Vibration perception thresholds in workers with long term exposure to lead

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Accepted 2 May 2000

Abstract

***Objectives*—To evaluate the impact of long term occupational exposure to lead on function of the peripheral nervous system as reflected by vibration perception threshold (VPT), measured with a portable vibrameter.**

***Methods*—217 Workers in a lead battery factory were required to have an annual blood lead measurement during each of the 5 years preceding this study. All were invited to take the VPT test. A total of 206 workers were studied. The associations were analysed between VPTs and current blood lead concentration, mean concentration of blood lead over the past 5 years, maximum blood lead concentration during the past 5 years, index of cumulative blood lead (ICL), time weighted index of cumulative blood lead (TWICL), and percentage of lifespan spent at work in the plant, as well as the other potential confounders. Ordinary multiple regressions, generalised additive models, and hockey stick regression analyses were used to explore the potential existence of a threshold effect of blood lead variables on VPT.**

***Results*—VPT at a frequency of 220 Hz ranged from 6 to 100 (10^{-2} *g*, or 0.098 m/s^2) with a mean (SD) of 19.8 (14.2) for the feet and from 4 to 43 with a mean (SD) of 10.2 (6.1) for the hands. The five variables of exposure to lead were all significantly correlated with VPT of the feet but not the hands. In multiple linear regression analyses, the mean of the blood lead concentrations and the TWICL were significantly associated with VPT of the feet. The relation between VPT of the feet and mean blood lead was shown to be a J shaped curve with a generalised additive model and local smoothing technique. In the hockey stick regression, evidence was found of a threshold effect at a mean blood lead concentration of 31 µg/dl. Above this threshold it was estimated that each increase of 1 µg/dl mean blood lead over 5 years would increase VPT of the feet by 0.29 (10^{-2} *g*) or 0.028 m/s^2 (at a frequency of 220 Hz) with other potential confounders held constant.**

***Conclusion*—This study suggests that measurement of vibration sensory threshold is a relatively effective tool for detecting lead neuropathy in field studies, and that lead might cause sensory neuropathy with an effect threshold corresponding to a 5 year mean blood lead concentration of 31 µg/dl.**

(*Occup Environ Med* 2000;**57**:588–594)

Keywords: blood lead; neuropathy; vibration perception threshold

The peripheral nervous system is one of the target organs in lead intoxication. Evidence of lead induced subclinical neuropathy based on nerve conduction velocity and electromyography has been published since the 1970s. In 1975, Seppalainen *et al* studied a group of workers with blood lead concentrations below 70 µg/dl and found electromyographic abnormalities and a reduction of nerve conduction velocity in the median and ulnar nerves.[1] The dose of lead associated with impairment of nerve conduction velocity and electromyography tended to decrease in subsequent studies. In 1976, Araki and Honma reported that the maximal motor nerve conduction velocity of the median and posterior tibia nerves was significantly delayed among lead workers with a blood lead range of 29–73 µg/dl (mean 45).[2] In a prospective study of 24 workers who were followed up for 1–2 years, Seppalainen and Hernberg reported asymptomatic impairment of nerve conduction velocity in a subgroup of workers with blood lead concentrations exceeding 30 µg/dl.[3] Other studies had also reported a decrease of nerve conduction velocity in workers with blood lead concentrations less than 50 µg/dl.[4–6] However, Nielsen *et al* and Triebig *et al* did not find an association between blood lead concentration and nerve conduction velocity among workers with blood lead concentrations over 70 µg/dl.[7 8]

One explanation for the contrasting results may be differences in study design and measurement devices. Also, most of the studies used current blood lead concentrations as the only biomarker of exposure, which may have obscured an effect related to chronic exposure. For lead to be toxic to the nervous system, chronic exposure to low concentrations of lead and cumulative doses may be an important issue. For example, with time weighted average (TWA) blood lead concentrations better correlation with nerve conduction velocity was found than with current blood lead concentrations.[8] In a recent study, Chia *et al* found a dose-response relation between nerve conduction velocity and cumulative blood lead concentration.[9] Similarly, in a study of asymptomatic lead workers who had blood lead concentrations from 17.4 to 58 µg/dl, Yeh *et al* found a linear correlation between nerve conduction velocity and an index of cumulative exposure to lead, which was calculated by a time integrated method.[10] These studies all found a more important relation between peripheral nerve changes to indices of chronic exposure to lead rather than to current blood lead concentrations.

