in a series of furniture production processes.

Workers serving in the same plant were examined on the same day. In total, 238 men and 60 women in 69 enterprises participated in the survey. The present survey on solvent exposures revealed that 25 men and 7 women were exposed to isopropyl alcohol together with acetone. As isopropyl alcohol is converted to acetone in vivo[3)], these workers were excluded from the analyses. Three subjects who were under treatment for diabetes were also excluded, as diabetes

may induce excretion of acetone in urine[4,5]. Thus, 211 men and 52 women were available for further analyses. The mean ages (± standard deviation) of the male and female workers were 40.7 ± 12.5 and 52.9 ± 7.9 years, respectively. Their service durations (mean±standard deviation) were 12.5 ± 10.2 and 16.3 ± 9.9 years.

All participants provided informed consents. The study protocol was retrospectively reviewed by the Ethics Committee, Occupational Health Service Center, Japan Occupational Safety and Health Association, Tokyo, Japan. The Committee considered the study to have met the review exemption criteria.

Each worker wore a diffusive sampler equipped with carbon cloth for solvents in general[6,7] and one with water as the adsorbent for methyl alcohol[8,9] for an entire 8-hour shift, and provided a spot urine sample at the end of the shift. The solvents adsorbed by the exposed cloth were extracted with carbon disulfide, which was then subjected to flame ionization detector-equipped gas-chromatographic (FID-GC) analysis on a capillary column[6,7]. Methyl alcohol in water was analyzed by the FID-GC method as previously described[9].

Production work started at 08:30 and finished at 17:00. Immediately after the end of the shift, each worker collected his/her urine sample in an air-tight glass bottle, 5 m*l* of which was transferred to a headspace (HS) vial within 1 hour after the collection, according to the procedures previously described[10]. The quantification limits (QLs) for solvent in air were 0.1 ppm in general (except for acetone and methyl alcohol for which 1.0 ppm was the QLs), and the QLs for solvents in urine were 1 μg/*l* in general (except that 0.1 mg/*l* for both acetone and methyl alcohol)[8,9].

Possible statistical differences in intercepts, slopes and correlation coefficients between two regression lines were examined after statistical procedures[11]. A probability of 5% was taken for statistical evaluation of significant differences.

Results

Solvent exposure

Nineteen types of solvents were detected, among which toluene and acetone were most frequently observed (Table 1). Of these solvents, 6 types of solvents, i.e., acetone, methyl alcohol, methyl ethyl ketone, methyl isobutyl ketone, toluene and xylenes, were selected as the solvents for which biological monitoring by means of urinalyses would be applicable for un-metabolized solvents[9,10,12,13].

It should be noted that the types of solvent mixtures varied depending on the works. The exposure intensity was generally low, i.e., 5 ppm or lower as geometric means when evaluated individually (Table 1), although some of the workers were exposed at much higher concentrations, e.g., toluene at 163 ppm. When evaluated as solvent mixtures taking advantage of the addictiveness formula[2], the worker with the highest exposure was a woman (Table 1).

Table 1. Solvent concentrations in workroom air[1] and in urine[2]

Solvents	Sex	No. of cases	Solvent concentration in air					Solvent concentration in urine				
			Unit	GM[3]	*p*[4]	GSD[3]	Max[3]	Unit	GM	*p*	GSD	Max
Acetone	Men	161	ppm	1.09	M	3.59	29.7	mg/*l*	1.15		1.75	8.3
	Women	47	ppm	0.67		4.99	51.5	mg/*l*	1.22		2.35	21.1
Methyl alcohol	Men	101	ppm	4.69		2.56	79.0	mg/*l*	2.93		1.87	11.4
	Women	34	ppm	5.53		2.62	106.1	mg/*l*	3.61		1.60	12.5
Methyl ethyl ketone	Men	88	ppm	0.42		2.91	5.6	μg/*l*	56.28		1.86	282.2
	Women	24	ppm	0.26		3.72	2.1	μg/*l*	50.13		1.56	112.0
Methyl isobutyl ketone	Men	76	ppm	0.59		3.10	15.1	μg/*l*	28.82		2.39	445.4
	Women	19	ppm	0.49		2.92	9.1	μg/*l*	26.64		2.37	288.3
Toluene	Men	211	ppm	3.07		3.58	103.9	μg/*l*	8.62		2.27	98.0
	Women	52	ppm	4.20		4.04	163.2	μg/*l*	14.04	W	2.43	225.7
Xylenes	Men	176	ppm	1.11	M	3.08	27.3	μg/*l*	5.51	M	2.07	43.0
	Women	39	ppm	0.69		3.35	9.1	μg/*l*	4.17		1.95	13.0
Mixture[5]	Men	211		0.11		3.44	2.12		0.34		1.74	1.78
	Women	52		0.14		3.36	3.44		0.49	W	1.85	4.81

[1] Eight-hour average concentration by diffusive sampling. [2] Concentrations in end-of-shift urine samples. [3] Geometric mean, geometric standard deviation, and the maximum. [4] The difference between men and women was significant; M for men>women, W for women >men. [5] Calculated by making use of the additiveness formula[2]. Xylenes were not taken into account when solvents in urine were evaluated because no BOEL values were set for un-metabolized xylenes in urine.

