Blood pressure is believed to become increased among residents exposed to lead, such as that emitted from house paint, gasoline, and other sources. Several reports are available concerning the lead-blood pressure relation in which confounding factors (age, sex, hypertensive heredity, nutrition, lead exposure level, etc) were adjusted by mathematical modelling. Harlan and colleagues described a close association between blood lead and systolic or diastolic blood pressure, based on the Second National Health and Nutrition Examination Survey data (NHANES II). We have also applied mathematical modelling to our survey data on 220 male workers, and found that diastolic blood pressure was increased in male workers with blood lead concentrations above 40 µg/dl. On the other hand, Harlan indicated that blood lead was closely related to systolic and diastolic pressures in males but not in females, based on multiple regression analysis. Female workers were normally not included or exposed to lower concentrations of lead, and no consensus for the relation between lead exposure and blood lead has been established.

We therefore examined the lead induced increase of blood pressure in female workers by the use of mathematical modelling.

### Methods

#### Study population

The study population consisted of 127 female crystal toy making workers (age range 17–44 years, mean (SD) 27.3 (5.4) years; duration of employment 0.8–25.0 years, mean 7.2 (4.6) years) and 70 female sewing workers (age range 16–58 years, mean 24.2 (6.4) years; duration of employment 0.1–11.4 years, mean 7.2 (4.6) years). All female workers were examined in each factory. Both factories were located in Beijing City, China. The working environment of the crystal toy making factory was contaminated with lead dust at concentrations of 0.39–1.91 mg/m³ (mean 0.92 (0.42)) that were much higher than the occupational exposure limit of 0.05 mg/m³ recommended by the American Conference of Governmental Industrial Hygienists. The suburban environment, the target site, was also seriously polluted with lead from automobile exhaust gases, although no precise data were available for the target site at the time of our survey. Table 1 presents the results of the biological indices of lead in workers.
Uric Acid (Dainabot), Glucose FA-Test (Wako), Cholesterol-FA Test (Wako), and Triglyceride G-FA Test (Wako), respectively. Plasma sodium and potassium were analysed by flame photometry, and chloride by the chloridometer.

Urine protein and glucose were determined with an automatic biochemical analyser, Abbott VP, using Tonein TP (Otsuka) and the Glucose FA-test (Wako). Urine amino acids and creatinine were estimated by the trinitrobenzene sulfonic acid method\(^{13}\) and Folin-Wu method,\(^{14}\) with the use of Abbott VP. Urine phosphorus, alanine aminotransferase, and alkaline phosphatase were assessed with an automatic biochemical analyser, Abbott VP, employing Phospha-B T est (Wako), GPT-FA T est (Wako), and Alkaline Phospha-FA T est (Wako) to detect lead induced lesions of the kidneys.\(^{15}\)

In order to avoid observation bias, all subjects and examiners were unaware of our concern about the relation between blood lead and blood pressure: all workers and doctors who measured blood pressure and familial heredity, and who took blood and urine samples, and the technician who measured biological parameters. Subjects were questioned on their familial hypertensive heredity in their routine health check interviews before being informed of the aim of this study, in order to diminish differential recall bias.

Statistical analysis
Twenty two parameters related to blood pressure were subjected to factor analysis for classifying into 10 factors. The parameters were age and duration of employment, hypertensive heredity (number of persons suffering from hypertensive disease), blood lead, plasma triglyceride, plasma cholesterol, plasma high density lipoprotein (HDL), plasma low density lipoprotein (LDL) (calculated after Freewald's formulae), haemoglobin, plasma \(\delta\)-aminolaevulinic acid (ALA), urine ALA, urine protein, urine glucose, urine amino acids, plasma creatinine, plasma urea nitrogen, ratio of plasma urea nitrogen to creatinine, fractional excretion of phosphorus (FEIP), plasma phosphorus, plasma calcium, urine calcium, and plasma alkaline phosphatase. Multiple forward regression analyses were employed for 10 representative parameters selected by factor analysis to evaluate the possible confounders, and multiple regression and the Pearson correlation procedure were used for evaluating the significance of the selected confounders. Multiple logistic regression analyses were employed for evaluating dose-effect and dose-response relations between blood lead and blood pressures after controlling for possible confounders. Some of the data, including blood lead concentrations, were missing because of insufficient sample volume for analyses. However, this is not related to the exposure or health status of workers. All analyses were performed using SAS 6.12 statistical software (SAS Institute, Cary, NC, USA).

