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## Evaluation of exposure to mixed solvents by analysis of urinary metabolites and solvents: content ranges

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## Abstract

To evaluate worker's exposure to mixed solvents, equations for the calculation of the biological hazard index, which is defined as biological levels tolerable for exposure to mixture, were developed. When biological levels of exposure indicators were not affected by coexposure, rules similar to those for airborne monitoring could be applied. Namely, when the components had additive effects, the biological hazard index was calculated from the concentration of urinary metabolites or parent solvents, by an equation which was essentially similar to the equation for the calculation of the hazard index. In the present study, the confidence limits of the biological hazard index and predictive limits for individual specimens were calculated. These equations could be used under the condition that the uptake, metabolism and elimination of solvents were practically unaffected by coexposure. When urinary metabolites or solvents of some components of a mixed solvent alone were determined and those of the remaining components were not determined, the concentration of urinary metabolites or solvents of remaining components were estimated from the airborne concentration of the other components.

**KEYWORDS:** evaluation, coexposure, organic solvents, urinary metabolites, content ranges

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## Evaluation of Exposure to Mixed Solvents by Analysis of Urinary Metabolites and Solvents: Content Ranges

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To evaluate worker's exposure to mixed solvents, equations for the calculation of the biological hazard index, which is defined as biological levels tolerable for exposure to mixture, were developed. When biological levels of exposure indicators were not affected by coexposure, rules similar to those for airborne monitoring could be applied. Namely, when the components had additive effects, the biological hazard index was calculated from the concentration of urinary metabolites or parent solvents, by an equation which was essentially similar to the equation for the calculation of the hazard index. In the present study, the confidence limits of the biological hazard index and predictive limits for individual specimens were calculated. These equations could be used under the condition that the uptake, metabolism and elimination of solvents were practically unaffected by coexposure. When urinary metabolites or solvents of some components of a mixed solvent alone were determined and those of the remaining components were not determined, the concentration of urinary metabolites or solvents of remaining components were estimated from the airborne concentration of the other components.

**Key words:** evaluation, coexposure, organic solvents, urinary metabolites, content ranges

In the workplace, exposure to mixed solvents is more common than exposure to a single solvent. Thus, there is a need for a method to estimate and evaluate the health risk of workers exposed to mixed solvents by monitoring urinary metabolites or parent solvents.

In 1970, Ogata *et al.* (1) proposed a method for the

evaluation of mixed exposure of volunteers to toluene and m-xylene by analyzing the urinary metabolites, hippuric acid and m-methyl hippuric acid. Currently, Ogata *et al.* (2-5) have developed an equation for evaluating exposure of workers to mixed solvents by analyzing metabolites in urine and proposed a "biological hazard index" (biol. haz. index) under the assumption that compounds have no cross effect on concentrations of urinary metabolites or parent solvents. The biol. haz. index indicates biological levels for tolerable exposure to solvent mixtures.

Following this, Ogata *et al.* reported a method of evaluation of exposure to solvents from the urinary excretions of workers coexposed to toluene, xylenes and methyl isobutyl ketone (6). In order to evaluate the overexposure to mixed solvents, considering personal differences in metabolic rates, calculations of the biol. haz. index and its ranges is necessary. With this in mind, the confidence limits of the mean and predictive limits for individual specimens of urinary excretions (metabolites and solvents) are described in the present paper. In a mixture containing many kinds of solvents in such materials as thinners, determination of the urinary excretions derived from all components of the mixed solvents are difficult, because critical methods of evaluating the urinary excretion of all solvents have not been developed and the biological exposure index (BEI) of their urinary excretion has not yet been reported. For evaluation of exposure to mixed solvents in such cases, a method has been devised to complement of the analysis of concentration of urinary excretions of undetermined components using the airborne concentration of these components.

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## Materials and Methods

The biol. haz. index was calculated by an equation based on the equation for the "hazard index" (haz. index) using airborne concentrations by the American Conference of Governmental Industrial Hygienist (ACGIH) (7).

The relationship was studied between concentrations of toluene or xylene in the air and hippuric acid or methylhippuric acid in the urine of subjects exposed to toluene or xylene (8). The number of subjects exposed to toluene was 84 and those exposed to xylene numbered 19 while the numbers of control subjects not exposed to any solvents was 84.

Subjects exposed to single solvents of toluene or xylene were classified into several groups on the basis of exposure to solvents, and their urinary hippuric acid or methylhippuric acid were determined. In each group, the mean value, confidence limits of the mean and predictive limits of the individual samples were calculated.

Regression lines were plotted to the means, to the confidence limits of the means and to the predictive limits of individual specimens of each group, according to the group mean method of Weisbrot (9) under the assumption that the relationship between concentrations of solvents in the air and those of metabolites in the urine is linear for relatively low air concentrations of solvents. The symbols of each of the parameters are listed in Table 1 as described later.

The standard values and examples used in the evaluation of exposure to mixed solvents of toluene or xylene were taken from the author's reports (8) of 1986 and of (1) 1970 with some modifications. Both reports described the relationship between concentrations of toluene or xylene in the air and hippuric acid and methylhippuric acid in the urine.

Statistical analyses were carried out with Lotus 1, 2, 3 software.

## Results

### *The Regression Line and Its Confidence Limits and the Predictive Limits of Individual Specimens*

To describe the relationship between concentrations of toluene or xylene in the air and hippuric acid or methylhippuric acid in the urine, regression lines were plotted

connecting the means, confidence limits of the means, and predictive limits of individual samples according to the group mean method of Weisbrot (8). Namely, subjects exposed to a single solvent of toluene or xylene were classified into several groups on the basis of similar exposure to solvents, and their urinary hippuric acid or methylhippuric acid were determined. In each group, the mean value, 97.5 % upper or 2.5 % lower confidence limit of the mean and 97.5 % upper or 2.5 % lower predictive limits of the individual samples were calculated.

The definitions of parameters are listed in Table 1.

Regression lines were plotted by connecting the means, the confidence limits of means and the predictive limits of individual specimens of each group. The 97.5 % upper confidence limits of mean and upper 97.5 % predictive limits of individual specimens of metabolites corresponding the subjects exposed to the threshold limit

**Table 1** A list of the symbols of the concentrations of excretions in the urine of subjects exposed to ith solvents

Concentrations of urinary excretions of an ith solvent: $UEC_i$ The mean concentration: $MC$ $ECM_i$ : $MC$ of $UEC_i$ from specimens $BCM_i$ : background concentrations for $ECM_i$ $ECM_{TLV_i}$ : $MC$ of $UEC_i$ corresponding to $TLV-TWA_i$ $BCM_{TLV_i}$ : background concentrations for $ECM_{TLV_i}$
The upper 97.5% predictive limit of concentrations (UPL): $ECUL_i$ : UPL of $UEC_i$ from specimens $BCUL_i$ : background concentrations for $ECUL_i$ $ECUL_{TLV_i}$ : UPL of $UEC_i$ corresponding to $TLV-TWA_i$ $BCUL_{TLV_i}$ : background concentrations for $ECUL_{TLV_i}$
The lower 2.5% predictive limit of a concentration (LPL): $ECLL_i$ : LPL of $UEC_i$ from specimens $BCLL_i$ : background concentrations for $ECLL_i$ $ECLL_{TLV_i}$ : LPL of $UEC_i$ corresponding to $TLV-TWA_i$ $BCLL_{TLV_i}$ : background concentrations for $ECLL_{TLV_i}$
The upper 97.5% confidence limit of the mean of the concentrations (UCLM) $ECULM_i$ : UCLM of $UEC_i$ from specimens $BCULM_i$ : background concentrations for $ECULM_i$ $ECULM_{TLV_i}$ : UCLM of $UEC_i$ corresponding to $TLV-TWA_i$ $BCULM_{TLV_i}$ : background concentrations for $ECULM_{TLV_i}$
The lower 2.5% confidence limit of the mean of the concentrations (LCLM) $ECLLM_i$ : LCLM of UEC from specimens $BCLLM_i$ : background concentrations of $ECLLM_i$ $ECLLM_{TLV_i}$ : LCLM of UEC corresponding to $TLV-TWA_i$ $BCLLM_{TLV_i}$ : background concentration for $ECLLM_{TLV_i}$
Unit: HA; g/g creatinine and MHA; g/g creatinine.

