The Relationship Between Blood Lead Levels and Neurobehavioral Test Performance in NHANES III and Related Occupational Studies

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SYNOPSIS

Objectives. The goals of this study were two-fold: (*1*) to assess the relationship between blood lead levels and neurobehavioral test performance in a nationally representative sample of adults from the third National Health and Nutrition Evaluation Survey and (*2*) to analyze the results from previously published studies of occupational lead exposure that used the same neurobehavioral tests as those included in the survey.

Methods. Regression models were used to test and estimate the relationships between measurements of blood lead and performance on a simple reaction time, a symbol-digit substitution, and a serial digit learning test in adults aged 20–59 years who participated the survey. Mixed models were used to analyze the data from the occupational studies.

Results. The blood lead levels of those participating in the survey ranged from 0.7 to 41.8 µg/dl. The estimated geometric mean was 2.51 µg/dl, and the estimated arithmetic mean was 3.30 µg/dl. In the survey, no statistically significant relationships were found between blood lead concentration and performance on the three neurobehavioral tests when adjusted for covariates. In the occupational studies, the groups exposed to lead consistently performed worse than control groups on the simple reaction time and digit-symbol substitution tests.

Conclusions. The results from the survey and the occupational studies do not provide evidence for impairment of neurobehavioral test performance at levels below 25 µg/dl, the concentration that the Centers for Disease Control and Prevention define as elevated in adults. The average blood lead level of the exposed groups in the occupational studies was 41.07 µg/dl, less than 50 µg/dl, the minimum concentration that the Occupational Safety and Health Administration requires for medical removal from the workplace. Given the evidence of impaired neurobehavioral performance in these groups, the 50 µg/dl limit should be reevaluated.

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Data from the third National Health and Nutrition Examination Survey (NHANES III) have been used to demonstrate that blood lead levels in the population of the United States have declined from 1976 to 1991.[1] The average decline was from 12.8 to 2.8 µg/dl in individuals aged 1–74 years. For children aged 1–5 years, the average decline was from 13.7 to 3.2 µg/dl in non-Hispanic white children and from 20.2 to 5.6 µg/dl in non-Hispanic black children. Steps that have been taken over the past three decades to eliminate common environmental sources of lead contamination, including lead in gasoline, house paint, solder, pottery glaze, and pipes, have dramatically reduced lead levels in the general population.[2]

Data from NHANES III also have been used to determine the relationship between blood lead concentration and the cognitive performance of children aged 6–16 years.[3] Decreases in average performance were found for arithmetic scores (0.7 points per µg/dl), reading scores (1.0 points per µg/dl), nonverbal reasoning (0.1 points per µg/dl), and short-term memory (0.5 points per µg/dl) as the blood lead concentration increased. Decreases in performance were found on all the tests at levels less than 10 µg/dl, and for the arithmetic and reading tests, decreases were found at levels less than 5 µg/dl.

In the present study, NHANES III data were used to assess the relationship between blood lead levels in adults and performance on the three computerized neurobehavioral tests included in the survey: simple reaction time, symbol-digit substitution, and serial digit learning. These tests also were used as components of larger test batteries in studies of individuals occupationally exposed to lead (e.g., workers in battery manufacturing plants and secondary lead smelters). The results of previously published occupational studies using these three tests also were analyzed and compared with the survey results.

METHODS

Subjects

The subjects in NHANES III were civilian, non-institutionalized individuals in the United States who were aged 2 months or older. The survey was conducted from 1988 through 1994. Approximately 40,000 individuals were selected to participate in the survey. Of these, 5,662 adults aged 20–59 years were selected to take the neurobehavioral tests, of which 4,937 (87.2%) completed all three tests.

Sampling

The sample design was a stratified, multistage probability design. In the first stage of sampling, 81 primary sampling units (PSUs) were selected. The PSUs were individual counties or adjacent counties. Thirteen of the largest PSUs were divided into 21 survey locations and the remaining 68 PSUs had one survey location. The 89 survey locations or *stands* were randomly divided into two phases. Phase I consisted of 44 locations visited from 1988 through early 1991. Phase II consisted of 45 locations visited from late 1991 through 1994. Later stages of sampling included selecting area segments within PSUs, households within area segments, and sample individuals within households. The subjects selected for neurobehavioral testing were individuals aged 20–59 years who had an exam at their stand's mobile examination center and had an odd-numbered survey identification number.

Blood lead

Venous blood samples were taken at mobile examination centers or during home examinations given to individuals who could not go to mobile examination centers. Blood lead was measured by atomic absorption spectrometry. The limit of detection for the blood lead measurements was 1 µg/dl. Values below the limit of detection were assigned a value of 1 µg/dl divided by the square root of two. More information about the blood samples, blood lead measurements, and the rest of the survey can be found in the NHANES III documentation and data.[4–6]

Neurobehavioral tests

The three tests that were administered are components of the Neurobehavioral Evaluation System 2.[7] The methods used for collecting the neurobehavioral data have been described in more detail previously.[8]

Simple reaction time. For this test, subjects pressed a button whenever a solid square was displayed in the center of the computer screen. A total of 50 trials were administered to each subject. The mean reaction time of trials 11 through 50 was calculated in milliseconds (ms). Values less than or equal to 50 ms or greater than or equal to 750 ms were considered outliers and were not included in the calculation. Subjects were usually administered 50 trials using their preferred hand; however, some subjects were administered 30 trials with their preferred hand and 20 trails with their non-preferred hand. The simple reaction time data for these subjects was not included in the statistical analyses.

