Estimation of Benchmark Dose for Bone Damage and Renal Dysfunction in a Chinese Male Population Occupationally Exposed to Lead

YI SUN1, DONGHONG SUN2, ZHIJUN ZHOU1,3, GUOYING ZHU3, LIJIAN LEI1, HAIYING ZHANG1,4, XIULI CHANG1 and TAIYI JIN1*

1Department of Occupational Health, School of Public Health, Fudan University, Shanghai 200032, China; 2Department of Occupational Health, Pudong Center for Health Inspection and Supervision, Shanghai 200135, China; 3Institute of Radiation Medicine, Fudan University, Shanghai 200032, China; 4Department of Occupational Health, School of Public Health, Guangxi Medical University, Nanning, Guangxi Province 530021, China

Received 28 June 2007; in final form 13 December 2007; published online 20 June 2008

Objectives: The aim of this study was to examine a possible relationship between lead nephropathy and its effects on the skeleton in male population occupationally exposed to lead in China.

Methods: One hundred and fifty-five lead-exposed male workers in a storage battery plant in Shanghai were selected as the exposed subjects while the 36 healthy male officers in the plant who were not occupationally exposed to lead were treated as the control. Blood lead (BPb) and urine lead were used as biomarkers for exposure. Z score, urine hydroxyproline (HYP), serum alkaline phosphatase (bone isoenzyme) (BALP) and serum osteocalcin (BGP) were used as biomarkers for bone effects. Urine N-acetyl-D-glucosaminidase (UNAG) and urine albumin (UALB) were applied as biomarkers of renal tubular and glomerular dysfunction. Bone mineral density was measured by the monophoton absorptiometry (SPA-4).

Results: It was found that there were linear correlate relationships between lead exposure and NAG, ALB, BALP, BGP, HYP, Z score \( (P < 0.01) \), after controlling confounders such as age and work year. NAG, ALB, BALP, BGP and HYP would increase with the increase of lead exposure. \( Z \) score would decrease with the increase of lead exposure. Of 21 subjects with osteoporosis, nine subjects were suffering from renal dysfunction. The prevalence of renal dysfunction (42.86%) was significantly higher in the subjects with osteoporosis than in those without osteoporosis \( (42.86\%) \) \( (\chi^2 = 7.310, P = 0.007) \). The prevalence of osteoporosis had relationship with renal tubular damage, but not with renal glomerular damage. This showed that glomerular dysfunction plays a smaller role than tubular dysfunction in the causation of bone damage. Benchmark dose in terms of BPb was calculated using Benchmark Dose Software Version 1.3.2 software. The benchmark dose lower limit of a one-sided 95% confidence interval (BMDL) for 10% excess risk was also determined. It was found that BMDL for BALP, UNAG, BGP, HYP, \( Z \) score and UALB of BPb increased sequentially. The BMDL values for UNAG \( (10.13 \mu g \text{ dL}^{-1}) \) were lower than those of \( Z \) score \( (14.17 \mu g \text{ dL}^{-1}) \).

Conclusions: The present study has thus demonstrated the combined adverse effects (osteoporosis and renal dysfunction) caused by occupational exposure to lead. There was a dose-response relationship between lead exposure and prevalence of osteoporosis, renal dysfunction and bone metabolism. The renal dysfunction might develop earlier than osteoporosis. Osteoporosis caused by lead was related to the change of bone metabolism and renal dysfunction, which was especially to tubular damage but not to glomerular damage.

Keywords: benchmark dose; biomarkers; bone metabolism; lead; osteoporosis; renal dysfunction

*Author to whom correspondence should be addressed. Tel: +66-21-54237214; fax: +66-21-64178160; e-mail: tyjin@shmu.edu.cn

527
INTRODUCTION

Lead (Pb) poisoning is an occupational hazard for workers of lead refineries, battery, painting, ceramic and printing workshops (Muter and Karl, 1995; Piomelli, 2000), as well as from exposure to contaminated food, water and the environment (Kocak et al., 1989). Lead accumulates gradually in the human body, where it gives rise to a number of adverse health effects and especially to osteotoxicity and nephrotoxicity (Nolan and Shaikh, 1992; Piomelli, 2000). Lead in blood is the most commonly used biological marker of lead dose. With a mean biological life of 30 days, lead in blood reflects current exposure to lead and the endogenous release of lead from the skeleton (Popovic et al., 2004). Most of the lead accumulated by humans over time is deposited in bone, and has a half-life of ~20 years (Rabinowitz, 1991). During both normal and increased bone turnover, e.g. during pregnancy, lactation and at menopause, skeletal lead stores can be mobilized (Franklin et al., 1997; Gulson et al., 1997, 1998; Silbergeld et al., 1988).

