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Review Article

Large Scale Biological Monitoring in Japan

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Abstract

According to a regulation issued by the Ministry of Labour of Japan, periodical bio-monitoring of workers exposed to lead and eight kinds of common organic solvents became mandatory as of October, 1989. The regulation states that each worker must be classified into one of three categories, distribution 1, 2 and 3, according to the level of the determinant in biological specimens. Distribution 3 consists of workers having exposure concentrations above the 1988-1989 biological exposure indices of the ACGIH with the exception of lead concentration in blood ($40 \mu g/100 mL$). Seven major laboratories analyzed the results. The total number of cases examined from 1989 to 1994 was about 661,000 for lead in the blood and about 4,173,000 for the urinary metabolites of eight organic solvents. The percentage of exposed workers in distribution 3 was 1.4% for blood lead and 0.2-2.4% for the urinary metabolites of the eight organic solvents. Data from the seven laboratories and about fifteen others entrusted with measurements showed that the percentage of exposed workers in distribution 3 for blood lead, urinary delta-amino-levulinic acid, urinary mandelic acid, N-methylformamide and 2,5-hexanedione has decreased with time. The data from the Labour Standard Bureau of the Ministry of Labour also showed similar results. However, data from institutions entrusted with a health survey showed that only the percentage of 2,5-hexanedione had decreased. In ambient monitoring, the percentage of workplaces in control class 3 for lead and styrene also decreased with time.

Introduction

In Japan, levels of exposure to industrial chemicals are declining as a result of automation and hermetization of production processes. However, the length of exposure is increasing because of prolongation of the working age[1-3]. Research pertinent to biological monitoring must account for this new problem of additional exposure time under low concentrations of chemicals.

In addition, ambient monitoring in Japan is based on area monitoring and not on personal monitoring[4]. Therefore, there is a need to survey the levels of determinants in biological specimens from workers.

The large-scale testing mandated by the new regulations requires implementation of a nationwide quality control program to ensure proper handling and analysis of biological specimens[5-7]. Until 1989, biological monitoring was not compulsory for all workers in Japan, but was used as further evaluation of suspected cases where the periodical health check of workers handling industrial chemicals showed possible exposure.

Basic principles of biological monitoring

Biological exposure monitoring consists of measuring the amounts of hazardous substances in workers' bodies and evaluating the environment and work conditions. This is because the amount of chemical absorbed by the body changes with the workload, with the degree of skin absorption and whether or not workers are wearing protective masks and/or clothes.

The amounts of chemicals found in the body are more closely related to health effects than the amounts of substances in the environment. Therefore, biological exposure monitoring also evaluates the state of health. Biological effect monitoring[8] is also intimately correlated with health effects. Both types of monitoring have agent specificity and aim to ensure the safety of the work environment, work conditions and workers' health from the adverse effects caused by chemicals (Fig. 1). Variations among workers in different countries caused by differences in genetic, environmental and habitual factors should be taken into consideration.

Biological monitoring in Japan

A Historical review of the biological monitoring in Japan is as follows.

The number of cases of biological monitoring performed in Japan in 1986 was about 7,000 out of 164,988 workers for lead in the blood and about 7,400 out of 350,000 workers for metabolites of major organic solvents (Fig. 2). Since 1989, about 160,000 workers handling lead and more than 350,000 workers handling eight organic solvents have received

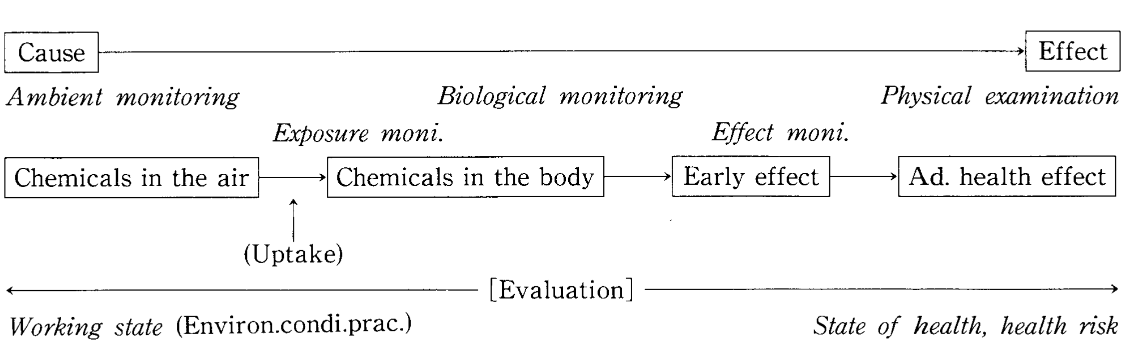

Fig. 1 Evaluation of biological monitoring data for decision making (Ogata[3])
Ad.: adverse; Environ. condi. prac.: work environment, work condition, work practice

biological monitoring annually or semiannually[1]. The Department of Industrial Health and Safety in the Ministry of Labour proposed amendments to the draft of the ordinance related to biological monitoring. Changes in the timing of urine sampling, procedures for the preservation of urine after collecting and the adjustment of the concentration of urinary determinants according to urine volume are described in the guideline[7].

