

Estimation of biological occupational exposure limit values for selected organic solvents from logarithm of octanol water partition coefficient

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Abstract: Estimation of biological occupational exposure limit values for selected organic solvents from logarithm of octanol water partition coefficient:

Toshio KAWAI, et al. Osaka Occupational Health Service Center, Japan Industrial Safety and Health Association—Objectives:

For several organic solvents (solvents in short), biological occupational exposure limits (BOELs) have been established for un-metabolized solvents in urine, based on the solvent exposure-urinary excretion relationship. This study was initiated to investigate the possibility of estimating a BOEL from the P_{ow} (the partition coefficient between n-octyl alcohol and water), a physico-chemical parameter. **Methods:** Data were available in the literatures for exposure-excretion relationship with regard to 10 solvents for men and 7 solvents for women. **Results:** Statistical analysis revealed that the slopes (after correction for molecular weights and logarithmic conversion) of the exposure-excretion regression lines linearly correlated ($p < 0.01$) with the log P_{ow} values of the respective solvents. No significant difference ($p > 0.05$) was observed between men and women, and it was acceptable to combine the data for the two sexes. Thus the log P_{ow} -log slope relation was represented by a single equation for both sexes. Based on the observations, procedures were established to estimate BOEL values from P_{ow} . Successful estimations of BOELs for styrene, tetrahydrofuran and m-xylene (a representative of xylene isomers) were calculated as examples. **Conclusions:** The present study proposed promising procedures for estimation of a BOEL from the P_{ow} . (J Occup Health 2015; 57: 359–364)

Key words: Biological occupational exposure limit, Exposure-excretion relationship, Octanol water partition coefficient (P_{ow}), Organic solvent, Regression analysis, Sex difference

Un-metabolized solvents in urine as a marker of exposure to solvents in concern¹⁾ has been gradually accepted as an indicator of occupational solvent exposure. For example, both the Japan Society for Occupational Health (JSOH)²⁾ and the American Conference of Governmental Industrial Hygienists (ACGIH)³⁾ in 2014 listed 7 solvents (i.e., acetone, dichloromethane, methyl alcohol, methyl ethyl ketone, methyl isobutyl ketone, tetrahydrofuran and toluene) in urine as quantitative markers of the occupational exposure (i.e., biological occupational exposure limits or BOELs for JSOH and biological exposure indices or BEIs for ACGIH) in 2014.

The typical procedures to establish an occupational exposure limit (OEL) are based on an analysis of the relationship between the 8-hour average intensity of exposure to a chemical and its health effects^{2, 3)}. In contrast, BOEL values for some solvents are based on the exposure-excretion relationship, i.e., the urinary solvent level (in end-of-shift samples) corresponding solvent exposure at the OEL level (e.g., in cases of toluene, toluene in the end-of-shift urine after 8-hour toluene exposure at OEL level)^{2, 3)}. That means that quantitative data are needed on solvent exposure intensity and resulting solvent levels in end-of-shift urine samples. Although urine sampling is not invasive, such a database is not always available for all solvents.

The present study was initiated to investigate the possibility to estimate a BOEL from a physico-chemical parameter of a solvent, such as P_{ow} (i.e., the partition coefficient between n-octyl alcohol and water). To do this, the regression line slopes in the relationship between solvent exposures and the levels

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of un-metabolized solvent in urine were obtained from published reports⁴⁻¹⁵, and the relation of log Slope (i.e., the logarithm of the slope of the regression line between the exposure and the excretion) with log P_{ow} were analyzed.

Materials and Methods

Database

Exposure-excretion relationship data for 10 solvents were obtained from previous publications of this group⁴⁻¹⁵; the relationship data included the intercepts, the slopes and correlation coefficients of the calculat-

ed regression lines between the 8-hour time-weighted average exposure intensity (in ppm) and the levels of un-metabolized solvents in end-of-shift urine samples (in $\mu\text{g/l}$ in general, but in mg/l for acetone and methyl alcohol), together with numbers of cases studied (Table 1). It should be added that the all correlation coefficients were statistically significant ($p < 0.01$). In these studies, 8-hour time-weighted average exposure to solvents was measured by diffusive sampling, and urine samples were collected at the end of the shift; routine procedures in solvent exposure monitoring were followed.