Un-metabolized solvents in urine

Solvent exposure concentrations and solvent concentrations detected in end-of-shift urine samples were subjected to correlation analyses (Table 2). The regression lines thus obtained were statistically compared[6] for possible differences between men and women. Intercepts were considered to represent the levels among non-exposed subjects. It was clear that no significant sex-related difference was detected in the intercepts for the 6 solvents. In the case of toluene, the correlation coefficients were significantly different between men and women. Both correlation coefficients for men and women were however statistically significant ($p<0.01$).

The slopes represent the increments due to exposure to each solvent, and are the determining factor for setting BOELs based on the exposure-excretion relationship. In practice, no significant difference was observed between men and women for 4 solvents, i.e., methyl alcohol, methyl ethyl ketone, methyl isobutyl ketone and xylene. There were significant differences in the cases of acetone and toluene (Table 2).

Discussion

To examine whether previous publications are in agreement with the findings on the different slopes for men and women, reports were retrieved for past studies in which the same methods as used in the present study were employed. Sex-related differences in the acetone exposure-excretion relationship (Table 2) were examined by comparison with previous study results[12], in which 38 male workers were exposed to acetone (in combination with styrene). Comparison of the study results with the values for women in Table 2 showed that intercepts (0.10 vs. 0.95 in mg/*l*), slopes (0.40 vs. 0.36 mg/*l*/ppm) and correlation coefficients (0.895 vs. 0.824) did not differ significantly ($p>0.05$) between the two groups. The slope for the acetone regression line for men in the present study (Table 2) was too shallow due to unknown reasons. The acetone levels in urine may increase in the case diabetes[4, 5], but unfortunately this could not be examined because no medical examination was conducted to detect subclinical cases of diabetes.

The slopes for toluene were also different between men and women in the present study (i.e., 0.96 vs. 1.26 μg/*l*/ppm for men and women, respectively; Table 2). Attention was paid to this observation because toluene is the most commonly used solvent[14] as found in the present survey (Table 1). For comparison with the present results for toluene-exposed women (Table 2), 3 groups of toluene-exposed male workers were cited from a previous publication[15]. The selection criteria were toluene exposures at the levels similar to that for the women (i.e. a geometric mean of about 3 ppm) and comparable numbers of cases (cases of workers in two workplaces were combined to obtain about 50 cases per group). In practice, three groups (Groups 1, 2 and 3) were available for comparison. The workers were engaged in printing and other tasks, and exposed to solvent mixtures including toluene.

The intercepts, the slops and the correlation coefficients were 4.24 μg/*l*, 1.39 μg/*l*/ppm and 0.832 for Group 1, 7.24 μg/*l*, 1.30 μg/*l*/ppm and 0.491 for Group

Table 2. Comparison of regression parameters between men and women

Solvents	Units for uriary conc.	Sex	No. of cases	Regression line parameter			Significant difference between men and women (p value)		
				Inter-cept	Slope	Corr. coeff.[1]	Inter-cept	Slope	Corr. coeff.
Acetone	mg/*l*	Men	161	0.90	0.20	0.711	ns	<0.01	ns
		Women	47	0.95	0.36	0.824			
Methyl alcohol	mg/*l*	Men	101	2.65	0.10	0.570	ns	ns	ns
		Women	34	3.20	0.08	0.721			
Methyl ethyl ketone	µg/*l*	Men	88	43.1	30.7	0.551	ns	ns	ns
		Women	24	43.7	20.7	0.525			
Methyl isobutyl ketone	µg/*l*	Men	76	12.9	25.65	0.896	ns	ns	ns
		Women	19	10.8	30.54	0.992			
Toluene	µg/*l*	Men	211	8.21	0.96	0.753	ns	<0.01	<0.01
		Women	52	8.92	1.26	0.885			
Xylenes	µg/*l*	Men	176	5.06	0.93	0.601	ns	ns	ns
		Women	39	4.01	0.71	0.478			

[1] All correlation coefficients are statistically significant ($p<0.01$).

