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Further examination of log P_{ow}-based procedures to estimate biological occupational exposure limits

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Abstract: Objectives: To test the reliability of the procedures (described in a previous article) for estimation of biological occupational exposure limits (BOELs). **Methods:** Data on four organic solvents (styrene, ethyl benzene, isopropyl alcohol and tetrachloroethylene) were obtained from recent publications and added to previously cited data for 10 organic solvents. Regression analysis was used for statistical evaluation. **Results and Discussion:** The previously reported results obtained using 10 solvents were reproduced by the analysis with 14 solvents. Repeated randomized division of the 14 sets into two subgroups of equal size followed by statistical comparisons did not show a significant difference between two regression lines. This reproducibility suggests that the procedures used to estimate BOELs may be applicable across many solvents, and this may be of particular benefit for protecting the health of workers who work with skin-penetrating solvents.
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Introduction

Biological exposure monitoring is an important tool to protect workers from the possible health effects of hazardous industrial chemicals, because this method can observe the severity of worker exposure irrespective of the route of exposure. In recent years, biological occupational exposure limits (BOELs) have been gaining increased attention[1-3]. With regards to organic solvent exposure, the attention has been focused on measurement of un-metabolized solvent in urine[4-6], due to the combination of a non-invasive sampling method and the availability of simple analytical procedures such as head-space gas-chromatography[4,5,7] or direct injection of the urine sample into a gas-chromatographic system (with use of a proper pre-column)[8] in the case of highly water-soluble solvents.

In the preceding report[9], procedures were developed to estimate BOEL by calculating the rate of the increase in un-metabolized solvent levels in response to respiratory exposure levels. This is done by calculating the slope of a regression line with the vapor exposure concentrations on the horizontal axis and urinary solvent concentrations on the vertical axis[9]. These values were then combined with the octanol-water partition coefficient (P_{ow}), a physico-chemical parameter of the solvent, and the molecular weight of the solvent for which an occupational exposure limit (OEL) is available, to estimate the BOEL.

The present study was conducted to approve the previously described procedures by re-examining the 10 chemicals used in the previous study[9] with 4 additional chemicals. The expected usefulness of the estimated BOEL values for exposure intensity evaluations of skin-penetrating solvents such as N,N-dimethylformamide[10,11] will be discussed.

Table 1. Regression line parameters for the four new solvents.

Solvent	No. of cases	Regression line[1] parameters			Reference No.
		Intercept (α)	Slope (β)	r	
Ethybenzene	130	0.98	0.79	0.86	12
Isopropyl alcohol	95	–70.0	40.0	0.80	8
Styrene	60	31	0.90	0.65	13
Tetrachloroethylene	50	207.4	2.64	0.48	14

[1] In the regression line $Y=\alpha+\beta X$, X is the 8-hour time-weighted average concentration in the exposed air in ppm, and Y is the concentration in the end-of-shift urine in μg/*l*.
r designates the correlation coefficient. The values were all statistically significant (p<0.01).

Table 2. Physico-chemical parameters for the additional four solvents

Solvent	Molecular weight[1]	CAS No[1]	Log P_{ow}[2]
Ethybenzene	106.17	100-41-4	3.15
Isopropyl alcohol	60.10	67-63-0	0.05
Styrene	104.15	100-42-5	3.05
Tetrachloroethylene	165.83	127-18-4	3.40

[1] Cited from the Organization for Economic co-operation and Development[15)].
[2] Cited from the National Institute of Technology and Evaluation[16)].

Table 3. Parameters of the four additional solvents used for regression analysis.

Solvent	Log P_{ow}	Log Slope[1]
Ethybenzene	3.15	0.872
Isopropyl alcohol	0.05	2.823
Styrene	3.05	0.937
Tetrachloroethylene	3.40	1.202

[1] Slope is given in units of nmole/*l*/ppm.

Materials and Methods

The study subjects were all male workers. Data on the original 10 solvents (acetone; 1-bromopropane; dichloromethane; 1,2-dichloropropane; methyl alcohol; methyl ethyl ketone; methyl isobutyl ketone; toluene; 1,1,1-trichloroethane; and xylenes) were cited from a previous publication[9)]. The data for male workers were cited from the original database employed in each report[8,9,12-14)]. In addition to the previously analyzed solvents, exposure-excretion data recently became available for four additional solvents: ethylbenzene[12)], isopropyl alcohol[8)], styrene[13)], and tetrachloroethylene[14)].