Table 1. Data used in the analysis; regression line parameters and references

Worker groups by solvent	No. of cases	Regression line ¹ parameters			Reference No.
		α	β	r	
Male workers					
Acetone A	161	0.90	0.200	0.71	4
Acetone B	38	10.00	0.400	0.90	5
Acetone C	60	0.32	0.201	0.91	6
Acetone D	45	0.40	0.208	0.84	7
Number-weighted average ³ for acetone			0.226		
Bromopropane, 1-	43	0.20	0.660	0.96	8
Dichloromethane	50	8.80	3.300	0.80	9
Dichloropropane, 1,2-	38	9.40	8.900	0.92	10
Methyl alcohol A	101	2.65	0.100	0.57	4
Methyl alcohol B	25	3.08	0.146	0.74	11
Number-weighted average ³ for methyl alcohol			0.109		
Methyl ethyl ketone	88	43.10	30.700	0.55	4
Methyl isobutyl ketone	76	12.90	25.650	0.90	4
Toluene A	211	8.21	0.960	0.75	4
Toluene B	473	2.30	1.340	0.67	12
Toluene C	294	11.30	0.650	0.60	13
Toluene D	115	2.20	1.520	0.84	14
Number-weighted average ³ for toluene			1.100		
Trichloroethane, 1,1,1-	50	0.21	1.330	0.94	15
Xylene	176	5.06	0.930	0.60	4
Female workers					
Acetone	47	0.95	0.36	0.82	4
Dichloromethane	19	3.6	3.03	0.96	9
Methyl alcohol	34	3.20	0.08	0.72	4
Methyl ethyl ketone	24	43.7	20.7	0.53	4
Methyl isobutyl ketone	19	10.8	30.54	0.99	4
Toluene	52	8.92	1.26	0.89	4
Xylene	39	4.01	0.71	0.48	4

¹ In the regression line $Y = \alpha + \beta X$, X is the 8-hour time-weighted average concentration in the exposed air in ppm, Y is the concentration in the end-of-shift urine in $\mu\text{g/l}$ in general (mg/l in the cases of acetone and methyl alcohol), α is the intercept (in $\mu\text{g/l}$ or mg/l), and β is the slope (in $\mu\text{g/l/ppm}$ or mg/l/ppm).

² Correlation coefficient. The correlations were all statistically significant ($p < 0.01$). ³ Case number-weighted average for acetone A, B, C and D, for methyl alcohol A and B, or for toluene A, B, C and D.

Molecular weights and CAS numbers were obtained from the database of e-ChemPortal (2004 version)¹⁶, and log P_{ow} values were obtained from the database of CHRIP (2014 version)¹⁷. The values are summarized in Table 2. Cases for m-xylene and styrene were also included for reference.

Ethical issues

Informed consent was obtained from each participating worker at the time of the surveys. It should be noted that no ethics committee had been established at the time of field surveys (i.e., the studies for databases) for reviewing the study design. Thus, the study design was retrospectively submitted in 2014 to the Ethics Committee in the Industrial Safety and Health Association (Tokyo Office), Japan for reviewing. The Committee confirmed that the data in the manuscript were all cited from previous publications, and that the study met with the exemption criteria.

Statistical analysis

Absence of significant differences ($p > 0.05$) between pairs of regression lines was confirmed by the comparison of intercepts, slopes and correlation coefficients¹⁸. The Excel Statics software¹⁹ was employed for equations of 95% lower and upper limit curves.

Results and Discussion

Comparison of regression lines among male and female workers

Database studies on male workers were found for 10 solvents through literature retrieval. Among them, two or more studies were available for 3 solvents, i.e., 4, 2 and 4 studies in the cases of acetone, methyl alcohol and toluene, respectively (Table 1). For these solvents, case number-weighted average of slope

values were taken as the representative slope values for the solvents (the values in italics in Table 1). In the case of women, database studies were available for 7 solvents, but only one database study was found per solvent. Thus, one regression line slope was available for each solvent, i.e., 10 solvents in the case of men and 7 solvents in the case of women (Table 3).