Symbol-digit substitution. During this test, subjects were presented with a grid that paired one of nine different symbols with one of the digits from one to nine. This grid appeared on the upper half of the computer screen. A similar grid was displayed on the bottom half of the screen; however, the same symbols were presented in a scrambled order and the spaces for the corresponding digits were left blank. Subjects entered the matching digit for each symbol. Five trials were conducted with a different pairing of digits and symbols for each trial. The first trial was a practice trial. The mean total latency of the four test trials was calculated in seconds (s). The total latency for each trial did not include the time it took to respond to the first item. The number of errors that occurred during the four test trials on items two through nine was also calculated.

Serial digit learning. For this final test, subjects were presented with a series of digits that were displayed one at a time on the computer screen. After all the digits were displayed, subjects entered the sequence of numbers in the order in which they were presented using the numeric keys on the keyboard. The first trial was a practice trial consisting of four digits. All subsequent trials contained the same eight-digit sequence. Testing continued until the subject responded correctly on two consecutive trials or until the subject attempted eight trials. The number of trials to reach the criterion was recorded. If the subject did not reach the criterion by trial eight, the number of trials was scored as an eight.

The total score was also calculated. This score represented the sum of the error scores for each trial. When a subject's response had fewer than six of the eight digits in the correct position, two points were added to the score. One point was added when either six or seven digits were in the correct position, and zero points were added when all eight digits were reported correctly.

Occupational studies

Many studies have investigated the effects of occupational exposure to lead using the three neurobehavioral tests included in NHANES III. The data from NHANES III are from a large, nationally representative sample. The occupational studies summarized in Table 5 were smaller, cross-sectional, and usually had control and exposed groups. Age, sex, and education were usually accounted for by adjustment, matching, or similarity. The subjects in these studies tended to be working age, working class, male, with a high school education or less. The occupational studies were conducted in various countries, including Australia, Canada, China, Finland, Italy, Japan, the United States, the Republic of Korea, Singapore, Sweden, and Venezuela. In these occupational studies, a whole battery of tests, such as the World Health Organization Neurobehavioral Core Test Battery, was usually given.[9] Due to time constraints, only three tests were administered in NHANES III. The methods of many of the occupational studies made reference to here have been reviewed previously.[10,11]

Statistical analysis

The computer programs SAS and SUDAAN were used to analyze the survey data.[12,13] The appropriate sample weights were used to take into account the probability of selection, non-coverage, and non-response. Design effects (DEFF) are included in the Tables because of the complex sample design. A *design effect* is the ratio of the variance of an estimate from a complex sample to the variance from a simple random sample.

Descriptive statistics were calculated, and regression analyses were performed between measures of neurobehavioral test performance and the log of the blood lead concentrations both unadjusted and adjusted for sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. All the covariates were classification variables except age, which was continuous.

Mixed linear models were used to analyze data from the occupational studies. Study was a random variable. The log of the blood lead level or a classification variable for exposure status also was included as a fixed effect.

S-PLUS was used to make the graphs. Simple linear least squares regression was used to smooth the data.[14]

RESULTS

NHANES III

The blood lead concentrations of the individuals taking the neurobehavioral tests in NHANES III ranged from 0.7 to 41.8 µg/dl. The estimated geometric mean of the concentrations was 2.51 µg/dl, and the estimated arithmetic mean was 3.30 µg/dl.

Average test performance as a function of blood lead intervals is shown in Table 1. Scatter plots of the mean reaction time from the simple reaction time test and the

Table 1. Blood lead and unadjusted test performance from NHANES III by blood lead intervals, *N*=5,662

Test Variable	*Blood lead interval (µg/dl)*	n[b]	*M*	*SE*	*DEFF*
Blood lead (µg/dl)	0.7[a]	568	0.70	0.00	9.52
	[1, 5)	3,688	2.57	0.04	5.41
	[5, 10)	979	6.75	0.05	1.34
	[10, 15)	148	11.79	0.15	2.49
	[15, 25)	49	18.76	1.07	4.88
	[25, 42)	11	31.77	2.02	1.34
Simple reaction time					
Mean reaction time (ms)	0.7[a]	528	238.30	3.34	2.30
	[1, 5)	3,249	232.76	1.30	2.78
	[5, 10)	793	233.41	3.74	3.56
	[10, 15)	121	220.06	4.14	1.51
	[15, 25)	39	249.71	8.17	0.63
	[25, 42)	11	243.17	23.61	1.00
Symbol-digit substitution					
Mean total latency (s)	0.7[a]	538	20.55	0.42	2.32
	[1, 5)	3,355	22.41	0.19	2.77
	[5, 10)	851	25.49	0.42	2.27
	[10, 15)	130	25.95	0.96	1.92
	[15, 25)	40	31.60	2.39	0.90
	[25, 42)	11	24.13	1.67	0.84
Number of errors	0.7[a]	538	1.09	0.17	3.10
	[1, 5)	3,355	1.13	0.06	2.67
	[5, 10)	851	1.43	0.11	1.63
	[10, 15)	130	1.35	0.25	1.70
	[15, 25)	40	2.44	0.40	0.65
	[25, 42)	11	0.88	0.65	1.42
Serial digit learning					
Trials to criterion	0.7[a]	529	4.44	0.14	2.40
	[1, 5)	3,281	4.59	0.07	3.72
	[5, 10)	815	4.97	0.13	2.86
	[10, 15)	126	5.14	0.40	3.67
	[15, 25)	39	5.96	0.34	1.14
	[25, 42)	10	4.94	0.84	1.26
Total score	0.7[a]	529	3.97	0.33	3.20
	[1, 5)	3,281	4.32	0.15	4.17
	[5, 10)	815	5.28	0.27	2.67
	[10, 15)	126	5.55	0.68	2.54
	[15, 25)	39	7.89	0.62	0.71
	[25, 42)	10	5.74	2.05	1.17

NOTE: For blood lead intervals, brackets indicate a closed bound, parentheses indicate an open bound.