The same methods were used to analyze the original and the new solvents. Diffusive sampling was used for determination of the 8-hour time-weighted average (TWA) intensity of exposure; and solvent levels in urine were measured by head-space gas-chromatographic analysis[8)], or by direct injection into a pre-column-equipped gas-chromatograph[9)]. The regression line parameters obtained from these measurements are summarized in Table 1. Physico-chemical data including molecular weights (MW) and octanol-water partition coefficients (P_{ow}), together with CAS numbers were obtained from the appropriate databases[15,16)] and are summarized in Table 2. Based on these data, the log P_{ow} and log slope[9)] were calculated as an indicator of the rate of unmetabolized solvent in urine over air-borne exposure concentration (Table 3). Data were evaluated using regression analysis followed by testing the differences in the parameters for statistical significance[17)].

Results

Exposure-excretion data for the additional 4 solvents (see Materials and Methods section) were used to calculate the slopes. The slopes together with P_{ow} values were combined with the previously reported 10 sets of data[9)] on the slope and P_{ow}, and subjected to analysis following the procedures described previously[9)]. The results are depicted in Fig. 1. The figure was drawn based on the original 10 solvents[9)] (shown by solid circles). The additional 4 cases are marked with open circles in the figure with the following identification numbers: 1 for ethylbenzene[12)], 2 for isopropyl alcohol[8)], 3 for styrene[13)] and 4 for tetrachloroethylene[14)]. Using all 14 solvents for the calculation resulted in a regression line equation of $Y=2.95-0.66X$ where X=log P_{ow} and Y=log slope (in nmole/*l*/ppm) (Equation 1). The correlation coefficient was −0.93, which was highly significant (p<0.01). The equation of the curve for the 95% upper limit was $Y=3.321-0.810X+0.043X^2$ (Equation 2), and the equation for the 95% lower limit was $Y=2.589-0.517X-0.043X^2$ (Equation

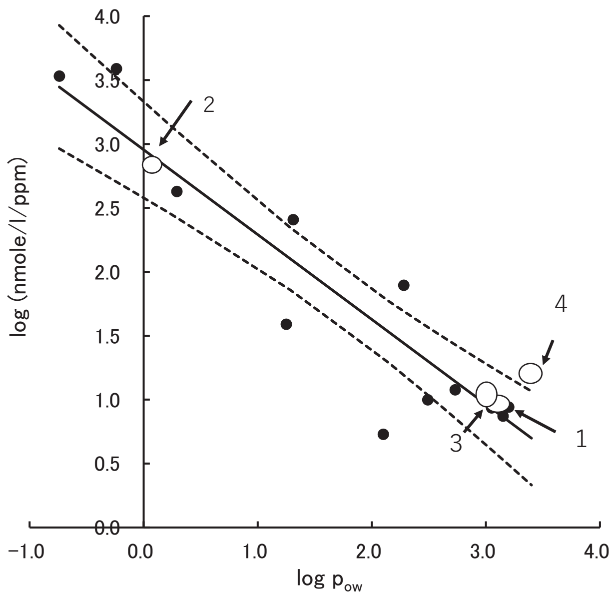

Fig. 1. Linear regression between log P_{ow} and log slope. The slope was calculated by relating the 8-hour TWA exposure to each solvent and excretion of un-metabolized solvent in the end-of-shift urine, as described in previous reports[6, 9]. The solid circles represent the 10 solvents used in the original study[9], and the open circles designate the additional 4 solvents presented in this work: 1=ethylbenzene, 2=isopropyl alcohol, 3=styrene, and 4=tetrachloroethylene. The line in the middle is the calculated regression line, and the two curves on both sides show 95% confidence range. The equations are presented in the Results section of the text.

Table 4. Comparison of pairs of regression lines

Pairs[1]	Regression line parameters		
	Intercept	Slope	r
10 [2]	3.02	–0.73	–0.92
14 [3]	2.95	–0.66	–0.93
A1	2.81	–0.62	–0.89
B1	3.06	–0.69	–0.96
A2	2.80	–0.63	–0.88
B2	3.05	–0.68	–0.95
A3	2.91	–0.60	–0.98
B3	3.16	–0.81	–0.88
A4	3.12	–0.68	–0.90
B4	2.85	–0.68	–0.96
A5	2.60	–0.54	–0.82
B5	3.22	–0.73	–0.99

r: correlation coefficient. p<0.05 for all pairs of intercepts, slopes and correlation coefficients.

[1] Pair to be compared. A and B are groups containing 7 solvents each after randomized division of the 14 solvents into Group A and Group B.

