FACTOR-ANALYTICAL OBSERVATION ON DOSE-RESPONSE RELATIONSHIP OF LEAD IN THE OCCUPATIONALLY NON-EXPOSED

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By the procedure of factor analysis, the interrelationships of parameters relevant to lead exposure were statistically investigated. The parameters were classified to three groups based on the results of these statistical analysis: the first group contained lead mobilized by CaEDTA and lead in blood, which were considered to be related to the body burden of lead; the second group, ALA-D in erythrocyte, δ -ALA in urine, coproporphyrin in urine and lead in urine, which should be the response to the body burden of lead; the third group, hemoglobin in blood.

It was supported that there might be specific biological reactions to lead in people free from occupational or accidental exposure to lead, though the extent of the reactions was supposed to be much less than that of occupationally-exposed lead workers. The influence of lead to blood hemoglobin level was not found under usual urban environments.

The biological significance seemed to be almost similar between lead in blood and lead mobilization test with the intravenous administration of CaEDTA from the viewpoint of dose-response relationship of lead. The regressions of urinary coproporphyrin and erythrocyte ALA-D activity on lead mobilized by CaEDTA or blood lead were supposed to be nearly linear in people free from occupational lead exposure.

In people without particular exposure to lead, the blood lead levels have been shown to have a logarithmic regression on estimated atmospheric exposure to lead,¹⁾ or a semi-logarithmic regression on a total absorption of lead, i.e. the amounts of lead absorbed from air, food and water²⁾ (Fig. 1). However, the atmospheric lead concentrations are not considered being suitable as a parameter for evaluation of the dose-response relationship of lead in those people, because the amount of lead absorbed from air was calculated to be much less than the amount absorbed through food.^{3,4)} Thus, the regression line^{1,2)} can not be applied with confidence to the exposure conditions below the value of approximately 2 $\mu\text{g}/\text{m}^3$.^{3,4)}

Then, the question comes across what parameters are desirable as an indicator of the dose of lead and whether the dose-response relationship of lead is linear or curvilinear in human subjects without the particular exposure to lead. Lately the mobilization yield

Fig. 1. Dose-response relationship of lead given by two authors.

The bPb and aPb mean the lead content in whole blood and atmospheric lead concentrations, respectively. The regression equations are rewritten from the original log or semilog scale to a normal scale and are shown in the lower range of atmospheric lead concentrations in this diagram. The Danielson's equation was calculated from the original diagram.

of lead by CaEDTA (mobilization test) has been considered being one of the best means of estimating, though indirectly, the active body burden of lead,⁵⁻⁷⁾ whereas the blood lead levels have still been accepted as the best of the "usual" parameters reflecting the exposure to lead.^{1,8-10)}

In this report, the author intended to estimate the dose-response relationship of lead in people free from the occupational or accidental exposure to lead based on the knowledge of the interrelationships of parameters relevant to lead exposure.

SUBJECTS AND METHODS

Subjects

The subjects consisted of 45 volunteered Japanese adults, 25 men and 20 women: 13 nurses, 10 office workers, 5 assistant nurses, 4 boilermen, 4 divers, 2 physicians, 2 drivers, 2 coalminers, 2 medical technicians and a guardman. All the subjects were under usual urban conditions where the daily average concentration of lead in the atmosphere

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ranged from 0.39 to 3.94 $\mu\text{g}/\text{m}^3$ with an average of 1.67 for 11 months.¹¹⁾ None of them had ever been exposed to lead occupationally or accidentally.

Collection of samples

Total amount of urine was collected for 24 hr to measure the urinary contents of lead (uPb) and delta-aminolevulinic acid (δ -ALA). After the collection of spot urine for the measurement of coproporphyrin (Copro.), intravenous infusion of CaEDTA was given to each subject for 1 hr in a dosage of 20 mg per kilogram body weight in 250 ml of 5% glucose solution. Since the start of infusion, the urine specimens were collected for 2 hr and the following 22 hr to analyse the urinary amounts of lead mobilized by CaEDTA in 2 hr and 24 hr (uPb_{2-hr mob.} and uPb_{24-hr mob.}, respectively). The blood samples were collected about six months after the administration of CaEDTA to investigate the activity of δ -ALA dehydratase in erythrocytes (ALA-D). Further six months had elapsed until the measurements of the lead content in the whole blood (bPb) and the hemoglobin level in blood (Hb).

