

## 가

### Abstract

#### Effect of Soft Drink on Urinary Hippuric Acid Excretion in Workers Exposed to Low dose Toluene

Yong Jin Lee

*Department of Preventive Medicine, College of Medicine, Soonchunhyang University*

**Objectives:** To investigate the effect of soft drink containing benzoic acid on the excretion of urinary hippuric acid after ingestion of soft drink containing benzoic acid before working (Ed-the deleted section is not an objective).

**Methods:** Fifty workers (male, 35; female, 15) exposed to toluene in Choongchung province area were studied. Urinary samples were collected on two days. On the first day, all study subjects were required to avoid any soft drink containing benzoic acid for the 24-hour period before urine collection. After emptying their bladder before starting work, the total volume of urine for the full shift period was collected and spot urine was collected at the end of the shift. On the second day, all workers were provided with soft drink containing benzoic acid before the shift and the same urine collection procedure was applied as on the first day.

The air concentrations of toluene for each workers was measured with personal air sampling with 3M organic solvent badge. Personal informations such as age, sex, smoking and drinking habit were collected by self-administered questionnaire method.

**Results:** The geometric mean of urinary hippuric acid without ingestion of soft drink containing benzoic acid was  $0.49 \pm 0.45$  g/g creatinine in total volume urine, and  $0.51 \pm 0.53$  g/g creatinine in spot urine, whereas the equivalent results with ingestion of soft drink were increased to  $0.92 \pm 0.61$  g/g and  $0.96 \pm 0.78$  g/g, respectively.

Stepwise multiple regression of urinary hippuric acid with air concentration of toluene, benzoic acid and other covariates revealed that 49% and 11% of urinary hippuric acid concentration in total volume urine analysis were attributed to the air concentration of toluene and benzoic acid, respectively, compared to 45% and 6% in spot urine analysis, respectively.

On the other hand, taking the difference of urinary hippuric acid before and after ingestion of soft drink containing benzoic acid as a dependent variable and taking the air concentration of

toluene, benzoic acid and other covariates as independent variables, stepwise multiple regression analysis revealed that 14% and 13% of urinary hippuric acid concentration in total volume urine analysis were attributed to the air concentration of toluene and benzoic acid, respectively, whereas only 9% of urinary hippuric acid concentration in spot urine analysis was attributed to the air concentration of toluene, (Ed- note that there is no respective comparison here).

**Conclusion:** Soft drink containing benzoic acid significantly affected the level of urinary hippuric acid after ingestion of soft drink before working. It is recommended that for the accurate elevation of urinary hippuric acid as an index of toluene exposure, detailed information on soft drink containing benzoic acid needs to be checked in the process of the health examination of toluene exposure workers.

**Key Words:** Hippuric acid, Benzoic acid, Toluene

가

(Clayton , 1981)

, , TDI, TNT, , 가

(La Dou, 1990;

, 1988).

(Ogata,

1985).

가 (Dodds , 1964).

가

가

, 가 ( ,

1986).

15~20%

, 80%

microsomal mixed function oxidase system benzoyl alcohol alcohol dehydrogenase aldehyde dehydrogenase system

(benzoic acid) 80% (hippuric acid) , 20% benzoyl glucuronide, o-cresol, m-cresol, p-cresol

가

(Cohr Stockholm, 1987; Carisson, 1982),

1. (D -benzoic acid 70 mg/dl, O -benzoic acid 50 mg/dl)

2000 8 2001 3

56

4 ~ 6

6 ~ 8

1

(high performance liquid chromatography; HPLC)

(20 =1 pack)

( ) {(pack/day}xyear}

(BMI) body mass index ( / 3)

2)

6 50

PC-SPSS 10.0

paired t-test

2.