Recent studies indicate that lead may exert both direct and indirect actions on bone turnover, indirectly via kidney dysfunction and directly on osteoblast and osteoclast function (Marika et al., 2000). On the long-lasting impact of lead on health, lead exposure interferes with bone formation and increases the risk of osteoporosis later in life. Lead inhibits osteoclastic bone resorption and osteoblastic bone formation. Moreover, lead may inhibit activation of vitamin uptake of dietary calcium and several regulatory aspects of cell function (Silbergeld et al., 1988). Some epidemiologic studies have also indicated that lead can impair kidney function (Staessen et al., 1992; Loghman Adhan, 1997). Chronic, low-level exposure to lead has been associated with increased excretion of low-molecular-weight proteins and lysosomal proteins (Alfven et al., 2002). Lead is nephrotoxic and can disturb vitamin D metabolism. However, no detailed study of the relationship between renal effects and bone damage in various population groups has been made.

The main aim of the present study is to examine a possible relationship between lead nephropathy and its effects on the skeleton in a lead-exposed male population working in a storage battery plant in China.

METHODS

Subjects

A storage battery plant is located in Shanghai, China. The main products in this plant are automobile storage battery which is made from lead and acid. The mean of lead dust concentration in atmosphere in workshop was 0.039 mg m$^{-3}$ (0.022–0.084 mg m$^{-3}$), which was often higher than permissible concentration-time-weighted average of national hygiene standard (lead fume: 0.03 mg m$^{-3}$; lead dust: 0.05 mg m$^{-3}$). For the lead dust concentration, there were no significant differences within and between workshops. There were no exposures to other nephrotoxic and bone altering chemical or metals, such as cadmium, etc.

The target population comprised people who worked in this plant. The study population was divided into two groups: namely exposure group and control group. One hundred and fifty-five male workers who were occupationally exposed to lead >1 year were selected to be the exposed population and constituted the exposed group. Their average age was 43.5 years old, and their work years were 18.07 ± 9.39 years. The control group was consisted of office faculty, who were not exposed to lead in work. The control group included 36 male subjects, whose average age was 45.0 years old. Subjects with impairment of liver, hyperparathyroidism and those who had received drugs known to alter bone metabolism were excluded. The drugs included cholestyramine, phenytoin, phenobarbital, rifampicin and corticosteroid. Subjects participating in the study completed a questionnaire to obtain information on height, weight, age age age, cigarette smoking, alcohol consumption, job position, work year, physical exercise, medical and drug history, etc. There were no restrictive diets (vegan) in the study population. Local ethics committees of Fudan University gave permission to perform the study. All participants in this study were informed about the content and the objectives of the study and gave their informed consent to participate.

Collection of samples and analytical method

Spot urine samples were collected from all participants after they had been instructed how to avoid contamination. Polyethylene containers were checked to be contamination free by testing with diluted nitric acid analyzed for lead. Every 1-ml urine sample was acidified with concentrated nitric acid and was used for assay lead. The rest of urine sample was used for urinary albumin (UALB), NAG and hydroxyproline (HYP). Collection of samples and analytical method

Urine lead (UPb) concentrations were measured by use of the standard addition method. A reference urine sample was inserted in each run of 10 samples. The value of the correlation coefficient was 0.8612 and the slope was 0.9236. Urine albumin (UALB) was measured by enzyme-linked immunosorbent assay (Neuman and Cohen, 1989) and NAG was measured as described by Price (1992). Urine HYP was measured using kits from the Nanjing Jiancheng Biological Engineering Institute. Creatinine was determined by the Jaffé reaction method (Hare, 1950). All urine
parameters were standardized to the concentration of creatinine in urine. ALB in urine was used as a glomerular damage index. Urine N-acetyl-β-D-glucosaminidase (UNAG) was used for tubular damage. Urinary HYP was used as bone metabolism damage index.

