

# Evaluation of lead exposure in workers at a lead-acid battery factory in Korea: with focus on activity of erythrocyte pyrimidine 5'-nucleotidase (P5N)

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## Abstract

**Objective**—To evaluate lead exposure among lead-acid battery workers in Korea, to evaluate in more detail the erythrocyte pyrimidine 5'-nucleotidase (P5N) test for lead exposure, and to evaluate the abnormal accumulation of erythrocyte pyrimidine nucleotides in the battery workers.

**Methods**—Activity of P5N and other biological variables were examined in 66 exposed workers in a lead-acid battery factory and in 26 non-exposed workers in Korea.

**Results**—At the factory the time-weighted average of 13 (72%) of 18 air samples for lead exceeded 0.05 (range 0.012–0.468) mg/m<sup>3</sup>. Blood lead concentration (PbB) in 39 of the 66 exposed workers was above 40 µg/dl, and the mean (SD) PbB in the exposed group was 45.7 (15.7) µg/dl. Compared with the non-exposed group, free erythrocyte protoporphyrin in the exposed group was significantly increased, whereas erythrocyte P5N activity and activity of erythrocyte δ-aminolevulinic acid dehydratase (ALAD) were significantly inhibited. Erythrocyte P5N activity had valid correlation biologically with PbB and with other biological variables, such as ALAD activity. In 28 exposed workers, the concentration of erythrocyte pyrimidine nucleotides (uridine 5'-diphosphate-glucose and cytidine 5'-triphosphate) correlated inversely with P5N activity and positively with PbB.

**Conclusions**—These findings show that the depression of erythrocyte P5N activity by lead exposure results in the accumulation of erythrocyte pyrimidine nucleotides. In general, the standard analysis of PbB performed in laboratories around the world remains the most useful index of recent exposure. The results indicate that the erythrocyte P5N activity test provides supporting evidence of lead exposure and shows the effect of lead on nucleotide metabolism.

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**Keywords:** erythrocyte pyrimidine 5'-nucleotidase (P5N); lead; nucleotide metabolism

Although the toxic effects of exposure to lead are well known, occupational lead poisoning

continues to occur worldwide. In the lead-acid battery industry, one of the largest users of lead, workers are at high risk of lead toxicity.<sup>1</sup> Although this risk has been thoroughly studied and controlled in most developed countries, in developing countries significant exposure to lead among lead-acid battery workers is still common.<sup>2,3</sup>

Erythrocyte pyrimidine 5'-nucleotidase (P5N), which catalyses the hydrolytic dephosphorylation of pyrimidine 5'-monophosphates, is inhibited by lead, and its activity is considered to be an indicator of lead exposure.<sup>4</sup> Also, it has been reported that the depression of P5N activity results in the accumulation of pyrimidine nucleotides in erythrocytes in clinical studies<sup>5</sup> and in rabbits treated with lead.<sup>6</sup> There are few reports concerning P5N activity on workers with occupational exposure to lead.<sup>7,8</sup>

## Methods

### MANUFACTURING PROCESS

Grids (the metallic lead lattices used in making battery plates) are manufactured with automatic casting machines. The grids are then pasted with lead oxide by machine. After drying, the pasted grids (plates) are converted electrically to lead peroxide and lead (plate forming process). Pairs of plates are separated and then cleaned by a brushing machine to get rid of excess metal and paste (plate finishing process). The finished plates are stacked to form battery elements, alternating negative and positive plates with an inert separator between each plate, and welded to form groups (cells) by machine. Cell connectors and battery terminals, cast from lead, are manually gas welded to the cells to complete the batteries (assembling process).

### SUBJECTS

Of the 85 workers in the plant, we selected 72 who had been exposed to lead for at least three months. Six of these were absent on the day of examination and thus could not be included in the study population, leaving 66 lead workers for examination.

As controls, we examined all 26 clerical workers from one section in another plant. None of them had any history of exposure to lead.

Heparinised venous blood samples and spot urine samples were collected from both groups.