A factor limiting the routine use of nerve conduction velocity and electromyographic tests in studies of lead toxicity is that they usually cause some discomfort and few of the instruments are portable to perform examinations in the field. Few studies have used these devices in field screening. Vibration perception threshold (VPT) instruments, however, have been used in field studies because they are painless, non-invasive, and easy to carry to the field. Vibration perception is conducted by fast or large diameter nerve fibres. It has been suggested that fast nerve fibres are sensitive to chronic exposure to lead.[11] However, in 1982, a study found no relation between VPT and current blood lead concentration,[7] perhaps because of the sensitivity of the device[12] and use of current blood lead concentration as an exposure index. Recently, the enhanced design of VPT devices (for example, the stability of the vibration head) has improved their sensitivity; and these devices are now applied in the field of occupational medicine.[13] Thus, VPT measurement of lead workers could be performed as a screening test for identifying people who need to be examined further by nerve conduction velocity and electromyography.

The aim of this study was to assess the relation between exposure to lead and peripheral nerve function, with repeated measurements of blood lead over a period of 5 years to construct indices of chronic exposure to lead and VPTs measured with a simple field device to signify peripheral nerve function.

Materials and methods

SUBJECTS

The current study was carried out in a lead battery factory, where workers were monitored from 1990 and 5 years thereafter with annual health examinations. To investigate the effects of cumulative exposure to lead, the study recruited workers who had entered the plant before or during 1991—that is, only workers who had worked in the plant for at least 5 years were included in the study. Among the 217 workers who met this criterion, 206 agreed to take the VPT test in 1995. None of the 206 workers had ever been exposed to organic solvents or had a history of head or nerve injuries or major neurological diseases (such as seizures or multiple sclerosis).

MEASUREMENT OF BLOOD LEAD

At each annual health examination, we collected venous blood samples by standard procedures. Each worker first washed his or her forearms with soap and fresh water. The antecubital area was then cleaned with 70% ethanol and cotton balls (no wipe package was used to avoid foil containing lead); and a 5 ml whole blood sample was collected (by venepuncture) in a lead free vacuum tube (Monoject, Sherwood Medical) containing ethylenediamine tetracetic acid (EDTA) as the anticoagulant. After pretreatment with a 1:4 solution of 0.1% Triton X 100 (Merck, scintillation grade) and 1.25% ammonium dihydrogen phosphate (Merck, puratronic grade) in a class 100 hood to which air was supplied and cleaned by a high efficiency particulate filter, the blood samples were analysed by Zeeman effect graphite furnace atomic absorption spectrometry (GF-AAS, Perkin-Elmer 5100 PC with AS 60 autosampler), with intralaboratory quality controls. With use of commercial standard materials (Betherning Institute, Bio-Rad), all coefficients of variation were less than 3% for measurements at high concentrations (70.5–82.7 µg/dl) and medium concentrations (37.1–45.3 µg/dl) and less than 5% for those at low concentrations (5.6–8.9 µg/dl) during these 5 years. Since 1985, the laboratory at the Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, has been participating in the blood lead proficiency testing programme between laboratories supervised by the US Centers for Disease Control and Prevention; the results of our measurements were all within the specified reference ranges, an indication that our blood lead measurements are relatively accurate.

EXPOSURE TO LEAD VARIABLES

Six indices of exposure to lead were developed for each worker.

(1) Current blood lead concentration measured at the time of the VPT test.

(2) The maximum blood lead concentration in the past 5 years.

(3) Mean concentrations of blood lead in the past 5 years 1991–5.

(4) Percentage of lifespan spent in the factory, which was calculated by dividing years in the factory by age (this variable was used instead of years at the factory to signify duration of exposure to minimise collinearity with age).

(5) Index of cumulative blood lead (ICL), calculated by integrating blood lead concentrations over each worker's employment time by the trapezoidal rule[14]:

$$ICL=\int PbB_t \cdot \Delta t=\sum 0.5(PbB_i + PbB_{i+1})\Delta t_i$$

expressed in (µg/dl)×year

Here PbB_i and PbB_{i+1} represent the *i*th and (*i*+1)th measurements of blood lead, taken Δt years apart.