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Table 2 Pertinent data to be used for calculation of equations

A-1. Standard values

Solvent-metabolite	TLV*	BEI	ECM <sub>TLV<sub>i</sub></sub>	ECULM <sub>TLV<sub>i</sub></sub>	ECUL <sub>TLV<sub>i</sub></sub>	BC <sub>TLV<sub>i</sub></sub>	BCULM <sub>TLV<sub>i</sub></sub>	BCUL <sub>TLV<sub>i</sub></sub>
T-HA	50	—	1.26	1.51	1.85	0.21	0.41	0.65
	100	2.5	2.31	2.61	3.05	0.21	0.41	0.65
X-MHA	100	1.5	2.10	2.40	2.80	0	0	0

Sol-Met	TLV	ECLLM <sub>TLV<sub>i</sub></sub>	ECLL <sub>TLV<sub>i</sub></sub>	BCLLM <sub>TLV<sub>i</sub></sub>	BCLL <sub>TLV<sub>i</sub></sub>
T-HA	50	1.01	0.67	0.01	-0.23
	100	2.01	1.57	0.01	-0.23
X-MHA	100	1.8	1.4	0	0

\* = Present threshold limit value (TLV) of toluene is 50ppm and TLV of xylene is 100ppm. Symbols are listed in Table 1.

A-2. Regression equations

Regression equations between solvent concentrations in air (x, ppm) and concentrations in urine (y, g/g creatinine) with correlation coefficient (r) or standard deviation (SD).

1. For toluene (x<sub>T</sub>) and hippuric acid (y<sub>H</sub>) systems;

Case	Regression equation & Corr. coeff.
Mean	y <sub>H1</sub> = 0.21 + 0.021x <sub>T</sub> r = 0.99
Upper 97.5% confidence limit of mean	y <sub>H2</sub> = 0.41 + 0.022x <sub>T</sub> r = 0.99
Upper 97.5% predictive limit of specimens	y <sub>H3</sub> = 0.66 + 0.024x <sub>T</sub> r = 0.98

2. For xylene (x<sub>V</sub>) and methylhippuric acid (y<sub>MH</sub>) systems;

Case	Regression equation & SD
Mean	y <sub>MH1</sub> = 0.021x <sub>V</sub> SD = 0.0005
Upper 97.5% confidence limit of mean	y <sub>MH2</sub> = 0.024x <sub>V</sub> SD = 0.0014
Upper 97.5% predictive limit of specimens	y <sub>MH3</sub> = 0.028x <sub>V</sub> SD = 0.0042

B. Specimens

Solvent-metabolite	C <sub>i</sub>	ECM <sub>i</sub>	ECULM <sub>i</sub>	ECUL <sub>i</sub>	BC <sub>i</sub>	BCULM <sub>i</sub>	BCUL <sub>i</sub>
T-HA	67	1.41	2.00	2.70	0.25	0.30	0.41
X-MHA	83	1.91	2.19	3.10	0	0	0

Unit: airborne concentrations; ppm and metabolite concentrations; g/g creatinine.

Data used in B. Specimens were obtained from Ref (1), Ogata *et al.*, 1970.

value-time weighted average (TLV-TWA) of solvents and the subjects not exposed were calculated, which as listed in Table 2A. These values obtained from volunteers coexposed to 83 ppm toluene and 67 ppm xylene are listed in Table 2B as specimen. As for the relationship between concentration of toluene in the air and hippuric acid in the urine, regression lines were plotted to the means, to the confidence limits of means and to the predictive limits of individual specimens of each group as shown in Fig. 1.

**Airborne Concentrations Tolerable for Exposure to Mixture**

According to the ACGIH proposal (7), workplace air containing multiple organic vapors was evaluated with the sum of fractions as follows:

$$\sum_{i=1}^n C_i / TLV_i = K \dots\dots\dots [1-1]$$

in which  $C_i$  denotes the airborne concentration of the  $i$ th component and  $TLV_i$  denotes the  $TLV-TWA$  for the same component. The symbol of  $K$  denotes the haz. index. If the  $K$  value exceeds 1, the workplace is deemed to exceed the exposure threshold for the mixed vapors.

### Equations Derived from Group Means and from Predictive and Confidence Intervals of Each Group for Evaluation of Mixed Exposure

#### A. All Components in the Mixture are Biologically Determined

##### 1. When biological levels are tolerable for exposure to mixture

In order to set up the following equations for this case, the interaction of mixture components should have no effect on the biological levels of urinary metabolites and parents solvents (excretions).

##### a. Equations made from group means

① *Calculation was made under assumption that the background of the standard and the specimens was not different.* We calculated the average concentration of hippuric acid (as a metabolite) in the urine of the worker's group classified by exposure concentrations of toluene (as a solvent) in the breathing zone. A regression line was plotted between the concentration of toluene in the breathing zone air and average concentrations of urinary hippuric acid described above (Fig. 1A).

In Fig. 1A,  $ECM_i$  and  $BCM_{TLV_i}$  denote the mean concentrations of excretions of an  $i$ th solvent in the urine and that of its background concentration of the hippuric acid in test groups, respectively, and the symbol  $ECM_{TLV_i}$  denotes the mean concentration of urinary excretions corresponding to  $TLV_i$ . In addition, the author used the symbol  $BCM_{TLV_i}$ , to indicate the background concentration of hippuric acid in the group calculating  $ECM_{TLV_i}$  as described later. In order to evaluate the extent of exposure for subjects exposed to mixed solvents from their urinary excretions, the following equation was formulated.

$$\sum_{i=1}^n (ECM_i - BCM_i) / (ECM_{TLV_i} - BCM_i) = K_B'' \dots \dots \dots [1-2],$$

where  $ECM_i$  and  $BCM_i$  denote the mean concentrations of excretions of an  $i$ th solvent in the urine and that of its

background concentration of the individual excrete, respectively. The symbols  $ECM_{TLV_i}$  and  $BCM_i$  denote the mean concentration of urinary excretions corresponding to  $TLV_i$  and that of its background concentration in Fig. 1A. The  $K_B''$  denotes the biol. haz. index-3. The  $ECM_{TLV_i}$  in [1-2] can be replaced by the biological exposure index of  $i$ th solvent ( $BEI_i$ ), because the  $BEI$  is defined as the level of industrial chemicals in biological specimens of workers exposed to chemicals in the same concentration as  $TLV-TWA$ . Therefore, we can formulate the following equation [1-3] from equation [1-2]:

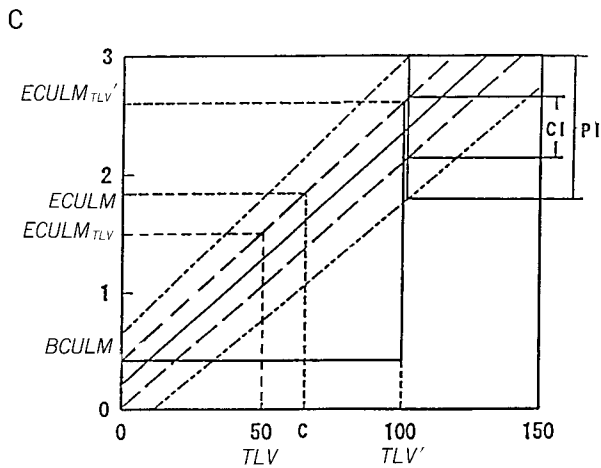
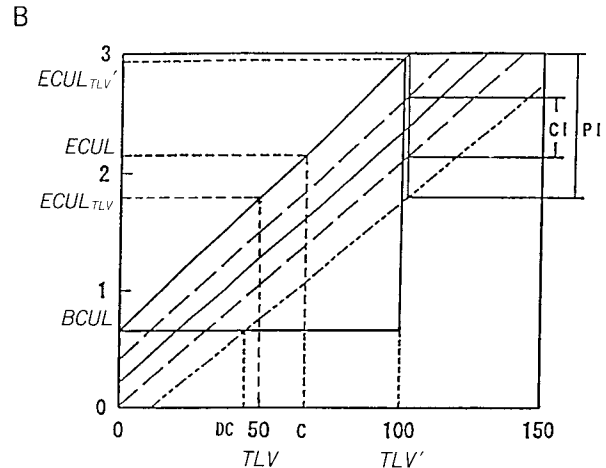
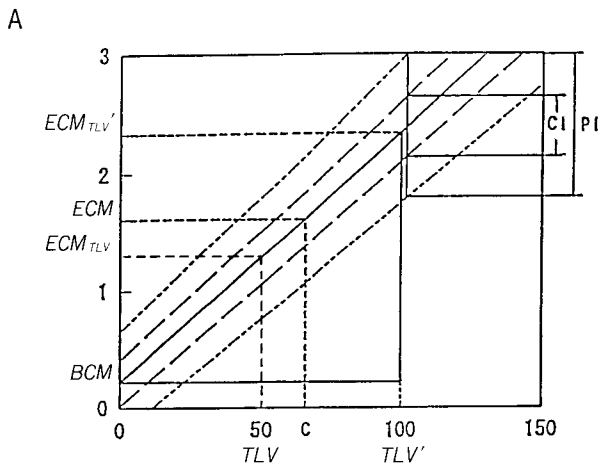
$$\sum_{i=1}^n (ECM_i - BCM_i) / (BEI_i - BCM_i) = K_B''' \dots \dots \dots [1-3],$$

where  $K_B'''$  denotes biol. haz. index-4.