The Ministry of Labour ordinances[5,6] also requires that employers report determinant levels to the workers. In order to determine the general condition in each workshop, the results from workers are to be classified into 3 groups according to provisional values set by the Ministry of Labour (Table 1) and the number of workers in each class is reported to the chief of the Labour Standards Inspec-

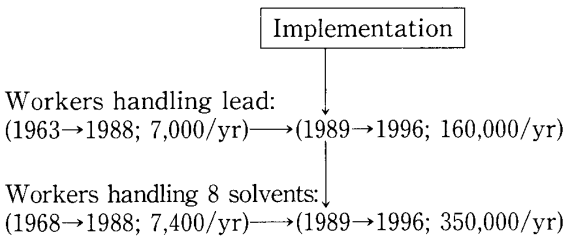

Fig. 2 Number of workers receiving biological monitoring before and after implementation (Ogata[1])

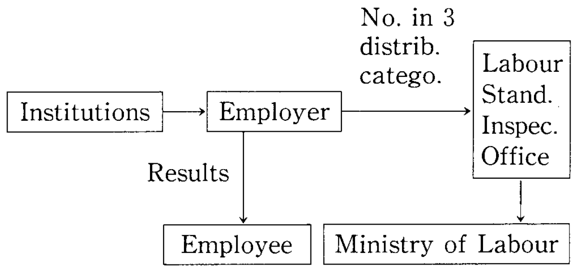

Fig. 3 The flow diagram of the reporting systems for biological monitoring in Japan
Institutions: institutions entrusted with health survey; Labour Stand. Inspec. Office: Labour Standard Inspection Office; No. in 3 distrib. catego.: Number of workers in 3 distribution categories (Ogata[1,2])

Table 1 Standard values for classifying the results of biological monitoring into three distribution ranges

	Chemicals-Determinants	Unit	Distribution		
			1	2	3
Lead	Blood lead	μg/dl	≦ 20	> 20- 40	> 40
	Urinary ALA	mg/L	≦ 5	> 5- 10	> 10
	Protoporphyrin in erythrocyte	μg/dl	≦100	>100-250	>250
Sol.	Toluene → Hippuric acid	g/L	≦ 1.0	> 1.0- 2.5	> 2.5
	Xylene → Methylhippuric acid	g/L	≦ 0.5	> 0.5- 1.5	> 1.5
	Styrene → Mandelic acid	g/L	≦ 0.3	> 0.3- 1.0	> 1.0
	N,N′-dimethylformamide → MFA	mg/L	≦ 10	> 10- 40	> 40
	Normal hexane → 2,5-hexanedione	mg/L	≦ 2	> 2- 5	> 5
	Trichloroethylene → TCA	mg/L	≦ 30	> 30-100	>100
	Trichloroethylene → TTC	mg/L	≦100	>100-300	>300
	Methyl chloroform → TCA	mg/L	≦ 3	> 3- 10	> 10
	Methyl chloroform → TTC	mg/L	≦ 10	> 10- 40	> 40
	Perchloroethylene → TCA	mg/L	≦ 3	> 3- 10	> 10
	Perchloroethylene → TTC	mg/L	≦ 3	> 3- 10	> 10

Sol: Solvents; ALA: Delta aminolevulinic acid; MFA: N-methylformamide; TCA: Trichloroacetic acid; TTC: Total trichloro compound tion Office and finally the Ministry of Labour (Fig. 3)[2].

After the results have been summarized, there will be a determination on the validity of the distribution ranges. At present, this means that the distribution ranges are not meant to discriminate between normal and abnormal levels for workers' health. Therefore, the distribution ranges are rather preliminary investigating levels than action levels for the implementation of large scale biological monitoring.

Analytical methods

Analytical methods: Appropriate analytical methods for biological monitoring were not described in the ordinance from the Ministry of Labour. Textbooks, describing the precise methods for biological monitoring of lead and organic solvents, were written by the authors[9,10] and published beforehand. A report from the National Federation of Industrial Health Organization in 1995 (Table 2) describes measurements of lead in the blood are performed by flameless atomic absorption spectrophotometry (97% of total) and measurements of δALA-U by spectrophotometry, including the methods of Tomokuni and Ogata (80%) and HPLC (20%). An increasing tendency to use HPLC was observed. Measurement of urinary hippuric acid, methylhippuric acid and mandelic acid was mostly carried out by high performance liquid chromatography (HPLC) (100 %, 100 % and 99%, respectively). Measurement of urinary n-methyl formaldehyde and urinary hexanedione was by gas-chromatography (GC) (97% and 97%, respectively). Measurement of urinary TTC was conducted by gas-chromatography (47%) and spectro photometry (54 %) and an increasing tendency toward gas-chromatography was observed. Similar results were obtained in the assay of TCA.

Data indicated that methods having better accuracy and precision are selected by practicing quality control programs[2,11,12].

Table 2 Analytical methods for legal biological monitoring estimated from the quality control program (1991 and 1995)

Chemicals-Determinants	Analytical methods
Lead	
Blood lead	AA (100 %), flameless AA (98.0 %*→ 96.9 %)
Urinary ALA	Spect. photometry (91.2%*→ 79.7%), HPLC (20.3%)
Protoporphylin in erythrocytes	Spect. fluorometry (95.2%*)[2]
Organic solvents	
Toluene → hippuric acid	HPLC (100%)
Xylene → methylhippuric acid	HPLC (100%)
Styrene → mandelic acid	HPLC (98.6%), Spect. photometry (1.4%)
N,N-dimethylformamide → MFA	GC (97.2%*)
Normal hexane → 2,5-hexanedione	GC (97.2%*→ 97.4%)
Tri, Tet, MC → TTC	GC (28.3%*→ 43.4%), Spect. photo. (69.7*→ 56.6%)
Tri, Tet, MC → TCA	GC (29.4%*→ 46.9%), Spect. photo. (68.6*→ 53.1%)