RESULTS
Possible confounders for blood pressure
From the 22 parameters, 10 representative parameters were chosen by factor analysis, one each from the above 10 factors, as follows: blood lead, age, hypertensive heredity, plasma cholesterol, plasma triglyceride, plasma low density lipoprotein, plasma urea nitrogen, urine protein, urine amino acids, and fractional excretion of phosphorus. The above parameters were then subjected to multiple forward regression analysis with a level of entry of 0.2. As table 2 shows, these parameters were applied to multiple regression analysis; the potent parameters modulating blood pressure were as follows: (1) for systolic blood pressure: blood lead, age, urine protein, and plasma triglyceride; (2) for diastolic blood pressure: blood
Table 3

<table>
<thead>
<tr>
<th>Blood lead concentration (µg/l)</th>
<th>Systolic blood pressure (SBP)</th>
<th>Diastolic blood pressure (DBP)</th>
<th>Pulse pressure (PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Control (&lt;11.4)</td>
<td>110.3 (9.8)</td>
<td>72.7 (6.0)</td>
<td>37.7 (7.0)</td>
</tr>
<tr>
<td>&lt;20 to 40</td>
<td>115.2 (7.5)</td>
<td>76.1 (5.6)</td>
<td>4.1 (0 to 8.5)</td>
</tr>
<tr>
<td>&gt;40 to 60</td>
<td>119.8 (13.1)</td>
<td>77.1 (13.1)</td>
<td>2.1 (1.0 to 6.8)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>125 mm Hg</td>
<td>80 mm Hg</td>
<td>50 mm Hg</td>
</tr>
</tbody>
</table>

Dose-effect relation between blood lead and blood pressure (table 3)

<table>
<thead>
<tr>
<th>Blood lead concentration (µg/l)</th>
<th>Systolic blood pressure (SBP)</th>
<th>Diastolic blood pressure (DBP)</th>
<th>Pulse pressure (PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Control (&lt;11.4)</td>
<td>70</td>
<td>2.1 (1.0 to 2.5)</td>
<td>0.0583</td>
</tr>
<tr>
<td>&lt;20 to 40</td>
<td>59</td>
<td>4.2 (1.0 to 2.5)</td>
<td>0.0079</td>
</tr>
<tr>
<td>&gt;40 to 60</td>
<td>47</td>
<td>7.5 (1.0 to 2.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt;60</td>
<td>47</td>
<td>7.5 (1.0 to 2.5)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Dose-response relation between blood lead and blood pressure (table 3)

<table>
<thead>
<tr>
<th>Blood lead concentration (µg/l)</th>
<th>Prevalence</th>
<th>Odds ratio (95% CI†)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (&lt;11.4)</td>
<td>7.1%</td>
<td>18.6%</td>
<td>0.0405</td>
</tr>
<tr>
<td>&lt;20 to 40</td>
<td>18.6%</td>
<td>4.26 (1.07 to 17.04)</td>
<td>0.0570</td>
</tr>
<tr>
<td>&gt;40 to 60</td>
<td>25.5%</td>
<td>7.48 (1.86 to 30.12)</td>
<td>0.0046</td>
</tr>
<tr>
<td>&gt;60</td>
<td>25.5%</td>
<td>7.48 (1.86 to 30.12)</td>
<td>0.0046</td>
</tr>
</tbody>
</table>

*Blood lead values on control workers were less than 11.4 µg/l, and those on exposed workers were more than 22.5 µg/l.
†Adjusted by the selected possible confounders for SBP, DBP, and PP in table 2.
data by the use of mathematical modelling in order to eliminate confounding factors that elevate blood pressure. In addition, although several authors did apply mathematical modelling, the blood lead might be relatively low. On the other hand, the occupational exposures to lead in some Asian and African countries are still higher than those in western countries.1 20-29 We therefore carried out an epidemiological survey on male lead workers, and found that lead exposure was the most potent factor in the diastolic blood pressure increase, and that diastolic blood pressure in the male workers with blood lead concentrations above 40 µg/dl was increased, after mathematical modelling. Other potent factors in raising blood pressure were hypertensive heredity and age.30

We carried out the present survey on lead induced increase of blood pressure in female workers, as it has been suggested by Harlan,18 that lead exposure did not raise blood pressure levels in females residents, and Wu and colleagues14 recently confirmed that lead exposure did not appear to raise blood pressure in female workers. Contrary to the works of Harlan10 and Wu and colleagues, however, our data yielded the following facts: (1) the potent factors increasing the systolic and diastolic blood pressures calculated by a combination of factor analysis and multiple forward regression analysis were blood lead, age, plasma triglyceride, and urine protein, and did not include hypertensive heredity in common (table 2); and (2) the systolic and diastolic blood pressures were increased in female workers with blood lead concentrations of 40-60 µg/dl or higher, as shown by dose-effect and dose-response relation data (table 3).