Equation [1-2] indicates that  $(ECM_i - BCM_i) / (ECM_{TLV_i} - BCM_i)$  is additive, if the interaction of mixture component have no effect on biological levels of urinary determinants (5). The relationship between haz. index ( $K$ ) and biol. haz. index-3 or biol. haz. index-4 ( $K_B''$  or  $K_B'''$ ) is as follows: The significance of  $K_B''$  related to  $K$  is shown in Fig. 1A. When data of the crossing point of  $C_i$  (exposure concentration of an  $i$ th solvent) and  $EC_i$  of a test worker lie on the standard regression line for the  $i$ th solvent passing through the crossing point of  $TLV_i$  and  $ECM_{TLV_i}$  and the point of  $BCM_i$  on the ordinate,  $C_i$  is proportional to  $(EC_i - BC_i)$  and  $TLV_i$  is proportional to  $(ECM_{TLV_i} - BCM_i)$  in the same ratio. When the equations of  $C_i = k_i(ECM_i - BCM_i)$  and  $TLV_i = k_i'(ECM_{TLV_i} - BCM_i)$  or  $TLV_i = k_i'(BEI_i - BC_i)$  are calculated provisionally,  $k_i = k_i'$  was obtained and the value of  $1/k_i$  or  $1/k_i'$  indicates the slope of the regression line. Namely, when data from test workers are on the regression line described above,  $k_i = k_i'$  and in such cases the following equation is formulated.

$$C_i / TLV_i = (ECM_i - BCM_i) / (ECM_{TLV_i} - BCM_i) \dots \dots \dots [1-4]$$

For estimating [1-4], it is desirable that the above crossing point lies on the regression line described above or, at least, in the confidence range of the group mean described later. In the equation [1-4],  $ECM_{TLV_i}$  can be replaced by  $BEI_i$  because  $BEI$  represents the level of determinants which are mostly to be observed in the specimens collected from healthy workers with inhalation exposure to the  $TLV_s$  as described above. Then



**Fig. 1** The relationship between concentration of toluene in breathing zone air and concentration of hippuric acid in urine. Workers were classified into several groups on the basis of exposure to toluene concentration and their hippuric acid concentrations were determined. Lines were fitted to the means, confidence limits of the mean and predictive limits of individual specimens in each group. Symbols CI and PI indicate the 95% confidence limit of the group mean and the 95% predictive limit of individual values, respectively. The current threshold limit (TLV) for toluene is 50ppm and TLV for toluene before 1991 (TLV') is 100ppm. Explanation of the symbols is contained in Table 1.

**A** The relationship between  $c/TLV$  and  $(ECM-BCM)/(ECM_{TLV}-BCM)$ .  
 $ECM_{TLV}$  is the concentration of hippuric acid corresponding to 50ppm TLV of toluene.  
 $ECM_{TLV}$  is mean concentration of hippuric acid corresponding to 50ppm TLV of toluene.  
 $ECM_{TLV}'$  is mean concentration of hippuric acid corresponding to 100ppm TLV' (used till 1991) of toluene.

**B** The relationship between  $c/TLV$  and  $(ECUL-BCUL)/(ECUL_{TLV}-BCUL)$ .  
 $ECUL_{TLV}$  is the 97.5% upper predictive limit of individual sample of concentration of hippuric acid corresponding 50ppm TLV of toluene.  
 $ECUL_{TLV}'$  is the 97.5% upper predictive limit of individual sample of concentration of hippuric acid corresponding 100ppm TLV' of toluene.  
 DC (cut off toluene concentration, which is used to discriminate exposure from nonexposure at a 2.5% level of error) on abscissa showed 45 ppm, suggesting that hippuric acid could be useful for urinary biological monitoring of 50ppm TLV of toluene.

**C** The relationship between  $c/TLV$  and  $(ECULM-BCULM)/(ECULM_{TLV}-BCULM)$ .  
 $ECULM_{TLV}$  is the 97.5% upper confidence limit of the mean of concentration of hippuric acid corresponding to 50ppm TLV of toluene.  
 $ECULM_{TLV}'$  is the 97.5% upper confidence limit of the mean of concentration of hippuric acid corresponding to 100ppm TLV' of toluene.

$$C_i/TLV_i = (ECM_i - BCM_i)/(BEI_i - BC_i) \dots\dots\dots [1-5]$$

is obtained.

The following equation of [1-6] or [1-7] was derived from the equations [1-2] and [1-4] or the equations [1-3] and [1-5] in such ideal case described above.

$$K = K_B'' \dots\dots\dots [1-6]$$

or

$$K = K_B''' \dots\dots\dots [1-7],$$

where the coefficient of  $K_B''$  or  $K_B'''$  stands for the biol. haz. index and is equal to  $K$  (haz. index) in the equation [1-1] which is the standard condition described above. To maintain occupational safety, the coefficient of  $K_B''$  or  $K_B'''$  calculated from individual data of urinary determinants or mean values of determinants of groups surveyed should be equal to or smaller than 1. When the coefficient of  $K_B''$  or  $K_B'''$  exceeds 1, the cause of the excessive values must be investigated and proper action must be taken to reduce the exposure.

② **Calculation made under the assumption that the background of the standard and the specimens is different.** In the equations [1-4] and [1-5], the equation was formulated under the assumption that background concentration of  $BCM_i$  is almost equal to  $BCM_{TLVi}$  or  $BCM_{BEi}$ . However, there

are cases in which the background levels of urinary hippuric acid in specimens ( $BCM_i$ ) and those in the standard ( $BCM_{TLVi}$  or  $BCM_{BEi}$ ) are not completely the same value as shown in Table 3 described later, because hippuric acid is derived from toluene inhaled and benzoic acid in food eaten.

Therefore, the background level of  $BCM_{BEi}$  or  $BCM_{TLVi}$  is inserted into the equation [1-4] or [1-5]. Thus, the value of  $ECM_i - BCM_i$  is changed into  $ECM_{TLVi} - BCM_{TLVi}$  in the equation [1-4] or [1-5] and the following equations were formulated, in which the increase in concentration of urinary excretions solely derived from increased concentration of solvent exposure (slopes of regression lines) was used for calculation. In these cases, the equation [1-8] or [1-9] is formulated as follows:

$$\sum_{i=1}^n (ECM_i - BCM_i) / (ECM_{TLVi} - BCM_{TLVi}) = K_B \dots\dots\dots [1-8]$$

or

$$\sum_{i=1}^n (ECM_i - BCM_i) / (BEI_i - BCM_{BEi}) = K_B' \dots\dots\dots [1-9],$$

where  $K_B$  and  $K_B'$  are biol. haz. index-1 and biol. haz. index-2, respectively.

In the equations [1-8] and [1-9] only increased amounts of excretions according to increased amounts of

solvent (slope of regression line) were taken in calculation.

The relationship between haz. index ( $K$ ) and biol. haz. index ( $K_B$  or  $K_B'$ ) is as follows:

In a similar manner to formulate [1-10] from [1-6], the following equations of

$$K = K_B \dots\dots\dots [1-10]$$

and

$$K = K_B' \dots\dots\dots [1-11]$$

were obtained when data of the crossing point of  $C_i$  and  $EC_i$  of a test worker lie on the standard regression line for the  $i$ th solvent

The  $K_B$  and  $K_B'$  were used in the sample calculation described later.