[a]0.7 is the limit of detection divided by the square root of two.

[b]Due to missing data, the total number of individuals for each test may be less than 5,662.

M = mean

SE = standard error

DEFF = design effect

mean total latency from the symbol-digit substitution test, both as a function of blood lead concentration, are shown in Figures 1 and 2.

Unadjusted slopes for the relationship between test performance and blood lead concentration are shown in Table 2. Adjusted slopes are shown in Table 3. The slopes were adjusted for sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. No statistically significant relationships between blood lead concentration and neurobehavioral test performance were found when the adjustments were made.

Adjustments were made for demographic and other factors based on a previous analysis of the data.[8] Including the covariates affected the slopes of the relationships between performance and blood lead. For simple reaction time, the slope became more negative. For the other two tests, positive slopes became smaller or negative. To determine which covariates affected the slopes the most, covariates were removed from the regression equations one at a time. When sex was removed from the model, the slope between simple reaction time and blood lead became more negative and statistically significant (slope=−13.69; p=0.007). For mean total latency, removing sex (slope=1.31; p=0.0001), age (slope=2.55; p=0.0000), or education (slope=0.93; p=0.0288) made the slope larger and statistically significant. For number of errors, removing sex made the slope more negative (slope=−0.27; p=0.0542) and removing age made the slope positive (slope=0.27; p=0.0683). For trials to criterion, removing age made the slope positive (slope=0.17; p=0.2551) and removing education made the slope less negative (slope=−0.01; p=0.9417). For total score, removing age made the slope positive (slope=0.27; p=0.4381) and removing education made the slope less negative (slope=−0.09; p=0.8217). As seen in Table 4, these covariates were also related to blood lead level. Males had a higher average blood lead concentration than females. The average blood lead concentration increased as age increased, and decreased as education level increased.

Occupational studies

The 26 occupational studies examined for this study are summarized in Table 5.[15–40] The average blood lead levels of the control groups in the studies ranged from 3.67 to 20.40 µg/dl, with the average blood lead level of the control groups being 11.42 µg/dl. The average blood lead levels of the exposed groups ranged from 24.00 to 72.00 µg/dl, with the average blood lead level of the exposed groups being 41.07 µg/dl.

Figure 1. Mean reaction time from the simple reaction time test from NHANES III as a function of blood lead concentration, *N*=4,741

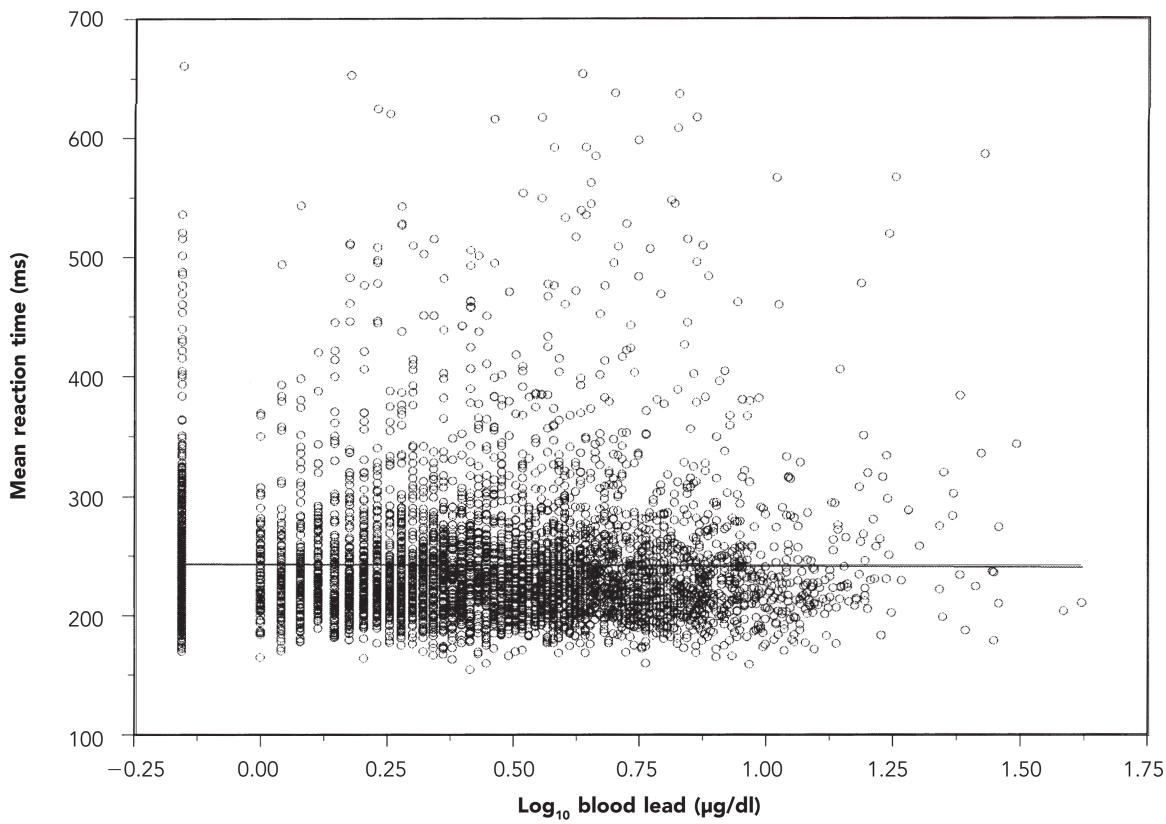


Table 2. Unadjusted slopes for test performance and $\log_{10}$ blood lead (µg/dl) from NHANES III