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Table 1 Environmental and biological variables in the exposed and non-exposed groups

	Casting and pasting (n = 5)	Plate forming and finishing (n = 17)	Assembling (n = 22)	Others† (n = 22)	Exposed group all (n = 66)	Non-exposed (n = 26)
Age	39 (7)	44 (7)*	39 (10)	39 (9)	40 (9)*	32 (12)
PbA (mg/m <sup>3</sup> ):	0.083 (0.04)	0.17 (0.19)	0.145 (0.149)	—	—	—
Range	0.04–0.154 (6)	0.012–0.468 (5)	0.015–0.411 (7)	—	—	—
Air samples (n)	—	—	—	—	—	—
PbB (µg/dl)	40.6 (8.8)*	49.2 (17.4)*	47.2 (11.6)*	42.6 (18.7)*	45.7 (15.7)*	10.8 (4.4)
Hb (g/dl)	14.3 (1.1)	14.1 (1.3)	14.0 (1.6)	14.3 (1.9)	14.2 (1.6)	14.6 (1.5)
FEP (µg/dl)	36.2 (18.9)	69.4 (48.1)	73.1 (38.5)*	73.8 (60.3)	69.6 (48.4)*	33.1 (12.3)
ALAD (µmol PBG/h/ml RBC)	0.348 (0.128)*	0.315 (0.147)*	0.309 (0.128)*	0.359 (0.164)*	0.330 (0.143)*	1.268 (0.329)
P5N (µmol uridine/h/g Hb)	10.08 (0.46)*	10.13 (2.71)*	10.44 (2.10)*	11.69 (2.65)*	10.75 (2.44)*	15.34 (1.90)
ALAU (mg/l)	2.8 (0.4)	5.6 (4.2)	3.7 (2.9)	2.9 (1.5)	3.9 (3.0)	3.6 (0.9)
CPU (µg/l)	63.6 (63.3)	74.7 (105.5)	72.3 (68.0)	74.6 (83.0)	73.0 (81.5)*	36.8 (60.0)
Duration (y)	4.1 (5.5)	6.1 (5.1)	8.3 (5.3)	2.9 (3.5)	5.6 (5.2)	—

\* P < 0.05, (no significant differences were found among the four exposed subgroups.) Values are mean (SD).

†Maintenance service workers, mechanics, and other unclassified workers.

#### ENVIRONMENTAL MONITORING

For personal breathing zone air samples, a trained technician selected 14 workers whose exposures were thought to be representative in each job category. At the same time, a total of four area samples were collected to obtain general background information near the main operation site in each production section. The air samples were collected on cellulose ester membrane filters (0.8 µm pore size, 37 mm diameter) with personal air samplers. Before use, each sampling system was calibrated to obtain a flow rate of 2 l a minute. Sampling was carried out for six hours excluding breaks. The Institute of Industrial Medicine, Soonchunhyang University, authorised industrial hygiene laboratory for the Korean industries that use lead analysed air lead (PbA) samples. This laboratory has participated in a national quality control programme,<sup>9</sup> applied to all Korean industrial hygiene laboratories. In this programme, the Industrial Health Research Institute of the Korean Industrial Safety Corporation was designated as the reference laboratory by the Korean government. This reference laboratory has participated in the American Industrial Hygiene Association proficiency analytical testing programme and has performed internal quality control programmes. The concentration of PbA was measured by flame atomic absorption spectrophotometry with the National Institute for Occupational Safety and Health (NIOSH) method 7082.<sup>10</sup> Four field blanks were included and analysis of air samples was corrected by field blanks. Spiked samples (n = 15) were prepared by spiking known amounts of lead on cellulose ester membrane filters.<sup>10</sup> Recovery rates of the spiked samples ranged from 90% to 99% (mean; 94%). The pooled coefficient of variation calculated for these measurements was 4%.