Taking the log P_{ow} values as the independent variables and log Slopes (after division by molecular weight to make on a molar basis) as the dependent variables, regression lines were calculated for the 7 solvents for men and women separately. Calculation gave an intercept of 3.041 for men and 3.026 for women, a slope of -0.708 for men and -0.710 for women, and a correlation coefficient of -0.955 for

Table 2. Parameters for solvents studied

Solvent	Molecular weight ¹	CAS No. ¹	Log P_{ow} ²
Acetone	58.09	67-64-1	-0.24
Bromopropane, 1-	122.99	106-94-5	2.10
Dichloromethane	84.93	75-09-2	1.25
Dichloropropane, 1,2-	112.99	78-87-5	2.28
Methyl alcohol	32.04	67-56-1	-0.74
Methyl ethyl ketone	72.11	78-93-3	0.29
Methyl isobutyl ketone	100.16	108-10-1	1.31
Styrene	104.15	100-42-5	3.05
Toluene	92.14	108-88-3	2.73
Trichloroethane, 1,1,1-	133.40	71-55-6	2.49
Xylene ³	106.18	108-38-3	3.20

¹ Cited from Organization for Economic Co-operation and Development¹⁶. ² Cited from National Institute of Technology and Evaluation¹⁷. ³ Represented by m-xylene.

Table 3. Selected parameters for regression analysis

Solvent	Log P_{ow}	Men		Women		Lg Slope ²
		Slope ¹	Log Slope	Slope ¹	Log Slope	
Acetone	-0.24	3.89×10^3	3.590	6.20×10^3	3.792	3.703
Bromopropane, 1-	2.10	5.37	0.730			0.730
Dichloromethane	1.25	38.86	1.590	35.68	1.552	1.571
Dichloropropane, 1,2-	2.28	78.77	1.896			1.896
Methyl alcohol	-0.74	3.40×10^3	3.531	2.50×10^3	3.398	3.470
Methyl ethyl ketone	0.29	4.26×10^2	2.629	2.87×10^2	2.458	2.552
Methyl isobutyl ketone	1.31	2.56×10^2	2.408	3.05×10^2	2.484	2.448
Toluene	2.73	11.940	1.077	13.67	1.136	1.107
Trichloroethane, 1,1,1-	2.49	9.97	0.999			0.999
Xylene	3.20	8.76	0.943	6.69	0.825	0.888

¹ Unit for the slopes; nmole//ppm. ² Log (arithmetic mean of the slope for men and the slope for women). The value for men was taken when only the values for men were available.

men and -0.931 for women. Comparison showed that there was no significant ($p>0.05$) difference between the men-women pairs of regression line parameters. When calculations were performed with 10 solvents for men and 7 solvents for women, and regression line parameters were compared between men and women, no significant difference ($p>0.05$) was detected (data not presented). Thus, it was considered that the two regression lines (one for men and one for women) could be combined by taking the average values. Thus the averages were taken for the 7 solvents for which slopes were available for both men and women. Slopes were available only for men in the cases of the remaining 3 solvents (i.e., 1-bromopropane, 1,2-dichloropropane and 1,1,1-trichloroethane; Table 3). Accordingly, 10 cases in total were employed for further statistical analyses.

The equation thus established together with the 95% upper and lower limits are depicted in Fig. 1. The equation for the regression line is $Y_1 = 3.017 - 0.736X$ ($r = -0.913$, $p < 0.01$; Eq. 1), where X is the $\log P_{ow}$ of the solvents and Y_1 is the logarithm of the slope in nmole/ppm for the solvents. The dotted curves to show the 95% lower (Y_2 ; Fig. 1) and upper limits (Y_3) were best ($R^2 > 0.999$) fit with quadratic equations of $Y_2 = 2.516 - 0.528X - 0.073X^2$ (Eq. 2) and $Y_3 = 3.517 - 0.945X + 0.073X^2$ (Eq. 3), respectively.