Test / *Variable*	n	*Slope*	*SE*	*DEFF*	df	t	p
Simple reaction time	4,741						
Mean reaction time (ms)		−3.71	3.62	2.86	49	−1.02	0.3106
Symbol-digit substitution	4,925						
Mean total latency (s)		5.58	0.39	1.61	49	14.25	0.0000
Number of errors		0.36	0.13	1.98	49	2.73	0.0087
Serial digit learning	4,800						
Trials to criterion		0.68	0.16	3.00	49	4.19	0.0001
Total score		1.63	0.38	3.58	49	4.35	0.0001

SE = standard error

DEFF = design effect

In the studies that used a simple reaction time test, the average reaction time of the exposed group was greater than the average reaction time of the control group in 12 studies.[16,17,20,21,25,27,29,30,32,37,39,40] In one study, the average reaction time of the exposed group was less than that of the control group.[31] Twelve of the studies compared the exposed and control groups with an inferential statistic.[16,17,20,25,27,29–32,37,39,40] Six studies reported a statistically significant ($p<0.05$) increase in the average reaction time of the exposed group.[17,25,27,32,37,39] Five studies reported an increase that was not statistically significant.[16,20,29,30,40] One study reported a decrease that was not statistically significant.[31]

Six of the studies using a simple reaction time test used correlation or regression analysis.[16,27,29,31,34,39] Four studies reported a direct relationship between mean reaction time and blood lead level.[16,29,31,39] One study reported an inverse

Figure 2. Mean total latency from the symbol-digit substitution test from NHANES III as a function of blood lead concentration, *N*=4,935

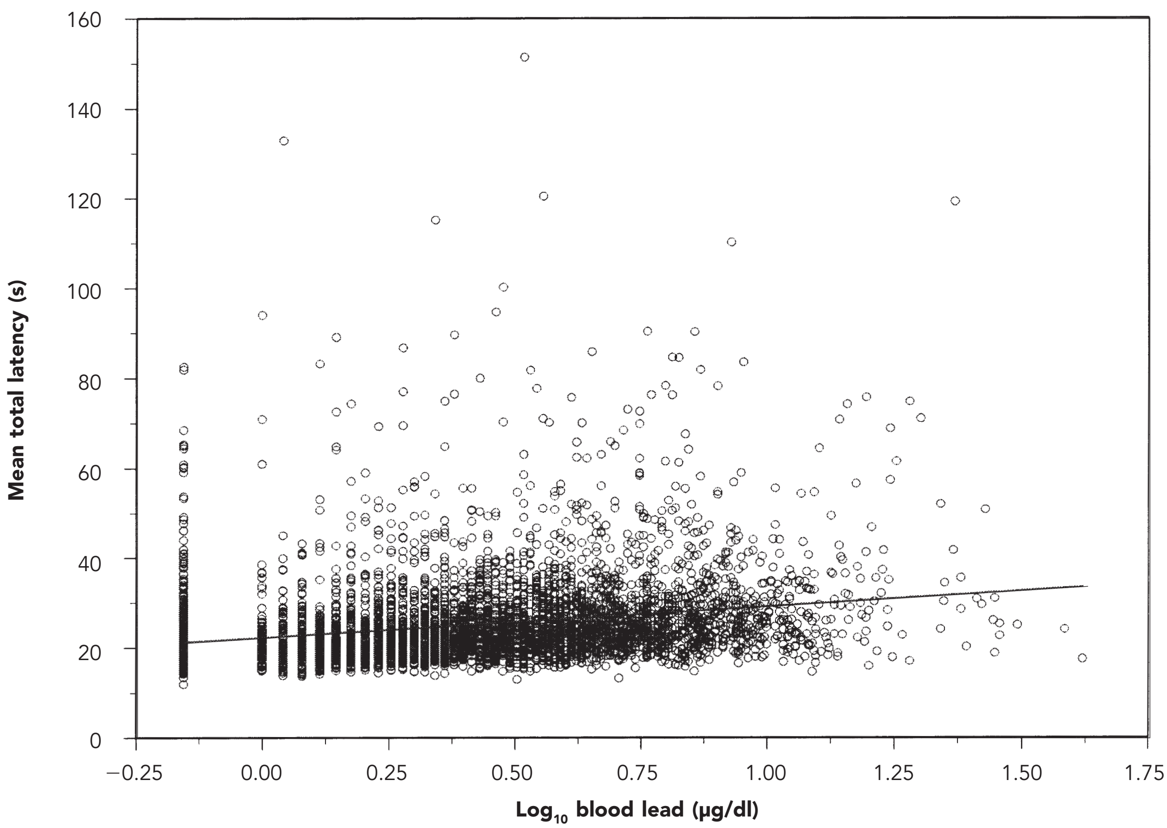


Table 3. Adjusted slopes[a] for test performance and $\log_{10}$ blood lead (µg/dl) from NHANES III

Test *Variable*	n	*Slope*	*SE*	*DEFF*	df	t	p
Simple reaction time	4,341						
Mean reaction time (ms)		−4.65	3.95	2.46	49	−1.18	0.2440
Symbol-digit substitution	4,509						
Mean total latency (s)		0.40	0.36	1.61	49	1.11	0.2745
Number of errors		−0.04	0.16	2.05	49	−0.23	0.8172
Serial digit learning	4,399						
Trials to criterion		−0.18	0.16	2.45	49	−1.15	0.2567
Total score		−0.45	0.38	3.34	49	−1.20	0.2361

[a]The slopes were adjusted for sex, age, education, family income, race-ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase.