**b. Equation derived from upper 97.5 % predictive limits of individual samples in a group of subjects exposed to similar concentrations**

① **Calculation made under the assumption that the background of the standard and the specimens is not different.** The

regression line between the concentrations of toluene and the upper or lower predictive limits of individual specimens of hippuric acid concentrations in the groups is shown in Fig. 1B. In this figure, the symbols of  $ECUL_i$  and  $BCUL_i$  denote the upper 97.5 % predictive limit of concentrations of individual excretions of  $i$ th solvent in the urine and the upper 97.5 % predictive limit of the background concentration of the individual excretion, respectively, and the symbols of  $ECUL_{TLVi}$  and  $BCUL_i$  denote the upper 97.5 % predictive limit of the concentration of urinary excretion corresponding to  $TLV_i$  and the upper 97.5 % predictive limit of the background concentration of urinary excrete corresponding to  $TLV_i$ . If the mixture components have additive effects,

$$\sum_{i=1}^n (ECUL_i - BCUL_i) / (ECUL_{TLVi} - BCUL_i) = K_{ULB}' \dots\dots\dots [2-1]$$

is formulated as in the case of the equation [1-2].

The relationship between  $K$  and  $K_{ULB}'$  is as follows:

When the crossing point of  $C_i$  (exposure concentration of  $i$ th solvent) and  $ECUL_i$  lies on the regression line passing through the crossing point of  $TLV_i$  and  $ECUL_{TLVi}$  and the point of  $BCUL_i$  on the ordinate as shown in Fig. 1B, namely, in the range where  $C_i$  is proportional to  $ECUL_i - BCUL_i$  and  $TLV_i$  is proportional to  $ECUL_{TLVi} - BCUL_i$  in the same ratio,



$C_i = k_2'(ECUL_i - BCUL_i)$  and  $TLV_i = k_2'(ECUL_{TLV_i} - BCUL_i)$ , where  $1/k_2$  is the slope of the regression line in Fig. 1B. Then  $(ECUL_i - BCUL_i)/(ECUL_{TLV_i} - BCUL_i) = C_i/TLV_i$ , and the following equation [2-2] can be derived:

$$\sum_{i=1}^n (ECUL_i - BCUL_i)/(ECUL_{TLV_i} - BCUL_i) = \sum_{i=1}^n C_i/TLV_i \dots\dots\dots [2-2]$$

Then the equation

$$K = K_{ULB}' \dots\dots\dots [2-3]$$

is derived from the equations [2-1] and [2-2]. The value of the coefficient of  $K_B''$  was calculated from the means of specimens and standards using the equation [1-4]. On the other hand, the value of the coefficient of  $K_{ULB}$  was obtained from the 97.5 % upper predictive limits of concentrations of determinants in the individual urine of specimens and standards using the equation [2-2]. Practical evaluation of  $K_{ULB}'$  in exposure to mixed solvent is described in the sample calculation.

② **Calculation made under the assumption that background levels of the standard and the specimens are different.** The following equation [2-4] is derived from [2-2] in a similar manner in which the equation of [1-10] is derived from the equation [1-6] in the case of that  $BCUL_i$  and  $BCUL_{TLV_i}$  are not the same.

$$\sum_{i=1}^n (ECUL_i - BCUL_i)/(ECUL_{TLV_i} - BCUL_{TLV_i}) = K_{ULB} \dots\dots\dots [2-4]$$

or

$$\sum_{i=1}^n (ECUL_i - BCUL_i)/(ECUL_{TLV_i} - BCUL_{TLV_i}) = \sum_{i=1}^n C_i/TLV_i \dots\dots\dots [2-5],$$

where  $BCUL_{TLV_i}$  is the predictive limit of the background concentration of the urinary excrete when the standard regression line is plotted.

Then the equation,

$$K = K_{ULB} \dots\dots\dots [2-6]$$

was obtained when data of the crossing point of  $C_i$  and  $ECUL_i$  of a test worker lies on the regression line made from the upper 97.5 % predictive limit of specimens for the *i*th solvent.

**c. Equations derived from the lower 2.5 % predictive limit**

Under assumption that the background of the standard and the specimens is different, the following equation [2-7] can be derived in a manner similar to that used for derivation of the equation [2-4].

$$\sum_{i=1}^n (ECLL_i - BCLL_i)/(ECLL_{TLV_i} - BCLL_{TLV_i}) = K_{LLB} \dots\dots\dots [2-7]$$

The definitions of the symbols of  $ECLL_i$ ,  $BCLL_i$ ,  $ECLL_{TLV_i}$  and  $BCLL_{TLV_i}$  are described in Table 1.

The relationship between  $K$  and  $K_{LLB}$  is as follows: When a crossing point of  $C_i$  and  $ECLL_i$  lies on the regression line passing through the crossing point of  $TLV_i$  and  $ECLL_i$  and  $BCLL_i$  on the ordinate, namely, in the range where  $C_i$  is proportional to  $ECLL_i - BCLL_i$ , and  $TLV_i$  corresponds to  $ECLL_{TLV_i} - BCLL_{TLV_i}$  (Fig. 1B),

$$\sum_{i=1}^n (ECLL_i - BCLL_i)/(ECLL_{TLV_i} - BCLL_{TLV_i}) = \sum_{i=1}^n C_i/TLV_i \dots\dots\dots [2-8].$$

Then the equation,

$$K = K_{LLB} \dots\dots\dots [2-9]$$

is derived from the equations [2-4] and [2-5].

It would be possible to use  $K_{LLB}$  as one means of screening workers exposed to  $K$  of solvent mixture from urinary excretions, because  $K_{LLB}$  is a coefficient of the lower 2.5 % predictive limit of concentrations of individual metabolites or parent solvents. In actual practice detailed explanation will be given in near future.

**d. Equations derived from upper 97.5 % confidence limit of the mean of each group**

① **Calculation was carried out under the assumption that the background levels of the standard and the specimens are not different.**

Then following equation [3-1] can be derived. The regression line between the concentration of toluene and the upper or lower confidence limits of the mean lines of hippuric acids in the groups is shown in Fig. 1C. In Fig. 1C, symbols  $ECULM_i$  and  $BCULM_i$  denote the upper 97.5 % confidence limit of the mean of the concentrations of solvent excretions in the urine of subjects exposed to the *i*th solvent and the upper 97.5 % confidence limit of the mean of the concentrations of

subjects not exposed to the  $i$ th solvent, respectively. The symbols  $ECULM_{TLVi}$  and  $BCULM_{TLVi}$  denote the upper 97.5 % confidence limit of the mean concentration of the urinary metabolites or solvents of subjects exposed to  $TLV_i$  and upper 97.5 % confidence limit of those unexposed to the  $i$ th solvent. Then the following equation of

$$\sum_{i=1}^n (ECULM_i - BCULM_i) / (ECULM_{TLVi} - BCULM_i) = K_{ULMB'} \dots \dots \dots [3-1]$$

is formulated as in the equation [2-1].

The relationship between  $K$  and  $K_{ULMB'}$  is as follows: When a point indicating  $C_i$  and  $ECULM_i$  obtained from a worker lies on the regression line passing through the point of  $TLV_i$  and  $ECULM_{TLVi}$  and the point of  $BCULM_i$  is on the ordinate, namely in the range where  $C_i$  is proportional to  $ECULM_i - BCULM_i$ , and  $TUV_i$  is proportional to  $ECULM_{TLVi} - BCULM_i$  in the same ratio (Fig. 1C), then the equations  $C_i = k_3 (ECULM_i - BCULM_i)$  and  $TLV_i = k_3 (ECULM_{TLVi} - BCULM_i)$ , where  $1/k_3$  is the slope of the regression line in Fig. 1C, are obtained. Therefore, the following equation,

$$\sum_{i=1}^n (ECULM_i - BCULM_i) / (ECULM_{TLVi} - BCULM_i) = \sum_{i=1}^n C_i / TLV_i \dots \dots \dots [3-2]$$

is derived.

