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INORGANIC COMPOUNDS

A meta-analysis of studies investigating the effects of lead exposure on nerve conduction

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Abstract Group means from nerve conduction studies of persons exposed to lead were used in a meta-analysis. Differences between the control and exposed groups, and the slopes between nerve conduction measurements and $\log_{10}$ blood lead concentrations were estimated using mixed models. Conduction velocity was reduced in the median, ulnar, and radial nerves in the arm, and in the deep peroneal nerve in the leg. Distal latencies of the median, ulnar, and deep peroneal nerves were longer. No changes in the amplitudes of compound muscle or nerve action potentials were detected. The lowest concentration at which a relationship with blood lead could be detected was 33.0 μg/dl for the nerve conduction velocity of the median sensory nerve. Lead may reduce nerve conduction velocity by acting directly on peripheral nerves or by acting indirectly, for example, on the kidney or liver.

Keywords Nerve conduction · Blood lead

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Introduction

There have been many studies investigating the effect of occupational lead exposure on nerve conduction velocity and many reviews of the individual studies. A decrease in the conduction velocity of a peripheral nerve indicates that the nerve has been damaged, for example, that the axons in a nerve have degenerated, or that they have become demyelinated.

One group that reviewed the literature (Zielhuis 1977) concluded that changes in nerve conduction velocity can occur in some workers with blood lead concentrations greater than 50 μg/dl.

Triebig and Büttner (1983) note that some studies show an inverse relationship between nerve conduction velocity and blood body burden, while others do not, and that proposals for threshold values range from 50 to 80 μg/dl.

Seppäläinen (1984) concluded that occupational exposure to lead slows motor and sensory nerve conduction velocity, and that the slowing occurs earlier in the arms than in the legs. The slowing occurs in workers whose blood lead concentrations are below 70 μg/dl, and in the 50–59 μg/dl range.

He (1985) noted that some studies show an effect of lead on the peripheral nerves at just above 30 μg/dl, and that the results of nerve conduction velocity studies are inconsistent, some showing a difference or relationship, and some not.

Ehle (1986) reviewed electrophysiological studies and concluded that, in subjects with blood lead concentrations not less than 60 μg/dl, a 7–8% decrease in nerve conduction velocity may occur in the median, posterior tibial, and sural nerves, but that no decrease is found in the ulnar and peroneal nerves.

A previous meta-analysis of nerve conduction velocity studies (Davis and Svendsgaard 1990) found that the

exposed groups had a lower overall nerve conduction velocity for the median motor (effect size = −0.553, $p = 0.0000$), median sensory (effect size = −0.475, $p = 0.0000$), ulnar motor (effect size = −0.251, $p = 0.0008$), and ulnar sensory (effect size = −0.265, $p = 0.0004$) nerves. Averaging across nerves, it was found that the effect size became less negative as blood lead concentration increased. In the highest blood lead category (>40 μg/dl), effect sizes were positive, indicating an increase in the nerve conduction velocity of the exposed groups.

Araki et al. (2000) reviewed the neurophysiological literature and concluded that a reduction in nerve conduction velocity occurs with blood lead concentrations as low as 30–40 μg/dl.

In the meta-analysis reported here, mixed models are used that include study as a random effect. Differences between control and exposed groups, and slopes between nerve conduction measurements and $\log_{10}$ blood lead concentrations are estimated. Means from published studies are used. The original measurement units are retained. By using a mixed model, it is not necessary to standardize group differences by dividing by a standard deviation. Comparisons between groups and between nerves become more straightforward and meaningful. By incrementing the highest blood lead concentration, it is possible to determine at what concentration a relationship between blood lead and a nerve conduction variable becomes consistently statistically significant.

Materials and methods

Studies

Studies were identified by searching the reference sections of review articles and the papers describing individual studies. Searches were made on Ovid and PubMed combining the terms "nerve conduction" and "blood lead". The last search was made on 19 September 2007.