SE = standard error

DEFF = design effect

relationship.[34] One of the direct relationships and the inverse relationship were statistically significant.[29,34] One study reported a relationship of unspecified direction that was not statistically significant.[27]

The group means from 11 of the studies using a simple reaction time test were used in a mixed model to estimate and test for a relationship between the log of the blood lead level and mean reaction time.[17,20,21,29–32,34,37,39,40] The means from three studies were not included in the analysis.[16,25,27] The slope was significantly greater than zero ($\beta=32.21$; standard error [SE]=11.31; $p=0.0293$). A scatter plot is shown in Figure 3. A second mixed model was done using a classification variable for exposure status. The mean of the exposed groups (306.29; SE=15.75) was significantly greater

Figure 3. Average mean reaction time from the occupational studies as a function of average blood lead concentration, $N=18$

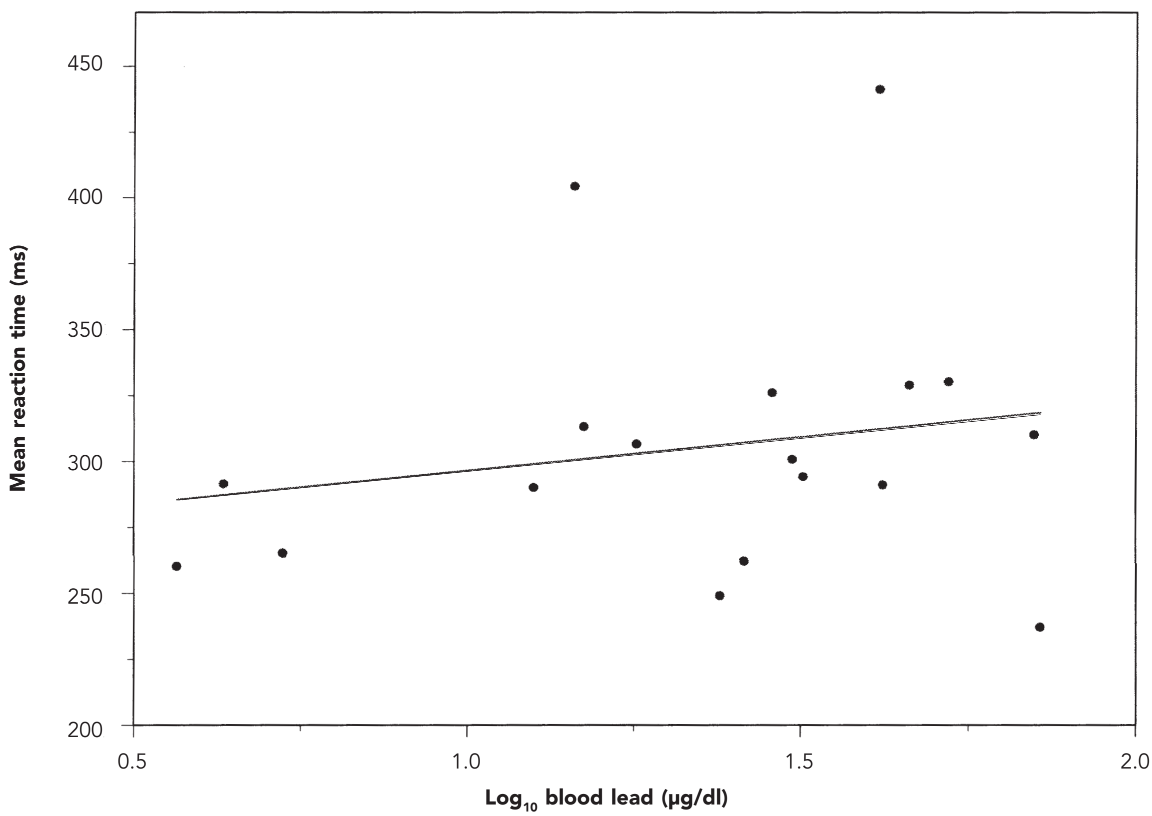


Table 4. Blood lead concentrations by levels of the covariates included in the regression models for individuals (*N*=5662) taking the neurobehavioral tests in NHANES III

	Blood lead (µg/dl)			
Variable	n[a]	*M*	*SE*	*DEFF*
Sex				
Male	2,505	4.22	0.13	4.05
Female	2,938	2.40	0.10	6.02
Age (years)				
20–29	1,703	2.69	0.12	4.92
30–39	1,548	3.14	0.14	3.12
40–49	1,282	3.51	0.13	2.90
50–59	910	4.38	0.20	3.03
Last grade attended				
0–8	887	4.27	0.29	5.32
9–11	937	4.10	0.18	3.29
12	1,802	3.29	0.11	2.54
13+	1,786	2.91	0.13	5.03
Family income				
<$10,000	817	4.07	0.32	4.51
$10,000–$29,999	2,206	3.46	0.11	2.88
$30,000–$49,999	1,182	3.16	0.13	3.20
$50,000+	843	2.86	0.17	4.43
Race/ethnicity				
Non-Hispanic white	1,886	3.18	0.12	3.64
Non-Hispanic black	1,681	3.85	0.13	2.83
Mexican American	1,645	3.60	0.12	2.65
Other	231	3.38	0.22	1.50
Computer or video game familiarity				
None	2,085	3.98	0.13	3.60
Some	2,203	3.10	0.12	4.42
A lot	685	2.72	0.15	2.58
Drinks with alcohol in last 3 hours				
0	4,911	3.28	0.10	6.36
1	45	6.02	0.56	0.78
2+	17	4.15	0.61	0.54
Test language				
English	4,319	3.26	0.11	5.96
Spanish	655	3.99	0.31	5.83
Survey phase				
I	2,620	3.74	0.12	3.87
II	2,823	2.88	0.13	8.20