Thus, the following equation [3-3] is obtained from [3-1] and [3-2].

$$K = K_{ULMB'} \dots \dots \dots [3-3]$$

② **Calculation was made under the assumption that the background of the standard and the specimens is different.** The following equation [3-4] is derived from [2-2] in a similar manner to which the equation of [1-10] is derived from equation [1-4] considering the case that  $BCUL_i$  and  $BCUL_{TLVi}$  are not the same. In the above case,

$$\sum_{i=1}^n (ECULM_i - BCULM_i) / (ECULM_{TLVi} - BCULM_{TLVi}) = K_{ULB} \dots \dots \dots [3-4]$$

or

$$\sum_{i=1}^n (ECULM_i - BCULM_i) / (ECULM_{TLVi} - BCULM_{TLVi}) = \sum_{i=1}^n C_i / TLV_i \dots \dots \dots [3-5]$$

is derived, where  $BCUL_{TLVi}$  is the predictive limit of the background concentration of the urinary excrete when the standard regression line is plotted.

Then the following equation of

$$K = K_{ULB} \dots \dots \dots [3-6]$$

is obtained when data of the crossing point of  $C_i$  and  $ECUL_i$  of a test worker lie on the regression line made from the upper 97.5 % predictive limit of specimens for the  $i$ th solvent.

**e. Equation derived from the lower 2.5 % confidence limit of the mean.**

Calculation was made under the assumption that background of the standard and the specimens is different. In a manner similar to that for the derivation of equation [3-1], the following equation [3-7] is obtained.

$$\sum_{i=1}^n (ECLLM_i - BCLLM_i) / (ECLLM_{TLVi} - BCLLM_{TLVi}) = K_{LLMB} \dots \dots \dots [3-7]$$

The relationship between  $K$  and  $K_{LLMB}$  is as follows:

When a point indicating  $C_i$  and  $ECLLM_i$  lies on the regression line passing through the point of  $TLV_i$  and  $ECLLM_{TLVi}$  and  $BCLLM_i$  are on the ordinate, the following equation is formulated.

$$\sum_{i=1}^n (ECLLM_i - BCLLM_i) / (ECLLM_{TLVi} - BCLLM_{TLVi}) = \sum_{i=1}^n C_i / TLV_i \dots \dots \dots [3-8]$$

Then the equation [3-9] is obtained from the equation [3-7] and [3-8].

$$K = K_{LLMB} \dots \dots \dots [3-9]$$

was obtained.

**2. Comparison between the haz. index ( $K$ ) and the biol. haz. index ( $K_B$ ), when biological levels of exposure are not affected by the coexposure.**

In the case that  $K$  is higher than  $K_B$ , or  $K$  is higher than  $K_{ULMB}$ , the following equation [4-1] or [4-2] is derived from the equation [1-6] or [1-7] for the group mean

$$\sum_{i=1}^n C_i / TLV_i > \sum_{i=1}^n (ECM_i - BCM_i) / (ECM_{TLVi} - BCM_{TLVi}) \dots \dots \dots [4-1]$$

or

$$\sum_{i=1}^n C_i/TLV_i > \sum_{i=1}^n (ECM_i - BCM_i)/(BEI_i - BCM_{BEI_i}) \dots\dots\dots [4-2]$$

In the equation [4-1] or [4-2] was formulated, ethanol intake several hours prior to or just before inhalation exposure to organic solvents and/or effect of wearing mask on workers exposure should be checked.

In the case that the equation of [4-1] is formulated, the following equation of [4-3] should be tested.

When the symbol *ECLL<sub>i</sub>*, indicating the lower 2.5 % predictive limit of the concentration of urinary determinants, was used instead of *ECM<sub>i</sub>*, equation [4-3] is derived.

$$\sum_{i=1}^n C_i/TLV_i > \sum_{i=1}^n (ECLL_i - BCLL_i)/(ECLL_{TLV_i} - BCLL_{TLV_i}) \dots\dots\dots [4-3]$$

Equation [4-1] is derived from *ECM<sub>i</sub>* of the group means of urinary determinants of solvents, and the equation [4-3] is derived from *ECLL<sub>i</sub>* of the lower 95 % predictive limit of the concentration of urinary determinants. Therefore, equation [4-1] is based on the comparison of *C<sub>i</sub>* with *ECM<sub>i</sub>*, and equation [4-3] is based on the comparison of *C<sub>i</sub>* with *ECLL<sub>i</sub>*. On the other hand, equation [4-3] can also be derived from equation [2-7].

In the cases that *K* is lower than *K<sub>B</sub>* or *K* is lower than *K<sub>ULMB</sub>*, the following [4-4] equation is derived from equation [1-6] and the [4-5] equation is derived from equation [1-7].

$$\sum_{i=1}^n C_i/TLV_i < \sum_{i=1}^n (ECM_{ii} - BCM_i)/(ECM_{TLV_i} - BCM_{TLV_i}) \dots\dots\dots [4-4]$$

and

$$\sum_{i=1}^n C_i/TLV_i > \sum_{i=1}^n (ECM_i - BCM_i)/(BEI_{BEI_i} - BC_{BEI_i}) \dots\dots\dots [4-5]$$

On the contrary, microsomal enzyme activity induced by chronic alcohol intake, or dermal absorption is considered in equations [4-4] and [4-5].

When the symbol *ECUL<sub>i</sub>*, indicating the lower 2.5 % predictive limit of the concentration of urinary determinants, was used instead of *ECM<sub>i</sub>* in equation [4-4], the following equation is derived:

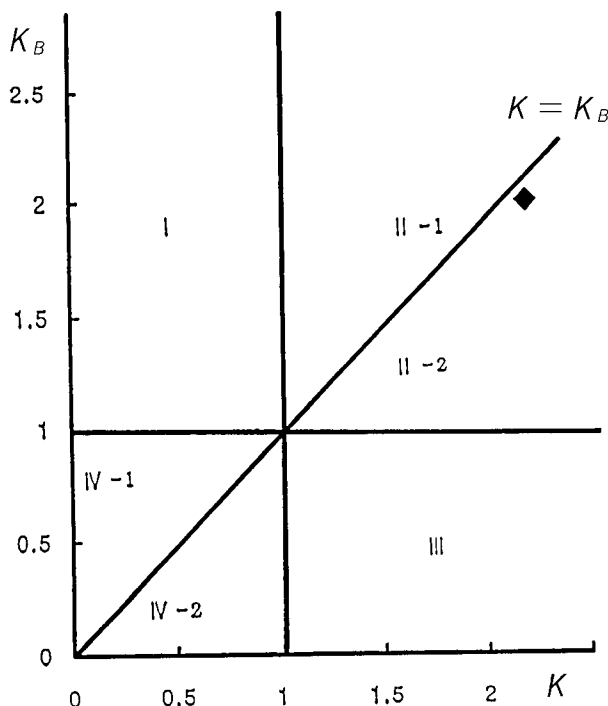


Fig. 2 Relationship between the *K* value and the *K<sub>B</sub>* values in workers exposed to solvent mixture.

Symbol ◆: Data described in the sample calculation based on the average value of urinary biological monitoring of subjects exposed to mixed solvents of 67ppm toluene and 83ppm xylene. *K* value was 2.17 and *K<sub>B</sub>* value was 2.01 (Table 3-1). The value was obtained from the sample calculation.

- (1) *K<sub>B</sub>* > 1 (I, II-1, II-2):  
A worker on different occasions exceeds the *BEI*. The cause of the excessive values must be investigated and proper action should be taken to reduce exposure.
  - (2) *K* > 1 (II-1, II-2, III):  
The value exceeds the *TLV*, which indicates airborne concentrations of solvents under which nearly all workers will be without adverse effects.
  - (3) *K<sub>B</sub>* > *K* (I, II-1, IV-1):  
Presence of dermal absorption or extra occupational exposure should be considered.
  - (4) *K<sub>B</sub>* < *K* (II-2, III, IV-2):  
Effect of a protecting mask on worker's exposure or ethanol intake several hours prior to exposure to solvents should be considered.
- In this case, the value of *K<sub>B</sub>* > 1 and *K* > 1, and *K* is slightly higher than *K<sub>B</sub>*.

$$\sum_{i=1}^n C_i/TLV_i < \sum_{i=1}^n (ECUL_i - BCUL_i)/(ECUL_{TLV_i} - BCUL_{TLV_i}) \dots \dots \dots [4-6]$$

On the other hand, equation [4-6] can also be derived from equation [2-5].

Fig. 2 shows the  $K$  and  $K_B$  values for workers exposed to a mixed solvent and the cases of  $K \geq 1$ ,  $K < 1$ ,  $K_B \geq 1$ ,  $K_B < 1$ ,  $K > K_B$  and  $K < K_B$ .