Data from 49 studies published in journal articles, proceedings, and technical reports were used. The studies are listed in the meta-analysis references section that follows the references section. The sample size per group had to be greater than one for a group to be included. Case reports of an individual were not included. Studies of children were not included. All the studies had subjects that were exposed to lead. Almost all of the exposures were occupational. In Vasilescu (1973) the exposed group included persons who had ingested alcohol that was made using lead pipes. In Verberk (1976) volunteers were asked to ingest lead acetate for 49 days.

Some studies did not measure blood lead or only measured it in the exposed group. Not all studies had measurements of all the nerve conduction variables. There were five studies in which repeated measurements were made. Only the first measurement was used except for the Verberk (1976) study in which subjects were experimentally exposed to lead for 49 days. In this case the last measurement was used. Seven studies did not have control groups. Eight studies had multiple control or exposed groups.

Nerves and nerve measurements

The nerves measured in the studies include the median, ulnar, and radial nerves in the arm, and the deep peroneal, superficial peroneal, posterior tibial, sural, and fibular nerves in the leg. For the median and ulnar nerves, "proximal" refers to the upper arm and "distal" refers to the hand, otherwise the measurements were made in the forearm. The term "motor" refers to motor fibers, the term "sensory" refers to sensory fibers, and the term "mixed" refers to a combination of motor and sensory fibers. Measurements of the radial nerve are made in the upper arm. For the nerves in the leg, "proximal" refers to the upper leg and "distal" refers to the foot, otherwise the measurements were made in the lower leg.

The velocities of the fastest conducting fibers are usually measured in nerve conduction studies. It is also possible to measure the slower conducting fibers using a partial antidromic block (Seppäläinen and Hernberg 1972). The term "slow fibers" refers to the measurement of the slower conducting nerve fibers using this or a similar technique.

"Latency" refers to the time between stimulus and response. For motor nerves the response is a compound muscle action potential (CMAP) in a muscle connected synaptically to the nerve being stimulated. The response for a sensory nerve is a compound nerve action potential (CNAP) measured at some point along the nerve. The amplitudes of the CMAPs and CNAPs are also measured in some studies.

Oh (2003, chapter 13) discusses physiological factors that affect nerve conduction. Nerve conduction velocity decreases as limb temperature decreases. Velocity also decreases as age increases in adults 20 years and older. Nerve conduction is faster in the proximal segments of limbs as compared to distal segments. Nerve conduction is slower in the lower limbs as compared to the upper limbs. Some studies find sex differences in nerve conduction velocity while others do not.

Limb temperature is an important variable that should be taken into account in nerve conduction studies. Fifteen studies used in the analysis reported the room temperature where testing was done. Eighteen studies reported the skin temperature of the limbs that were tested. Seven studies reported controlling limb temperature by warming or