[a]Due to missing blood lead measurements or missing values for covariates, the total number of individuals for each variable may be less than 5,662.

M = mean

SE = standard error

DEFF = design effect

than the mean of the control groups (283.32; SE=15.88), $p=0.0092$.

In the studies using a digit-symbol substitution test, which differs from the digit-symbol test in that it requires subjects to draw symbols on paper versus keying digits on a computer, the average number of symbols drawn by the exposed group was less than the average number in the control group in 14 studies.[15,18,20,21,23–25,28,29,32,35,37,39,40] In two studies, the average number of symbols drawn by the exposed group was greater.[26,31] Eleven studies reported a statistically significant decrease in the average number of symbols drawn by the exposed group.[15,18,20,23,25,28,29,32,35,37,39] Three studies reported a decrease that was not statistically significant.[23,24,40] No study reported a statistically significant increase. One study reported a statistically significant decrease in the average number of digits entered by the exposed group.[30] One study did not report the measure used for the test, but indicated that the exposed and control groups were not statistically significantly different.[36] One study reported a statistically significant increase in the average response latency of the exposed group.[38]

Thirteen of the studies using a digit-symbol substitution test used correlation or regression analysis.[15,18,19,22–24,26,29,31,33,35,36,39] One study reported a direct relationship between the number of symbols drawn and the blood lead level.[31] Seven studies reported an inverse relationship.[15,18,19,23,26,35,39] The direct relationship was not statistically significant. Two of the inverse relationships were statistically significant.[15,23] Four studies reported a relationship of unspecified direction that was not statistically significant.[22,24,29,33] One study reported a relationship of unspecified direction between an unspecified measure of test performance and blood lead level that was not statistically significant.[36]

The group means from 15 of the studies that used a digit-symbol substitution test were used in a mixed model to estimate and test for a relationship between the log of the blood lead level and the number of symbols drawn.[15,18,20,21,23–25,29,31,32,33,35,37,39,40] The means from seven studies were not included in the analysis.[19,22,26,28,30,36,38] The slope was significantly less than zero ($\beta=-10.04$; SE=2.20; $p=0.0008$). The scatter plot is shown in Figure 4. A second mixed model was done using a classification variable for exposure status. One additional study was included in this analysis.[28] The mean of the exposed groups (41.52; SE=1.72) was significantly less than the mean of the control groups (48.70; SE=1.76), $p<0.0001$.

One study reported results from a serial digit learning test.[30] The average number of correct responses was less in the exposed group as compared with the control group. The difference was not statistically significant.

DISCUSSION

The Centers for Disease Control and Prevention's (CDC) Adult Blood Lead Epidemiology and Surveillance program defines an *elevated blood lead* in an adult as 25 µg/dl or greater, and the Occupational Safety and Health Administration's (OSHA) *level for medical removal* from the workplace is 50 µg/dl or greater.[42,43] Eleven individuals in the survey that took the neurobehavioral tests had a blood lead concentration 25 µg/dl or greater. None were greater than 50 µg/dl.

Table 5. Summary of 26 occupational studies, *N*=4,033 total subjects

Study	Group	n	Blood lead mean (μg/dl)	Simple reaction time test, scored by mean reaction time (ms)				Digit-symbol substitution, scored by number of symbols				Serial digit learning test, scored by number correct	
				M	p	r or β	p	*M*	p	r or β	p	*M*	p
Grandjean 1978[15]	Control	22	16.6[a]					54[a]		*r*=0.29[b]	<0.05		
	Exposed	42	45.6[a]					48[a]	<0.01				
Haenninen 1978[16]	Control	24	11.9	1448.0[c]									
	Exposed	49	32.3	1482.0[c]	≥0.05	*r*=0.04	≥0.05						
Repko 1978[17]	Control	55	18.0	306.4									
	Exposed	85	46.0	328.7	<0.05								
Valciukas 1978[18]	Control	25	NR					38.6					
	Exposed	90	51.2[d]					31.8	<0.05	*r*=0.061[e]	≥0.05		
Valciukas 1980[19]	Control	265	NR					NR					
	Exposed	23	28.2					NR		*r*=−0.03	0.44		
	Exposed	28	38.5					NR		*r*=−0.03	0.44		
	Exposed	90	51.2					NR		*r*=−0.06	0.31		
Bleecker 1983[20]	Control	20	NR	223.0[a]				54.5[a]					
	Exposed	13	72.0[a]	237.0[a]	0.52			48.0[a]	0.04				
Hogstedt 1983[21]	Control	27	14.5	404.0				40.0					
	Exposed	49	41.4	441.0				37.3					
Baker 1984[22]	0–20[f]	26	NR					49.00		β=NR	0.74		
	21–40[f]	97	NR					53.54					
	41–60[f]	28	NR					48.50					
	61–80[f]	9	NR					50.56					
Campara 1984[23]	Control	20	20.4					41.8					
	Exposed	20	31.7					39.8	≥0.05	*r*=−0.33	<0.05		
	Exposed	20	52.2					29.4	<0.01				
Araki 1986[24]	Control	12	13.0					41.0		*r*=NR	≥0.05		
	Exposed	19	42.0					35.0	≥0.05				
Jeyaratnam 1986[25]	Control	36	14.50	37.9[g]				59.9					
	Exposed	49	48.69	50.7[g]	<0.001			48.9	<0.001				
Parkinson 1986[26]	Control	181	7.2[h]					8.72[i]					
	Exposed	288	40.1[h]					9.36[i]	≥0.05	β=−0.007	≥0.05		
Williamson 1986[27]	Control	59	NR	NR[j]									
	Exposed	59	48.90	NR[j]	<0.05	β=NR	≥0.05						

