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# Relationship Between Blood Lead Level and Urinary ALA Level in Workers Exposed to Very Low Levels of Lead

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**Abstract: The relationship between blood lead (PbB) level and urinary delta-aminolevulinic acid (ALAU) level was examined in a total of 3,636 lead-exposed workers in a periodic medical examination in 1992, in accordance with the Ordinance on Prevention of Lead Poisoning. The results were consistent with previously reported results[2, 4] in that ALAU level was found to increase with an increase in PbB level above 22.4 μg/dl (1.35 as a logarithmic value) and to rise markedly above 35.5 μg/dl (1.55). On the contrary, the geometric means of ALAU levels appeared to decrease with an increase in PbB levels within a range between a logarithmic value of 0.15 (1.4 μg/dl) and 1.25 (17.8 μg/dl). Because the earliest sign of the adverse health effects of lead is reported to occur at a PbB level of 20 μg/dl, the relationship between PbB level and ALAU level was examined at PbB levels below 20 μg/dl. A regression formula was obtained, Y (log ALAU (mg/l)) = −0.0570X (log PbB (μg/dl)) + 0.4099. This result indicates that ALAU level decreases with a concomitant increase in PbB level lower than 20 μg/dl.**

**Key words:** Blood lead level, Urinary ALA level, Low lead exposure, Workers, Heme synthesis

Delta-aminolevulinic acid (ALA) is synthesized from glycine and succinyl CoA by the action of delta-aminolevulinic acid synthetase (ALAS). Porphobilinogen (PBG) is biosynthesized from ALA by the action of delta-aminolaevulinic acid dehydratase (ALAD). Lead exposure promotes the activity of ALAS and inhibits the activity of ALAD. The effects of ALAS induction and ALAD inhibition result in an increased blood ALA level and subsequently in an increased urinary excretion of urinary ALA (ALAU)[1]. Selander *et al.*[2] and Haeger-Aronsen[3] reported that the relation between blood lead (PbB) level and ALAU level follows a curved regression. Selander *et al.*[2] reported that the following regression equation held: log (ALAU (mg/100 ml)) = 0.0157 (PbB (μg/100 ml)) − 1.0985. Haeger-Aronsen[3] also reported that ALAU level can be expressed as the following function of PbB level: log (ALAU (mg/100 ml)) = 0.01294 (PbB (μg/100 ml)) − 0.8605. It has been recognized that the ALAU level increases markedly with PbB level above 40 μg/dl[2, 4]. However, Roels *et al.*[5] reported that ALAU level did not change with an increase in PbB level below a range of 30–45 μg/dl. Therefore, it can be surmised that exposure of workers to very low levels of lead does not increase ALAU level. It is well known that lead exposure affects the hematogeneous system and induces anemia[6]. However, exposure of workers to low levels of lead does not induce anemia. Makino *et al.*[7] found that workers exposed to low levels of lead could be classified into two groups according to their median PbB and ALAU levels, and that the hematocrit value, amount of hemoglobin, and erythrocyte counts were significantly lower in workers whose blood lead levels ranged from 1–15 μg/dl than in those whose blood lead level ranged from 16–39 μg/dl.