#### BIOLOGICAL MONITORING

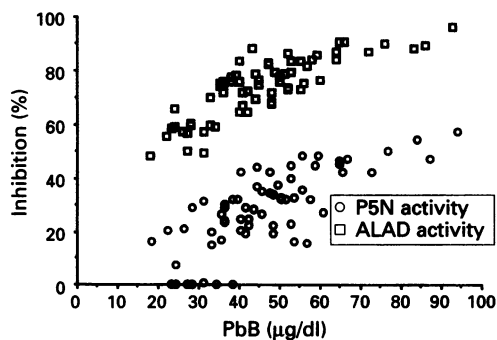
Activity of P5N was determined by the method of Tomokuni and Ichiba<sup>11</sup> with high performance liquid chromatography (HPLC, model LC-5A, Shimadzu, Kyoto, Japan). Nucleotides were extracted from the whole blood as follows: whole blood (1 ml) was

deproteinised by adding 2 ml of 0.6 N HClO<sub>4</sub> and centrifuged at 1200 g for five minutes. The supernatant (2 ml) was neutralised with 2 ml of 0.2 M K<sub>2</sub>CO<sub>3</sub>. Nucleotides were separated with HPLC by linear gradient elution with a low concentration eluent of 0.007 M KH<sub>2</sub>PO<sub>4</sub> at pH 3.90 and a high concentration eluent of 0.25 M KH<sub>2</sub>PO<sub>4</sub> and 0.50 M KCl at pH 4.50.<sup>5</sup> Nucleotide standards were purchased from Sigma Chemical Company, USA.

Activity of erythrocyte δ-aminolevulinic acid dehydratase (ALAD) was measured with the method of Haas *et al.*<sup>12</sup> Lead concentration in whole blood (PbB) was analysed with flameless atomic absorption spectrophotometry.<sup>13</sup> The accuracy was checked by inclusion of a whole blood reference sample (BCR No 196, Community Bureau of Reference, CEC, Belgium) in the sample series. Free erythrocyte protoporphyrin (FEP) was determined with the method of Piomelli.<sup>14</sup> Urinary coproporphyrin (CPU) was measured with the fluorometric HPLC method of Tomokuni and Hirai.<sup>15</sup> Urinary δ-aminolevulinic acid (ALAU) was determined with the colorimetric method of Tomokuni and Ogata,<sup>16</sup> after a threefold dilution with distilled water. Packed cell volume was measured by the capillary method, and haemoglobin (Hb) concentration by the cyanmethaemoglobin method. All urine analyses were done on spot samples, and the data were corrected to a specific gravity of 1.024.

#### STATISTICAL ANALYSES

The significance of the difference in the variables between the exposed group as a whole and the non-exposed group was tested by *t* tests. Among five groups (four exposed subgroups and one non-exposed group) significance was tested by a one way analysis of variance (ANOVA). If the ANOVA showed significance at P < 0.05, Scheffe's multiple comparison test was used to identify which subgroup or group was significantly different from which other subgroups or groups. Relations between PbB or P5N and other biological variables were evaluated with Pearson's correlation coefficients.



Relation between the inhibition of P5N or ALAD activity and blood lead concentration in 66 battery workers.

## Results

### LEAD EXPOSURE IN THE LEAD-ACID BATTERY FACTORY

Table 1 shows the concentrations of biological variables in the exposed and non-exposed groups. The difference in PbB between the four exposed subgroups and the non-exposed group was significant. There were no significant differences in mean PbB among the four exposed subgroups. PbB in 39 (59%) of the 66 exposed workers exceeded 40 µg/dl, the upper limit recommended by the World Health Organisation for adult male workers.<sup>17</sup> In nine (14%) of the exposed workers PbB was above 60 µg/dl.

Table 1 also summarises the PbA concentrations at the lead-acid battery factory. In this survey, 13 (72%) of 18 air samples for lead exceeded the United States time weighted average permissible exposure limit of 0.05 (range 0.012–0.468) mg/m<sup>3</sup>. All of the mean PbA values in the three processes were above the permissible exposure limit. A highest mean concentration of PbA and PbB were found in the section where plate forming and finishing were done.

Compared with the non-exposed group, FEP in the exposed groups was significantly increased, whereas P5N and ALAD activity were significantly inhibited. The difference in Hb and ALAU between the exposed and non-exposed groups was insignificant. Mean CPU was higher in the exposed than in the non-exposed group.