2, and 1.08 μg/*l*, 1.22 μg/l/ppm and 0.757 for Group 3, respectively. None of the slopes of regression lines for the 3 male groups, 1.22 to 1.39 μg toluene/l/ppm, differed from that for women, 1.26 μg toluene/l/ppm in the present study (Table 2). Additional comparison of slope of the regression line for the present toluene-exposed male group, 0.96 μg toluene/l/ppm, with that for the combination of Groups 1, 2 and 3, 1.36 μg toluene/l/ppm, revealed that the slope for the male group in the present study (Table 2) was unusually shallower than it should be. Thus, it appeared quite likely that there would also be no sex-related difference in the slopes.

There are several limitations in the present study. First of all, workers were exposed to solvent mixtures and not to one single solvent. Thus, the possibility of solvent interaction in kinetics cannot be ruled out, although mixture exposure is the typical type of exposure in various industries[16,17]. The numbers of workers studied were biased toward men, i.e., more male cases than less female cases. This is however due to tradition of male workers and not female workers being expected to serve in hazardous environments such as workplaces using solvents. The exposure concentrations were generally lower than the current occupational exposure limits[2] for each solvent which is good from the view point of occupational health. Another limitation in the study design was the inability to conduct surveys on the same weekdays. Because the production schedules varied depending on the plants, it was not possible to carry out the survey on a fixed day of the week, e.g., the survey was conducted on Monday in one plant, whereas it was conducted on Thursday in another plant. The difference in days of the week on which the survey was conducted might have affected solvent accumulation in the bodies of the participating workers. However, the men and women in one plant were examined on the same day.

Conclusions

The present survey results did not indicate clear diffidences between men and women in terms of the exposure-excretion relationship. The observed differences for the cases of acetone and toluene were not supported by previous publications. It is apparently desirable to carry out further studies for possible sex-related differences in the exposure-excretion relationship.

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Conflicts of interest: The authors declare that they have no conflicts of interest.

References

1) Ikeda M. Solvents in urine as exposure markers. Toxicol Lett 1999; 108: 99–106.
2) Japan Society for Occupational Health. Recommendation of occupational exposure limits (2013–2014). J Occup Health 2013: 55; 422–41.
3) Kawai T, Yasugi T, Horiguchi S, et al. Biological monitoring of occupational exposure to isopropyl alcohol vapor by urinalysis for acetone. Int Arch Occup Environ Health 1990; 62: 409–13.
4) Laffel L. Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Res Rev 1999; 15: 412–26.
5) Wang Z, Wang C. Is breath acetone biomarker to diabetes? A historical review on breath acetone measurements. Breath Res 2013. (doi: 10.1088/1752-7155/7/3/1037 109).
6) Hirayama T, Ikeda M. Applicability of activated carbon felt to the dosimetry of solvent vapor mixture. Am Ind Hyg Assoc J 1979; 40: 1091–6.
7) Kawai T, Yasugi T, Mizunuma K, et al. Comparative evaluation of urinalysis and blood analysis as means of detecting exposure to organic solvents at low concentrations. Int Arch Occup Environ Health 1992; 64: 223–34
8) Uchida Y, Kawai T, Yasugi T, Ikeda M. Personal monitoring sampler for acetone Vapor exposure. Bull Environ Contam Toxicol 1990; 44: 900–4.
9) Kawai T, Yasugi T, Mizunuma K, Horiguchi S, Hirase Y, Ikeda M. Methanol in urine as a biological indicator of occupational exposure to methanol vapor. Int Arch Occup Environ Health 1991; 63: 311–8.
10) Kawai T, Mizunuma K, Okada Y, Horiguchi S, Ikeda M. Toluene itself as the best urinary marker of toluene exposure . Int Arch Occup Environ Health 1996; 68: 289–97.
11) Ichihara K. Statistics for Bioscience. Nankodo Publishers, Tokoyo. 1995 (in Japanese).
12) Kawai T, Yasugi T, Uchida Y, Iwami O, Ikeda M. Urinary excretion of un-metabolized acetone as an indicator of occupational exposure to acetone. Int Arch Occup Environ Health 1990; 62: 165–9.
13) Kawai T, Zhang Z-W, Takeuchi A, et al. Methyl isobutyl ketone and methyl ethyl ketone in urine as biological markers of occupational exposure to these solvents at low levels. Int Arch Occup Environ Health 2003; 76: 17–23.
14) Nagasawa Y, Ukai H, Okamoto S, et al. Organic solvent use in enterprises in Japan. Ind Health 2011; 49: 534–5.
15) Kawai T, Ukai H, Inoue O, et al. Evaluation of biomarkers of occupational exposure to tolune at low levels. Int Arch Occup Environ Health 2008; 81: 253–62.