Industrial Health 2010, **48**, 154–163 **Original Article**

Validation of Urine Density Correction in Cases of Hippuric Acid and Un-metabolized Toluene in Urine of Workers Exposed to Toluene

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Abstract: To investigate if it is appropriate to apply urine density correction when a urine sample is dense or dilute. Data on hippuric acid (HA-U), toluene (Tol-U), creatinine (CR) and specific gravity (SG) in end-of-shift urine samples and exposure to air-borne toluene were cited from previous publications. In practice, 837 cases were available, and they were classified into dense, intermediate and dilute groups taking 0.3 and 3.0 g/l of CR and 1.010 and 1.030 of SG as cut-off points. Lines of regression of HA-U and Tol-U (as observed, CR-corrected or SG-corrected) with air-borne toluene were calculated for each density groups, and correlation coefficients (CCs) were compared. The dense groups gave CCs similar to those of the intermediate groups. Dilute versus intermediate group comparison also gave promising results. These conclusions were however based primarily on the findings with observed values, because the numbers of cases in the dilute or dense group were limited when CR- or SG-correction was applied. Literature survey showed that urine density correction does not always improve the correlation between solvents in air and exposure makers in urine. It was concluded that no correction for urine density may be necessary in evaluating HA-U and Tol-U in dense (and probably also dilute) urine samples as markers of occupational toluene exposure. Just in case when correction for urine density is desired for any reason, SG-correction may be recommended.

Key words: Creatinine, Hippuric acid, Specific gravity, Toluene, Urine density correction

Introduction

Urine is one of the most popular materials for biological monitoring of occupational exposure to various chemicals, typically organic solvents[1)]. Quite different from blood, however, density of urine from the same person may vary depending on physiological conditions such as perspiration, water intake etc. Accordingly, possible correction for urine density has been the subject of long-standing concern as to be discussed later. There are two common proposals for the correction, i.e., correction for creatinine concentration (CR)[2)] and for a specific gravity of urine (SG)[3, 4)]. The application of the correction has been however criticized as it does not reduce variation and therefore does not always improve the correlation between the external doses and urinary exposure marker levels[5, 6)]. Our study group also has reported that the correlation with intensity of exposure to air-borne chemicals is as close with observed (non-corrected) values of uri-

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nary metabolite levels as with density-corrected values to suggest no need of density correction[7–14]. In contrast, surveys for past publications[15–17] showed that it is a common practice to correct urinary levels of markers (e.g., cadmium, and β_2-microglobulin) for CR in environmental toxicology of cadmium. For example, cadmium concentrations in urine (as corrected for CR) of residents in non-polluted areas correlate with cadmium levels in the sediments of regional rivers[18].

Whether or not correction for urine density is recommended, it happens sometimes in real world that a urine sample of critical importance carries very dark or light color to suggest extensive condensation or dilution, respectively. Thus, any method for correcting urine density is desired for better evaluation of analyte levels in the sample.

The present study was initiated to investigate whether it is plausible or not to make correction for urine density in terms of either CR or SG, and if so, which is better the CR-correction or SG-correction. For this purpose, a database was established from several publications for a large toluene-exposed population, and correlation of hippuric acid and un-metabolized toluene in urine (HA-U and Tol-U, respectively) with air-borne toluene among a group of high (dense, as evaluated in terms of CR or SG) or low (dilute) urine density was compared with that among a group of intermediate urine density.

Subjects, Materials and Methods

Ethical issue

The Ethics Committee of Kyoto Industrial Health Association approved the study protocol. Each of the participants agreed to join the survey.

Solvent-exposed workers, collection of urine samples, and urinalysis for hippuric acid, unmetabolized toluene, CR and SG

The surveys were carried out on the second half of working weeks. Time-weighted average exposure of each worker to organic solvents was monitored by diffusive sampling[19] mostly for 8 h, and carbon disulfide extract of the exposed carbon was analyzed by gas-chromatography as previously described[20]; the limit of detection (LOD) was 0.1 ppm, common to various solvents. Workers were exposed primarily to toluene, but co-exposures to other solvents were also noted, as to be described later. Thus, the additiveness formula[21, 22] was employed for evaluation of combined exposure to multiple solvent vapors. The formula is the SUM = $\sum Ci/OELi$, in which i =1 to n (n being the total number of solvents exposed together), Ci is the measured concentration for the ith solvent, and OELi is the corresponding occupational exposure limit[22].