1)

dent's t-test one way ANOVA

multiple correla-

organic vapor monitor(3M 3500) tion

가

gas chro-

matography(Shimadzu 14-A FiD)

step-

wise multiple regression test

2)

(total vol- 1. (spot

ume urine)

urine) 2

15 (30%) 35 (70%),  
(62.0%), 40 31  
19 (38.0%)

36.0±11.6 . 25 (50.0%) .  
 (BMI) 20~24.9† 26 (52.0%) 99 mg/dl  
 , 20 12 (24.0%), 25 가 12 13 (26.0%), 100~149 mg/dl  
 (24.0%) . 6~8 22 (44.0%), 150 mg/dl 15  
 29 (58.0%), 4~5.9 21 (42.0%) (30.0%) 132.6±60.0 mg/dl  
 . 45 g 27 20 ppm  
 (54.0%), 45 g 가 40 (80.0%)  
 11 (22.0%), 12 (24.0%) .  
 10 pack · year 13 (26.0%), 9.6±15.1 ppm, 9.6±15.3 ppm  
 10 pack · year 12 (24.0%) (Table 1).

**Table 1.** Summary of study subjects

Variables	No. (%)	Mean ± SD
Sex		
Male	35 (70.0)	
Female	15 (30.0)	
Age (years)		36.0 ± 11.6
<40	31 (62.0)	
40	19 (38.0)	
BMI (body mass index) (kg/m <sup>2</sup> )		
<20	12 (24.0)	
20~24.9	26 (52.0)	
25	12 (24.0)	
Exposure time (hrs/day)		
4~5.9	21 (42.0)	
6~8	29 (58.0)	
Alcohol amount (g/week)		
Non-drinker	12 (24.0)	
1~44.9	11 (22.0)	
45	27 (54.0)	
Smoking (pack/day * year)		
Non-smoker	25 (50.0)	
<10	12 (24.0)	
10	13 (26.0)	
Benzoic acid (mg/dl)		132.6 ± 60.0
<100	13 (26.0)	
100~149	22 (44.0)	
150	15 (30.0)	
Concentration of toluene in air (ppm)		9.6 ± 15.1 (first day)
<20	40 (80.0)	9.6 ± 15.3 (second day)
20~100	10 (20.0)	
Total	50 (100.0)	

가

2. tinine, 100~149 mg/dl 0.33±0.42  
g/g·creatinine, 150 mg/dl  
0.68±0.42 g/g·creatinine  
가

가

,  
가 , (p<0.05)

, 가, 0.43±0.44 g/g·  
creatinine, 0.44±0.67 g/g·creatinine  
(Table 3).

가, 4.

, 가  
가  
(p<0.05).

가  
가 (p<0.05).

0.49±0.45  
g/g·creatinine, 0.51±0.53 g/g·creatinine  
0.92±  
0.61 g/g·creatinine, 0.96±0.78 g/g·creati-  
nine  
가 (p=0.000)  
(Table 2).

3.

, 가  
99 mg/dl 0.31±0.42 g/g·crea-

(Table 4).

**Table 2.** Comparison of Urinary hippuric acid concentration by several characteristics in toluene exposed workers with or without drinking soft drink (g/g.creatinin)