Wu and colleagues12 reported a lack of evidence of lead induced increase of blood pressure in female workers, probably as a result of the short exposure (0.5-17 years, mean 3.1 (3.2) years). Indeed, it is true that their observed blood lead concentrations (n = 110, 45 (18) µg/dl) were lower than ours (35 (14) µg/dl), and the exposure period of our female workers (0.8-25 years, 7.2 (4.6) years) was longer than theirs (0.5-17 years, 3.1 (3.2) years). Nevertheless, the duration of lead exposure was not selected by multiple forward regression analyses. These findings imply that the exposure period did not contribute much to the lead induced increase of blood pressure.

Other factors increasing blood pressure
Age also contributed to systolic, diastolic, and pulse pressures (table 2). Systolic and diastolic pressures were significantly increased in female workers above 30 years old (data not shown), as was observed in male workers.7

Lilis and colleagues24 and Wedeen25 suggested that lead induced renal dysfunction might lead to a blood pressure increase in workers. In the present survey on female workers, however, while blood lead was significantly associated with urine amino acids or plasma creatinine (p = 0.0079, p = 0.0191), these parameters were not selected as possible confounders by multiple forward regression analyses. Urine protein was significantly associated with systolic/diastolic/pulse blood pressures (table 2), but partial correlations (PCs) indicated no associations between blood lead and urine protein on blood pressure (systolic blood pressure: PC = -0.0928, p = 0.2142; diastolic blood pressure: PC = -0.0989, p = 0.1982; pulse pressure: PC = -0.0614, p = 0.4118). Furthermore, as was shown in table 2, no parameters indicating renal function other than urine protein were selected by multiple forward regression analyses. It is difficult to conclude therefore that the observed blood pressure increase was related to lead induced renal dysfunction, such as glomerular or tubular dysfunction.

However, plasma triglyceride was significantly and closely associated with systolic and diastolic blood pressures and pulse pressure, respectively, even though no significant partial correlation was found between blood lead and plasma triglyceride on systolic/diastolic/pulse blood pressure. Although low density cholesterol was significantly associated with diastolic blood pressure, the partial correlation between low density cholesterol and blood lead was negatively significant (PC = -0.2661, p = 0.0004). All the above confounding results may suggest that lead induced changes of lipoprotein metabolism could induce an increase of blood pressure, but the mechanism is not fully elucidated. Kuz'minskaya reported that potent atherosclerosis occurred in pigeons given cholesterol 600 mg/day and lead 25 mg/kg simultaneously over a period of 3.5 months, compared to the pigeons of the control, cholesterol, and lead groups. Sroczynski and colleagues16 gave lead acetate to rats intravenously at a dose of 20 mg Pb/kg every other day for three months, and found increased concentrations of plasma cholesterol and lipoprotein T fraction. Sroczynski and colleagues17 noted cholesterol deposition in the inner, median, and outer layers of the aorta in rats administered lead acetate at a dose of 20 mg Pb/kg every other day. Revis and colleagues22 reported that the plasma high density lipoprotein was increased in pigeons given food containing lead chloride at a dose level of 0.8 mg/kg over a period of six months. Tarug and colleagues observed greatly increased concentrations of plasma cholesterol ester in rabbits given food containing 0.5% lead acetate over a period of 45 days. Their findings appear to provide support for our proposal concerning the mechanism of lead induced increase of blood pressure, whereby lead induced changes in lipoprotein metabolism may play an important role in the lead induced blood pressure increase in female workers.

Limitations of the study
In view of the nature of the cross sectional study, there are some limitations of this study. The temporal causality has not been established, and past exposure to lead was hard to be estimated. Furthermore, we cannot exclude the possibility of unexpected factors that were not evaluated and can confound the effect of lead exposure.

Conclusion
A possible explanation of the results of the study is that lead induced changes in lipoprotein metabolism may play an important role in the lead induced blood pressure increase in female workers, especially at concentrations higher than 40 µg/dl.

ACKNOWLEDGEMENTS
The authors are grateful to Prof. Koichi Nakamura of Jichi Medical School for his advice in revising the manuscript from the viewpoint of the epidemiologist. The present study was supported by the International Lead Zinc Research Organization, Inc. (ULH-389 to KN Namiyama), Research Triangle Park, NC.


11. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents and biological exposure indices. ACGIH, Cincinnati, Ohio, 1997.


Lead induced increase of blood pressure in female lead workers

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*Occup Environ Med* 2002 59: 734-738
doi: 10.1136/oem.59.11.734

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