Urine samples were collected at the end of shift with due care to minimize possible loss of toluene in sampling procedures[23], and analyzed for hippuric acid (HA-U, U standing for urine) and un-metabolized toluene (Tol-U) by high-performance liquid chromatography[24] and by head-space gas-chromatography[25], respectively. CR concentration was measured by colorimetry, and SG by refractometry. The limit of detection (LOD) was 2 mg/l for HA-U and 2 μg/l for Tol-U, and 0.1 ppm for air-borne organic solvents in general.

In practice, data were cited from Takeuchi *et al.*[26] (277 cases), Ukai *et al.*[27] (124 cases) and Kawai *et al.*[28] (520 cases). In addition, a set of 50 new cases (all men) were included in the database. These new cases were engaged in the production of small painted containers, and were exposed primarily to toluene at 4.4 ppm as a geometric mean and 147 ppm as the maximum. Co-exposures to xylenes, ethylbenzene, ethyl acetate and butyl acetate were noted, and the SUM after the additiveness formula was 0.16 as GM and 2.94 as the maximum. Out of the combination of the four groups (with 971 cases), 96 cases were excluded because air-borne or urinary marker levels were below the corresponding LODs. Furthermore, a preliminary analysis revealed that all workers who offered dense or dilute urine samples (for definition, see below) were exposed ≤36.8 ppm toluene. For better comparability, 38 cases exposed to toluene at >37 ppm were excluded. In practice, complete sets of data on HA-U, Tol-U, CR, SG and solvent exposure were available for 837 cases for statistical evaluation. The subjects were all men at the ages of 20 to 60 yr.

HA-U and Tol-U were expressed as observed (i.e., HA-U_{ob} and Tol-U_{ob}), or after correction for CR[2] (HA-U_{cr} and Tol-U_{cr}), or for SG (HA-U_{sg} and Tol-U_{sg}, taking 1.016 as a standard SG of urine[3, 4]). In some instances, SG was expressed in terms of factor G[29] which is defined as factor G = (SG–1.000) × 1,000.

With regard to urine density correction, Aitio[30] considered unlikely that correction for urine density will give accurate results when urine is very dilute (i.e, CR <0.3 g/l or SG <1.010) or very concentrated (i.e., CR>1.0 g/l or SG >1.030). Cioffi *et al.*[31] also reported that urine SG ranges between 1.010 and 1.025 under normal conditions. Following the criteria of Aitio[30], the 837 cases were classified into dilute (low-density), intermediate and dense (high-density) groups when the CR was <0.3, ≥0.3 to ≤1.0 and >1.0 g/l (classification by CR concentration), or the SG of urine was <1.010, ≥1.010 to ≤1.030, and >1.030 (or <10, ≥10 to ≤30, and >30 when factor G was employed; classification by SG). In cases of observed values, those with CR<0.3 or SG<1.010 were classified as dilute, and CR>3.0 or SG>1.030 as dense, respectively; others were classified as intermediate.

Statistical analysis

HA-U, Tol-U, and air-borne toluene were distributed log-normally so that geometric means (GMs) and geometric standard deviations (GSDs) were taken as representative parameters of the distribution, together with medians (MEDs), and the maximum concentrations, as necessary. CR and SG (expressed in terms of factor G which is defined as described above) were distributed normally and expressed in terms of arithmetic means (AMs) and arithmetic standard deviations (ASDs).

Statistical significance of the differences was examined by *t*-test (as a parametric examination with an assumption of normal or log-normal distribution) or Mann-Whitney test (as non-parametric evaluation). When necessary, two simple regression lines were compared in terms of correlation coefficients (CC) after Ichihara[32)].