Variable	Total volume urine		Spot urine	
	Without	With	Without	With
Sex				
Male	0.47 ± 0.41	0.92 ± 0.58 <sup>†</sup>	0.49 ± 0.50	0.97 ± 0.77 <sup>†</sup>
Female	0.53 ± 0.54	0.93 ± 0.70 <sup>†</sup>	0.57 ± 0.60	0.94 ± 0.85*
Age (years)				
<40	0.37 ± 0.31	0.78 ± 0.47 <sup>†</sup>	0.41 ± 0.42	0.84 ± 0.64 <sup>†</sup>
40	0.69 ± 0.57 <sup>†</sup>	1.16 ± 0.73 <sup>†</sup>	0.68 ± 0.64	1.15 ± 0.96*
BMI (body mass index) (kg/m <sup>2</sup> )				
<20	0.42 ± 0.48	0.71 ± 0.61 <sup>†</sup>	0.43 ± 0.53	0.67 ± 0.61
20~24.9	0.52 ± 0.49	1.06 ± 0.62 <sup>†</sup>	0.55 ± 0.54	1.11 ± 0.89 <sup>†</sup>
25	0.49 ± 0.35	0.85 ± 0.55*	0.50 ± 0.53	0.92 ± 0.64 <sup>†</sup>
Exposure time (hrs/day)				
4~5.9	0.32 ± 0.32	0.66 ± 0.58 <sup>†</sup>	0.35 ± 0.46	0.69 ± 0.69 <sup>†</sup>
6~8	0.61 ± 0.49 <sup>†</sup>	1.11 ± 0.56 <sup>†§</sup>	0.70 ± 0.59	1.16 ± 0.85* <sup>†</sup>
Alcohol amount (g/week)				
Non-drinker	0.78 ± 0.57 <sup>b</sup>	1.03 ± 0.74	0.79 ± 0.65	1.01 ± 0.92
1~44.9	0.28 ± 0.23 <sup>a</sup>	0.78 ± 0.40 <sup>†</sup>	0.34 ± 0.28	0.85 ± 0.61 <sup>†</sup>
45	0.45 ± 0.40 <sup>a†</sup>	0.94 ± 0.63 <sup>†</sup>	0.45 ± 0.51	0.98 ± 0.80 <sup>†</sup>
Smoking (pack/day × year)				
Non-smoker	0.58 ± 0.51	1.01 ± 0.65 <sup>†</sup>	0.56 ± 0.55	1.05 ± 0.85 <sup>†</sup>
<10	0.27 ± 0.25	0.70 ± 0.54 <sup>†</sup>	0.45 ± 0.57	0.88 ± 0.83*
10	0.51 ± 0.41	0.96 ± 0.57 <sup>†</sup>	0.47 ± 0.48	0.86 ± 0.61*
Benzoic acid ingestion (mg/d $\theta$ )				
<100	0.54 ± 0.56	0.85 ± 0.65 <sup>†</sup>	0.54 ± 0.57	0.82 ± 0.83*
100~149	0.43 ± 0.37	0.77 ± 0.56 <sup>†</sup>	0.46 ± 0.57	0.90 ± 0.72 <sup>†</sup>
150	0.53 ± 0.46	1.21 ± 0.58 <sup>†</sup>	0.56 ± 0.45	1.17 ± 0.85
Concentration of toluene in air (ppm)				
<20	0.37 ± 0.34	0.78 ± 0.48 <sup>†</sup>	0.38 ± 0.37	0.76 ± 0.58 <sup>†</sup>
20~100	0.95 ± 0.54 <sup>§</sup>	1.51 ± 0.75* <sup>†</sup>	1.03 ± 0.74 <sup>†</sup>	1.75 ± 1.00* <sup>†</sup>
Total	0.49 ± 0.45	0.92 ± 0.61 <sup>†</sup>	0.51 ± 0.53	0.96 ± 0.78 <sup>†</sup>

\* : p&lt;0.05, † : p&lt;0.01 by paired t-test between without and with group

† : p&lt;0.05, § : p&lt;0.01 by student t-test or ANOVA of within group

<sup>a, b</sup> : the same letter was significantly different by Duncan test

가

가

(p&lt;0.01)

Y=0.325+0.017 Toluene

가

가

**Table 3.** Comparison of difference of hippuric acid concentration without and with ingestion of soft drink on variables (g/g.creatinin)