Analytical methods

The blood and urinary content of lead before and after the administration of CaEDTA were measured by atomic absorption spectrophotometry (Perkin-Elmer 403); ALA-D, by the method of Weissberg *et al.* (1971)¹²⁾; δ -ALA, by the method of Wada *et al.* (1971)¹³⁾; Copro., by fluorescence spectrophotometry (Hitachi, MPF-2A); Hb, by the cyanmethemoglobin method; creatinine in the urine, by Jaffe's reaction; specific gravity of urine, by refractometry.

Statistical analysis

The factor analysis was performed by the use of Hitac 8700, the University of Tokyo. The factor loadings are extracted by multiplying eigenvectors by the square root of corresponding eigenvalues through the method of principal component analysis.^{14,15)}

RESULTS

1. Classification of the parameters indicative of lead exposure by factor analysis

Thirty nine people, i.e. 21 men and 18 women, who were examined for all the eight parameters are selected for the analysis. The means and standard deviations of the eight parameters are as listed in Table 1. The urinary contents of uPb, δ -ALA, uPb_{2-hr mob.} and uPb_{24-hr mob.} are expressed in four ways such as the total amount (μg or mg), the concentration ($\mu\text{g}/\text{l}$ or mg/l), the corrected concentration to a specific gravity of urine ($\mu\text{g}/\text{l}$, SG 1.020 or mg/l, SG 1.020) and the corrected concentration by urinary creatinine content ($\mu\text{g}/\text{g}$, Cn or mg/g, Cn); the Copro., in the latter three ways. The bPb is also corrected to bPb/Hb, which has been reported to have no sexual difference.¹⁶⁾ In cases of uPb, ALA-D, δ -ALA, Copro., uPb_{2-hr mob.} and uPb_{24-hr mob.}, the values are transformed into logarithm to normalize the distribution. In men and women respectively,

Table 1. Means and standard deviations of parameters related to lead exposure.

Variables		Men (21)		Women (18)		Men & Women (39)	
		Mean	SD	Mean	SD	Mean	SD
1) bPb:	$\mu\text{g}/100\text{ g}$	12.0	4.3	7.4	2.5	9.9	4.2
	$\mu\text{g}/\text{g}$, Hb	0.784	0.262	0.610	0.207	0.704	0.251
2) log uPb:	$\mu\text{g}/24\text{ hr}$	1.115	0.397	1.066	0.217	1.092	0.323
	$\mu\text{g}/\text{l}$, SG 1.020	0.828	0.472	1.017	0.208	0.915	0.381
	$\mu\text{g}/\text{g}$, Cn	0.906	0.425	1.102	0.236	0.997	0.360
3) log ALA-D:	u.	1.582	0.136	1.577	0.155	1.580	0.143
4) log δ -ALA:	$\text{mg}/24\text{ hr}$	0.506	0.143	0.383	0.190	0.449	0.175
	mg/l , SG 1.020	0.339	0.161	0.338	0.194	0.339	0.175
	mg/g , Cn	0.288	0.157	0.425	0.198	0.351	0.188
5) log Copro.:	$\mu\text{g}/\text{l}$, SG 1.020	1.663	0.320	1.687	0.197	1.674	0.267
	$\mu\text{g}/\text{g}$, Cn	1.573	0.307	1.691	0.238	1.627	0.280
6) Hb:	g/dl	15.3	1.1	12.3	1.0	13.9	1.9
7) log uPb _{2-hr mob.} :	$\mu\text{g}/2\text{ hr}$	1.047	0.204	0.899	0.194	0.978	0.211
	$\mu\text{g}/\text{l}$, SG 1.020	1.841	0.171	1.839	0.184	1.840	0.175
	$\mu\text{g}/\text{g}$, Cn	1.934	0.182	1.980	0.182	1.956	0.181
8) log uPb _{24-hr mob.} :	$\mu\text{g}/24\text{ hr}$	1.951	0.175	1.679	0.185	1.826	0.224
	$\mu\text{g}/\text{l}$, SG 1.020	1.739	0.184	1.614	0.195	1.681	0.197
	$\mu\text{g}/\text{g}$, Cn	1.725	0.187	1.711	0.191	1.719	0.186

Number of cases, examined, is shown in parentheses. SD means standard deviation; SG, specific gravity of urine; Cn, creatinine.

the eight parameters are analysed. In men and women combined, bPb/Hb is selected instead of bPb which is omitted together with Hb because of highly significant sexual difference ($p < 0.001$). To check the reproducibility of the analysis, the three expressions of the urinary contents of uPb, δ -ALA, Copro., uPb_{2-hr mob.} and uPb_{24-hr mob.} are separately analysed together with other parameters in men, women, and men and women combined.