The blood was sampled in 3-ml evacuated heparinized and metal-free tube. An aliquot of ~1 ml was acidified with concentrated nitric acid and was used for assay lead. All samples were stored frozen at −20°C until analysis. In total, 2 ml blood was used to separate serum. Serum alkaline phosphatase (bone isoenzyme) (BALP) was measured as described by Tan et al. (2005). Serum osteocalcin (BGP) was assayed using a radioimmunoassay method. Serum alkaline phosphatase (bone isoenzyme) and osteocalcin were used as bone metabolism damage indexes.

Bone densitometry and quality control, definition of Z score and osteoporosis

Bone mineral density was measured in each subject by single photon absorptiometry (SPA, SPA-4 densitometer; Chinese Measurement Technology Institute, Beijing, China) at the distal one-third of the radius and ulna. Measurement precision, expressed as the coefficient of variation, was within 2%. The system was calibrated every day. The machine operator was experienced and all the bone measurements were made by a veteran operator. Repetition of the measurements in the same person eight times showed that the repeatability of the results was 99.66% as described by Wang et al. (2003). The change in forearm bone density was used as a marker of bone damage.

Individual variables of bone mineral density in the subjects were also expressed as a Z score, i.e. the number of standard deviation (SD) from the mean of sex- and age-matched controls. After standardization by age and sex, Z-score values were computed according to the formula: Z score = (X – Xm)/SD, where Xm is measured bone density, Xm is group mean for the same age and sex group in a normal resident population in Shanghai and SD is the standard deviation in the same group. In this study, we use bone mineral density of the normal residents in Shanghai as the baseline bone mineral density. A common definition of osteoporosis, namely Z score < −2, was used (Consensus Development Conference, 1993; Stein et al., 1996; Chalkley et al., 1998).

The BMD method

The benchmark dose (BMD) was defined by Crump (1984) as a lower confidence limit corresponding to a moderate increase in risk (1–10%) above the background risk. In the present set of data, we used 5% level of risk above background in BMD and lower confidence limit of BMD (BMDL) procedures to estimate the lower confidence limit of the population critical concentration of blood lead (BPb), based on occupational population data of UNAG, UALB, HYP, BALP, BGP and Z score. Benchmark Dose Software (BMDS) Version 1.3.2 (US, Environmental Protection Agency) was used for calculation of the BMD and BMDL.

Statistical analysis

Database management and statistical analysis were performed using Epi-Info (Centers for Disease Control, Atlanta, GA, USA) and SPSS 13.0 (SPSS Inc, Chicago, IL, USA) software. The data in age, weight, height, body mass index (BMI), serum osteocalcin and alkaline phosphatase (bone isoenzyme) were normal distribution, and the results were expressed as the arithmetic mean ± SD. BPb, UBPb, NAG, ALB and HYP are expressed as the geometric mean. Means and proportions were compared by using the standard normal F test and χ² test for trends, respectively. The criterion significance level was set at P < 0.05. Also, partial correlate analysis was used to assess the relationship between NAG, ALB, BALP, BGP, HYP, Z score and BPb, after adjusting for confounding variables such as age and work year.

RESULTS

Characteristics of the subjects

Table 1 showed that for the main characteristics, such as age, weight, height, BMI, current smokers, pack-years of smoking, alcohol consumers and units of alcohol per month, there were no significant differences between the exposure group and the control group. Amounts of alcohol were converted to units per month (1 unit of alcohol = 9 g). Thus, the participants in the two groups had similar baseline characteristics apart from lead exposure.

The levels of BPb, UBPb, HYP, BALP, BGP and NAG in exposure group were significantly higher than those in the control group (P < 0.05). The level of ALB in the exposure group was higher than that in the control group, but with no significantly statistical difference (P > 0.05). The average bone mineral density in exposure group was lower than that in the control group, but with no significantly statistical difference (P > 0.05).

Osteoporosis, bone metabolism modification, renal dysfunction and lead exposure

BPb and UBPb are used as biomarkers of lead exposure and internal dose in this study. Because age and work year could be potential confounders (Newitt, 1994), we did partial correlate analysis to assess the variation of NAG, ALB, BALP, BGP, HYP and Z score in function of the variation of BPb and
UPb, after correcting for confounding variables such as age and work year. Table 2 displays that there were linear correlate relationships between BPb, UPb and NAG, ALB, BALP, BGP, HYP and $Z$ score, after controlling confounders such as age and work year. NAG, ALB, BALP, BGP and HYP would increase with the increase of lead exposure. $Z$ score would decrease with the increase of lead exposure.