**B. Only Some of All Kinds of Mixtures are Biologically Determined**

Equations for complement of concentrations of undetermined exposure indicators are formulated. When the concentrations of urinary metabolites or parent solvents of some solvents in a mixed solvent are not measured, the following equation can be used for evaluation of exposure to all solvents under the assumption that the compounds have no effect on the concentration of urinary metabolites or parent solvents.

In  $n$  class solvents, when the concentration of urinary metabolites or parent solvents derived from  $m$  class solvents are measured and the concentration of urinary determinants from remaining  $n-m$  class solvents are not measured, following equations [5-1] ~ [5-10] are useful for evaluation of mixed exposure.

① **The ratio of the airborne concentration  $C$  to TLV is used instead of the concentration of urinary metabolites or parents solvents to biological exposure indices for the remaining  $n-m$  class solvents.** When the all components (number  $n$ ) are composed of  $j$  components (number  $m$ ) and  $k$  components (number of  $m+1$  to  $n$ ), the next equation is formulated.

$$\sum_{i=1}^n (ECM_i - BCM_i)/(BEI_i - BCM_{BEI_i}) = \sum_{j=1}^m (ECM_j - BCM_j)/(BEI_j - BCM_{BEI_j}) + \sum_{k=m+1}^n C_k/TLV_k \dots \dots \dots [5-1],$$

where the symbol of  $k$  indicates  $n-m$  class compounds in which concentration of the urinary metabolites or parent solvents has not been determined. Therefore,  $k$  is different from  $K$  of the haz. index.

② **The ratio of urinary concentration of metabolites or parents solvents to BEIs is used for complementation of undetermined sol-**

**vents.** The equations [5-2] ~ [5-10] described below can be useful as an complementary method for undetermined biological exposure indicators of solvents.

The ratio of remaining solvents is estimated under the assumption that the relationship between each concentration of remaining solvents in the air and that of the metabolite or solvent in the urine produced a linear equation.

$$\sum_{i=1}^n (ECM_i - BCM_i)/(BEI_i - BCM_{BEI_i}) = \sum_{j=1}^m (ECM_j - BCM_j)/(BEI_j - BCM_{BEI_j}) + \sum_{k=m+1}^n (ECM_k - BCM_k)/(BEI_k - BCM_{BEI_k}) \dots \dots \dots [5-2]$$

From the equation of

$$\sum_{j=1}^m C_j/TLV_j = \sum_{j=1}^m (ECM_j - BCM_j)/(BEI_j - BCM_{BEI_j}) \dots \dots \dots [5-3]$$

and

$$\sum_{k=m+1}^n C_k/TLV_k = \sum_{k=m+1}^n (ECM_k - BCM_k)/(BEI_k - BCM_{BEI_k}) \dots \dots \dots [5-4],$$

the next equation of [5-5] is derived from equations [5-3] and [5-4].

$$\sum_{j=1}^m C_j/TLV_j; \sum_{k=m+1}^n C_k/TLV_k = \sum_{j=1}^m (ECM_j - BCM_j)/(BEI_j - BCM_{BEI_j}); \sum_{k=m+1}^n (ECM_k - BCM_k)/(BEI_k - BCM_{BEI_k}) \dots \dots \dots [5-5]$$

From equations [5-2] and [5-5], the following equation

$$\sum_{i=1}^n (ECM_i - BCM_i)/(BEI_i - BCM_{BEI_i}) = \sum_{j=1}^m (ECM_j - BCM_j)/(BEI_j - BCM_{BEI_j}) \times (\sum_{k=m+1}^n C_k/TLV_k + \sum_{j=1}^m C_j/TLV_j) \div \sum_{j=1}^m C_j/TLV_j \dots \dots \dots [5-6]$$

is derived.

The values of biol. haz. index were obtained from the following equation [5-7] or [5-8]:

$$\sum_{i=1}^n (ECM_i - BCM_i) / (ECM_{TLVi} - BCM_{TLVi}) = K_B \dots\dots\dots [5-7]$$

or

$$\sum_{i=1}^n (ECM_i - BCM_i) / (BEI_i - BC_{BEIi}) = K_{B'} \dots\dots\dots [5-8]$$

is calculated by the equation of

$$\sum_{j=1}^n (ECM_j - BCM_j) / (ECM_{TLVj} - BCM_{TLVj}) \times \sum_{j=1}^m C_i / TLV_i \div \sum_{j=1}^m C_j / TLV_j \dots\dots\dots [5-9]$$

or

$$\sum_{j=1}^m (ECM_j - BCM_j) / (BEI_j - BC_{BEIj}) \times \sum_{i=1}^n C_i / TLV_i \div \sum_{j=1}^m C_j / TLV_j \dots\dots\dots [5-10]$$

③ *The m class of solvents out of n class of all solvents are used for evaluation, and the ratios of the concentrations of m solvents to their TLVs are compared with the ratios of urinary excretions to their BEIs.*

$$\sum_{j=1}^m C_j / TLV_j > \sum_{j=1}^m (ECM_j - BCM_j) / (ECM_j - BC_{TLVj}) \dots\dots\dots [6-1]$$

or

$$\sum_{j=1}^m C_j / TLV_j > \sum_{j=1}^m (ECM_j - BCM_j) / (BEI_j - BC_{BEIj}) \dots\dots\dots [6-2]$$

In equation [6-1] or [6-2], ethanol intake several hours prior to exposure or just before inhalation of exposure to organic solvents should be taken into consideration as described in equation [4-1] or [4-2].

$$\sum_{j=1}^m C_j / TLV_j < \sum_{j=1}^m (ECM_j - BCM_j) / (BEI_j - BC_{BEIj}) \dots\dots\dots [6-3]$$

In the equation [6-3], the presence of dermal absorption of solvents and/or airway absorption of solvents passed through a mask is considered.

$$\sum_{j=1}^n C_j / TLV_j > \sum_{j=1}^n (ECLL_j - BCLL_j) / (ECLL_{TLVj} - BCLL_{TLVj}) \dots\dots\dots [6-4]$$

Namely  $K > K_{LLB}$  should be checked when equation [6-1] or [6-2] holds.

$$\sum_{j=1}^n C_j / TLV_j < \sum_{j=1}^n (ECUL_j - BCUL_j) / (ECUL_{TLVj} - BCUL_{TLVj}) \dots\dots\dots [6-5]$$

Namely  $K < K_{ULB}$  should be checked when equation [6-3] holds.

Equation [6-1] is based on the comparison of the ambient concentrations of solvents,  $C_i$ , with the mean concentration of urinary determinants,  $ECM_i$ . On the other hand, equation [6-4] is based on the comparison of  $C_i$  with the lower 2.5% predictive limit of individual specimens of  $ECLL_i$ , and equation [6-5] is based on the comparison of  $C_i$  with  $ECUL_i$ . Therefore, personal differences in the concentration of urinary determinants are taken into consideration in equations [6-4] and [6-5].

**Sample Calculation**

In previous report (1), Ogata *et al.* described the urinary excretion of hippuric acids and m-methyl hippuric acids in persons coexposed to vapors of toluene and m-xylene. The report also indicated the minimum effect of coexposure on excretion rates of metabolites. The values described in the report are listed in Table 2B. The values in Table 2B were substituted into the equations [1-1], [1-2] and [1-3], and the following biol. haz. index was calculated.

For calculation, the BEI value of hippuric acid for 50 ppm toluene has not been documented. Therefore, for calculation, the author used equations based on a TLV of 50 ppm toluene and 100 ppm xylene. Those based on a TLV of 100 ppm toluene and 100 ppm xylene were expressed in equations in square brackets as follows:

**A. Haz. Index (K)**

The haz. index was calculated by equation [1-1] as follows:

$$(83/100) + (67/50) = 2.17$$

$$[(83/100) + (67/100) = 1.50]$$

**B. Biol. Haz. Index (K<sub>B</sub>)**

The biol. haz. index was calculated by equations [1-2] and [1-3] as shown in Table 3-1. The average values of metabolite concentrations in the urine of a group of specimens,  $ECM_{TLVi}$ , and BEI were used for calculation.