Correlation matrices are shown in Table 2. Each correlation matrix contains two sets of submatrix where the urinary contents of uPb, δ -ALA, Copro., uPb_{2-hr mob.} and uPb_{24-hr mob.} are expressed in two ways, i.e. the corrected concentration by urinary creatinine and the corrected concentration to a specific gravity of urine.

As is shown in Table 3, the proportion of the first principal component to the total variance is from 28 to 33% in men, women, and men and women combined; the second component, 17 to 21%; the third, 14 to 16. Sixty three to sixty six per cent of the information is involved in the three components. And up to the third component, the eigenvalues are beyond 1.0. So, the extraction of factors is stopped in the third component.

Factor matrices and a plain consisting of the first factor (FC 1) and the second factor (FC 2) of men and women combined are shown in Table 4 and Fig. 2, respectively. The analysis of eight parameters including bPb and Hb in women is shown in Fig. 3.

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Table 2. Correlation matrices of parameters related to lead exposure.

A. Men (n=21)

1)	2)	3)	4)	5)	6)	7)	8)	Correlation coefficient
1.000	0.160	0.354	0.221	0.463†	-0.320	0.041	0.258	1) bPb
-0.031	1.000	0.295	-0.049	0.123	-0.285	0.157	0.253	2) log uPb
0.354	0.091	1.000	0.032	0.048	-0.333	0.151	0.297	3) -log ALA-D
0.247	-0.187	0.192	1.000	0.452†	-0.207	0.283	0.169	4) log δ -ALA
0.472†	0.377	0.085	0.317	1.000	-0.383	0.408	0.331	5) log Copro
-0.320	-0.223	-0.333	-0.372	-0.333	1.000	-0.194	0.139	6) -Hb
0.048	0.147	0.426	-0.104	0.321	-0.096	1.000	0.455†	7) log uPb _{2-hr mob.}
0.127	0.025	0.307	-0.020	0.257	0.114	0.499†	1.000	8) log uPb _{24-hr mob.}

B. Women (n=18)

1)	2)	3)	4)	5)	6)	7)	8)	Correlation coefficient
1.000	0.096	-0.132	0.094	0.166	-0.025	0.390	0.336	1) bPb
0.159	1.000	0.135	0.311	0.257	0.131	0.284	0.253	2) log uPb
-0.132	0.088	1.000	0.462	0.195	0.189	0.026	-0.338	3) -log ALA-D
0.121	0.159	0.383	1.000	0.287	-0.083	0.221	0.260	4) log δ -ALA
-0.102	-0.020	0.107	0.193	1.000	0.459	0.118	0.184	5) log Copro.
-0.025	0.120	0.189	-0.045	0.013	1.000	0.238	0.119	6) -Hb
0.555†	0.288	0.110	0.205	-0.168	0.250	1.000	0.717†††	7) log uPb _{2-hr mob.}
0.404	0.285	-0.284	0.408	0.032	0.049	0.420	1.000	8) log uPb _{24-hr mob.}

C. Men and women (n=39)

1)	2)	3)	4)	5)	6)	7)	Correlation coefficient
1.000	-0.016	0.102	-0.025	0.216	0.118	0.304	1) bPb/Hb
-0.117	1.000	0.222	0.171	0.206	0.217	0.223	2) log uPb
0.102	0.084	1.000	0.255	0.110	0.091	0.019	3) -log ALA-D
0.136	-0.070	0.295	1.000	0.411††	0.277	0.186	4) log δ -ALA
0.226	0.302	0.090	0.255	1.000	0.309	0.255	5) log Copro.
0.256	0.167	0.265	0.038	0.140	1.000	0.566†††	6) log uPb _{2-hr mob.}
0.338†	0.004	0.002	0.192	0.148	0.437††	1.000	7) log uPb _{24-hr mob.}

Urinary contents of uPb, δ -ALA, Copro., uPb_{2-hr mob.}, and uPb_{24-hr mob.} are expressed in the corrected concentration by urinary creatinine content and the corrected concentration to a specific gravity of urine above and below the diagonal, respectively. A dagger (†), a double dagger (††), and a triple dagger (†††) indicate statistical significance at 5%, 1% and 0.1% levels, respectively.