Results

Basic parameters of exposures for the total 837 cases

The analyses for air-borne solvents showed that the workers were exposed primarily to toluene, but also to several other solvents (i.e., xylenes, ethylbenzene, ethyl acetate and butyl acetate) depending on the workshops. Accordingly, the co-exposures (including that to toluene) were evaluated in terms of the SUM after the additiveness formula. The distribution parameters for air-borne toluene, the SUM, HA-U, Tol-U, CR and SG are summarized in Table 1.

The over-all toluene exposure level was rather low with GM and MED of 2.8 ppm and 3.4 ppm, respectively, although the maximum was as high as 36.8 ppm. Correspondingly, the GM HA-U_{ob} and Tol-U_{ob} were rather low (299 mg/l and 6.7 μg/l, respectively) whereas the maximum values were high (3,081 mg/l and 270 μg/l). Because both AM CR and SG (in terms of G) were in excess of 1 g/l and 16, respectively, both values for HA-U and Tol-U after CR or SG corrections were nominally smaller than the observed values.

Comparison of regression lines after correction for CR or SG with the line without correction

Regression lines were calculated with air-borne toluene concentration after HA-U and Tol-U were corrected for none, CR or SG, and the CCs thus calculated were examined for statistical significance (Table 2). It was clear that the differences were insignificant for all pairs (p>0.05); one possible exception was that the CC for Tol-U_{cr} (0.502) was barely (0.05<p<0.10) smaller than that for Tol-U_{ob} (0.593), but the difference (Δ) was small (Δ=0.091) and both CCs were statistically significant (p<0.01).

Exposure parameters after classification into three urine density groups

When the observed values (i.e., HA-U_{ob} and Tol-U_{ob}) for the total 837 cases were classified into dense, intermediate and dilute urine groups (the top one-third in Table 3), the distribution of cases in the three groups were markedly biased, i.e., a majority (720 cases or 86%) was in the intermediate group and those in the dense (87 cases, 10%) or dilute group (30 cases, 4%) were limited. The intensity of exposure to air-borne toluene was nevertheless comparable among the three groups when examined by *t*-test (after logarithmic conversion) and Mann-Whitney test (for non-parametric evaluation), respectively.

The distribution of the cases was more biased when classified in terms of CR, i.e., 27, 800 and 10 cases (3%, 96%, and 1%) in the dense, intermediate, and dilute groups, respectively (the middle one-third in Table 3), but less so with SG, i.e., 80, 728 and 29 cases (10%, 87%, and 3%) in the three groups, respectively (the bottom one-

Table 1. Exposure marker levels

Parameter	Solvents in air		Urinary markers							
	Toluene (ppm)	SUM[d]	Creatinine (g/l)	Specific gravity (G[a])	HA-U_{ob} (mg/l)[b]	HA-U_{cr} (mg/g cr)	HA-U_{sg} (mg/l)[c]	Tol-U_{ob} (μg/l)[b]	Tol-U_{cr} (μg/g cr)	Tol-U_{sg} (μg/l)[c]
GM	2.57	0.15	1.48[e]	22.4[e]	298.6	231.4	224.3	6.73	5.22	5.06
GSD	3.33	3.27	0.73[e]	6.5[e]	2.45	2.26	2.27	2.92	3.26	2.98
MED	3.40	0.18	1.39	23	303	238	229	7.20	5.37	5.33
Max	36.8	3.66	4.78	41	3,081	1,884	1,972	270.3	206.3	173.0

A total of 837 cases were analyzed.
[a]Factor G is defined as factor G = (SG–1.000) × 1,000.
[b]LOD: 2 mg/l for HA-U and 2 μg/l for Tol-U.
[c]A SG of 1.016 is taken as a standard.
[d]The SUM after the additiveness formular; for details, see Materials and Methods section.
[e]AM and ASD are given in place of GM and GSD, respectively.