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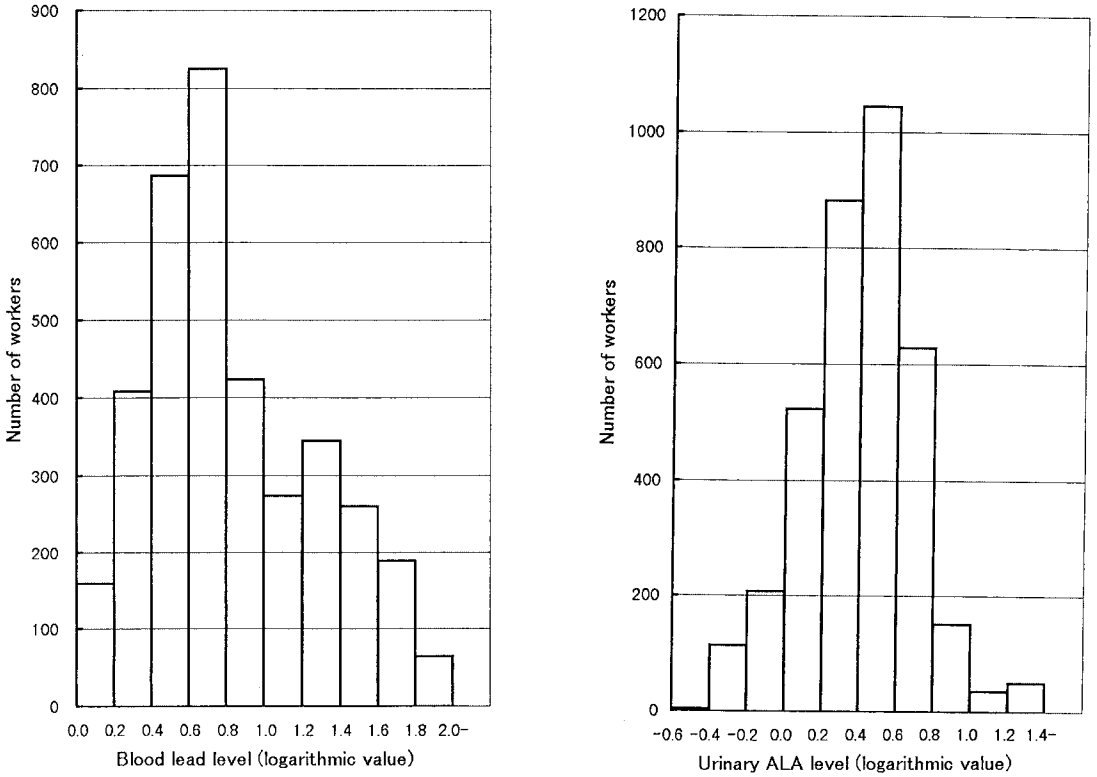


**Fig. 1. Histograms of blood lead levels and urinary ALA levels.**

Recently, there has been much concern over the adverse health effects of low-level lead exposure. For example, neurological disorders have been identified in workers exposed to a PbB level of 20 $\mu$g/dl[8–10]. WHO/IPCS reported that clinical lesions are caused at a PbB level of 20 $\mu$g/dl or higher[1]. In the present preliminary report, therefore, we examine the relationship between PbB and ALAU levels among workers exposed to low levels of lead, that are thought to be below the threshold required to induce the earliest adverse health effect.

A total of 3,636 lead-exposed workers were examined for PbB and ALAU in a periodic medical examination of the Japan Industrial Safety and Health Association in 1992 in accordance with the Ordinance on Prevention of Lead Poisoning. The workers, almost all of whom were male, were engaged in the manufacture of pigments, stabilizers, or batteries or in soldering work. The PbB and ALAU levels were transformed into logarithmic values, and the geometric mean of ALAU level was plotted against the logarithmically-transformed PbB level. The relationship between PbB and ALAU levels was represented by a linear regression for the 2,924 workers with PbB level lower than 20 $\mu$g/dl, because this value is thought to be a threshold for inducing the most sensitive adverse health effect. The subjects' PbB levels were determined using a flameless atomic absorption spectrophotometer. The ALAU levels were measured by means of the Mauzerall-Granick method[11]. Quality control of the PbB and ALAU measurements was ensured by internal quality control and external quality assessment[12].

Distributions of PbB and ALAU levels of the 3,636 workers are shown in Fig. 1. Neither distribution followed a logarithmic normal distribution curve according to the Kolmogorov-Smirnov test. The median values of PbB and ALAU were 5.2 $\mu$g/dl (range: 0.9 to 132.8 $\mu$g/dl) and 2.6 mg/l (range: 0.34 to 134 mg/l).

The relationship between PbB and ALAU levels was examined as follows. The geometric mean of each ALAU level was calculated for each narrowly divided range of logarithm-scaled PbB levels, as shown in Fig. 2. The divided spans ranged from 0.05 (1.1 $\mu$g/dl) to 1.95 (89.1 $\mu$g/dl) with a logarithmic increment by a step of 0.1. The mean value of ALAU level appeared to decrease with a concomitant increase in PbB level within the range between a logarithmic value of 0.15 (1.4 $\mu$g/dl) and 1.25 (17.8 $\mu$g/dl). The geometric mean of ALAU at a PbB level of 17.8 $\mu$g/dl (1.25 as a logarithmic value) was significantly lower than the geometric