(6) Time weighted index of cumulative blood lead (TWICL), calculated by dividing ICL by the summation of employment time[15]:

$$TWICL=\{\sum 0.5(PbB_i+PbB_{i+1})\Delta t_i\}/\sum \Delta t_i$$

For indices (5) and (6), reliable measurements of blood lead began in 1991. Workers with no existing records of blood lead concentrations before 1990 were assigned a value of 15 µg/dl from birth to the date of hire, a figure based on the mean concentration of blood lead in a population survey of Taiwan, 1984.[16] For each worker who started employment before 1991, the value of the first blood lead measured by our laboratory (usually in 1991) was assumed to be representative of the blood lead concentrations from 3 months after the date of first employment until the date of the first blood lead measurement. We assumed that blood lead concentrations had gradually increased to this value from the date of employment. In fact, the industrial hygiene of the plant had changed little until we intervened in 1990[17]; thus, before 1991, blood lead concentrations of workers in this plant could be rationally assumed to have reached equilibrium, similar to the first measurement in our laboratory.

OTHER LABORATORY TESTS

Serum alanine transaminase for liver function screen, serum creatinine, fasting blood glucose, urinary protein and sugar, and complete blood counts were assessed during annual health examinations. Specimens taken on the examination day were immediately transported to the central laboratory of Provincial Tao-Yuan General Hospital for analyses. Workers with abnormal laboratory data, including haemoglobin less than 12 mg/dl for women or 14 mg/dl for men, serum creatinine greater than 2.0 mg/dl, urinary protein strongly positive (+++), serum alanine transaminase greater than 35 IU/l, urinary sugar positive, or fasting glucose more than 140 mg/dl, were further examined in the out patient department of Provincial Tao-Yuan General Hospital. If a worker was diagnosed with abnormal renal or liver function or with diabetes or major neurological diseases, he or she was not included in the present data analysis.

VIBRATION PERCEPTION THRESHOLD TEST

The VPT was measured with a vibrameter (Technoque, Tokyo, Japan) with the frequency of vibration fixed at 220 Hz and the unit of measurement one-hundredth gravity (10^{-2} *g*, or 0.098 m/s^2). The intensity of stimulation ranged from 0 (minimum) to 999 (maximum). Two sites, the distal phalanx of the left index finger and the left big toe, were tested for each worker. A standard protocol was used called "method of limits yes-no procedure" which shows an acceptable measure of reproducibility and validity.[18] During the test, a practice trial was given to ensure that each worker understood the test. Stimuli were then increased gradually from the minimum until each worker reported feeling a vibrating sensation, and the score of intensity unit was recorded. The mean of three tests for a site represented the VPT value of the site. Room temperatures were always kept above 27°C. All workers were tested by the same technician trained in neurological examination. This method had been successfully applied in a study of workers with exposure to styrene in Taiwan.[19]

QUESTIONNAIRE

A short questionnaire on job, medical history, and working history, history of nerve disorders and limb injuries, and alcohol and cigarette consumption was administered before the annual health examination. The workers reported the frequency of smoking and drinking per week during the past 3 months; and the questionnaire was reviewed and checked for completeness by an occupational physician when the annual health examination was performed. Although none of the workers ever used portable vibration tools—such as a hand carried electric saw—at work, some occasionally cut lead plates with static electric saws fixed on the work tables. In the questionnaire, each worker was asked whether such vibration tools were used at work. The use of vibration tools was coded as a binomial variable (yes *v* no) to model its effect on our analysis. None of the workers ever used vibration tools involving their feet. Alcohol consumption estimated as absolute alcohol ingestion (g) was calculated by a semiquantitative method that was the product of drinking frequency (per week), volume, and the percentage of alcohol consumed from the drink. Subjects were categorised as: non-drinker, less than 100 g (about 3.5 oz) a week, moderate drinker, 101 to 200 g (about 7.0 oz) a week, and heavy drinker, greater than 200 g a week.

DATA ANALYSIS

Because in the initial analysis of the distribution of the outcome variables, hand and foot vibration perception thresholds were both skewed to the right, natural log transformation of these two outcome variables was performed. After transformation, the variables were normally distributed. Mean (SD) were used to present continuous variables, including age, body height, work duration, and blood lead variables. Blood lead concentrations in each year were normally distributed. In bivariate analyses, Student's *t* test was used to compare continuous variables, and a χ^2 test was used for testing categorical variables.