Table 2. Regression lines[a] for HA-U and Tol-U, and comparisons among them

Y[b]	(Unit)	Intercept	Slope	CC[c]	p for CC	p for difference in CC	
$HA\text{-}U_{ob}$	mg/l	356	16.1	0.219	<0.01		
						ns[d]	
$HA\text{-}U_{cr}$	mg/g cr	263	11.2	0.232	<0.01		ns[d]
						ns[d]	
$HA\text{-}U_{sg}$	mg/l	258	10.2	0.212	<0.01		
$Tol\text{-}U_{ob}$	μg/l	2.41	1.83	0.593	<0.01		
						ns[e]	
$Tol\text{-}U_{cr}$	μg/g cr	2.75	1.51	0.502	<0.01		ns[d]
						ns[d]	
$Tol\text{-}U_{sg}$	μg/l	2.41	1.31	0.567	<0.01		

[a]X is air-borne toluene (in ppm). Y is either HA-U or Tol-U as shown in the table.
[b]ob, cr and sg stand for observed values, values corrected for creatinine concentration, and values corrected for a specific gravity of 1.016, respectively.
[c]CC stands for correlation coefficients.
[d]$p>0.10$.
[e]$0.05<p<0.10$.

Table 3. Parameters of groups after classification into three groups

Correction for Parameter (Unit)		Geometric mean					Median					Maximum		
		Dense[a]	p[b]	Intermediate[a]	p[b]	Dilute[a]	Dense[a]	p[c]	Intermediate[a]	p[c]	Dilute[a]	Dense[a]	Intermediate[a]	Dilute[a]
No correction														
Count		87		720		30	87		720		30	87	720	30
Toluene	(ppm)	2.4	ns	2.6	ns	2.6	3.3	ns	3.4	ns	3.4	36.8	36.1	23.1
CR	(g/l)	2.7	>>	1.4	>>	0.3	2.7	>>	1.3	>>	0.3	4.8	3.0	0.8
SG	(G)	32.8	>>	21.8	>>	7.7	33.0	>>	23.0	>>	8.0	41.0	30.0	15.0
Creatinine concentration														
Count		27		800		10	27		800		10	27	800	10
Toluene	(ppm)	3.4	ns	2.5	ns	3.6	3.8	ns	3.4	ns	4.6	17.3	36.8	23.1
CR	(g/l)	3.5	>>	1.4	>>	0.2	3.4	>>	1.4	>>	0.3	4.8	3.0	0.3
Specific gravity														
Count		80		728		29	80		728		29	80	728	29
Toluene	(ppm)	2.3	ns	2.6	ns	2.5	3.3	ns	3.4	ns	3.4	36.8	36.1	23.1
SG	(G)	33.3	>>	21.9	>>	7.4	33.0	>>	23.0	>>	8.0	41.0	30.0	9.0

[a]A total of 837 cases were devided into the dense, intermediate and dense groups; for classification criteria, see the Materials and Methods section.
[b]p for the difference from the intermediate group value by un-paired t-test after logarithmic conversion; << for $p\leq0.01$, and ns for $p>0.05$.
[c]p for the difference from the intermediate group value by Mann-Whitney test; << for $p\leq0.01$, and ns for $p>0.05$.
[d]CR for creatinine and SG for specific gravity. Arithmetic means are shown in place of geometric means.

third in Table 3). The levels of air-borne toluene were comparable among the three groups in both cases.

Comparison of correlation coefficients for the dilute or dense group with that for the intermediate group

Analyses were first conducted with $HA\text{-}U_{ob}$ and $Tol\text{-}U_{ob}$. Regression lines were calculated between the air-borne toluene and $HA\text{-}U_{ob}$ or $Tol\text{-}U_{ob}$ for each of the dense, intermediate and dilute groups, and the CC for the dense (or dilute) group was compared with that for the intermediate group (the top one-third in Table 4). The CC for the intermediate group was taken as the reference, and the comparison was made to examine if the CC for the dense (or dilute) group differed from that for the intermediate group.