Variables	DHAT (Mean ± S.D)	DHAS (Mean ± S.D)
Sex		
Male	0.45 ± 0.49	0.48 ± 0.74
Female	0.39 ± 0.32	0.36 ± 0.49
Age (years)		
<40	0.41 ± 0.35	0.43 ± 0.50
40	0.46 ± 0.57	0.46 ± 0.90
BMI (body mass index) (kg/m <sup>2</sup> )		
<20	0.29 ± 0.30	0.23 ± 0.68
20~24.9	0.53 ± 0.45	0.55 ± 0.78
25	0.36 ± 0.52	0.42 ± 0.29
Exposure time (hrs/day)		
4~5.9	0.33 ± 0.35	0.33 ± 0.51
6~8	0.50 ± 0.49	0.53 ± 0.78
Alcohol amount (g/week)		
Non-drinker	0.25 ± 0.44	0.22 ± 0.75
1~44.9	0.49 ± 0.26	0.50 ± 0.47
45	0.49 ± 0.49	0.52 ± 0.71
Smoking (pack/day × year)		
Non-smoker	0.42 ± 0.52	0.48 ± 0.73
<10	0.42 ± 0.38	0.43 ± 0.60
10	0.45 ± 0.35	0.38 ± 0.66
Benzoic acid ingestion (mg/dℓ)		
~99	0.31 ± 0.42 <sup>a†</sup>	0.27 ± 0.64
100~149	0.33 ± 0.42 <sup>a</sup>	0.44 ± 0.49
150~	0.68 ± 0.42 <sup>b</sup>	0.61 ± 0.90
Toluene in air (ppm)		
~19	0.40 ± 0.32	0.38 ± 0.57
20~100	0.56 ± 0.77	0.71 ± 0.98
Total	0.43 ± 0.44	0.44 ± 0.67

DHAT : Difference of hippuric acid in total volume urine (-without)

DHAS : Difference of hippuric acid in spot urine (with-without)

† : p&lt;0.05, † : p&lt;0.01 by student t-test or ANOVA of within group

<sup>a, b</sup> : the same letter was significantly different by Duncan test

0.023 Toluene 가 , Y=0.310+  
 가 , 38% 가  
 (Table 5).

**Table 4.** Correlation matrix among variables

	HAS1	HAS2	DHAS	HAT1	HAT2	DHAT	Tol1	Tol2	BA	Age	BMI	Alcohol
HAS2	.528**											
DHAS	-.171	.746**										
HAT1	.833**	.527**	-.042									
HAT2	.749**	.840**	.388**	.687**								
DHAT	.184	.620**	.575**	-.070	.677**							
Tol1	.626**	.659**	.274	.586**	.698**	.364**						
Tol2	.614**	.671**	.297*	.581**	.700**	.374**	.999					
B.A	.089	.230	.198	.078	.309*	.345*	-.034	-.032				
Age	.273	.333*	.173	.344*	.406**	.209	.421**	.419**	-.069			
BMI	-.015	.022	.037	.015	-.009	-.027	.232	.232	-.048	.264		
Alcohol	-.207	.048	.217	-.225	-.030	.187	-.072	-.073	.241	-.239	.014	
Smoking	-.079	-.182	-.149	-.073	-.075	-.030	-.214	-.221	.195	.033	.012	.266

\*\* : p<0.01, \* : p<0.05

- HAS1: Hippuric acid without ingestion of soft drink in spot urine in Toluene exposed workers
- HAS2 : Hippuric acid with ingestion of soft drink in spot urine in Toluene exposed workers
- HAT1 : Hippuric acid without ingestion of soft drink in total volume urine in Toluene exposed workers
- HAT2 : Hippuric acid with ingestion of soft drink in total volume urine in Toluene exposed workers
- Tol1 : concentration of toluene in first day
- Tol2 : concentration of toluene in second day
- DHAS : Difference of hippuric acid in spot urine (with-without)
- DHAT : Difference of hippuric acid in total volume urine (with-without)
- B.A : Benzoic acid
- BMI : Body mass index

**Table 5.** Stepwise multiple regression of urine hippuric acid concentration in toluene exposed workers without ingestion of soft drinks containing benzoic acid on selected variables

	Variable	Partial R <sup>2</sup>	Coefficient	F value	Significance
HAT1	Constant		0.325		0.000
	Toluene	0.344	0.017	25.160	0.000
HAS1	Constant		0.305		0.000
	Toluene	0.392	0.022	30.910	0.000

HAT1: Hippuric acid without ingestion of soft drink in total volume urine  
 HAS1: Hippuric acid without ingestion of soft drink in spot urine

가

Y=0.203+0.027 Toluene+0.003 Benzoic acid  
 가 , 가 Y=-

49%, 11% 0.027+ 0.011 Toluene +0.003 Benzoic acid  
 가 가

14%,  
 Y=0.189+0.034 Toluene+0.003 Benzoic acid 13%  
 가 가 (p<0.05),

45%,  
 6% Y=0.321+0.014 Toluene  
 (Table 6). 가  
 9%(p<0.05) (Table 7).