Pearson correlation was used to present the relation between vibration perception thresholds and lead variables, work duration, height, and age. Multiple linear regression analyses were performed to find the association between VPT and variables of exposure to lead, including blood lead variables and percentage of lifespan in the work, as well as potential confounders, including age, sex, height, smoking, alcohol consumption, and handling vibration tools. The statistical software package, SAS 6.12,[20] was used in the data analysis.

As well as the multiple regression analyses, generalised additive models and scatter plots, adjusted with other confounders, were used to examine the curved shape of the relation between VPTs (natural log transformed) and lead variables.[21–23] The aim of these techniques is to look for a dose-response curve and identify whether a threshold effect is present. Because the extrapolation of first available blood lead concentration was used in the calculation of ICL and TWICL, ICL, and TWICL were discarded, and mean concentration of blood lead was used as the only lead variable in the dose-response curved analysis. The computer software package S-Plus 4.5 was used in the analysis.[24] Once a threshold was identified by visual inspection of the fitted curve, "hockey stick" regression analysis was applied to the

Table 1 Characteristics of workers with long term exposure to lead

Characters	*Participants n (%) or mean (SD)*	*Non-participants n (%) or mean (SD)*
Number	206	11
Male workers	100 (48.5%)	4 (36.4%)
Smoking:		
Non-smokers	134 (65.1%)	7 (63.6%)
Smokers	56 (27.2%)	4 (36.4%)
Ex-smokers	16 (7.8%)	0
Use of vibration tool (yes *v* no)	12 (5.8%)	0
Age (y)	40.5 (7.1)	33.0 (7.3)
Working duration (years)	12.6 (6.6)	8.2 (7.0)
Life span in the work (%)	31.0 (14.4)	26.0 (25.7)
Height (cm)	158.7 (8.4)	158.2 (8.1)
Current PbB (μg/dl)	28.3 (12.7)	22.5 (14.7)
Max PbB (μg/dl)	39.2 (14.5)	32.4 (16.5)
Mean of PbB (μg/dl)	31.8 (12.4)	24.1 (12.2)
TWICL (μg/dl)	32.4 (12.5)	24.0 (11.1)
ICL (year*μg/dl)	425.5 (320.0)	189.5 (54.2)
VPT on hands (10^{-2} g)	10.2 (6.1)	—
VPT on feet (10^{-2} g)	19.8 (14.19)	—
Alcohol consumption (g/week):		
1–100	10 (4.9%)	—
101–200	13 (6.3%)	—
>200	4 (1.9%)	—

p Values from χ^2 test for categorical variables and *t* test for continuous variables.
PbB=blood lead concentration; Max PbB=the maximum of the blood lead concentrations in the 5 years; TWICL=time weighted index of cumulative exposure to lead; ICL=index of cumulative lead exposure; VPT=vibratory perception threshold.

data. In general, a hockey stick regression uses two different curves to fit two regions of a data set[25 26]:

For some lead variable x_0 (cut off point or threshold),

$$VPT=\beta_0+\text{covariates for } x\leqslant x_0,$$
$$=\beta_0+\beta_1(x-x_0)+\text{covariates for } x>x_0$$

In this study, the lower portion of a hockey stick signifying blood lead concentrations below the cut off point or threshold was assumed to have no relation to VPT, whereas a linear relation was assumed for the concentrations above the joint point.

Results

The total number of workers with more than 5 working years at the plant was 217; 206 (94.9%) of whom participated in the nerve examination in 1995. Characteristics of participants and non-participants are shown in table 1. The 11 non-participants were younger, had worked for fewer years, and had lower mean blood lead concentration, ICL, and TWICL. Of the 217 workers, about 35% (64 male and 12 female workers) were current or former smokers. This percentage is similar to the adult smoking rate in Taiwan.[27] Rate of alcohol consumption is low in Taiwanese Chinese[28] In our study population, about 13% of workers (20 male and seven female workers) had an absolute alcohol ingestion of more than 100 g a week by semi-quantitative calculation.