AA: atomic absorption spectrometry; HPLC: high performance liquid chromatography; GC: gas-chromatography; Spect.photo.: spectrophotometry; ALA: delta aminolevulinic acid; MFA: N-methylformamide; Tri: trichloroethylene; Tet: tetrachloroethylene; MC: methyl chloroform; TTC: total trichloro compound; TCA: trichloroacetic acid; *: percentage in 1991
(Data from the National Federation of Industrial Health Organization)

Reporting to authorities after biological monitoring

The determinants (substances measured) and distribution ranges for the implementation of biological monitoring are shown in Table 1. In order to know the determinant levels in the biological specimens of workers in each workshop, each worker is tested and the determinant levels in the workers are classified into one of three categories, distribution 1, 2 and 3, according to values provisionally set by the Ministry of Labour. The number of workers in each category is reported to the chief of the Labour Standards Inspection Office and finally the Ministry of labour (Fig. 3). The values classifying the distribution 3 from the distribution 2 are set corresponding values to the biological exposure indices (BEIs) recommended by the ACGIH in 1989 except that lead in blood is set 40 μg per dl of blood. The values classifying the distribution 2 from the distribution 1 are set from 1/3 to 1/2 of the BEIs or of the value for classification of the distribution 2 and 3. These values are useful when the levels of the BEIs are decreased in conjunction with decrease the levels of the threshold limit values-time weighted average (TLV-TWA).

Biological monitoring in Japan after implementation of the ordinance from the Ministry of Labour

In Japan, analytical chemists in institutions entrusted with health surveys and those in laboratories entrusted with the task of analyzing have measured determinants in the specimens from workers.

1) Comparison of the data among four organizations

The results from four organizations that analyzed specimens or reported analytical results are listed in Table 3, A-D.

The Table (A) is the report of the National

Table 3 **Percentage of workers in the 3 distribution classes as reported the National Federation of Industrial Health Organization and the seven major laboratories**
Survey was performed in September 1993.

	Organization														
	A: Nation. Feder. Indust. Health Organization Distribution from institutes*				B: Report from Labour Standard Bureau Ministry of Labour***			C: Nation. Feder. Indust. Health Organization Distribution from laboratories**				D: Seven Major Laboratory (Apl-Sep)			
Subjects	1	2	3	No.case	1	2	3	1	2	3	No.case	1	2	3	No.case
Lead	%	%	%		%	%	%	%	%	%		%	%	%	
Blood lead	95.0	3.8	1.1	122,673	94.4	4.6	1.0	93.5	5.5	0.9	103,992	94.8	4.1	1.1	56,108
ALA-U	96.8	3.0	0.1	122,509	97.5	2.3	0.1	96.4	3.2	0.3	110,222	97.0	2.6	0.4	56,508
Org. solvents															
Tol. → HA	90.1	8.2	1.6	279,634	92.1	6.4	1.1	90.1	8.6	1.1	285,101	86.2	11.4	2.4	138,373
Xyl. → MHA	98.2	1.5	0.1	168,087	98.7	1.1	0.2	99.0	0.8	0.0	184,838	98.9	1.0	0.1	89,213
Sty. → MA	88.7	8.7	2.5	28,052	92.0	6.2	1.8	92.1	6.0	1.8	22,752	93.3	5.0	1.7	11,860
DMF → MF	96.8	2.0	1.1	13,005	96.1	3.3	0.6	96.4	3.0	0.6	20,632	94.5	4.4	1.1	10,555
HXN → HD	97.9	1.7	0.2	38,350	99.0	0.9	0.1	98.8	1.0	0.2	57,333	99.5	0.5	0.1	28,634

*: institutes entrusted with health survey; **: laboratories entrusted with measurement; ***: Labour Standard Bureau, Ministry of Labour (1994). Biological monitoring, p.242, General Guidebook on Industrial Health, Rōdō eisei no Shiori, in Japanese; Tol. → HA: toluene → hippuric acid; Xyl. → MHA: xylene → methylhippuric acid; Sty. → MA: styrene → mandelic acid; DMF → MF: N,N'-dimethylformamide; HXN → HD: n-hexane → 2,5-hexanedione

Federation of Industrial Health Organization (NFIHO) from institutes entrusted from health surveys. Data were obtained from the large number of institutes, however, there are some differences in accuracy and precision of assay methods among them.

The Table (B) is reports from the Labour Standard Bureau in the Ministry of Labour, which would be expected to cover almost all cases from employers. However, these reports published were covered only 1992 and 1993 and do not include the results of the time study.

The Table (C) is the reports from the NFIHO and includes the results from the seven major laboratories plus other laboratories. The number of cases is a little smaller than (A), because the latter included results from institutes which do not belong to the NFIHO.

Table (D) is data from the seven major laboratories after they computed and classified their results. The seven major laboratories tested about sixty percent or more of the specimens from workers in Japan.

The percentage of workers in distribution 3 for lead in the blood are similar as shown in Table 3 A–D, while the percentage for urinary δ-ALA is a little higher for table B and D than Table A and C. For mandelic acid, Table B, C and D are similar and lower than Table A.

In addition, scientists in the NFIHO have a research group for analytical methods which maintains quality control over the accuracy and precision of the procedures used by the members who reported results for Table (D).

For the survey of the time study of biological monitoring, the primary source of data was the seven major laboratories of Table (D), while results from Tables (A) and (C) were used as supplemental data.