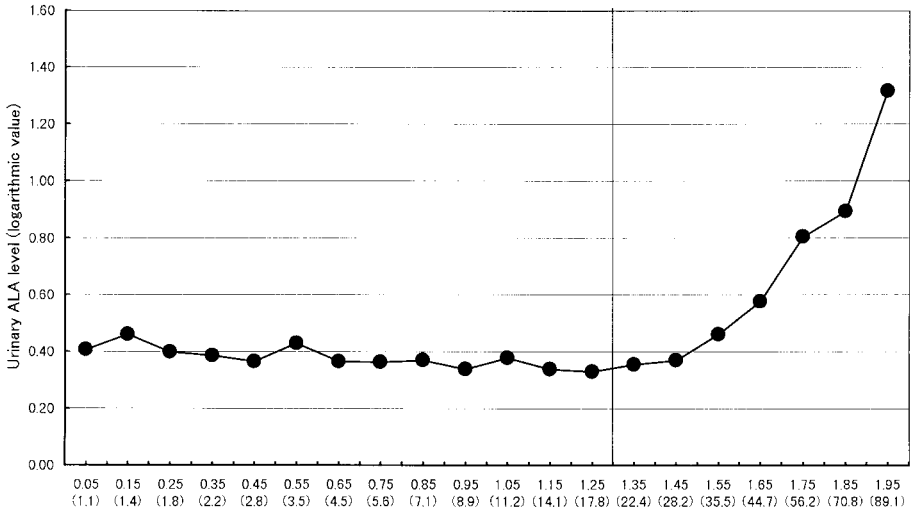


**Fig. 2. Relationship between mean urinary ALA level and blood lead level.**
Lower and upper numericals on the abscissa indicate PbB level and its logarithmic value, respectively. A vertical line indicates a PbB level of 20 $\mu$g/dl.

means of ALAU at the PbB levels of 1.1 and 1.4 $\mu$g/dl (0.05 and 0.15 as logarithmic values, respectively) ($p<0.05$ by t-test). Our results were consistent with the reported results[2, 4] in that ALAU level was found to increase with an increase in PbB levels above 22.4 $\mu$g/dl (1.35 as a logarithmic value) and to rise markedly above 35.5 $\mu$g/dl (1.55). The relationship between PbB level and ALAU level was examined for 2,924 workers with PbB level lower than 20 $\mu$g/dl (1.30 as a logarithmic value). A linear regressison was obtained:Y (log ALAU (mg/l)) = $-$ 0.0570X (log PbB ($\mu$g/dl)) + 0.4099. The coefficient of regression was negative and statistically significant ($p<0.001$ by t-test). The result indicates that ALAU level decreases with a concomitant increase in PbB level at PbB levels lower than 20 $\mu$g/dl. This result is coincident with our earlier report[7] that the blood lead level had a significant positive correlation with hematocrit value ($p<0.001$), amount of hemoglobin ($p<0.001$) and erythrocyte count ($p<0.001$) for PbB levels lower than 40 $\mu$g/dl.

It has been recognized that ALAU is associated with the synthesis of ALA by ALAS and PBG synthesis from ALA by ALAD[1] and that ALAU level increases with an increase in PbB level above 20 $\mu$g/dl. No relationship between ALAU and PbB has been obtained for PbB levels less than 20 $\mu$g/dl, which is considered to be a threshold for inducing adverse health effects. In the present preliminary study involving a large number of lead-exposed workers, it was found that ALAU level increased with a concomitant decrease in PbB level below 20 $\mu$g/dl.

Therefore, it can be inferred that below a threshold PbB level of 20 $\mu$g/dl at which the earliest signs of adverse health effect[8–10] appear, ALAU levels exhibit the opposite trend to the clear positive relationship between ALAU and PbB above 20 $\mu$g/dl. However, we do not yet have an explanation for such trend at low levels of lead exposure. Such U-shaped relationships between lower doses of hazardous chemicals and biological responses have been reported for dioxins and endocrine- disrupting chemicals[13]. It is possible that a more clearly discernible U-shaped relationship between low-level lead exposure and ALAU level may be obtained by excluding other confounding factors such as gender, age and smoking habit for majority of the 3,636 lead-exposed workers. Further study is necessary to examine how heme synthesis is affected exposure of workers to lead at very low levels.

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