Table 2 gives the matrix of Pearson correlation coefficients and p values. The five variables of exposure to lead were all significantly correlated with foot VPT, whereas none was correlated with hand VPT. Both of the VPTs were significantly correlated with age. Age and working duration were significantly correlated with each other (r=0.405, p<0.001); however, percentage of lifespan in this work (worklife) was not correlated with age, but highly correlated with work duration. Thus, we used worklife as the variable of working duration in the next step of analysis. Mean concentration of blood lead, TWICL, and maximum concentration of blood lead was closely correlated with the other variables. Because the calculation of TWICL adopted some assumption, the values were close to mean concentration of blood lead. Also, due to the tendency of blood lead concentrations to decline during the 5 years, mean concentration of blood lead and TWICL were closer to maximum concentration of blood lead than to the current blood lead concentration.

Multiple linear regression analyses (table 3) showed that no blood lead variable was significantly associated with hand VPT, after adjustment for potential confounders. Worklife was negatively associated with hand VPT (model 6); age was positively related to hand VPT in every model. Adjusted potential confounders, including sex, body height, smoking, alcohol consumption, and use of hand vibration tools, were non-significant and changed little in the varying models; thus, the coefficients were omitted from the table. Table 4 shows the relation between foot VPT and variables of exposure to lead. Mean blood lead concentration (model 3) and TWICL (model 5) were significantly associated with foot VPT, whereas current blood lead concentration, maximum blood lead concentration in the 5 years, and ICL were not significant in models 1, 2, and 4, respectively. In these multiple regression analyses, age always had the most significant correlation with VPT, with older people having higher thresholds. Similarly, insignificant potential confounders were omitted from the table.

Scatter plots with local smoothing techniques for foot VPT versus mean concentration of blood lead, after adjustment of potential confounders by generalised additive models,

Table 2 Correlation coefficient matrix of lead parameters, body height, work duration, life span in the work (%), and VPTs on hands and feet (natural log transformed) in a group of workers exposed to lead long term

	TWICL	*Mean PbB*	*Max PbB*	*Current PbB*	*Height*	*Age*	*Duration*	*Worklife*	*LNHD*	*LNFT*
ICL	0.69**	0.63**	0.57**	0.51**	0.13	0.32**	0.79**	0.74**	−0.02	0.16*
TWICL		0.97**	0.92**	0.76**	0.14*	0.06	0.19**	0.18**	0.06	0.21**
Mean PbB			0.95**	0.86**	0.16*	0.05	0.15*	0.14*	0.07	0.21**
Max PbB				0.77**	0.15*	0.04	0.12	0.10	0.08	0.19**
Current PbB					0.20**	−0.01	0.13	0.13	0.01	0.15*
Height						−0.11	0.11	0.16*	−0.10	0.11
Age							0.41**	0.09	0.26**	0.33**
Duration								0.94**	−0.08	0.08
Worklife									−0.17*	−0.01
LNHD										0.47**

* p<0.05; ** p<0.01.
Worklife=life span in work (%); LNHD and LNFT=natural log transformed values of VPT on hands and feet, respectively.

Table 3 Multiple regression analyses for the association of hand VPT (natural log transformed) with lead exposure indices and potential confounders in a group of workers exposed to lead long term (all models were adjusted for sex, body height, smoking, alcohol, and use of hand vibration tools)

Independent variables	Model 1 β (SE)	Model 2 β (SE)	Model 3 β (SE)	Model 4 β (SE)	Model 5 β (SE)	Model 6 β (SE)
Current PbB (μg/dl)	0.0020 (0.0029)					
Max PbB (μg/dl)		0.0035 (0.0026)				
Mean PbB (μg/dl)			0.0036 (0.0032)			
ICL (year*μg/dl)				−0.0001 (0.0001)		
TWICL (μg/dl)					0.0029 (0.0032)	
Life span in the work (%)						−0.5375 (0.2460)*
Age (y)	0.0189 (0.0048)**	0.0184 (0.0048)**	0.0186 (0.0048)**	0.0207 (0.0051)**	0.0186 (0.0048)**	0.0192 (0.0048)**

* p<0.05; ** p<0.01.
β=Regression coefficients (SEs).