Table 1 Control groups and exposed groups summary statistics

Variable nerve	Control groups						Exposed groups					
	Studies	*n*	Mean	Std	Min	Max	Studies	*n*	Mean	Std	Min	Max
Age (years)	20	25	39.2	8.9	26.8	70.2	36	46	38.4	5.8	26.8	53.5
Duration (years)	2	2	8.8	5.7	4.8	12.8	23	29	7.7	4.7	0.1	21.7
Blood lead (μg/dl)	21	25	15.7	6.8	4.5	38.0	39	50	53.0	23.0	15.6	133.0
Conduction velocity (m/s)												
Median motor	26	26	59.1	2.2	55.1	63.6	32	42	55.9	2.9	46.9	61.5
Median motor, slow fibers	1	1	49.7		49.7	49.7	1	1	50.1		50.1	50.1
Median motor, proximal	0	0					1	1	59.7		59.7	59.7
Median sensory	11	11	62.9	3.1	56.3	67.1	12	17	61.0	3.1	52.7	65.9
Median sensory, proximal	2	2	60.0	1.4	59.0	61.0	3	3	62.0	6.1	56.3	68.5
Median sensory, distal	12	12	50.7	3.9	45.7	57.2	15	24	47.2	4.3	35.6	56.8
Median mixed	1	1	68.3		68.3	68.3	1	1	66.6		66.6	66.6
Median mixed, proximal	0	0					1	1	69.0		69.0	69.0
Ulnar motor	24	28	58.1	2.4	53.7	64.5	30	39	56.5	3.4	44.7	61.5
Ulnar motor, slow fibers	8	8	46.3	6.0	33.2	54.0	10	16	43.0	3.8	34.3	49.9
Ulnar sensory	6	6	62.2	2.9	57.9	66.4	7	11	59.9	2.3	56.4	63.4
Ulnar sensory, distal	5	5	50.9	4.4	44.9	54.6	5	9	50.7	4.1	42.4	54.3
Ulnar mixed, proximal	1	1	53.1		53.1	53.1	1	1	52.3		52.3	52.3
Radial motor	6	6	63.4	4.7	59.0	71.7	9	10	58.0	6.9	44.8	67.0
Radial sensory	2	2	55.9	5.2	52.2	59.6	2	2	53.6	5.2	50.0	57.3
Deep peroneal motor	21	25	51.2	2.4	47.6	56.2	27	38	49.1	3.8	41.0	58.5
Deep peroneal motor, slow fibers	2	2	44.5	5.7	40.4	48.5	2	6	40.9	2.2	39.1	45.2
Deep peroneal motor, proximal	1	1	52.7		52.7	52.7	1	1	52.5		52.5	52.5
Deep peroneal motor, distal	1	1	50.2		50.2	50.2	1	1	50.6		50.6	50.6
Deep peroneal sensory	1	1	56.3		56.3	56.3	1	1	57.1		57.1	57.1
Superficial peroneal sensory	1	1	55.5		55.5	55.5	1	1	53.0		53.0	53.0
Posterior tibial motor	7	7	49.3	3.4	44.6	55.5	9	15	47.8	2.3	43.4	51.6
Posterior tibial sensory	1	1	43.9		43.9	43.9	2	2	48.1	9.2	41.6	54.6
Posterior tibial sensory, distal	0	0					1	1	48.6		48.6	48.6
Sural sensory	7	7	49.3	5.9	42.8	58.7	8	14	45.8	4.7	37.8	55.6
Sural sensory, distal	1	1	35.5		35.5	35.5	1	5	34.1	1.5	32.8	36.4
Fibular motor	0	0					1	3	47.0	1.2	45.7	48.1
Latency (ms)												
Median motor, distal	13	13	3.4	0.3	2.8	4.0	16	25	4.0	0.6	3.2	5.5
Median sensory, proximal	1	1	10.2		10.2	10.2	1	1	10.8		10.8	10.8
Median sensory, distal	3	3	2.5	0.5	2.0	3.0	4	4	3.2	1.3	2.2	5.1
Ulnar motor	1	1	7.6		7.6	7.6	1	1	7.8		7.8	7.8
Ulnar motor, distal	7	7	2.9	0.5	2.4	3.8	11	13	3.2	0.5	2.6	3.9
Ulnar sensory, distal	3	3	2.5	0.6	2.0	3.2	5	5	2.8	0.5	2.0	3.3
Radial motor, distal	2	2	3.4	0.6	3.0	3.9	2	2	3.7	0.9	3.1	4.4
Deep peroneal motor, distal	8	8	4.0	0.7	2.6	5.1	10	13	4.7	0.8	3.1	6.3
Posterior tibial motor, distal	3	3	5.1	0.3	4.9	5.4	4	4	5.5	0.8	4.6	6.3
Posterior tibial sensory	1	1	8.4		8.4	8.4	2	2	7.9	2.4	6.2	9.6
Sural sensory	3	3	3.5	0.5	3.0	4.0	4	4	3.6	0.6	2.9	4.3
CMAP amplitude (mV)												
Median motor	5	5	11.3	2.7	8.6	14.2	6	6	10.1	4.8	4.5	15.6
Median motor, distal	1	1	14.9		14.9	14.9	1	1	13.4		13.4	13.4
Ulnar motor	2	2	11.8	5.5	7.9	15.7	3	3	9.2	6.1	3.8	15.9