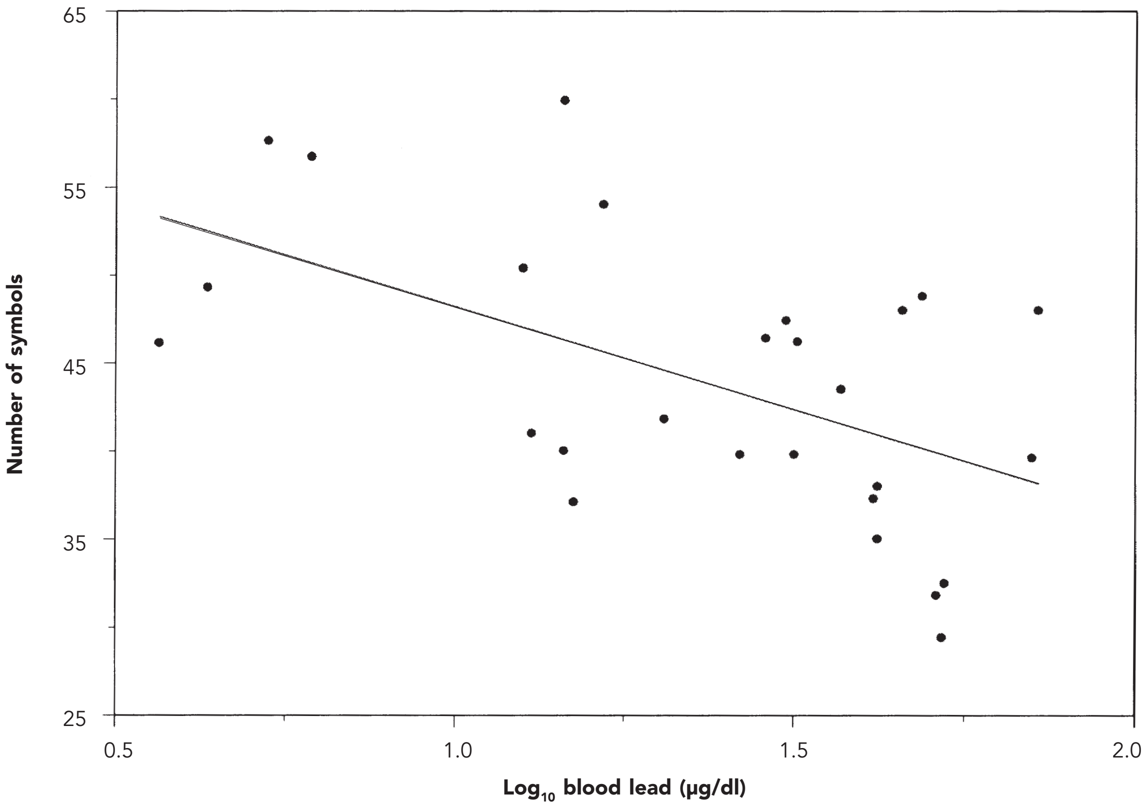
continued on p. 248

Table 5 (continued). Summary of 26 occupational studies, N=4,033 total subjects

Study	Group	n	Blood lead mean (μg/dl)	Simple reaction time test, scored by mean reaction time (ms)				Digit-symbol substitution, scored by number of symbols				Serial digit learning test, scored by number correct	
				M	p	r or β	p	*M*	p	r or β	p	*M*	p
Zhang 1991[28]	Control	49	NR					53.53					
	Exposed	78	NR					48.23	<0.01				
Hu 1994[29]	Control	26	NR	280.0				51.08					
	Exposed	39	52.63	330.0	≥0.05	β=0.0615	<0.05	32.49	<0.01	β=NR	≥0.05		
Bolla 1995[30]	Control	52	NR	241.0				34.9[k]				17.3	
	Exposed	190	24.0	249.0	≥0.05			32.7[k]	<0.01			15.7	≥0.05
Maizlish 1995[31]	Control	47	15	313.0		β=0.34	0.32	37.1		β=0.05	0.35		
	Exposed	43	42	291.0	0.06			38.0	0.33				
Tang 1995[32]	Control	23	3.67	260.0				46.13					
	Exposed	23	70.55	310.0	<0.05			39.61	<0.05				
Bleecker 1997[33]	Exposed	80	26.4					39.8		β=NR	≥0.10		
Bleecker 1997[34]	Exposed	78	26.1	262.0[l]		β=−8.00	<0.01						
Chia 1997[35]	Control	97	6.14[m]					56.7					
	Exposed	50	37.1[m]					43.5	0.001	*r*=−0.094	≥0.05		
Lucchini 2000[36]	Control	86	8.11					NR[n]		*r*=NR	≥0.05		
	Exposed	66	27.5					NR[n]	≥0.05				
Niu 2000[37]	Control	34	12.6096	289.9773				50.3864					
	Exposed	44	28.7373	325.8529	0.030			46.4118	0.000				
Proctor 2000[38]	Control	49	NR					59.2[o]					
	Exposed	11	NR					65.6[o]	<0.05				
Schwartz 2001[39]	Control	135	5.3	265.0				57.6					
	Exposed	803	32.0	294.0	<0.05	β<−0.0001[p]	≥0.05	46.2	<0.05	β= -0.0443	≥0.05		
Barth 2002[40]	Control	53	4.32	291.2				49.3					
	Exposed	47	30.8	300.6	0.17			47.4	0.20				