The comparison of CCs for $HA\text{-}U_{ob}$ between the dense and intermediate groups (the top one-third in Table 4) revealed that the CCs did not differ significantly ($p>0.05$) from each other. The CC for the dilute group was also not different from that for the intermediate group,

Table 4. Regression of HA-U and Tol-U in the dense or dilute groups with air-borne toluene in comparison with those in the intermediate group

Correction for Markers[a] (Unit)	Group	No. of cases	CC	p for CC[d]	p for diff.[c]
None (i.e, as observed)					
HA-U_{ob}	Dense	87	0.23	<0.05	ns
(mg/l)	Intermediate	720	0.23	<0.01	
	Dilute	30	–0.20	ns	ns[e]
Tol-U_{ob}	Dense	87	0.70	<0.01	<0.01
(μg/l)	Intermediate	720	0.59	<0.01	
	Dilute	30	0.59	<0.01	ns
Creatinine					
HA-U_{cr}	Dense	27	0.33	ns	ns
(mg/g cr)	Intermediate	800	0.23	<0.01	
	Dilute	10	–0.15	ns	ns
Tol-U_{cr}	Dense	27	0.55	<0.01	ns
(μg/g cr)	Intermediate	800	0.54	<0.01	
	Dilute	10	0.33	ns	ns
Specific gravity					
HA-U_{sg}	Dense	80	0.21	ns	ns
(mg/l)	Intermediate	728	0.23	<0.01	
	Dilute	29	–0.20	ns	ns[e]
Tol-U_{sg}	Dense	80	0.70	<0.01	ns
(μg/l)	Intermediate	728	0.59	<0.01	
	Dilute	29	0.54	<0.01	ns

[a]Abbreviations are: HA-U_{ob} or Tol-U_{ob} for hippuric acid or toluene in urine as observed, HA-U_{cr} or Tol-U_{cr} for hippuric acid or toluene in urine as corrected for creatinine (CR) concentration, and HA-U_{sg} or Tol-U_{sg} for hippuric acid or toluene in urine as corrected for a specific gravity (SG) of 1.016, respectively.
[b]Grouped by urine density to the dense, intermediate, and dilute groups; for details of classification, see the Materials and Methods section.
[c]p value for the difference from the intermediate group values; ns for $p>0.05$.
[d]p value for significance of the CC; ns for $p>0.05$.
[e]$0.05<p<0.10$.

although the CC for the dilute group was statistically insignificant ($p>0.05$). In case of Tol-U_{ob}, the difference in CCs between the dense and intermediate groups was statistically significant ($p<0.01$), whereas no significant difference ($p>0.05$) was observed in CCs in case of the intermediate versus dilute group comparison. Scatter diagrams for HA-U_{ob} with calculated regression lines are depicted in Fig. 1 for visual understanding of the cases.

The comparison in CCs between the dense and intermediate groups and between the dilute and intermediate groups after CR concentration of HA-U (i.e., HA-U_{cr}; the middle one-third in Table 4) showed no significant difference ($p>0.05$) between the groups for HA-U_{cr}, and the same was also the case for Tol-U_{cr}. Nevertheless the comparison both in HA-U_{cr} and Tol-U_{cr} was hampered by the fact that only 27 and 10 cases were available in the dense and dilute groups, respectively, for the calculation of CCs, and over-all evaluation was difficult to make.

Relatively large numbers of cases were available for the dense (80 cases) and dilute groups (29 cases) when corrected for a SG of 1.016 (the bottom one-third in Table 4). The results of the dense versus intermediate group comparison in CCs were essentially the same with the findings after CR-correction.

Discussion

The present observation on HA-U (Table 4) suggests that CCs are similar between the dense and intermediate groups irrespective of density correction. It is also the