2) Survey of biological monitoring data[13-19] from the seven major laboratories

Of workers exposed to lead tested between 1989 to 1995, the average percentage in distribution 3 was 1.4 for lead concentration in the blood and 0.40 for δ-ALA concentration in the urine. The former was higher than the latter (Table 4). This can be explained by the fact that the boundary between distribution 2 and distribution 3 for lead concentration in the blood was established as 40 μg/100 mL of blood, whereas that for urinary δ-ALA was established at a value equivalent to 50 μg/100 mL of blood. For the urinary metabolites of workers exposed to eight major solvents, the average percent in distribution 3 was 2.3%

Table 4 **Average percentage of workers in the 3 distribution classes as reported by seven major laboratories**
Survey was performed semiannually from October 1989 to September 1995.

Subjects	Distribution (%)			No. case
	1	2	3	
Lead				
Blood lead	93.5	6.1	<u>1.4</u>	660,963
Urinary ALA	95.5	4.1	0.4	654,704
Org. solvents				
Tol. → HA	89.4	9.1	1.4	1,639,569
Xyl. → MHA	98.9	0.9	0.2	1,044,242
Sty. → MA	90.5	7.2	<u>2.3</u>	140,333
DMF → MF	94.7	3.9	1.3	114,622
HXN → HD	98.7	1.0	0.3	333,344
MC → TTC	94.6	3.6	1.7	220,787
TRI → TTC	96.8	2.6	0.7	106,014
MC → TCA	92.4	5.3	<u>2.2</u>	97,878
TRI → TCA	96.4	2.9	0.8	46,535
PERC → TCA	93.0	4.6	<u>2.4</u>	35,282
Total				5,488,605

Values underlined are the values indicating relative higher ratio of distribution 3 among determinants in this table. Abbreviations are the same as those described in Table 2 and 3.

for mandelic acid, 2.4% for trichloroacetic acid from tetrachloroethylene, and 2.2% for total trichlorocompound acid from methylchloroform (trichloroethane).

3) Ambient and biological monitoring in Japan after implementation of biological monitoring

(1) Standards for ambient and biological monitoring in Japan

As shown in Fig. 4, control class 3 is defined as the level at which the estimated value of the average concentration of airborne toxic substances in a unit work-area

(Ambient monitoring) (Biological monitoring)
(Stationary moni.) (Personal moni.)
ALVs——*TLVs*——*BEIs*
Control 3 (Exceed ALVs)
Distribution 3 (Exceed BEIs)

Fig. 4 Relationship between control 3 and distribution 3
ALVs: Administrative Level Values
(Exceed ALVs): Average conc. exceed ALVs

Table 5 Changes in the percentage of workplaces in control 3 and workers in the distribution 3 with time, from October 1989 to December 1993

Year	AM (workplaces) control 3 (%)		BM (workers) distribution 3 (%)		
	[89-93]	[92-93] / [89-91]	(89-93)	(92-93) / (89-92)	(92-95) / (89-92)
Pb[1)]	10.2	0.78	1.47	0.61	0.60
Tol.	2.2	0.67	1.40	0.93	1.07
Xyl.	0.9	0.96	0.19	0.43	0.43
Styr.	7.1	0.12	2.60	0.55	0.55
DMF	1.0	ne	1.50	0.50	0.54
Hex.	6.2	0.55	0.38	0.43	0.38
MC[2)]	1.8	0.62	0.62[4)]	ne	ne
Tri.[2)]	6.9	0.76	0.72[4)]	ne	ne
Tet.[3)]	6.2	0.85	0.85[4)]	ne	ne

1) BM; lead in blood and the ratio for U-ALA was 0.77.; 2) TTC; 3) TCA; 4) 1992-1993; AM: Ambient monitoring; BM: Biological monitoring; 89: 1989; 91: 1991; ne: not examined

exceeds the administrative level. The administrative level corresponds almost exactly to the Threshold Limit Values and Time Weighted Average (TLV-TWA)[20)] of the ACGIH. Distribution 3 consists of workers having a level of concentrations above the Biological Exposure Indices (BEIs)[21)] of the ACGIH. BEIs represent levels of determinants which are most likely to be observed in specimens collected from healthy workers who have been exposed to chemicals to the same extent as a worker with inhalation exposure to the TLVs. Thus, the percentage of unit work-areas in control class 3 should roughly correspond to the percentage of workers in distribution 3. However, the percentage of unit work-areas in control class 3 is higher than that of workers belonging to distribution 3 in lead and solvents in (Table 5) as described later. One of the reason is that workers wear protective masks[2)].

(2) Trend of the results of biological monitoring with time

a. Data from seven major laboratories

Semiannual variations in the percentage of workers in distribution 3 for lead and organic solvents as reported by seven major laboratories are shown in Table 6A. The results of a further analysis comparing the results of earlier test (1989-1991; test 1-6) with those of later test (1992-1993; test 7-12) are calculated and shown in Table 5. The percentage of distribution 3 for a determinant by the later test was divided into that for the same determinant by the earlier test. These ratios for blood lead, urinary hexanedione, urinary N-methylformamide and urinary mandelic acid were 0.60, 0.38, 0.54 and 0.55, respectively. The results indicate that the percentage of distribution 3 for a determinant had a tendency to decrease with time.

One of the cause of this decline was an improvement of the working condition

Table 6 Change in the percentage of workers in the distribution 3 from October 1989 to September 1995

Survey was performed semiannually by 7 major laboratories (A), that from 1990 to 1993 by laboratories selected by the National Federation of Industrial Health Organization (NFIHO) (B), from 1990 to 1993 by institutes selected by NFIHO (C) and 92-94 from Labour Standard Bureau (LSB) (D).