Table 4 Multiple regression analyses for the association of foot VPT (natural log transformed) with lead exposure indices and potential confounders in a group of workers exposed to lead long term (all models were adjusted for sex, body height, smoking, and alcohol)

Independent variables	Model 1 β (SE)	Model 2 β (SE)	Model 3 β (SE)	Model 4 β (SE)	Model 5 β (SE)	Model 6 β (SE)
Current PbB (μg/dl)	0.0047 (0.0033)					
Max PbB (μg/dl)		0.0053 (0.0029)				
Mean PbB (μg/dl)			0.0074 (0.0035)*			
ICL (year*μg/dl)				−0.0001 (0.0001)		
TWICL (μg/dl)					0.0099 (0.0047)*	
Life span in the work (%)						−0.3742 (0.2746)
Age (y)	0.0275 (0.0054)**	0.0271 (0.0054)**	0.0270 (0.0054)**	0.0283 (0.0057)**	0.0280 (0.0054)**	0.0279 (0.0054)**

* p<0.05; ** p<0.01.
β=regression coefficients (SE).

are presented in figure 1. We found a J shaped curve of foot VPT versus mean blood lead with an inflection point around 30 μg/dl. Above the point, a positive linear relation between foot VPT and mean blood lead was noted. Thus, a potential threshold effect was identified.

Figure 2 shows a hockey stick regression curve with an inflection point at a mean concentration of blood lead of 31 μg/dl. The inflection point was determined by iterative hockey stick regression models (table 5). We used model R^2 value and Akaike information criterion that has an expected value close to the SSE/n (mean of the sum of error squared) to select the optimal model fitting. Hastie and Tibshirani called Akaike information criterion the predicted error squared, which can be used for both selection of degrees of freedom or model selection in testing hypotheses.[29] A small Akaike information criterion value means small error in the model fitting. The smallest Akaike information criterion was found when we fitted a mean blood lead concentration of 31 μg/dl, which also gave the greatest R^2 value. The hockey stick regression coefficient was 0.0145, which means that an increase of 1 μg/dl of mean blood lead in 5 years will increase foot VPT by 0.29 (10^{-2} *g*) or 0.028 m/s² at the 220 Hz band when mean blood lead is greater than 31 μg/dl, with all potential confounders held constant.

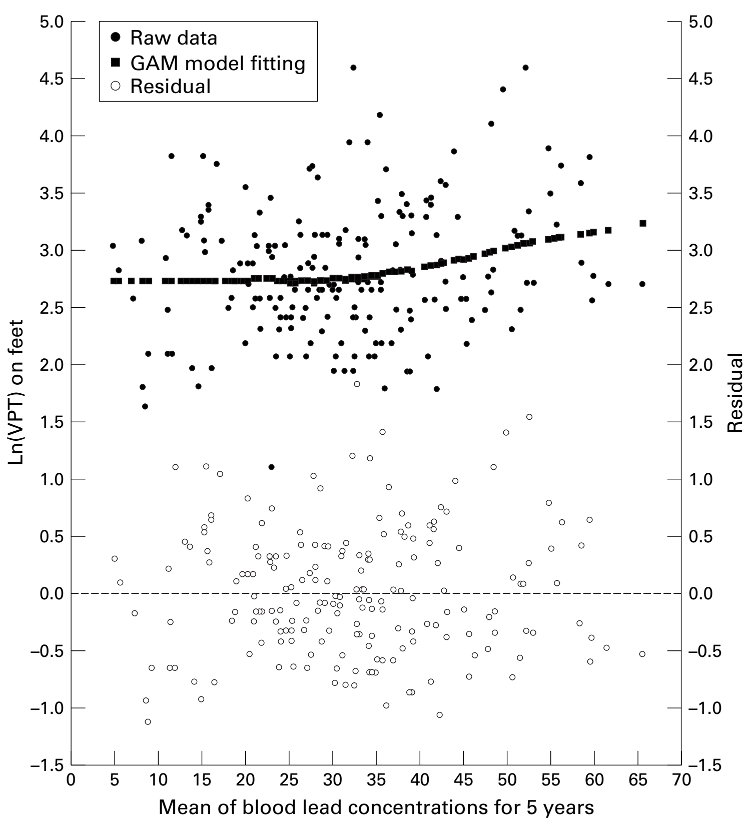

Figure 1 Generalised additive model fitting.