Table 1 continued

Variable nerve	Control groups						Exposed groups					
	Studies	*n*	Mean	Std	Min	Max	Studies	*n*	Mean	Std	Min	Max
Radial motor	1	1	6.8		6.8	6.8	1	1	2.5		2.5	2.5
Deep peroneal motor	7	7	7.2	1.9	4.1	10.5	8	8	5.5	2.6	1.8	8.4
Deep peroneal motor, proximal	1	1	4.0		4.0	4.0	1	1	3.1		3.1	3.1
Deep peroneal motor, distal	3	3	7.2	2.7	4.6	10.0	3	3	6.8	3.2	3.7	10.0
Posterior tibial motor	1	1	11.5		11.5	11.5	2	2	8.2	5.2	4.6	11.9
CNAP amplitude (μV)												
Median sensory	2	2	19.0	13.0	9.8	28.2	3	3	13.2	8.7	5.2	22.4
Median sensory, proximal	1	1	3.5		3.5	3.5	1	1	3.1		3.1	3.1
Median sensory, distal	4	4	28.1	6.8	19.2	35.7	6	11	27.3	8.9	15.9	41.6
Ulnar sensory, distal	2	2	18.4	8.1	12.7	24.1	2	2	19.6	10.4	12.3	26.9
Deep peroneal sensory	1	1	7.6		7.6	7.6	1	1	7.0		7.0	7.0
Superficial peroneal sensory	1	1	3.6		3.6	3.6	1	1	5.5		5.5	5.5
Posterior tibial sensory	1	1	1.2		1.2	1.2	2	2	3.0	2.5	1.3	4.8
Sural sensory	4	4	14.4	3.0	10.7	17.7	5	7	11.7	3.5	6.9	16.9

Studies number of studies; *n* number of groups; *Std* standard deviation; *Min* minimum; *Max* maximum

cooling. Eight studies reported adjusting nerve conduction measurements to a common temperature. The most commonly used method for adjustment is that of de Jesus et al. (1973).

For an introduction to the methods of nerve conduction studies see Iyer (1993). Ehle (1986) reviewed the methodology of many of the studies used in the analysis.

Statistical analysis

The data that were analyzed consisted of group means that were reported in a paper or that were calculated from the results of individuals that were reported in a paper. Mixed linear models were used to analyze the data. Study was a random variable. A classification variable for exposure status or the log base 10 of the mean blood lead concentration was included as a fixed effect.

The model used to compare exposed and control groups was

$$y_{ijk} = \mu + \tau_i + \delta_j + \varepsilon_{ijk}.$$

y_{ijk} is the mean nerve conduction measurement, μ is the grand mean, τ_i is the effect of exposure, $i = 1 =$ control, $i = 2 =$ exposed. δ_j is the random effect of study j, ε_{ijk} is a random error. For most cells, $k = 1$, however, in some studies there was more than one control or exposed group, so k was greater than one.

The model used for blood lead concentration was

$$y_{ij} = \alpha + \beta x_i + \delta_j + \varepsilon_{ij}.$$

y_{ij} is the mean nerve conduction measurement, α is the intercept, β is the slope. x_i is the log base 10 of the mean blood lead concentration of group i. Values from the control and exposed groups were included. δ_j is the random effect of study j, ε_{ij} is a random error.

In order to determine the lowest concentration of blood lead at which a relationship could be detected, two variables for blood lead were created. If the lead value was less than or equal to a cutoff value, the first lead variable was assigned the value and the second lead variable was set to zero. If the lead value was greater than the cutoff value, the first lead variable was set to zero and the second lead variable was assigned the value. The cutoff value varied from the next to lowest value of blood lead to the highest value and was incremented in steps of 0.1. The slopes of the two lead variables were calculated at each step. The lowest blood lead value at which a relationship could be detected was defined as the cutoff value for which the slope of the first blood lead variable was statistically significant ($p < 0.05$) at the cutoff value and at all subsequent greater values.