(A) Data from 7 major laboratories

Subjects	Distribution 3 (%)												
No. test	(1) '89 1st	(2) '90 1st	(3) '90 2nd	(4) '91 1st	(5) '91 2nd	(6) '92 1st	(7) '92 2nd	(8) '93 1st	(9) '93 2nd	(10) '94 1st	(11) '94 2nd	(12) '95 1st	m
I. *Lead*													
B-Lead	2.1	2.1	1.8	1.4	1.6	1.1	1.0	0.9	1.2	0.7	1.1	1.1	1.3
U-ALA	0.7	0.5	0.5	0.3	0.5	0.4	0.4	0.4	0.3	0.2	0.3	0.4	0.4
II. Solvents													
T → HA	1.1	1.7	1.2	1.7	1.4	1.5	1.4	1.5	1.1	1.6	1.2	2.0	1.4
X → MHA	0.2	0.3	0.2	0.3	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.2
St → MA	5.0	3.4	2.4	2.4	2.4	2.8	1.9	2.0	1.1	2.0	1.5	1.7	2.4
DF → MF	2,6	1.7	1.7	1.5	1.6	1.7	0.8	1.1	0.8	1.3	0.8	1.1	1.4
H → HD	0.9	0.2	0.4	0.3	0.7	0.3	0.2	0.1	0.3	0.1	0.3	0.1	0.3
MC → TCA	-	-	-	-	-	-	2.6	2.1	1.1	2.1	1.7	1.3	1.8
Tr → TCA	-	-	-	-	-	-	0.8	0.7	0.7	1.5	1.0	1.9	1.1
TET → TCA	-	-	-	-	-	-	3.1	1.5	3.0	1.1	1.4	3.3	2.2
MC → TTC	-	-	-	-	-	-	1.4	1.8	1.8	2.4	2.2	2.6	2.0
Tr → TTC	-	-	-	-	-	-	0.5	0.4	0.5	0.4	0.8	1.2	0.6

m: mean Solvent: organic solvents; 1st: period from April to September; 2nd: period from October to March in the next year. Abbreviation of solvents is described in Table 2 and 3.

(B), (C), (D) Reports of NFIHO from laboratories (B) and institutes (C), and from Labour Standard Bureau (LSB) (D)

	Laboratories (B)				Institutes (C)				L.S.B. (D)		
	'90	'91	'92	'93	'90	'91	'92	'93	'92	'93	'94
No. (B), (C)	13	11	16	18	189	196	210	229			
I. *Lead*	%	%	%	%	%	%	%	%	%	%	%
B-Lead	2.2	1.4	1.1	0.9	1.1	1.2	1.1	1.1	1.2	1.0	0.9
U-ALA	0.5	0.4	0.3	0.3	0.4	0.1	(1.8)	0.1	0.2	0.1	0.1
II. *Solvent*											
T → HA	1.3	1.5	1.4	1.1	1.6	1.6	1.6	1.6	1.2	1.1	1.2
X → MHA	0.2	0.2	0.1	0.0	0.2	0.2	0.2	0.1	0.2	0.2	0.2
St → MA	2.3	2.5	2.2	1.8	3.1	2.9	5.0	2.5	2.2	1.8	1.2
DF → MF	1.6	1.6	1.2	0.6	1.0	0.8	0.8	1.1	0.6	0.6	0.5
H → HD	0.6	0.5	0.2	0.2	0.4	0.2	0.2	0.2	0.2	0.1	0.1
MC → TCA	2.1	1.4	2.1	2.7	1.3	0.6	0.8	0.9	0.4*	0.6	0.4
Tr → TCA	0.0	0.3	1.8	0.9	0.6	1.6	1.7	1.8	0.9*	0.6	0.4
TET → TCA	3.8	3.2	3.2	1.7	3.5	0.7	1.0	0.9	1.5*	1.0	0.8
MC → TTC	2.5	1.2	1.0	2.3	0.9	0.6	0.8	0.6	-	0.4	0.4
Tr → TTC	1.7	0.2	0.9	0.4	1.7	1.3	1.7	1.9	-	1.1	1.1

*: TCA or TTC

because the results of biological monitoring inform both employers and employees about the actual state of the work environment, working method and workers. Also, the employers and workers know, in a very real way, the amount of body exposure to which they are being subjected from the industrial chemicals in biological specimens. Namely, the educational effect of biological monitoring on employers and workers contributes to the improvement of the working conditions.

A time study of the percentage of workers handling lead that are in distribution 3 as determined by lead in the blood and by delta-aminolevulinic acid in the urine is shown in Fig. 5. A time study of the percentage of workers handling styrene, N,N′-dimethylformamide and n-hexane that are in distribution 3 as determined by urinary mandelic acid, N-methylformamide and 2,5-hexanedione, respectively, is shown in Fig. 6.

The regression line as shown in Fig. 7 indicates a close correlation with 0.80 correlation coefficient, between the percentage of workers in distribution 3 as determined by lead in the blood and delta-aminolevulinic acid (δ-ALA) in the urine.

b. The results reported by three other organizations

The data from three other organizations are listed in Table 6 (B). A decreasing tendency was observed in the percentages of workers belonging to distribution 3 for lead in the blood, urinary δ-ALA, urinary mandelic acid, urinary N-methylformamide and 2, 5-hexanedione. The results are similar to those obtained from the seven major laboratories shown in Table 6 (A). In the data from the institutions, only a decreasing tendency for hexanedione was apparent.