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Table 3. Eigenvalues and cumulative proportion of total variance.

Principal component	Type 1			Type 2		
	CP 1	CP 2	CP 3	CP 1	CP 2	CP 3
Men:						
Eigenvalue	2.67	1.34	1.23	2.49	1.59	1.22
Cumulative proportion	0.33	0.50	0.66	0.31	0.51	0.66
Women:						
Eigenvalue	2.43	1.66	1.12	2.28	1.51	1.21
Cumulative proportion	0.30	0.51	0.65	0.28	0.47	0.63
Men and women combined:						
Eigenvalue	2.29	1.23	0.99	2.02	1.24	1.13
Cumulative proportion	0.33	0.50	0.64	0.29	0.47	0.63

Urinary contents of uPb, δ -ALA, Copro., uPb_{2-hr mob.}, and uPb_{24-hr mob.} are expressed in the corrected concentration by urinary creatinine content and the corrected concentration to a specific gravity of urine in Type 1 and Type 2, respectively.

Table 4. Factor matrices of men and women combined.

Factor loadings	Type 1			Type 2		
	FC 1	FC 2	FC 3	FC 1	FC 2	FC 2
1) bPb/Hb	0.35	0.49	-0.74	0.59	0.42	0.09
2) log uPb	0.48	-0.34	0.20	0.21	-0.82	0.35
3) -log ALA-D	0.33	-0.60	-0.51	0.44	-0.22	-0.55
4) log δ -ALA	0.59	-0.45	0.08	0.49	0.02	-0.68
5) log Copro.	0.67	-0.09	-0.10	0.54	-0.46	-0.01
6) log uPb _{2-hr mob.}	0.73	0.23	0.31	0.68	0.03	0.34
7) log uPb _{24-hr mob.}	0.70	0.49	0.17	0.66	0.36	0.35

Urinary contents of uPb, δ -ALA, Copro., uPb_{2-hr mob.}, and uPb_{24-hr mob.} are expressed in the corrected concentration by urinary creatinine content and the corrected concentration to a specific gravity of urine in Type 1 and Type 2, respectively.

As is obvious from Figs. 2 and 3, the parameters can be classified to three groups. The first group contains uPb_{24-hr mob.}, uPb_{2-hr mob.}, bPb and bPb/Hb; the second group, ALA-D, δ -ALA, Copro. and uPb; the third, Hb. The first group is considered to be related to the body burden of lead; the second group, the response to the body burden of lead.

2. "Dose-response relationship"

The dose-response relationship of lead is estimated from the following standpoint: The relationships between the parameters considered to be reflecting the body burden of lead, i.e. uPb_{24-hr mob.}, uPb_{2-hr mob.} and bPb, and those related to the biochemical responses, i.e. ALA-D, δ -ALA, Copro. and Hb.

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Fig. 2. A plain consisting of the first and second factors in type 1 of men and women combined.

Fig. 3. A plain consisting of the first, second and third factors in type 1 of women.

(a) The first factor (FC 1) and the second factor (FC 2)

(b) The second factor (FC 2) and the third factor (FC 3)

Fig. 4. Regression equations among seven parameters related to lead exposure.

Regression equations are obtained from men and women combined except for the last two from men. An asterisk (*) indicates statistical significance at 5% level.

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As was shown in the previous report of the present author, the correlation matrices of all the parameters disclosed small in the extent, but significant correlation between the parameters except for Hb.³⁾

The regression equations obtained previously and concomitantly in the process of factor analysis are shown in Fig. 4 in a normal scale. As is clear from the figure, $uPb_{24-hr\ mob.}$, bPb/Hb and uPb have nearly linear regression curves on $uPb_{24-hr\ mob.}$. The same statement holds true for the relationship between δ -ALA and Copro.. As to the "dose-response relationship", Copro. has nearly linear regression curves on $uPb_{24-hr\ mob.}$ and bPb . ALA-D has a slightly concave regression on $uPb_{2-hr\ mob.}$

3. Relationships between three expressions of urinary contents

Through the procedure of factor analysis, all the three expressions of urinary contents of uPb , δ -ALA, Copro., $uPb_{2-hr\ mob.}$ and $uPb_{24-hr\ mob.}$ are analysed concurrently with bPb/Hb and ALA-D in men and women combined. The cumulative proportion of total variance is 56 per cent up to the third component, in which the extraction of factors is stopped.