All calculations were done with SAS® (Release 9.1, SAS Institute, Inc., Cary, NC). The mixed procedure was used to estimate the mixed models. The method of estimation was residual maximum likelihood. SigmaPlot® (Version 9.01, Systat Software, Inc., Point Richmond, CA) was used to make the graphs. Simple linear least squares regression was used to fit the data in the graphs.

Results

In the 49 studies, there were 1,629 subjects in the control groups (849 males, 230 females) and 2,825 subjects in the

exposed groups (1,717 males, 255 females). The sex of the subjects was not always reported.

Table 1 shows the means of age, duration of employment or exposure, blood lead, and the nerve conduction measurements for the exposed and control groups. There were not enough group means to estimate the parameters of the mixed models for many of the nerve conduction measurements, so they do not appear in subsequent tables.

Table 2 shows the results of the mixed models comparing the means of the exposed and control groups. For conduction velocity, the mean of the exposed groups was statistically significantly less than the mean of the control groups for the median motor, median sensory, distal median sensory, ulnar motor, slow fibers of the ulnar motor, ulnar sensory, distal ulnar sensory, radial sensory, and deep peroneal motor nerves. The mean of the exposed groups was statistically significantly greater than the mean of the control groups for the median, ulnar, and deep peroneal motor distal latencies, and the ulnar sensory distal latency. There were no statistically significant differences for the amplitudes.

Table 2 Estimated differences between the control groups and exposed groups means

Variable nerve	Studies	*n*	Difference	SE	DF	*t*	*p*	LCL	UCL
Conduction velocity (m/s)									
Median motor	32	68	−3.09	0.47	35	−6.51	0.0000	−4.05	−2.12
Median sensory	12	28	−2.32	0.79	15	−2.95	0.0099	−3.99	−0.64
Median sensory, proximal	3	5	−1.00	1.45	1	−0.69	0.6135	−19.39	17.38
Median sensory, distal	15	36	−3.01	1.10	20	−2.74	0.0125	−5.30	−0.72
Ulnar motor	30	67	−1.69	0.53	36	−3.21	0.0028	−2.76	−0.62
Ulnar motor, slow fibers	10	24	−2.90	0.93	13	−3.12	0.0082	−4.90	−0.89
Ulnar sensory	7	17	−2.47	0.74	9	−3.36	0.0084	−4.13	−0.81
Ulnar sensory, distal	5	14	−1.65	0.69	8	−2.38	0.0446	−3.25	−0.05
Radial motor	9	16	−5.03	2.40	6	−2.09	0.0812	−10.91	0.85
Radial sensory	2	4	−2.26	0.04	1	−56.50	0.0113	−2.77	−1.75
Deep peroneal motor	27	63	−2.28	0.67	35	−3.41	0.0017	−3.63	−0.92
Deep peroneal motor, slow fibers	2	8	−1.51	0.76	5	−1.98	0.1043	−3.46	0.45
Posterior tibial motor	9	22	−1.56	0.79	12	−1.96	0.0731	−3.28	0.17
Sural sensory	8	21	−1.94	1.07	12	−1.82	0.0944	−4.28	0.39
Sural sensory, distal	1	6	−1.44	1.67	4	−0.86	0.4366	−6.07	3.19
Latency (ms)									
Median motor, distal	16	38	0.50	0.16	21	3.22	0.0041	0.18	0.83
Median sensory, distal	4	7	0.06	0.03	2	1.84	0.2074	−0.09	0.21
Ulnar motor, distal	11	20	0.14	0.05	8	2.63	0.0302	0.02	0.27
Ulnar sensory, distal	5	8	0.10	0.02	2	4.79	0.0409	0.01	0.18
Radial motor, distal	2	4	0.30	0.20	1	1.51	0.3718	−2.18	2.77
Deep peroneal motor, distal	10	21	0.32	0.14	10	2.37	0.0394	0.02	0.63
Posterior tibial motor, distal	4	7	0.20	0.33	2	0.59	0.6145	−1.23	1.62
Sural sensory	4	7	−0.06	0.03	2	−1.94	0.1922	−0.19	0.07
CMAP amplitude (mV)									
Median motor	6	11	−0.26	1.01	4	−0.26	0.8091	−3.06	2.54
Ulnar motor	3	5	0.13	0.04	1	3.85	0.1616	−0.31	0.58
Deep peroneal motor	8	15	−1.40	0.65	6	−2.17	0.0729	−2.99	0.18
Deep peroneal motor, distal	3	6	−0.44	0.25	2	−1.72	0.2278	−1.53	0.66
CNAP amplitude (μV)									
Median sensory	3	5	−2.40	3.93	1	−0.61	0.6507	−52.37	47.56
Median sensory, distal	6	15	−1.09	4.80	8	−0.23	0.8257	−12.16	9.98
Ulnar sensory, distal	2	4	1.19	1.61	1	0.73	0.5970	−19.34	21.71
Sural sensory	5	11	−0.65	0.91	5	−0.71	0.5098	−2.99	1.70