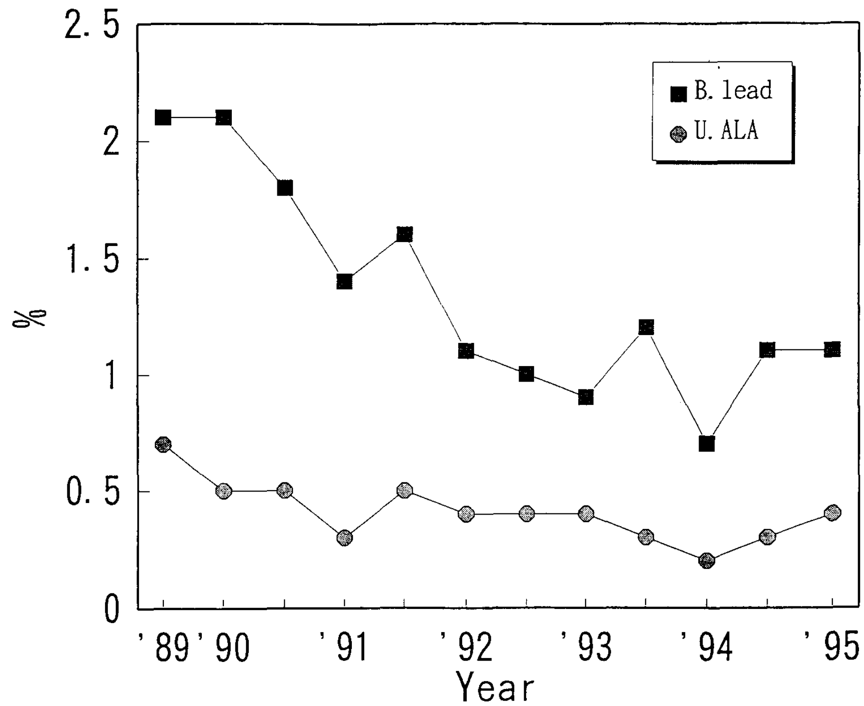

Fig. 5 Changes in the percentage of workers handling lead in distribution 3 with time
The symbol of B. lead is percentage of distribution 3 classified by lead concentration in their blood. The symbol of U.ALA is that classified by urinary delta aminolevulinic acid from 1989 to 1995.

(3) Trends in ambient monitoring with time

A time study showing the percentage of workplaces in control class 3 from 1989 to 1993 is listed in Table 7. In workplaces using lead, the percentage has decreased from 13.5

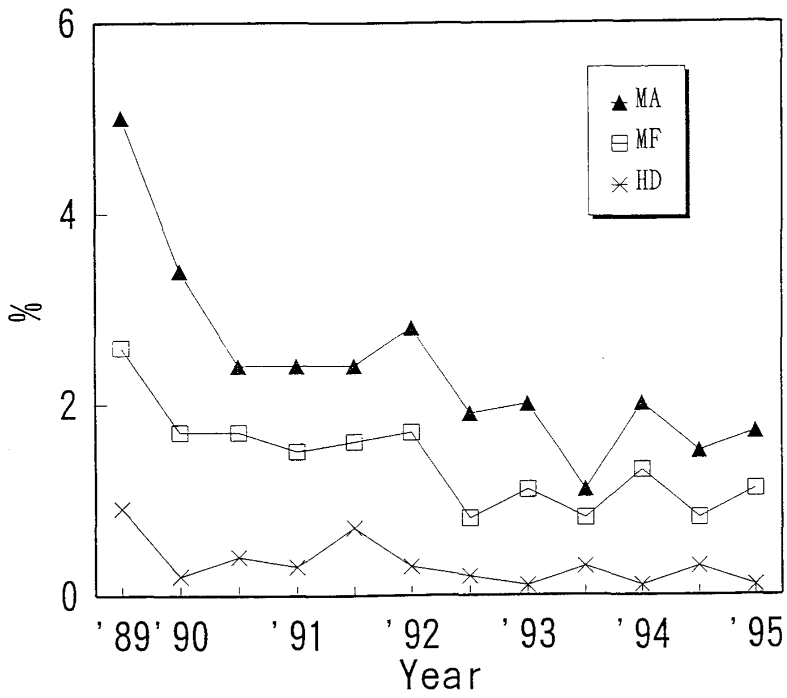

Fig. 6 **Change in the percentage of workers handling organic solvents in distribution 3**
The symbol MA is the ratio of workers handling styrene and belonging distribution 3 classified by urinary mandelic acid. The symbol of MF is the ratio of workers handling N,N′-dimethylformamide and belonging distribution 3 classified by N-methylformamide. The symbol of HD is the ratio of workers handling n-hexane and distribution 3 classified by urinary 2-5 hexanedione.