Discussion

Few studies have focused on peripheral nerve toxicity of lead with VPT changes and applied non-linear models in lead neurotoxicity. Our study suggests that measurement of VPT can be an effective tool for detecting lead neuropathy in field studies. The results also showed a potential threshold effect at a 5 year mean blood lead concentration of 31 μg/dl. Similar threshold effects have been found in previous studies. For example, a threshold of 30 μg/dl was found for slowed motor nerve conduction velocity among children[26] and workers.[30] There is evidence that sensory nerve fibres are more sensitive to lead than motor fibres.[11 31] Thus, we suggest the use of a VPT test as a screening tool for workers with moderate to high exposure to lead.

The association of VPT and exposure to lead was studied as early as 1982.[7] That cross sectional study showed no evidence of association between VPT and current blood lead concentrations. Our study also showed no association between VPT and current blood lead concentrations in a population in which the highest blood lead was 69 μg/dl, possibly because of the inability of the current blood

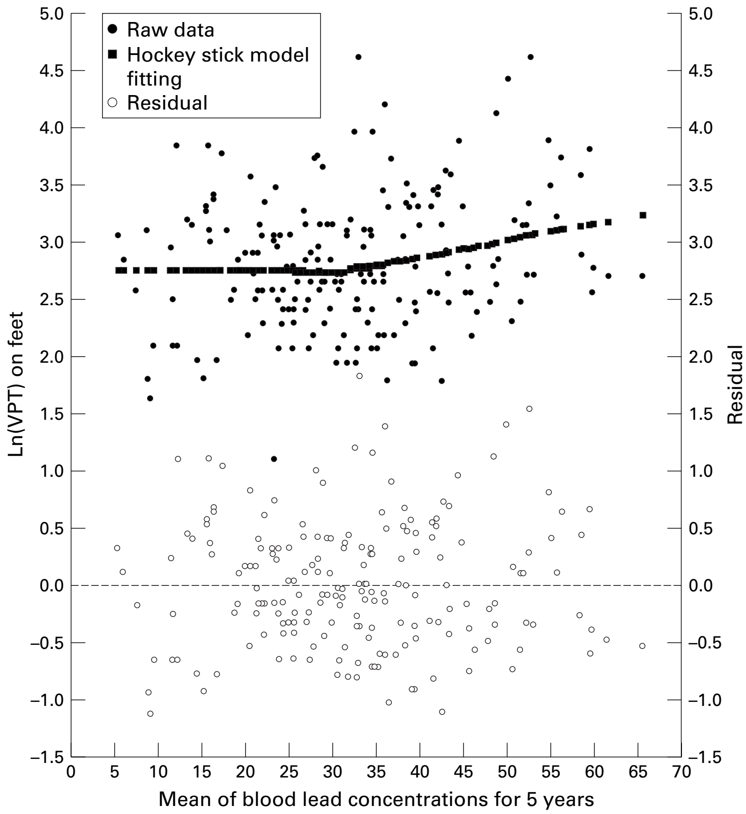

Figure 2 Hockey stick regression fitting.

Table 5 Comparison of different inflection points in hockey stick regression analyses

Mean PbB	*Hockey stick regression coefficient (SE)*	R^2	*AIC**
25	0.0114 (0.0046)	0.1886	55.2946
28	0.0127 (0.0050)	0.1893	55.2476
30	0.0139 (0.0054)	0.1905	55.1672
31	0.0145 (0.0056)	0.1908	55.1471
32	0.0151 (0.0058)	0.1906	55.1569
33	0.0156 (0.0061)	0.1901	55.1896
34	0.0162 (0.0063)	0.1898	55.2153
35	0.0168 (0.0067)	0.1892	55.2506

*AIC=Akaike information criterion.

lead concentrations to represent chronic exposure. Kovala *et al* found that foot VPT was significantly correlated with indicators of long term exposure, including tibial lead and time integrated blood lead (equal to ICL)[12] However, in this study, we found that foot VPT was weakly related to ICL. One of the possible reasons could be that ICL could not differentiate between short term high exposure and long term low exposure. For example, a worker who has worked for 10 years and has an annual blood lead concentration of 20 µg/dl (under the threshold) has the same ICL (200 years×µg/dl) as another who has worked for 5 years and has a blood lead concentration of 40 µg/dl (over the threshold) each year; but the second exposure would carry a higher risk of nerve damage. In this case, it was suggested that TWICL was a better predictor of VPT than ICL, because TWICL could be considered as time adjusted for measurements of exposure to lead over a threshold. Consequently, our study shows that foot VPT was sensitive to TWICL and mean blood lead concentration over the past 5 years.