**Table 6.** Stepwise multiple regression of urine hippuric acid concentration in toluene exposed workers with ingestion of soft drinks containing benzoic acid on selected variables

	Variable	Partial R <sup>2</sup>	Coefficient	F value	Significance
HAT2	Constant		0.203		0.160
	Toluene	0.491	0.027	46.221	0.000
	Benzoic acid	0.110	0.003	12.958	0.001
HAS2	Constant		0.189		0.354
	Toluene	0.449	0.034	39.205	0.000
	Benzoic acid	0.063	0.003	6.134	0.017

HAT2: Hippuric acid with ingestion of soft drink in total volume urine

HAS2: Hippuric acid with ingestion of soft drink in spot urine

**Table 7.** Stepwise multiple regression of differences of urinary hippuric acid concentration on toluene exposed workers with ingestion of soft drinks containing benzoic acid on selected variables

	Variable	Partial R <sup>2</sup>	Coefficient	F value	Significance
DHAT	Constant		-0.027		0.849
	Toluene	0.139	0.011	7.782	0.008
	Benzoic acid	0.128	0.003	8.570	0.006
DHAS	Constant		0.321		0.005
	Toluene	0.088	0.014	4.633	0.036

DHAT: Difference of hippuric acid in total volume urine (with- without)

DHAS: Difference of hippuric acid in spot urine (with-without)

가  
methyl  
benzene, methyl benzol  
가  
20%  
80% 2  
24  
(Carisson, 1982)  
가  
o-cresol  
150 Gotoh (1990)  
4  
가 Hiromi (1987) 4  
가  
Bolum (1987)  
가 가  
1993 (1996)  
, 가  
(  
1993)  
1.0~3.0 g/ ,  
3.0 g/ 가  
2000 , 가  
2 가  
2.5 g/g · creatinin  
(  
, 2000). 가  
(American Conference of Governmental  
Industrial Hygienists)  
100 ppm  
2.5  
g/g · creatinin (ACGIH, 1992).  
가  
가  
(Ogata, 1985) 가

가 49%,

11%

가

45% 6%

가

가

가

가

가

가

가

가 14%,

가 13%

가

가 9%

가 가

가

가

가

가  
가

가

가

:

가

:

50

가

2 가 가

가

1999;11(4):516-26.

1999;9:

: 1.

17-26.

0.49±0.45

. 1993.

g/g · creatinine,

0.51±0.53 g/g · crea-

. 2000.

tinine

0.92±0.61 g/g · crea-

1987;20(2):228-

tinine,

0.96±0.78 g/g · creatinine

35.

가

가가

(p<0.05).

1996;8(3):526-34.

2.

o-Cresol

1988;27(2):4-11.

가

1988;27(3):6-10.

가 49%,

1986;25(4):115-19.

11%,

45% 6%

가

1993;5(2):205-14.

3.

2000;33(1):45-50.

ACGIH. Threshold limit value and biological exposure indices for 1991- 1992. pp 65-6.

가 14%,

Baelum J, Dossing M, Hansen SH, Lundqvist GR, Andersen NT, et al. Toluene metabolism during exposure to varying concentrations combined with exercise. *Int Arch Occup Environ Health* 1987;59(3):281-94.

가 13%

가

Baselt RC. *Biological monitoring methods for industrial chemicals*. CA Biomedical Publications1980.

가 9%

Bavazzano P, Perico A, Li Donni V, Colzi A. Occupational exposure and individual factors influencing urinary elimination of hippuric acid. *G Ital Med Lav* 1994;16(1-6):57-61.