**Relationship between osteoporosis and renal dysfunction due to lead**

According to the 10% prevalence rate in the control group, the cut-off points (NAG, 13.783 U g$^{-1}$ Cr; ALB, 12.628 mg g$^{-1}$ Cr) were used for determining the prevalence of renal dysfunction indexes. Subjects with renal dysfunction were defined as just one of the two effect markers abnormal. Table 3 shows that among 21 subjects with osteoporosis, nine were suffering from renal dysfunction. The prevalence of renal dysfunction (42.86%) was significantly higher in the subjects with than in those without osteoporosis (17.65%) ($\chi^2 = 7.310, P = 0.007$). Table 4 shows that the prevalence of osteoporosis was significantly different between different tubular dysfunction groups ($\chi^2 = 8.296, P = 0.004$). In contrast, no significant change in the prevalence of osteoporosis was found in the different glomerular dysfunction groups ($\chi^2 = 1.681, P = 0.195$). This demonstrated that tubular dysfunction played an important part, and glomerular dysfunction played a smaller part in the bone–renal relationship.

### Table 1. Characteristics of study population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers ($n$)</td>
<td>36</td>
<td>155</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.0 ± 9.8</td>
<td>43.5 ± 8.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.3 ± 10.2</td>
<td>69.2 ± 9.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.8 ± 4.6</td>
<td>170.8 ± 5.3</td>
</tr>
<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>24.2 ± 2.9</td>
<td>23.7 ± 2.8</td>
</tr>
<tr>
<td>Current smokers</td>
<td>25 (69.4%)</td>
<td>121 (78.1%)</td>
</tr>
<tr>
<td>Pack-years of smoking$^a$</td>
<td>76.6 (0.0~182.5)</td>
<td>97.4 (0.0~282.9)</td>
</tr>
<tr>
<td>Alcohol consumers</td>
<td>22 (61.1%)</td>
<td>100 (64.5%)</td>
</tr>
</tbody>
</table>

$^a$ Geometric mean value and 95% confidence intervals of GM.

**Table 2. Correlate relationship between lead exposure and renal dysfunction/bone damage**

<table>
<thead>
<tr>
<th></th>
<th>BPb Correlation coefficient</th>
<th>$P$-value</th>
<th>UPb Correlation coefficient</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAG</td>
<td>0.638</td>
<td>0.000</td>
<td>NAG</td>
<td>0.754</td>
</tr>
<tr>
<td>ALB</td>
<td>0.445</td>
<td>0.000</td>
<td>ALB</td>
<td>0.459</td>
</tr>
<tr>
<td>BALP</td>
<td>0.601</td>
<td>0.000</td>
<td>BALP</td>
<td>0.598</td>
</tr>
<tr>
<td>BGP</td>
<td>0.359</td>
<td>0.000</td>
<td>BGP</td>
<td>0.332</td>
</tr>
<tr>
<td>HYP</td>
<td>0.604</td>
<td>0.000</td>
<td>HYP</td>
<td>0.826</td>
</tr>
<tr>
<td>$Z$ score</td>
<td>−0.316</td>
<td>0.000</td>
<td>$Z$ score</td>
<td>−0.489</td>
</tr>
</tbody>
</table>

**Table 3. Osteoporosis and renal dysfunction in a population occupationally exposed to lead and a control group**

<table>
<thead>
<tr>
<th>Kidney damage</th>
<th>Osteoporosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>9</td>
</tr>
<tr>
<td>−</td>
<td>12</td>
</tr>
</tbody>
</table>

$\chi^2 = 5.841, P = 0.016$

The cut-off points (NAG, 13.783 U g$^{-1}$ Cr; ALB, 12.628 mg g$^{-1}$ Cr) were used for determining kidney damage. For tubular damage, urinary NAG was used. For glomerular damage, urinary ALB was used.

**The values of BMD and BMDL of BPb for different indicators**

According to the methods used by Jin et al. (2004), the dose–response relationships were described
between BPb and the renal dysfunction/bone metabolism indicators and the BMD calculated. The geometric mean concentration of different BPb level (7.08, 14.64, 24.08, 38.32 μg dl⁻¹) was used in the quantal regression model to estimate the value of the BMDL₀·₀₅ for different renal dysfunction and bone metabolism indicators using the EPA program based on Crump’s principle (Crump, 1984). The estimated parameters and corresponding values of BMDL₀·₀₅ are presented in Table 5.