From equation [1-2], using  $ECM_{TLVi}$  as a standard

**Table 3** Equation for the evaluation of mixed exposure to organic solvents by their urinary metabolites

I. Values obtained from equations calculating means of mixed exposure

	(1) $c^a$	(2) $T^b$	$c/T$	$ECM_i^c$	(a) $ECM_i$ $-BCM_i^d$	$BEI^e$	(b) $BEI$ $-BCM_{BEI_i}^d$	$a/b$	$ECM_{TLV_i}^f$	(c) $ECM_{TLV_i}$ $-BCM_{TLV_i}^d$	$a/c$
T-HA	67	50	1.34	1.41	1.16	ne	ne	ne	1.26	1.05	1.10
T-HA *	67	100	0.67	1.41	1.16	2.50	2.29	0.51	2.31	2.10	0.55
X-MHA	83	100	0.83	1.91	1.91	1.50	1.50	1.27	2.10	2.10	0.91
Total			2.17					ne			2.01
			1.50*					1.78*			1.46*
			(K)					(K <sub>B'</sub> )			(K <sub>B</sub> )

 $a$ : Average concentrations in breathing zone air of workers (ppm). $b$ : TLV-TWA. $c$ : Average concentrations in urinary excretions of  $i$  solvent (HA and MHA). $d$ :  ${}^pBCM_{BEI_i}$  and  ${}^pBCM_{TLV_i}$ : The values were 0.25, 0.21 and 0.21, respectively, and symbols indicating background levels are  $ECM_i$ ,  $ECM_{BEI_i}$  and  $ECM_{TLV_i}$ . $e$ : Biological exposure indices. $f$ : Concentrations of urinary excretions corresponding to the TLV of our previous report (8).

T = toluene, X = xylene, HA = hippuric acid and MHA = methylhippuric acid.

These symbols are described in Table II.

\* Calculation was made under the assumption that TLV was 100 ppm.

Unit: (1) and (2), ppm; (a) (b) and (c), g/g creatinine.

The equations used were [1-1] for  $c/T$ , [1-2] for  $(a/b)$  and [1-3] for  $(a/c)$ .

ne: not examined.

2. Values obtained from equations calculating upper confidence and upper predictive limits for mixed solvents

1) The upper confidence for mean ( $K_{ULMB}$ )

	(d)			(e)		d/e
	$ECULM_i$	$BCULM_i$	$ECULM_i$ $-BCULM_i$	$ECULM_{TLV_i}$	$BCULM_{TLV_i}$	$ECULM_{TLV_i}$ $-BCULM_{TLV_i}$
T-HA	2.00	0.30	1.70	1.51	0.41	1.10
T-HA *	2.00	0.30	1.70	2.62	0.41	2.21
X-MHA	2.19	0.00	2.19	2.40	0.00	2.40
						2.46
						1.69*
						(K <sub>ULMB</sub> )

The equation used is [3-1] for d/e. Symbols are described in Table I.

2) The upper predictive limit for individual specimens ( $K_{ULB}$ )

	$ECUL_i$	$BULL_i$	(f) $ECUL_i$ $-BULL_i$	$ECUL_{TLV_i}$	$BCUL_{TLV_i}$	(g) $ECUL_{TLV_i}$ $-BCUL_{TLV_i}$	f/g
T-HA	2.70	0.41	2.29	1.85	0.65	1.20	
T-HA *	2.70	0.41	2.29	3.05	0.65	2.40	
X-MHA	3.10	0.00	3.10	2.80	2.80	2.80	
						3.02	
						2.06*	
						(K <sub>ULB</sub> )	

The equation used is [2-4] for f/g.

To be continued.

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Table 3-2

3) The lower confidence limit of mean ( $K_{LLMB}$ )

	$ECLLM_i$	$BCLLM_i$	(h) $ECLLM_i$ - $BCLLM_i$	$ECLLM_{TLV_i}$	$BCLLM_{TLV_i}$	(i) $ECLLM_{TLV_i}$ - $BCLLM_{TLV_i}$	h/i
T-HA	0.82	0.20	0.62	1.01	0.01	1.00	0.62
T-HA *	0.82	0.20	0.62	2.01	0.01	2.00	0.31
X-MHA	1.63	0.00	1.63	1.80	0.00	1.80	0.91
Total							1.53 1.22* ( $K_{LLMB}$ )

The equation used is [3-4] for h/i.

4) The lower predictive limit for individual specimens ( $K_{LLB}$ )

	$ECLL_i$	$BCLL_i$	(j) $ECLL_i$ - $BCLL_i$	$ECLL_{TLV_i}$	$BCLL_{TLV_i}$	(l) $ECLL_{TLV_i}$ - $BCLL_{TLV_i}$	j/l
T-HA	0.12	0.09	0.03	0.67	-0.23	0.90	0.03
T-HA *	0.12	0.09	0.03	1.57	-0.23	1.80	0.02
X-MHA	0.72	0.00	0.72	1.40	0.00	1.40	0.51
Total							0.54 0.53* ( $K_{LLB}$ )

The equation used is [2-6] for j/l.

$K_B$  was  $(1.41 - 0.25)/(1.26 - 0.21) + 1.91/2.10 = 2.01$  and  $K_B'$  was  $[(1.41 - 0.25)/(2.31 - 0.21) + 1.91/2.10 = 1.46]$ .

From equation [1-3], using  $BEI$  as a standard

the equation of  $[(1.41 - 0.25)/(2.5 - 0.21) + 1.91/1.5 = 1.78]$  was obtained.

To maintain occupational safety, the values of the coefficient of  $K_B''$  and  $K_B'''$  obtained from equations [1-2] and [1-3] should be equal to or less than the  $K$  value.

In this instance, the values  $K$  and  $K_B$  exceed 1, therefore, the cause of the excessive values must be investigated and proper action should be taken to reduce the exposure to mixed solvents.

### C. Confidence and Predictive Limits of Concentrations of Urinary Determinants from Specimens

When  $ECUML_i$  and  $BCUML_i$  of specimens shown in Table 2B and the standard exposure listed in Table 2A were substituted into equation [3-1], the 97.5

% upper confidence limit of mean ( $K_{ULMB}$ ) was calculated as shown in Table 3-2, 1).

$$2.00 - 0.30)/(1.51 - 0.41) + 2.19/2.40 = 2.46$$

$$[(2.00 - 0.30)/(2.62 - 0.41) + 2.19/2.40 = 1.69]$$

These data indicate that the upper 97.5 % predictive limit of the mean of this instance also exceeds 1.

When  $ECUL_i$  and  $BCUL_i$  of specimens (Table 2B) and the standard exposure listed in Table 2A were substituted into equation [2-4], the 97.5 % upper predictive limit of individual specimens ( $K_{ULB}$ ) was calculated as shown in Table 3-2, 2).

$$(2.70 - 0.41)/(1.85 - 0.65) + 3.10/2.80 = 3.02$$

$$[(2.70 - 0.41)/(3.10 - 0.65) + 3.10/2.80 = 2.06]$$

The data indicate that the upper 97.5 % predictive limit of individual specimens of this instances also exceeds 1 referred to the standard exposure listed in Table 2A. The 97.5 % lower confidence limit of mean ( $K_{LLMB}$ ) was calculated to be 1.53 and [1.22] using the similar method to calculation of  $K_{ULMB}$  and the results are shown in Table

3-2, 3). The 97.5 % lower predictive limit of individual specimens ( $K_{LLB}$ ) was calculated to be 0.54 and [0.53] using the similar method to calculation of  $K_{ULB}$  and the results are shown in Table 3-2, 4).

#### D. Comparison of One Datum in a Specimen with the Standard Group

The other methods of comparison are as follows: The values of the coefficient of  $K_B$  (2.01) exceed 1 as described above which suggests that the  $K_B$  values calculated from the mean value of a group of specimens were larger than the  $K_B$  values of standard. Then, the comparison of mean value of examples with the upper 97.5 % predictive limit of individual specimens of the standard was taken into consideration.

When a datum of 1.41 g/g cr of hippuric acid and 1.91 g/g cr of methyl hippuric acid obtained from the mean value of a group of specimens was substituted into  $ECULM_i$  in equation [3-1], the next equation of  $(1.41 - 0.30)/(1.51 - 0.41) + 1.91/2.4 = 1.81$  was calculated. The value of 1.81 of  $K_{ULMB}$  for exposure to  $TLV$  of 50ppm toluene and 100ppm xylene was obtained.

When the above datum of specimens was substituted into  $ECUL_i$  in equation [2-4], the next equation of  $(1.41 - 0.41)/(1.85 - 0.65) + 1.91/2.8 = 1.51$  was calculated. The value of 1.51 of  $K_{ULB}$  for exposure to  $TLV$  of 50 ppm toluene and 100ppm xylene was obtained.