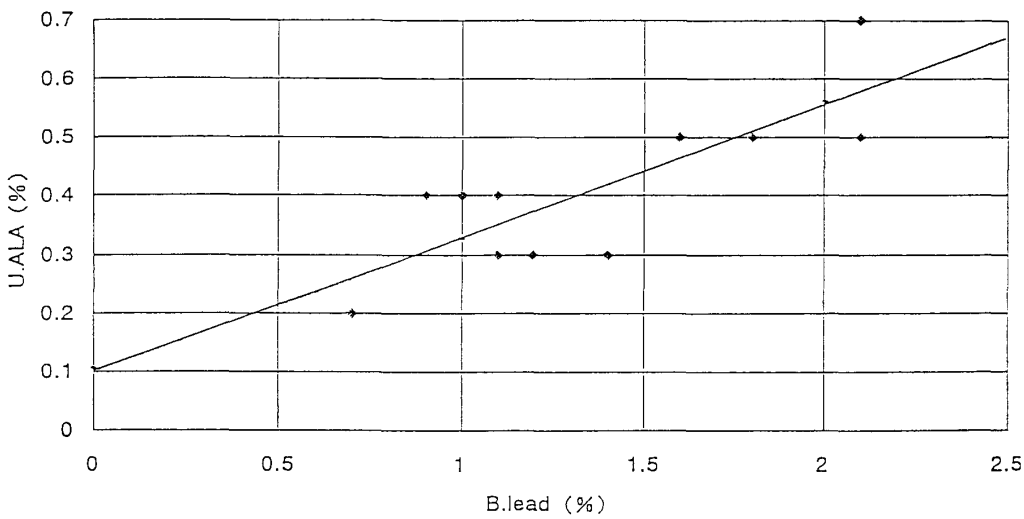

Fig. 7 **Regression equation between the ratio of numbers of workers handling lead in the distribution 3 classified by lead concentration in their blood (x) and that in the distribution 3 classified by urinary δ-ALA concentrations (y)**
$y = 0.102 + 0.228x$, Correlation coefficient $= 0.804$ ($p < 0.01$)

Table 7 Changes in the percentage of workplaces in control 3 from October 1989 to December 1993

Workplaces	Control 3 (%)					
No. test	[1]	[2]	[3]	[4]	[5]	[1-5]
Year	1989	1990	1991	1992	1993	89-93
Month	9±2	10±2	10±2	10±2	11±2	
Lead	13.5	9.2	10.8	12.2	5.3	10.2
Tol.	1.6	3.4	2.6	0.5	2.7	2.2
Xyl.	1.9	0.0	0.8	1.7	0.0	0.9
Styr.	22.7	1.7	8.5	0.0	2.5	7.1
DMF	0.0	0.0	0.0	0.0	5.0	1.0
Hex.	8.0	1.8	12.8	6.6	1.6	6.2
MC[1)]	2.7	1.9	1.7	0.7	1.8	1.8
Tri.[1)]	5.3	7.2	10.4	4.5	7.1	6.9
Tet.[2)]	6.8	4.6	8.5	4.5	6.7	6.2

1) TTC; 2) TCA; 3) 92-93; 4) lead in blood and the ratio for U-ALA was 0.77.; AM: Ambient monitoring; BM: Biological monitoring
Values underlined are the cases indicating markedly decreasing tendency among time shift of determinants tested.

in 1989 to 5.3 in 1993. In workplaces using styrene, the percentage has decreased from 22.7 in 1989 to 2.5 in 1993. Fig. 8 also shows these results.

The percentage of workplaces in control class 3 in a more recent period (tests 4-5; 1992-1993) was compared to those of an earlier period (tests 1-3; 1989-1991). The ratios were calculated and listed in Table 5. The ratio is 0.78 for workshop using lead, 0.12 for workshop using styrene and 0.55 for workshop using n-hexane. The results indicated that the number of workshops affected by these industrial chemicals is decreasing.

Ambient monitoring of toluene and xylene was conducted for each solvent separately and biological monitoring for hippuric acid and methylhippuric acid was done in the urine of workers exposed to single and mixed solvents of toluene and xylene. Therefore, time study data for both these solvents are unreliable.

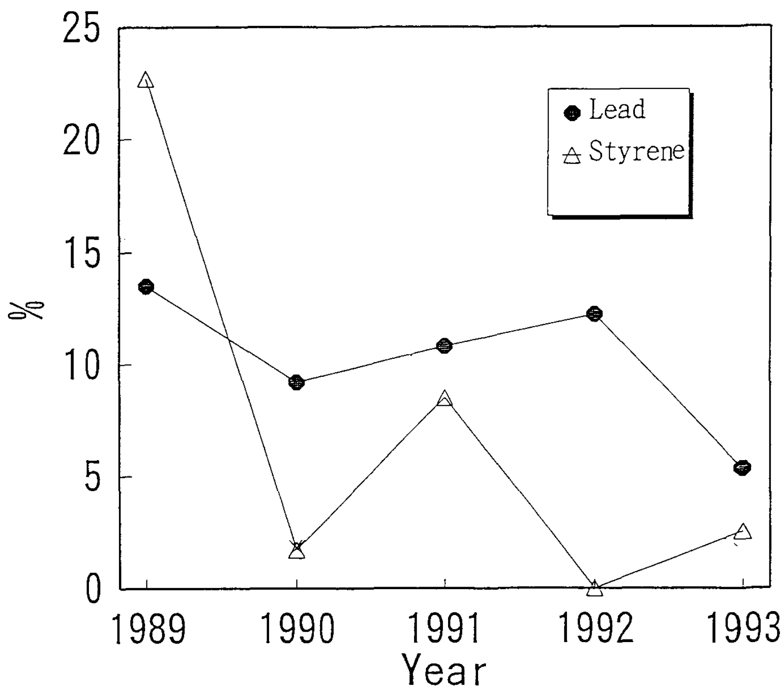

Fig. 8 Changes in the percentage of workplaces in control 3 from 1989 to 1993
Symbols of Lead and Styrene are workplaces using lead and styrene, respectively.

(4) Trends in the results of biological and ambient monitoring with time according to equations set up by the least square method

The trend in the percentage of workers handling lead and organic solvents in distribution 3 was investigated during 1989-1995 and 1989-1993 by the following method.