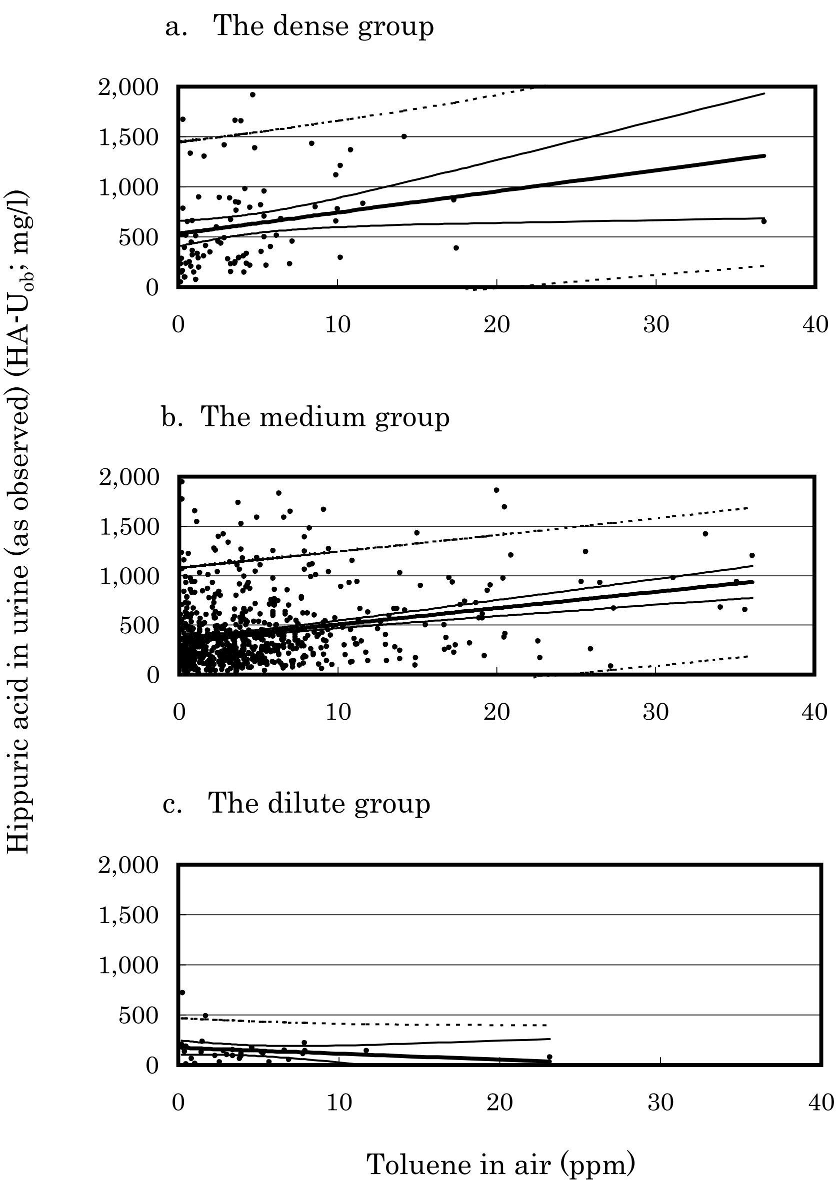

Fig. 1. Correlation of hippuric acid in end-of-shift urine (observed values; HA-U$_{ob}$) with time-weighted average exposure to air-borne toluene.
a. The dense group, b. The intermediate group, c. The dilute group.
The lines in the middle are calculated regression lines, and the dotted curves on both sides show the 95% confidence ranges of the regression lines. Each dot represents one case.

case for Tol-U, with one exception that CCs for Tol-U$_{ob}$ were different between the dense and intermediate groups (p<0.01). In cases of comparison of the dilute groups with the intermediate groups, general evaluation is difficult to make due to limitation in the numbers of cases available for the dilute groups, being more serious for CR-corrected dilute group (n=10) than for other two dilute groups (n=29 or 30). Thus, the present evaluation on the dilute groups should be taken inconclusive, and further studies with more cases of dilute urine samples are apparently desired. In this sense, the affirmative results with the observed value analysis (Table 4) may be taken as encouraging. One of the difficulties with HA-U (irrespective of urine density correction) was poor correlation of HA-U with air-borne toluene in the dilute group (the top one-third in Table 4). This should be due, at least in part, to the fact that HA is physiologically present in urine and the level is elevated after consumption of some foods or drinks such as benzoate-containing soft drinks[33–35].