Parameters	Communality*				
	0.1	0.3	0.5	0.7	0.9
$uPb_{24-hr\ mob.}$				N	Cn SG
$uPb_{2-hr\ mob.}$		N	SG	Cn	
uPb					SG N Cn
δ -ALA		N	SG Cn		
Copro.			N	Cn SG	
bPb/Hb		•			
ALA-D		•			

Fig. 5. Relationships among three expressions of urinary contents related to lead exposure.

*: the communality has been obtained by summing up the square of factor loadings of the first, second and third factors through factor analysis.

Cn: corrected concentration by urinary creatinine content.

SG: corrected concentration to a specific gravity of urine.

N: not-corrected concentration.

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As is obvious from Fig. 5, the most amount of information of $\text{uPb}_{24\text{-hr mob.}}$, uPb and $\delta\text{-ALA}$ is involved in the corrected concentration by creatinine content among the three expressions of urinary contents; that of $\text{uPb}_{24\text{-hr mob.}}$ and Copro., in the corrected concentration to a specific gravity of urine; the least amount of information is involved in the not-corrected concentration except for uPb . Owing to the influence of multiple variables of other parameters which are closely related, the communality of bPb/Hb and ALA-D is smaller in extent in this analysis than that in the above analysis (Fig. 2) where the single expression of each parameter is used as a variable.

DISCUSSION

The factor analysis of parameters relevant to the exposure to lead was reported in occupationally exposed lead workers by Suzuki, S. and Suzuki, T. (1974).¹⁷⁾ They applied the method to two sets of "lead exposure indicators" i.e., uPb , $\delta\text{-ALA}$, Copro., Hb et al. ; and found that the indicators had a complex structure after the discontinuation of the exposure and that Copro. had a noticeably different character from other indicators. Their results were not consistent with those obtained by the present author, i.e., Copro. was classified to the same group as $\delta\text{-ALA}$ and uPb in this study. The present author considers that any influence other than lead, e.g. liver diseases,¹⁸⁾ should be evaluated in their study. In this connection, the present author is preparing a report on lead workers where the character of Copro. is very similar to that of $\delta\text{-ALA}$.^{19,22)}

Following points were elucidated by the present study:

Firstly, the existence of small in extent, but significant biological reactions to lead in the occupationally non-exposed people which was suggested by Hernberg and Nikkanen (1970)²⁰⁾ and the present author (1973),³⁾ was supported by the present analysis, which separated the parameters related to the body burden of lead (dose-factor) from those related to the response to lead (response-factor).

Secondly, the lead under usual urban environments was not considered to influence to the hemoglobin level.

Thirdly, the behaviour of the blood lead level was almost consistent with that of the mobilization test. This finding shows that both the parameters have biologically close character in terms of the dose-response relationship of lead.

Fourthly, the urinary lead content was classified to the group indicative of the response to lead, together with ALA-D , $\delta\text{-ALA}$ and Copro., rather than to the group relevant to the dose-factor. This finding may signify that the urinary lead excretion is under great influence of daily exposure to lead in the usual, non-occupational environments, e.g., food and air.

Fifthly, Copro. had significant correlations with parameters related to the body burden of lead, with which $\delta\text{-ALA}$ had not. This result coincides with a prospective study by Tola *et al.* (1973),²¹⁾ contrary to that in most publications on lead workers.

Sixthly, the responses of urinary coproporphyrin content and erythrocytes $\delta\text{-ALA}$

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dehydratase activity to deposit of lead, if present, were supposed to be nearly linear in people without the particular exposure.

Lastly, it was shown that the corrected concentration by creatinine content or that to a specific gravity of urine reflected the exposure level of lead better than the not-corrected concentration in people free from occupational lead exposure.

The dose-response relationship of lead in human beings should be investigated in the whole range of the "active" body burden of lead. So, the present results will be compared with those of occupationally exposed lead workers in the author's next paper.²²⁾

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