The values of  $K_{ULMB}$  and  $K_{ULB}$  indicate that the mean values exceed not only the mean or upper 97.5 % confidence limit of the mean but also the upper 97.5 % predictive limit of the individual samples of the standard value for both a  $TLV$  of 50ppm toluene and 100ppm xylene.

When the above datum of specimens was substituted into  $ECLLM_i$  of equation [3-7],  $(1.41 - 0.20)/(1.01 - 0.01) + 1.91/1.8 = 2.27$ . The value of 2.27 of  $K_{LLMB}$  for exposure to a  $TLV$  of 50ppm toluene and 100ppm xylene was obtained.

When the above datum of specimens was substituted into  $ECLL_i$  of equation [2-7],  $(1.41 - 0.09)/(0.67 + 0.23) + 1.91/1.4 = 2.83$ . The value of 2.83 of  $K_{LLB}$  for exposure to a  $TLV$  of 50ppm toluene and 100ppm xylene was obtained.

In this case, the relationship of  $K_{LLB} > K_{LLMB} > K_{ULMB} > K_{ULB}$  was obtained.

A  $K_{LLB}$  (2.83) of a worker described above exceeds 1, and the value exceeds the 97.5 % predictive range of the standard samples from workers exposed to  $TLV$  of 50 ppm toluene and 100ppm xylene. Therefore, a  $K_{LLB}$  is

useful for screening workers exposed to  $TLV$  of mixed solvents taking individual differences into account. In this case, the  $K_{LLB}$  should not exceed 1.

#### E. Complementary Method

When some data for confidence and predictive limits of specimens are lacking, the background data of the standard value can be useful as an appropriate values. When the concentrations of methyl hippuric acids but not hippuric acid are available as factors for equations [1-2] and [1-3], the complementary method can be used substituting the appropriate values from Table 2A and B into equations [5-9] and [5-10]. When  $ECM_{TLVi}$  in equation [5-9] was used,

$$(1.91/2.1) \times (83/100 + 67/50)/(83/100) = 2.37$$

was obtained. The value from equation [1-2] was 2.01. When 100ppm toluene was used as a  $TLV$ ,

$$[(1.91/2.1) \times (83/100 + 67/100)/(83/100) = 1.64]$$

was obtained. The value from equation [1-2] was 1.46.

When  $BEI_i$  for a  $TLV$  of 100ppm toluene in equation (35) was used,  $K_B'$  was

$$[(1.91/1.5) \times (83/100 + 67/100)/(83/100) = 2.30]$$

The value from equation [1-3] was 1.78.

#### Discussion

There have been reports that the numbers of workshops using mixed solvents in Japan are relatively large. For example, Mori *et al.* (11) reported that the number of workshops using mixed solvents accounts for 79.2 % of the 237 workshops in the Kyushu district. Their report suggested that many organic solvents are used in mixture in Japan.

In order to evaluate mixed exposure, individual metabolic differences taken into account, the confidence and predictive lines should be straight by the present method. However, in our previous report (6), the regression lines were plotted by the method of Snedecor and Cochran (10). Using this method the lines we plotted for the confidence lines of the regression line and predictive lines of individual samples were not straight. Therefore, we used the values in our another previous paper (8) instead of the report (6). In the present paper, regression line, confidence lines and predictive lines were straight, because these lines were depicted by the method of Weisbrot (9). His method is as follows: Workers were



classified into several groups by their exposure concentration. In each group, the mean value, confidence limits of the mean and predictive limits of individual samples were calculated and the straight lines were drawn by the least square method from the mean, confidence limits of the mean and predictive limits of the individual samples of each group.

The equations in the present paper were made under the assumption that uptake, distribution, metabolism and elimination are not affected by coexposure. These conditions are usually met at low exposure, showing the values of the haz. ind. ( $k$ ) are not much greater than 1, rather than longer duration of exposure. In the report describing volunteers' exposure to 50 ppm toluene and 40 ppm xylene, equivalent to 1.4 of the  $k$  and 1.3 of the  $K_B$  value, did not alter urinary concentrations of both solvent by Tardiff *et al.* (13), which is described later.

Currently, the  $TLV$  of toluene has been changed from 100 ppm to 50 ppm, however,  $BEI_s$  of urinary hippuric acid, o-cresol and toluene have not been documented. Therefore,  $TLV_s$  for toluene of 50 ppm and 100 ppm were used in this study.

In the present study, urinary hippuric acids were used as biological determinants of toluene exposure. The cut-off value, which is used to discriminate the exposure from the non-exposure, was 43 ppm (Fig. 1B) for hippuric acids (with a 2.5% level of error) which is below the current  $TLV$  of 50 ppm toluene. Moreover, o-cresol is one of the metabolites whose background value is not affected food intake though it is affected by tobacco smoking. The  $K_B$  value of hippuric acids was 0.35 evaluated by hippuric acid and was 0.42 evaluated by o-cresol, the former being slightly lower than the latter. Therefore, we used hippuric acid as the major determinant. The use of urinary toluene as a determinant for evaluation will be reported in the future.

As to the metabolic rates of mixed solvents from the pharmacokinetic point of view, two factors should be taken into consideration. One is the instance in which little interaction of the metabolic rates of components is observed in workers exposed to mixed organic solvents (1, 12, 13) and the other is when marked mutual effects are observed on the metabolic rates in workers exposed to mixed solvents containing two or more components (13-15). In these cases, use of the adjustment factor "f" was described by the author and others (2-5).

A study made by Ogata *et al.* (1) considered the former case in which volunteers were coexposed to a

vapor of 67 ppm toluene and 83 ppm m-xylene for 3 h in an artificial exposure chamber and their urinary hippuric acid and m-methylhippuric acid were determined. The results suggested that simultaneous exposure did not alter the rates of excretion of both metabolites from those for separate exposure.

Kawai *et al.* (12) monitored urinary metabolites of workers exposed to a mixture of 11.0 ppm toluene, 7.1 ppm styrene and 32.6 ppm methanol and reported that no change in metabolism was induced by combined exposure at these low exposure levels.

Ogata *et al.* (6) examined the concentrations of urinary hippuric acid, m-methylhippuric acid and methyl isobutyl ketone at the end of shift in the urine of workers who had been exposed to 15.2 ppm toluene, 13.9 ppm xylenes and 16.7 ppm methyl isobutyl ketone (6). Regression equations were set up between the ambient concentrations of each compound in a mixed solvent to which workers were simultaneously exposed and the urinary concentration of the metabolites or parent solvents corresponding to the solvent to which they were exposed. The values of the slopes and intercepts of these equations obtained were not significantly different from the corresponding values of regression equations for the three groups of workers, each of which was exposed to only one of the solvents. These results indicated that each component had a minimal pharmacokinetic effect on the concentrations of urinary metabolites or solvents of the other solvents.

Recently, Tardif *et al.* (13) showed that simultaneous exposure to 50 ppm toluene and 40 ppm xylene for 7 h in a controlled exposure chamber did not produce any interactions on the concentrations of the solvents themselves in blood and exhaled air as well as in the urinary concentrations of hippuric acid and methylhippuric acid. Then the  $K$  values was calculated to be 1.4 and  $K_B$  value was to be 1.3. The same authors (13) also showed that simultaneous exposure to 95 ppm toluene and 80 ppm xylene (2.7 of  $K$  value) for 4 h did affect the concentration of parent solvents in blood and in exhaled air; there was a significant delay in the urinary excretion of the hippuric acid but not of the m-methylhippuric acid. These results indicate that there is a threshold level below which metabolic interaction of solvents does not occur, indicating that interaction among mixed components is dependent on concentrations of mixed solvents rather than duration of exposure. These four reports suggest that mutual metabolic interactions among multiple components of solvents

is not likely to occur in humans who are exposed to mixtures such as toluene and xylene, or toluene, xylene and methanol (12) in lower concentration ranges than those reported in the above studies.

In the present report, the author has reported a basic method for the evaluation of biological monitoring of a mixed exposure. The methods for calculation of the biol. haz. index and its ranges are described. When the concentrations of some metabolites and/or solvents in urine are not determined, a complementary method using their airborne concentrations is also described.

Therefore, its application is limited to those cases in which the kinds of solvents and the concentration range of those solvents have been reported.

A more generalized application of the equation will be reported after further experimental and field data have been taken into account.

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