[2] Original 10 solvents.

[3] Original 10 solvents + additional 4 solvents.

3).

The reproducibility of the regression line is essential for the broad application of this procedure for BOEL estimation. To test the reproducibility of the correlation equation, the regression line calculated with the original 10 solvents was compared with the regression line obtained using all 14 solvents. It was found that the slopes, the intercepts and the correlation coefficients were all statistically similar (p>0.05 for the difference, refer to the top pair in Table 4). Thus, the addition of four new cases did not produce significant changes in the regression line.

The consistency of the regression line was further examined by performing internal comparisons among the 14 cases. For this purpose, the 14 cases were randomly divided into two groups (Group A and Group B, n=7 for each), and the regression line parameters for Group A were compared with those for Group B. This comparison after randomized division into two groups was repeated five times, and no significant difference (p>0.05) was detected between the slopes, intercepts and correlation coefficients in any of the five tests (refer to the bottom 5 pairs in Table 4).

Thus, it was concluded that the correlation equation (Equation 1) is quite stable and universally applicable to various solvents.

Discussion

The advantage of utilizing biological monitoring in occupational health is that this method can not only monitor respiratory exposure but also dermal exposure (oral exposure to industrial chemicals is not common by nature). It should be noted that quantification and prevention of dermal absorption is much more difficult than that of respiratory exposure. Another problem is the difficulty in setting OELs for air-borne levels in cases of skin-penetrating solvents. Health effect data are usually influenced by simultaneous cutaneous absorption, and are not necessarily only attributable to air-borne exposures. It should be added that absorption through healthy skin is known to take place for many industrial chemicals[1-3].

It is possible that there may be medically relevant health effects for certain chemicals even if air-borne levels are well controlled and below OELs. Equation 1 (see

Table 5. Estimated biological occupational exposure limits for selected solvents.

Solvents	MW[1]	Log P_{ow}[2]	CAS No.	OEL[3] (ppm)	Estimated BOEL[4] (mg/*l* urine)		
					95% LL[5]	Average	95% UL[6]
1-Butyl alcohol	74.1	0.88	71-36-3	50	0.468	0.871	1.625
N,N-Dimethylformamide	73.1	–0.87	68-12-2	10	0.743	2.496	8.373
N,N-Dimethylacetamide	107.15	–0.77	127-19-5	10	0.798	2.552	8.146
2,2-Dichloroethyl ether	143.0	1.29	111-44-4	15	0.152	0.269	0.478
Ethyleneglycol monoethyl ether	90.1	–0.32	110-80-5	5	0.255	0.668	1.750
Methyl n-butyl ketone	100.2	1.98	591-78-6	5	0.031	0.055	0.097

[1] MW: Molecular weight. Values are cited from the Organization for Economic Co-operation and Development[15)].
[2] P_{ow}: Octanol-water partition coefficient. Values are cited from the National Institute of Technology and Evaluation[16)].
[3] OEL: Occupational exposure limits, established by the Japan Society for Occupational Health[1, 2)].
[4] BOEL: Biological occupational exposure limit, estimated by the described method[9)] using equations given in the Results section, i.e., Equation 1 (for average), Equation 2 (for 95% upper limit), and Equation 3 (for the 95% lower limit).
[5] LL: Lower limit.
[6] UL: Upper limit.

above and Fig. 1) allows the BOEL to be estimated from the molecular weight, P_{ow}, and OEL of a particular chemical. The use of BOELs as a guideline for evaluating the potential risk of dermal absorption may contribute to better occupational health for workers using skin-penetrating industrial chemicals. The estimated BOEL for selected organic solvents and related chemicals are presented as examples in Table 5.

For example, N, N-dimethylformamide is an organic solvent used for synthetic leather material production[10,11)] and other processes. However, this solvent can penetrate protective gloves made from a variety of materials to reach skin surface, making it difficult to prevent the risk of dermal absorption. When urinary levels exceed the estimated BOEL, it is highly likely that the excess exposure is taking place.

The analyses in this study were based on male workers. However, because the exposure-urinary excretion relationships do not differ significantly between men and women in the same working conditions[18)], the results observed in men may also be applicable to women.

Conclusions

The procedures for BOEL estimation used in this study yielded reproducible results when different solvents are tested, suggesting that this method may be broadly applied. The use of estimated BOEL may be recommended for exposure control of skin-penetrating solvents, and may be applicable to both sexes.

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Conflicts of interest: None declared.

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