### RELATION BETWEEN PbB AND P5N ACTIVITY OR OTHER BIOLOGICAL VARIABLES

In 66 battery workers, the correlation coefficients between PbB and ALAD, P5N, ALAU, FEP, CPU, packed cell volume, and Hb were -0.826 ( $P < 0.001$ ), -0.735 ( $P < 0.001$ ), 0.648 ( $P < 0.001$ ), 0.584 ( $P < 0.001$ ), 0.501 ( $P < 0.001$ ), 0.232 ( $P > 0.05$ ), and 0.176 ( $P > 0.05$ ), respectively. The correlation coefficients between P5N and ALAD, log ALAU, log FEP, CPU, packed cell volume, and Hb were 0.729 ( $P < 0.001$ ), -0.531 ( $P < 0.001$ ), -0.481 ( $P < 0.001$ ), -0.420 ( $P < 0.001$ ), -0.235 ( $P > 0.05$ ), and -0.185 ( $P > 0.05$ ), respectively.

We compared the degree to which lead inhibited P5N and ALAD activity (figure).

Table 2 Correlation coefficients between nucleotide concentration and P5N or PbB in 28 lead workers

Nucleotide	P5N	PbB
AMP	-0.051	0.062
UDPG	-0.656*	0.678*
NADP	-0.242	0.251
UDP	-0.034	-0.190
CDP	-0.320	0.079
ADP	-0.080	0.185
GDP	0.315	-0.104
UTP	0.114	0.015
CTP	-0.421*	0.403*
ATP	0.281	-0.088
GTP	0.153	0.001

\* $P < 0.05$ . AMP, adenosine 5'-monophosphate; UDPG, uridine 5'-diphosphate-glucose; NADP, nicotinamide adenine dinucleotide phosphate; UDP, uridine 5'-diphosphate; CDP, cytidine 5'-diphosphate; ADP, adenosine 5'-diphosphate; GDP, guanosine 5'-diphosphate; UTP, uridine 5'-triphosphate; CTP, cytidine 5'-triphosphate; ATP, adenosine 5'-triphosphate; GTP, guanosine 5'-triphosphate.

The percentage of inhibition of P5N and ALAD activity was calculated with the mean value of the non-exposed group as a base. In specimens in which P5N activity was higher than the mean value of the non-exposed group, enzyme inhibition was treated as 0%. The PbB dose-response curves for ALAD and P5N showed similar patterns. The inhibitory effect of lead exposure was higher on ALAD than on P5N over the whole range of PbB concentrations. At 18 µg/dl of PbB, 48% of ALAD activity was inhibited, and most of the activity was inhibited above 40–50 µg/dl. These findings show that ALAD activity is quite sensitive to lead exposure.<sup>18</sup>

Table 2 shows the relation between the concentration of erythrocyte nucleotides and P5N activity or PbB. The amount of uridine 5'-diphosphate-glucose (UDPG) correlated positively with PbB and inversely with erythrocyte P5N activity. Similar results were obtained for the cytidine 5'-triphosphate analysis.

## Discussion

Few studies of lead-acid battery workers in developing countries have been reported in recent years. Although our study has some limitations as a small scale, cross sectional study, our survey showed a high prevalence of increased concentrations of PbB of battery workers in Korea. Concentrations of PbB in the battery workers in this study were found to be higher than those in workers at a large United States battery manufacturer, where only 6% of PbB concentrations exceeded 60 µg/dl.<sup>19</sup> But they were lower than those found in Jamaican battery manufacturers, where 28% of the workers exceeded 60 µg/dl,<sup>2</sup> and those found at a battery factory in Sudan, where 95% of the workers had PbB concentrations above 40 µg/dl.<sup>3</sup> In battery manufacture, lead dust or fume from manual work in the process of casting and pasting, and also in the process of assembling, is the major source of exposure.<sup>20</sup> The high PbB concentration (80.7 (14.7) µg/dl) of casting and pasting workers in Sudan, and the higher PbA concentration in the process of assembling in Jamaica, suggest that different battery production technologies (machine or manual)

contribute to the differences in PbB concentrations in Korea, Sudan, and Jamaica.<sup>2,3</sup> The low PbB concentrations in lead-acid battery workers in the United States is most likely related to application of more automated production procedures, greater use of engineering control of lead exposures, more comprehensive application of environmental and personal monitoring, and greater regulatory attention to this problem.