The equation of the first degree was calculated by the least square method as followings; $p=\alpha+\beta t$, where t is number of year and p is the percentage in distribution 3. The factors, α and β, in the above equation are listed in Table 8. The trend in percentage of workshops using lead and organic solvents control 3 was investigated during 1989-1993 and the factors of equations set up are also described in Table 8.

The data in the table indicate that there is a decreasing tendency in the percentage of workers in distribution 3 for lead in blood and delta aminolevulinic acid, 2,5-hexanedione, mandelic acid and methylhippuric acid in urine. The results are paralleled with the decreasing tendency in the percentage of workshop in control 3 for lead and parent solvents in air.

Table 8 Factors of the straight lines depicted between years and percent of the control 3 in ambient monitoring and the distribution 3 in biological monitoring by the least square method

Class	Chemicals	No.	α*	β**	Mean square of error
Cont. 3	Lead	5	12.88	−1.34	7.43
Distri. 3	Pb-B	12	1.86	−0.17	0.09
Distri. 3	ALAU	12	0.55	−0.05	0.009
Distri. 3	Pb-B	9	2.07	−0.30	0.04
Distri. 3	ALAU	9	0.58	−0.07	0.008
Cont. 3	HX	5	7.76	−0.80	27.00
Distri. 3	HD	12	2.03	−0.23	0.11
Distri. 3	HD	9	2.20	−0.35	0.09
Cont. 3	Styr	5	15.50	−4.21	56.27
Distri. 3	MA	12	3.63	−0.45	0.41
Distri. 3	MA	9	3.96	−0.68	0.39
Cont. 3	Xy	5	1.30	−0.21	0.94
Distri. 3	MHA	12	0.26	−0.03	0.002
Distri. 3	MHA	9	0.27	−0.04	0.003
Distri. 3	NMFA	12	2.03	−0.23	0.109
Distri. 3	NMFA	9	2.21	−0.35	0.087

*: Intercept; **: Slope; Distri. 3 N=12: 1989-1995; Distri. 3 N=9: 1989-1993 Cont. 3 N=5: 1989-1993

(5) Discussion about the results of biological monitoring with respect to time

The data from three organizations indicate a decreasing tendency, over time, of the percentage of workers in distribution 3 for blood lead, urinary δ-ALA, mandelic acid, methylformamide and 2,5-hexanedione, as shown in Table 5 and 6 and Fig. 5 and 6.

One reason is improvements in the workplace environment and work procedures. Supporting this premise is the fact that the percentage of workplaces in control class 3 for lead, styrene, N,N′-dimethylformamide and n-hexane has also decreased (Table 5 and 7 and Fig. 8). However, the worker populations for biological monitoring and workplaces for ambient monitoring do not correspond exactly because separate examination systems were employed.

Another reason why the percentage of workers in distribution 3 has declined is that biological monitoring has sensitized both employers and employees to the effects of biological contamination by industorial chemicals. Specifically, they pay closer attention to the amounts of industrial chemicals in the body of workers and this educational effect has led to improved work conditions (Fig. 5 and 6), as well as improving working environment. Also greater accuracy in the analysis of samples has been achieved by improving analytical procedures, e.g. the method for determining urinary δ-ALA has been changed from spectrophotometry, measuring δ-ALA and aminoacetone, to high performance liquid chromatography, measuring only δ-ALA.

Procedures need to be continually updated (follow up study) to ensure the safety of the workers.

Evaluation of large-scale biological monitoring and problems encountered

There has been continual improvement of the procedures for biological monitoring as well as ambient monitoring since 1989, when large scale biological monitoring was started. One of the reasons is that many employers and employees have become aware of the need to protect workers from the effects of hazardous chemicals. However, some problems arose in the implementation of large scale biological monitoring.

First, concentrations for the biological exposure indices will be lowered as the concentrations of the Threshold Limit Values (TLVs-TWA) are lowered. So far, the limiting levels for control 2 and 3 have not changed except that the TLV-TWA and administrative level in Japan of toluene was lowered from 100 ppm to 50 ppm in October, 1995. Some of other limiting values will be decreased in the near future, though lowering the limit for inclusion in distribution 2 will help in some cases.

Second, because the urinary metabolites of workers exposed to mixed solvents are included in large scale biological monitoring, new methods must be developed on evaluation of worker's exposure to mixed solvents using their concentration of metabolites or parent solvents in urine. Preliminary work on this ploblem has been done by the authors[2,3,22−25].

Third, workshops are classified control 3 in ambient monitoring if average values of concentrations at measuring stations exceed the administrative level by A sampling and/or levels by B samplings exceed one and half times the administrative level. The A and B sampling are defined as follows;

A sampling is done at not less than five proper sampling points in accordance with the regulations of the Ministry of Labor.

The sampling points for B sampling using 1.5× ALVs as the standard are also described in the Working Environment Measurement Law[4]. The law requires that samples be taken at points at which and at a time when the manufacturing process and working conditions indicate that the workers are being subjected to the greatest exposure.

Our previous report[26] in some workshops using organic solvents described that solvent concentrations in breathing zone air of workers is higher than ambient concentrations by A sampling and is lower than concentrations by B sampling which almost equals to average of concentrations by A and B sampling. There is an intimate correlation between air concentrations determined by A sampling and those in the breathing zone of workers[27]. Therefore, air concentrations determined by A sampling give one of good indicators of the amount of worker exposure, in workplaces where solvent concentration in air is relatively homogeneous.

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