[a]Median
[b]Standardized so that a positive correlation indicates a decreasing number of symbols
[c]Cumulative reaction time (μs)
[d]Value reported in Valciukas et al., 1980[19]
[e]Multiple correlation coefficient for an inverse relationship
[f]Grouped according to blood lead ranges in μg/dl
[g]Units not reported
[h]Value reported in Ryan et al., 1987[41]
[i]Standard score
[j]The mean of the exposed group was greater than the mean of the control group.
[k]Number of digits
[l]Median reaction time
[m]Geometric mean
[n]Measure not reported
[o]Total latency (s)
[p]Standardized so that a negative slope indicates an increasing reaction time
M = mean
NR = not reported

Figure 4. Average number of symbols drawn from the occupational studies as a function of average blood lead concentration, *N*=27



When adjusted for covariates, no statistically significant relationships between blood lead concentration and neurobehavioral test performance were found. All but one adjusted slope was negative. Negative slopes indicate an improvement in performance. The results of the analysis of the NHANES III data do not provide evidence for impairment of neurobehavioral test performance in adults at levels below 25 μg/dl, or at lead concentrations currently found in the general adult population of the United States. The lack of relationship found here may be due to a lack of toxicity of lead in adults at the levels investigated, a sample size or study design that did not allow enough precision to detect a relationship, or neurobehavioral tests that are not sensitive to the toxicity of lead at the levels investigated.

Children in the NHANES III sample showed decreases in cognitive performance at blood lead levels less than 5 μg/dl.[3] The adults in NHANES III did not show lead-related decreases in performance. The geometric mean of the blood lead concentration of the children, 1.9 μg/dl, was less than the geometric mean for adults taking the neurobehavioral tests, 2.51 μg/dl. Children are considered to be more susceptible than adults to the toxic effects of lead exposure due to the immature state of their nervous systems, the increased tendency to ingest inappropriate products, and a higher absorption rate of lead relative to adults.[44] It is also possible that the tests used for the children (i.e., the arithmetic and reading subtests of the Wide Range Achievement Test and the block design and digit span subtests of the Wechsler Intelligence Scale for Children) are more sensitive to lead toxicity than the neurobehavioral tests used for adults.[45,46]

The analysis of the occupational studies shows that the exposed groups consistently performed worse on the simple reaction time and digit-symbol substitution tests. The average blood lead level of the control groups was 11.42 μg/dl, greater than the arithmetic mean from the NHANES III data (3.30 μg/dl) and less than the CDC limit (25 μg/dl). The average blood lead level of the exposed groups was 41.07 μg/dl, greater than 25 μg/dl and less than 50 μg/dl, the minimum concentration OSHA requires for medical removal from the workplace. The results of the analysis of the occupational studies indicate that the OSHA limit should be reevaluated.

A digit-symbol test was usually administered in the occupational studies. A symbol-digit test was used in three of the occupational studies and in the NHANES III.[30,36,38] The digit-symbol test is a paper and pencil test in which the subject responds by drawing symbols. The number of correct symbols is used as a measure of performance: the more correct symbols drawn, the better the performance. The symbol-digit test is an adaptation of the paper and pencil test and is administered on computers. The subject responds by entering numbers on a keypad. The number of correct digits entered or the time it takes to enter the digits, called the latency, are used as measures of performance: the greater the number of correct digits or the smaller the latency, the better the performance. Two of the occupational studies using a symbol-digit test reported statistically significant decrements in performance, a decrease in the number of digits entered and an increase in latency.[30,38] The third study reported no statistically significant difference in an unspecified measure.[36]

Previous reviews of studies have indicated that neurophysiological measurements such as nerve conduction velocity can be affected by blood lead levels of 30 μg/dl and that neurobehavioral function can be affected at 40 μg/dl.[47,48] A meta-analysis of studies comparing the nerve conduction velocities of lead-exposed and control groups found a statistically significant decrease in velocity (effect size=−0.369) for the combined median and ulnar, sensory and motor nerves of the exposed groups.[49] The average blood lead levels of the exposed and control groups were not calculated in this analysis. Previous meta-analyses of neurobehavioral data also indicate an effect of lead.[50,51] In one of these, statistically significant decreases in performance were found for block design (effect size=−0.31; blood lead=41 μg/dl), logical memory (effect size=−0.39; blood lead=38 μg/dl), Santa Ana with preferred hand (effect size=−0.20; blood lead=44 μg/dl), and digit-symbol substitution (for two groups effect size=−1.04; blood lead=44 μg/dl and effect size=−0.25; blood lead=45 μg/dl), but not for simple reaction time (effect size=0.50).[50] Thus, previous summaries of neurophysiological and neurobehavioral data also indicate that the OSHA limit should be reevaluated.

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