A comparison of the rather high PbA concentrations measured in the Korean factory with those reported in other published surveys<sup>2,3,19,21</sup> indicates that high and low exposure processes in battery manufacture may vary with the factory. No significant differences were found between the four sections in biological indices such as PbB, FEP, P5N, and ALAD. These findings show that the workers in the factory were exposed to similarly high concentrations of lead regardless of the section in which they worked. The workers may move about the plant and thereby receive bystander exposure from adjacent processes conducted in the same building that did not have adequate, separate ventilation systems for each process.

P5N was first reported by Valetine *et al* in 1974 in their description of haemolytic anaemia.<sup>22</sup> The enzyme in red cell cytosol catalyses the hydrolytic dephosphorylation of pyrimidine 5'-monophosphates but is ineffective on purine nucleotides. The reaction is thought to be a necessary step in the degradation of ribosomal RNA in maturing red cells. Through this mechanism, the erythrocyte is able to diffuse pyrimidine nucleotides as soluble nucleosides and retain purine nucleotides as a source of ATP. The accumulated pyrimidine nucleotides in red cells are thought to shorten the cells' life span in lead poisoning,<sup>23</sup> although details remain unknown. Activity of P5N is inhibited by lead, and it is considered an indicator of lead exposure.<sup>4,24</sup> In our study the mean (SD) erythrocyte P5N activity of 26 normal subjects was 15.34 (1.9)  $\mu\text{mol}$  uridine/h/g Hb, similar to the 16.2 (2.5)  $\mu\text{mol}$  uridine/h/g Hb reported by Sakai *et al*.<sup>25</sup> The validity of P5N activity was also estimated by the method of Zielhuis and Verberk.<sup>26</sup> If the lower limit for normal P5N activity is 11.54  $\mu\text{mol}$  uridine/h/g Hb (-2 SD), then the sensitivity is 88%, as 37 out of 42 subjects with PbB  $\geq 40$   $\mu\text{g}/\text{dl}$  were below it. The specificity of P5N is 82%, as 41 out of 50 subjects with PbB  $< 40$   $\mu\text{g}/\text{dl}$  were above it. Validity (sensitivity + specificity) is 1.70. These results are comparable to the findings of Tomokuni *et al*,<sup>27</sup> where sensitivity was 73% and specificity was 93%. In our study the erythrocyte P5N activity was found to be a valid biological correlate with PbB, although further study is indicated to determine its sensitivity and specificity in a large population. Activity of P5N also correlated highly with other biological variables such as ALAD activity, which we found to be a more sensitive indicator of lead exposure than P5N activity (figure). The erythrocyte ALAD activity test has one disadvantage: it must be carried out immediately after

blood sampling because this enzyme is vulnerable and inactivated during storage. By contrast, erythrocyte P5N is stable for at least seven days in blood stored at 4°C.<sup>28</sup> As the assay of P5N can be carried out with stored samples, erythrocyte P5N activity seems to be more suitable than erythrocyte ALAD activity for screening lead exposure. Our results also showed that erythrocyte UDPG and CTP concentration correlated positively with PbB and inversely with P5N activity. Thus, the depression of erythrocyte P5N activity by lead exposure results in the accumulation of erythrocyte pyrimidine nucleotides such as UDPG and CTP. Although the role of these accumulated pyrimidine nucleotides in the red cells of the battery workers remains sketchy, our study shows that lead has a definite effect on nucleotide metabolism.

In general, the standard analysis of PbB performed in laboratories around the world remains the most useful index of recent exposure.<sup>29</sup> Our results indicated that the erythrocyte P5N activity test provides supporting evidence of lead exposure and shows the effect of lead on nucleotide metabolism.

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