We found that when UNAG is used as an indicator of renal dysfunction, the BMDL₀·₀₅ of BPb is 10.13 μg dl⁻¹, which is lower than the estimated values for Z score (14.17 μg dl⁻¹), indicator of osteoporosis. The BMDL₀·₀₅ of BPb based on BALP, UNAG, BGP, HYP, Z score and UALB increased sequentially. BALP gave the lowest value (8.59 μg dl⁻¹) and UALB gave the highest value (16.57 μg dl⁻¹).

**DISCUSSION AND CONCLUSIONS**

In our study, UPb and BPb were used as the biomarkers of lead exposure and internal dose. Table 1 shows that, UPb and BPb levels in exposure group were higher than those in control group, which indicates that there was a higher internal dose of lead in the exposure group. Thus, occupational exposure to lead could increase the body burden of lead.

Lead is a potential risk factor for osteoporosis because lead could disturb skeleton function. Bone lead storage and release follow the general physiology of bone Ca metabolism (Silbergeld, 1991) and lead is incorporated into the mineral matrix of bone (Wittmers et al., 1988). There are several experimental studies, both in vivo and in vitro, suggesting that lead may affect osteoblast and osteoclast function both directly and indirectly (Pounds et al., 1991; Klein and Wirin, 1993; Puzas et al., 1999; Ronis et al., 2001). However, there are not yet sufficient data to establish the role lead plays in bone growth or development of bone diseases, i.e. decreased bone density, increased risk of fractures or osteoporosis. The three most likely mechanisms for lead-induced osteoporosis are decreased bone mass, increased bone resorption and changes in skeletal structure. It has been found that increased lead exposure is associated with decreased bone density (Escribano et al., 1997; Gruber et al., 1997; Puzas et al., 1999) and decreased bone strength on rats (Ronis et al., 2001). In present study, the results showed that the prevalence of osteoporosis increased significantly following lead exposure. It might be concluded that lead exposure could accelerate bone loss with aging and cause osteoporosis. Because there are many factors in human body affecting bone metabolism, the compensation effect inside human body makes it less obvious the bone damage resulting from low-level lead exposure. With the increase of lead exposure, the bone damage induced by lead will occur. Compared with BPb, UPb has a more closed relationship with osteoporosis. The reason is probably that osteoporosis usually happens after chronic low-level exposure to lead.

Serum osteocalcin (BGP) and alkaline phosphatase (bone isoenzyme) (BALP) are the two most commonly used biomarkers of bone formation, and urine HYP is the biomarker of bone reabsorption (Xiao, 2004). Previous studies have shown that low levels of Pb²⁺ can displace Ca²⁺ from osteocalcin and lead was shown to have a much higher affinity for osteocalcin than that of Ca²⁺. Lead can inhibit the binding of osteocalcin to hydroxyapatite and inactivate osteocalcin. Hence, the bone calcification process was affected (Dowd et al., 2001). The osteocalcin level in serum correlates positively with that in bone. Studies have shown that long-time high-level

Table 4. Stratum analysis of glomerular damage in kidney and osteoporosis

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Tubular damage</th>
<th>With glomerular damage</th>
<th>Without glomerular damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>19</td>
<td>140</td>
</tr>
</tbody>
</table>

χ² (total) = 9.977, P = 0.000
χ² (glomerular) = 1.681, P = 0.195
χ² (tubular) = 8.296, P = 0.004

Table 5. BMDL estimates of BPb (μg dl⁻¹) for renal dysfunction/bone metabolism indicators

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>b0</th>
<th>b1</th>
<th>BMD</th>
<th>BMDL₀·₀₅</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BALP</td>
<td>191</td>
<td>-2.995</td>
<td>0.069</td>
<td>10.75</td>
<td>8.59</td>
<td>4.14</td>
<td>0.126</td>
</tr>
<tr>
<td>NAG</td>
<td>191</td>
<td>-3.567</td>
<td>0.087</td>
<td>12.24</td>
<td>10.13</td>
<td>0.37</td>
<td>0.833</td>
</tr>
<tr>
<td>BGP</td>
<td>191</td>
<td>-2.843</td>
<td>0.051</td>
<td>13.26</td>
<td>10.56</td>
<td>0.66</td>
<td>0.718</td>
</tr>
<tr>
<td>HYP</td>
<td>191</td>
<td>-3.997</td>
<td>0.098</td>
<td>13.97</td>
<td>10.84</td>
<td>0.61</td>
<td>0.737</td>
</tr>
<tr>
<td>Z score</td>
<td>191</td>
<td>-3.394</td>
<td>0.053</td>
<td>18.04</td>
<td>14.17</td>
<td>0.64</td>
<td>0.727</td>
</tr>
<tr>
<td>ALB</td>
<td>191</td>
<td>-3.979</td>
<td>0.068</td>
<td>19.94</td>
<td>16.57</td>
<td>1.59</td>
<td>0.451</td>
</tr>
</tbody>
</table>