:

Carisson A. Exposure to toluene uptake distribution and elimination in man. *Scad J Work*

- Environ Health 1982;8:43-55.
- Clayton GD, Clayton FE. *Patty's industrial hygiene and toxicology*. 3th ed. New York, John Wiley & Sons. 1981. pp3283-91.
- De Rosa E, Bartolucci GB, Sigon M, Callegaro R, Perbellind L, et al. Hippuric acid and ortho-cresol as biological indicators of occupational exposure to toluene. *Am J Indust Med* 1987;11: 529.
- Dodds J, Santostefano S. Comparison of cognitive functioning of glue-sniffers and non sniffers. *J Pediat* 1964;64:565-70.
- Dossing M, Belum J, Hansen SH, Lundqvist GR. Effect of ethanol, cimetidine and propranolol on toluene metabolism in man. *Int Arch Occup Environ Health* 1984;54(4):309-15.
- Gotoh M, Ogino K, Kobayaashi H, Hobara T. Effects of soft drink intake on the concentration of urinary hippuric acid in workers exposed to toluene. *Jap J Industr Health* 1990;32:28-9.
- Hiroshi Michitsuji, Akio Ohara. Effect of intake of refrigerants in excretion of hippuric acid in urine. *松仁會醫誌* 1987;26(1):105-16.
- Hjelm EW, Lof A, Sato A, Colmsjo A, Lundmark BO, et al. Dietary and ethanol induced alterations of the toxicokinetics of toluene in humans. *Occup Environ Med* 1994 Jul;51(7): 487-91.
- Hjelm EW, Naslund PH, Wallen M. Influence of cigarette smoking on the toxicokinetics of toluene in humans. *Toxicol Environ Health* 1988;25(2):155-63.
- Inoue O, Seiji K, Watanabe T, Chen Z, Huang MY, et al. Effect of smoking and drinking habits on urinary o-cresol excretion after occupational exposure to toluene vapor among Chinese workers. *Am J Ind Med* 1994;25(5):697-708.
- Inoue O, Seiji K, Watanabe T, Nakatsuka H, Jin C, et al. Effect of smoking and drinking on excretion of hippuric acid among toluene exposed workers. *Int Arch Occup Environ Health* 1993;64(6):425-30.
- Moszczyński P. The effect of cigarette smoking on the indexes of immunity and acute phase reaction in subjects with occupational exposure to organic solvents. *Cent Eur J Public Health* 1993;1(1):41-5.
- Ogata M. Indices of biological monitoring with special reference to urinalysis for metabolites of organic solvents. *Jap J Indust Health* 1985;27: 229-41.
- Sanchez E, Fernandez-D' Pool J. Liver function in patients exposed to a toluene in a hydrocarbon processing plant. *Invest Clin* 1996;37(4):256-70.
- Seki Y. Methods of sampling industrial solvents in air. *Jap J Ind Health* 1972;14:138-39.
- Sugita M, Aikawa H, Suzuki K, Yamasaki T, Minowa H, et al. Urinary hippuric acid excretion in everyday life. *Tokai J Exp Clin Med* 1988;13(4-5):185-90.
- Tahti H, Karkkainen S, Pyykko K, Rintala E, Kataja M, et al. Chronic occupational exposure to toluene. *Int Arch Occup Environ Health* 1981;48(1):61-9.
- Van Roosmalen PB, Drummond I. Simultaneous determination by gas chromatography of the major metabolites in urine of toluene, xylenes and styrene. *Brit J Industr Med* 1978;35:56-60.
- Villanueva MB, Jonai H, Kanno S, Takeuchi Y. Dietary sources and background levels of hippuric acid in urine: comparison of Philippine and Japanese levels. *Ind Health* 1994;32(4):239-46.
- Wallen M. Toxicokinetics of toluene in occupationally exposed volunteers. *Scand J Work Environ & Health* 1986;12:588-93.
- Yin S, Li G, Hu Y, Zhang X, Jim C, et al. Symptoms and signs of workers exposed to benzene, toluene or the combination. *Industrial Health* 1987;25:113.
- Zuppi C, Messana I, Formi F, Rossi C, Giardina B, et al. Influence of feeding on metabolite excretion evidenced by urine <sup>1</sup>H NMR spectral profiles: a comparison between subjects living in Rome and subjects living at arctic latitudes. *Clin Clim Acta* 1998;278(1):75-9.