The high correlation coefficient for Eq. 1, -0.913 suggested that there existed a close correlation between $\log P_{ow}$ and \log Slope. In the case that a BOEL is to be established based on the linearity

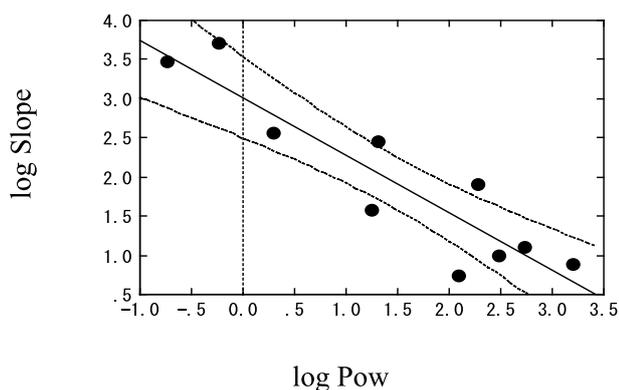


Fig. 1. Linear regression between $\log P_{ow}$ and \log slope for relation between the 8-hour time-weighted average exposure to each solvent and excretion of un-metabolized solvent in the end-of-shift urine. See the text and Table 1 for details. The unit for the slope was nmole//ppm. Each of the 10 dots represents one solvent. The solid line in the middle is the calculated regression line, whereas the two dotted curves show the upper and lower 95% confidence limits, respectively. For equations, see the Results section.

between the time-weighted average solvent concentration in air and the solvent concentration in end-of-shift urine, it is possible to estimate the BOEL from the OEL once the slope of the regression line is estimated. It should be added that the background excretion of the solvent (i.e., solvent in urine from non-exposed subjects) is substantially lower than the levels observed in the urine of workers exposed to the solvent at the OEL level (except for the case in which the target chemical is physiologically excreted, e.g., the case of urinary acetone).

Proposed procedure to estimate a BOEL from $\log P_{ow}$

It should be noted that the applicability of the following procedures is limited in principle to the cases in which the endogenous excretion of the target solvent is nil in urine from non-exposed subjects.

1. Search a proper database for the $\log P_{ow}$ of the solvent.
2. Insert the $\log P_{ow}$ to Eq. 1 to calculate Y_1 . The equation will give an estimate for the slope (α) of the regression line between the solvent concentration in air (C_{air}) and the concentration in urine (C_{urine}) so that $C_{urine} = \alpha \times C_{air}$. Insertion of the $\log P_{ow}$ into Eq. 2 and Eq. 3 will give the 95% lower and upper limits of the variation in the estimated slope (α_{-95} and α_{+95}).
3. Calculate the slope from \log Slope.
4. Insert the OEL value in the following three equations of
 $C_{urine} = \alpha \times C_{air}$, $C_{urine} = \alpha_{-95} \times C_{air}$, and
 $C_{urine} = \alpha_{+95} \times C_{air}$
5. As C_{urine} is calculated in nmole, apply the molecular weight of the solvent to convert it to traditional units (mg/l or μ g/l).

Agreement of the estimated biological occupational exposure limits with existing BOELs (or BEIs)

Calculations were made for the estimated exposure limits together with their 95% confidence limits for the solvents listed in Table 1. The results (together with data for styrene, tetrahydrofuran and m-xylene) are presented in Table 4.

Comparison of the calculated estimates with the existing BOELs and BEIs suggested that agreement was very good for toluene (both JSOH and ACGIH), acetone (ACGIH) and methyl alcohol (JSOH). The 95% intervals were too wide to carry any practical meaning in BOEL (or BEI) estimation.

Of particular interest is the case of xylene (represented by m-xylene), for which neither a BOEL nor a BEI has been set. Good agreement of the estimate was observed with the BOEL and BEI in the case of toluene. Xylene (a structural homologue) has a greater molecular weight and a higher P_{ow} than toluene (Table

Table 4. Estimation of biological occupational exposure limits (BOELs) and biological exposure indices (BEIs)