Model: ln(P/1 – P) = b0 + b1 × dose. Excess risk at BMD is 0.05. P-values were obtained from the chi-square test, with the Pearson goodness-of-fit test; if P > 0.05, then the equation is a good fit.
lead exposure increases the excretion of HYP in urine. Lead increases the resolving speed of bone collagen. With the lead exposure time increasing, lead accumulated in bone increases and the resolving of collagen increases. In this study, it has been showed that the bone metabolism indexes (BALP, BGP, HYP) would increase significantly with the increase of lead exposure. We can conclude that lead exposure could accelerate the bone formation and bone reabsorption. Hence, bone loss and osteoporosis could happen in the lead-exposed population.

Information about renal dysfunction and lead exposure has been reported (Hong et al., 1980; Benett, 1985; Batuman, 1993), including interstitial fibrosis, tubular atrophy and decreased glomerular filtration, as well as its irreversible and asymptomatic evolution as a consequence of the exposure (Nolan and Shaikh, 1985; Batuman, 1993), including interstitial fibrosis, albuminuria, and glomerular damage. Some ALB excretion results from decreased tubular reabsorption. NAG and ALB would increase significantly following lead exposure. In the present study, it has been shown that nine of 21 subjects with osteoporosis suffered from kidney damage and there was a significant difference in the prevalence of renal dysfunction compared with those without osteoporosis. The measurement of urinary parameters might be an indication that the bone effects are a risk. It has also been found that renal tubular dysfunction might play a more important role than glomerular dysfunction in osteoporosis induced by lead.

This study documents the dose–response relationship between lead exposure (BPb, UPb) and both osteoporosis and bone metabolism, as well as between lead exposure and indicators of renal dysfunction. The BMDS procedure was used to quantitatively calculate the lower confidence limit of the BMD (BMDL-05) of BPb for a 5% level of risk above the background level based on occupational population data. Recently, Gaylor et al. (1998) have redefined the BMD as the point estimate of the dose corresponding to a specified low level of risk and suggested that the concept of BMDL could be used as a replacement for the no observed adverse effect level or lowest observed adverse effect level. The BMDL is typically calculated using the lower 95% confidence limit on the dose–response curve to a 1–10% level if risk above the background. In the present study, we used this procedure like in a previous study (Jin et al., 2004). Our results showed that the BMDL-05 of BPb based on BALP, UNAG, BGP, HYP, Z score and UALB increased sequentially. Surprisingly in the study, it was found that the BMDL value for UNAG (10.13 µg dl\(^{-1}\)) was lower than the BMDL value for Z score (14.17 µg dl\(^{-1}\)). These results suggest that lead-induced renal dysfunction might appear earlier than osteoporosis. BALP gave the lowest BMDL value (8.59 µg dl\(^{-1}\)). It suggests that the serum BALP could be regarded as a sensitive biomarker of bone metabolism. The BMDL for UALB was highest (16.57 µg dl\(^{-1}\)), which could be concluded that renal glomerular dysfunction was later than tubular dysfunction, and might play a smaller role than tubular dysfunction in the causation of bone damage.

In conclusion, this study showed that the occupational lead exposure could cause osteoporosis and renal dysfunction and might affect bone metabolism. There was a dose–response relationship between lead exposure and prevalence of osteoporosis, renal dysfunction and bone metabolism. The renal dysfunction might develop earlier than osteoporosis. Osteoporosis caused by lead was related to renal dysfunction and the change of bone metabolism. With respect to renal dysfunction, osteoporosis was especially related to tubular damage but not to glomerular damage.

FUNDING

This study was funded by the European Commission PHIME program, no. 016253 (Food).

REFERENCES


Franklin CA, Inskip MJ, Baccanale CL et al. (1997) Use of sequentially administered stable lead isotopes to investigate...