In our study, the threshold effect was found by mean blood lead concentration over the past 5 years but not by TWICL, probably because of the time gap without available blood lead data in our study (mean work duration was 12 years but we have blood lead data only for the most recent 5 years), which required extrapolation of blood lead at the time of first employment and led to an error in the estimation of TWICL in our study. However, mean blood lead was highly correlated with TWICL, because blood lead was measured annually in Taiwan. For workers with moderate to high blood lead concentrations, especially higher than the threshold of recent 5 year blood lead concentrations (31 µg/dl), VPT would be an appropriate measure to predict lead neuropathy.

The vibrameter used in this study is a simple device with a fixed frequency of 220 Hz. There were some different hardware devices with various reported vibration units, such as decibel (dB), acceleration (*g* or cm/s^2) and log µm of peak to peak. Lack of standardised equipment and reported units may limit comparability. Relatively limited data on sensitivity and specificity of these kinds of devices were available. When compared with electrophysiological measures, VPT (log µm of peak to peak) was reported to have a sensitivity of 86% (under the specificity of 90%).[32] Our study, however, was conducted on workers exposed long term without any overt clinical signs. The sensitivity and specificity of vibrameters to detect subclinical lead neuropathy still need to be established.

Age is an important confounder of the relation between VPT (both hand and foot) and chronic lead neuropathy as reflected by some studies that showed increased VPT with older age.[18] Some studies reported that age had a linear relation with log transformed VPT values.[21] In our study, age was the only significant factor in all models, and the results were similar to the previous studies. The coefficient of age (per year) in our linear regression model 3 (table 4) was 0.027, which is close to the coefficient presented in the paper by Skov *et al* (0.025).[21] However, with adjustment of age and the other potential confounders, we found that lead seemed to have a significant non-linear relation. Workers with mean blood lead greater than the inflection point (31 µg/dl) had a hockey stick regression coefficient about twice as great as the coefficient for the non-hockey stick linear regression (0.0145: 0.0074). In our study, such an effect was apparent on nerves in the legs but not in the arms. A possible reason is that axons from the spinal cord to the toes are longer than those to the fingers and are more vulnerable to a poor surrounding environment—for example, ischaemia, or exposure to lead. A similar finding was reported among diabetic patients in Taiwan, which also showed a significant increase of VPT in the feet with an effect that was more apparent than that in the hands.[33]

In our study, smoking and alcohol consumption were not related to VPT in bivariate and multiple linear regression analyses. Alcohol consumption was reported to significantly increase VPT at 125 Hz.[34] However, studies in Taiwanese workers exposed to styrene[19] or lead (this study) at 220 Hz did not show such an effect, because that study included relatively few moderate to heavy drinkers. In general, the impact of smoking on VPT is equivocal. A VPT of 125 Hz on the fingertip has been significantly correlated with cigarette smoking in a Japanese study[35]; however, this result was a simple correlation and did not adjust for other potential confounders. Another study of workers with vibration induced white fingers found that smoking produced no significant effect.[36] Also, height did not correlate with VPT of the feet in our study, although such a correlation has been shown in the study by Skov *et al*.[21] The effect of height on VPT in that study also resulted in a J shaped curve, with a more apparent effect if height was above 5.8 feet. Workers in our study had a mean height of 5.2 feet (SD=0.27), which is in the range that seemed not positively related to foot VPT in the study of Skov *et al*. Thus, shorter heights and a smaller variation in our study population than those in workers in the United States may contribute to these findings.

In summary, our study suggests that workers with a 5 year mean blood lead concentration more than 30 μg/dl should have their peripheral nerve function examined carefully, including fast sensory nerve fibres. The VPT screening test is non-invasive, painless, and easy to perform in the field, and it has the potential to be developed for occupational physicians to screen for subclinical lead neuropathy at the workplace.

This work was supported by the Department of Health, the Executive Yuan, Taiwan, Republic of China (DOH-87-HR-504). HH was in part supported by the United States National Institute of Environmental Health Sciences Center Grant ES-00002. We thank research assistants Shih-Yuan Chang, Lan-Yin Mu, and Su-Yuan Chen. We also appreciate the cooperation of workers and employers.

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