Within such limitations, the present findings appear to suggest that correction of HA-U and Tol-U in dense (but not dilute) urine samples for urine density may not always improve correlation with air-borne toluene. With regard to choice between CR correction or SG correction, if necessary or desired, correction for SG rather than that for CR concentration might be recommended, knowing that CR in urine decreases in advanced ages[36, 37] and that the effects of aging are more remarkable on CR concentration than on SG[38]. It should be considered however that CR and SG correlate significantly (p<0.01) with each other[38], and therefore the criticism on CR correction may also be applicable to correction for SG.

CR is known to be excreted through glomeruli[39], whereas the SG may be determined as a result of balance between glomerular filtration and tubular re-absorption of various compounds. HA will be excreted into urine via organic anion transport system in proximal tubular cells[40]. Excretion of un-metabolized toluene into urine is generally believed as a result of simple diffusion. Nevertheless, the difference in the excretion mechanism was not reflected in the results of the present study.

Because the present study results suggested lack of improvement after CR- or SG-correction (Table 4), it was thought important to make literature survey to examine if the density-corrected values give better correlation than the values without correction. Research groups which reported values under three correction conditions in parallel (i.e., observed values, values corrected for CR and values corrected for SG) are limited (e.g., CR-corrected values only[41–44]). The available 37 cases (counted by analytes in urine) with CCs under more than two correction conditions are listed in Table 5. Among them, no CC with air-borne toluene was reported for SG-corrected values in case of Anger and Krämer[50] and it was also the case for observed values in De Rosa *et al*.[51]. The types of air-borne solvents were various but the reports were most abundant for toluene. In 8 reports, the mother compound itself was monitored as an exposure marker in urine, while metabolites were analyzed in other cases. When the CCs were compared among the former 8 reports, it was observed that the CCs for observed values were significantly greater (p=0.022) than the CCs for CR-corrected values although not different from the CCs for SG-corrected values. In case of the remaining 33 cases (excluding incomplete sets of De Rosa *et al*.[51] and Anger and Krämer[50]), CCs calculated with CR- or SG-corrected values did not differ from the CCs with observed values (p>0.05). The lack of difference was also the case when the evaluation was made with toluene exposure cases only (n=17). In other words, correction for urine density does not improve the CC, as previously discussed[5, 6]. The present observation (Table 2) is also on line with this opinion.

In conclusion, it appears that no correction for urine density is necessary in evaluating HA-U and Tol-U in dense urine samples as markers of occupational exposure to air-borne toluene. No general conclusion was achieved for dilute urine samples. Just in case it is desired for any reason to make correction for urine density, SG-correction may be recommended, whereas CR-correction should not be applied to the case of aged workers in particular.

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Table 5. Correlation coefficients by chemicals exposed and by correction for urine density; observation in selected reports