Solvent	Japan Society of Occupational Health ^{2,3)}				American Conference of Governmental Industrial Hygienists ^{4,5)}			
	OEL (ppm)	BOEL (mg/l)	Estimation (mg/l)		TLV (ppm)	BEI (mg/l)	Estimation (mg/l)	
			Estimate	(95% LL – 95%UL)			Estimate	(95% LL – 95%UL)
Acetone	200	40	18.2	(5.1 – 65.1)	250	25	22.7	(6.3 – 81.4)
Dichloromethane	50	0.2	0.53	(0.24 – 1.20)	50	0.3	0.53	(0.24 – 1.20)
Methyl alcohol	200	20	23.4	(4.7 – 115.8)	200	15	23.4	(4.7 – 115.8)
Methyl ethyl ketone	200	5	9.2	(3.3 – 25.6)	200	2	9.2	(3.3 – 25.6)
Methyl isobutyl ketone	50	1.7	0.57	(0.25 – 1.27)	20	1	0.23	(0.10 – 0.51)
Styrene	20	— ¹	0.012	(0.004 – 0.043)	20	— ¹	0.012	(0.004 – 0.043)
Tetrahydrofuran	200	2	6.9	(2.6 – 18.1)	50	2	1.7	(0.7 – 4.5)
Toluene	50	0.06	0.047	(0.016 – 0.14)	20	0.03	0.02	(0.006 – 0.56)
Xylene ²	50	— ¹	0.026	(0.006 – 0.092)	100	— ¹	0.05	(0.013 – 0.185)

¹ Both BOEL and BEI are yet to be proposed. ² m-Xylene is taken as a representative of three isomers.

2). Thus, the estimate (after rounding of the value) of 0.02 mg/l for a 50 ppm OEL or 0.05 mg/l for a 100 ppm TLV sounds quite reasonable.

Styrene (or styrene monomer) is another possible candidate for estimation of BOEL value in urine. Both JSOH and ACGIH gave a BOEL or BEI, respectively, for styrene in blood but not for styrene in urine^{2,3)}. Tentative application of the estimation procedures to styrene with an OEL of 20 ppm²⁾ gave an estimate of 0.012 mg/l for the BOEL (Table 4). By structural analogy of styrene (i.e., vinylbenzene) to toluene (methylbenzene), application of head-space gas-chromatography may be possible for analysis of styrene in urine. Styrene is a reactive chemical and may polymerize automatically (to form polystyrene). The risk of polymerization during sample collection and analysis processes, however, should be minimal at the expected concentration in biological samples.

Tetrahydrofuran (CAS No. 109-99-9) was the only solvent that was not in the present study database (Tables 1 and 2). The estimated biological exposure limit was 1.7 mg/l in response to TLV of 50 ppm (BEI=2 mg/l), whereas it was 7.1 mg/l for an OEL of 200 ppm (BOEL=2 mg/l). Perusal of publication records made it clear that an OEL had been published as early as in 1988 (the BOEL was set in 2008). It may be that the revision of the OEL has been delayed and that the OEL should be updated as early as possible.

Possible limitations of the study

There are several possible limitations in this study. As excretion of un-metabolized solvents in urine primarily depends on the diffusion, no difference in the velocity of biotransformation was taken

into account. In combining multiple databases, no specific adjustment was applied except for the number of cases in each database study (i.e., by application of the number-weighted average for the representative slope in men). Exposure intensities were different within and across solvents, and there were differences in the physical burdens on workers (and therefore differences in respiration rate) among the workplaces, but no corrections for these factors were technically possible. No correction for number of workers was made across solvents, and equal weight was given across the 10 solvents; otherwise, the results would have been more influenced by common solvents such as acetone and toluene. Finally, the variation in overall estimation (Table 4) was considerable, although the correlation coefficient between log P_{ow} and log Slope was as high as >0.9. This may be inherent to human studies, especially in field survey-based occupational health studies.

Conclusion

A statistical analysis-based procedure was established to estimate a BOEL for un-metabolized solvent in urine from a physico-chemical parameter of log P_{ow} . The application of the procedure revealed a close agreement of the estimate with the BOEL and the BEI in the case of toluene, the BEI in the case of acetone and the BOEL in the case of methyl alcohol. Based on the estimation procedure, a proposal was made for BOEL for xylene. It is inherent to field survey-based studies that the variation tends to be substantial. Nevertheless, the method developed in the present study may be a promising tool to establish BOELs for un-metabolized solvents which will be excreted in urine.

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

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