References / Authors	Solvents in air	GM (ppm)	Max (ppm)	No. of cases	Analytes in urine	Correlation coefficients with		
						OB[a]	CR[a]	SG[a]
Urinalysis for the mother chemical								
Kawai *et al*.[7)]	Acetone	8[b]	45	26	Acetone	0.90	0.81	0.89
Ukai *et al*.[45)]	Dichloromethane	9.9	270	61	Dichloromethane	0.91	0.84	0.90
Kawai *et al*.[10)]	Methanol	15.9	178	34	Methanol	0.86	0.72	0.68
Kawai *et al*.[25)]	Toluene	3.9	98	115	Toluene, un-metabolized	0.84	0.78	0.75
Kawai *et al*.[12)]	Toluene	2.1	12	30	Toluene, un-metabolized	0.65	0.70	0.72
Takeuchi *et al*.[26)]	Toluene	4.2	54	97	Toluene, un-metabolized	0.74	0.67	0.75
Kawai *et al*.[46)]	Toluene	2.3	132	294	Toluene, un-metabolized	0.60	0.30	0.43
Ukai *et al*.[27)]	Toluene	10.4	121	122	Toluene, un-metabolized	0.83	0.72	0.83
Urinalysis for a metabolite								
Inoue *et al*.[47)]	Benzene	NR[c]	210	152	Phenylmercapturic acid	0.72	0.76	0.72
Kawai *et al*.[11)]	Dimethylformamide	1.8	4.5	116	Monomethylformamide	0.72	0.67	0.71
Kawai *et al*.[9)]	Hexane	10.0[b]	80	36	2,5-Hexanedione[d]	0.87	0.41	0.83
Kawai *et al*.[48)]	Hexane	9.6	81	123	2,5-Hexanedione[d]	0.83	0.73	0.79
Kawai *et al*.[12)]	Hexane	2.2	4.7	30	2,5-Hexanedione[d]	0.70	0.68	0.65
Kawai *et al*.[8)]	Isopropyl alcohol	25[b]	66	133	Acetone	0.84	0.43	0.65
Mizunuma *et al*.[13)]	Methyl methacrylate	6.1	112	32	Methanol	0.93	0.82	0.81
Mizunuma *et al*.[14)]	Methylchloroform	2.7	45	50	Total trichloro-compounds	0.78	0.75	0.75
Kawai *et al*.[25)]	Toluene	3.9	98	115	Hippuric acid	0.52	0.67	0.70
Kawai *et al*.[25)]	Toluene	3.9	98	115	*o*-Cresol	0.54	0.60	0.62
Inoue *et al*.[49)]	Toluene	8.3	86	122	Benzylmercapturic acid	0.73	0.74	0.74
Angerer and Krämer[50)]	Toluene	63.2[b]	151	33	Hippuric acid	0.74	0.56	NR[c]
Angerer and Krämer[50)]	Toluene	63.2[b]	151	33	*o*-Cresol	0.65	0.52	NR[c]
Kawai *et al*.[35)]	Toluene	12.2	130	45	Benzyl alcohol	0.80	0.56	0.70
Ukai *et al*.[27)]	Toluene	10.4	121	122	Benzylmercapturic acid	0.66	0.56	0.63
Ukai *et al*.[27)]	Toluene	10.4	121	122	*o*-Cresol	0.81	0.74	0.80
Ukai *et al*.[27)]	Toluene	10.4	121	122	Hippuric acid	0.85	0.80	0.84
De Rosa *et al*.[51)]	Toluene	39.1	59	18	Hippuric acid	NR[c]	0.75	0.79[e]
De Rosa *et al*.[51)]	Toluene	39.1	59	18	*o*-Cresol	NR[c]	0.57	0.58[e]
Hasegawa *et al*.[52)]	Toluene	32.5[b]	130	74[f]	Hippuric acid	0.80	0.61	0.77
Hasegawa *et al*.[52)]	Toluene	32.5[b]	130	56[g]	Hippuric acid	0.83	0.79	0.83
Hasegawa *et al*.[52)]	Toluene	32.5[b]	130	74[f]	*o*-Cresol	0.61	0.40	0.49
Hasegawa *et al*.[52)]	Toluene	32.5[b]	130	56[g]	*o*-Cresol	0.63	0.61	0.62
Inoue *et al*.[53)]	Toluene	25.0	550	452	Hippuric acid	0.73	0.79	0.81
Inoue *et al*.[53)]	Toluene	25.0	550	452	*o*-Cresol	0.70	0.75	0.75
Inoue *et al*.[54)]	Toluene	13.1	86	46	Benzylmercapturic acid	0.43	0.49	0.49
Inoue *et al*.[49)]	Toluene	8.3	86	122	Benzylmercapturic acid	0.73	0.74	0.74
Inoue *et al*.[49)]	Toluene	8.3	86	122	Hippuric acid	0.58	0.58	0.63
Inoue *et al*.[49)]	Toluene	8.3	86	122	*o*-Cresol	0.63	0.63	0.66

[a]OB, CR, and SG for observed values, values corrected for creatinine concentration, and values corrected for a specific gravity of 1.016, respectively, unless otherwise specified.
[b]Median in the place.
[c]NR for not reported.
[d]2,5-Hexanedione without hydrolysis.
[e]Corrected for 1.024.
[f]Men only.
[g]Women only.

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