Difference = exposed groups mean − control groups mean

Studies number of studies; *n* number of groups; *SE* standard error; *DF* denominator degrees of freedom; *LCL* 95% lower confidence limit; *UCL* 95% upper confidence limit

Table 3 Estimated slopes between the nerve conduction variables and $\log_{10}$ blood lead (μg/dl)

Variable nerve	Studies	*n*	Slope	SE	DF	*t*	*p*	LCL	UCL
Conduction velocity (m/s)									
Median motor	28	46	−6.05	0.99	17	−6.11	0.0000	−8.14	−3.96
Median sensory	11	23	−6.01	1.27	11	−4.73	0.0006	−8.80	−3.21
Median sensory, distal	12	21	−4.69	1.86	8	−2.52	0.0356	−8.98	−0.41
Ulnar motor	26	50	−3.68	1.26	23	−2.93	0.0076	−6.28	−1.08
Ulnar motor, slow fibers	8	16	−3.69	2.48	7	−1.49	0.1802	−9.56	2.17
Ulnar sensory	7	15	−7.19	1.34	7	−5.35	0.0011	−10.37	−4.02
Ulnar sensory, distal	5	11	−2.21	2.44	5	−0.90	0.4082	−8.49	4.08
Radial motor	7	9	−0.73	4.57	1	−0.16	0.8996	−58.78	57.33
Radial sensory	2	4	−3.77	0.74	1	−5.12	0.1228	−13.11	5.58
Deep peroneal motor	21	43	−7.16	1.36	21	−5.28	0.0000	−9.98	−4.34
Deep peroneal motor, slow fibers	2	8	−2.19	2.17	5	−1.01	0.3583	−7.77	3.38
Posterior tibial motor	8	16	−3.39	2.45	7	−1.38	0.2087	−9.18	2.40
Sural sensory	6	14	−1.78	1.54	7	−1.16	0.2848	−5.42	1.86
Sural sensory, distal	1	6	−2.44	3.25	4	−0.75	0.4955	−11.47	6.60
Latency (ms)									
Median motor, distal	12	24	0.58	0.18	11	3.12	0.0097	0.17	0.98
Median sensory, distal	4	6	0.12	0.07	1	1.83	0.3189	−0.73	0.98
Ulnar motor, distal	10	15	0.30	0.10	4	3.12	0.0355	0.03	0.57
Ulnar sensory, distal	5	7	0.12	0.06	1	1.93	0.3049	−0.68	0.93
Deep peroneal motor, distal	8	13	0.26	0.20	4	1.35	0.2480	−0.28	0.81
Posterior tibial motor, distal	4	6	−0.62	0.86	1	−0.73	0.5994	−11.51	10.26
Sural sensory	4	6	−0.11	0.12	1	−0.90	0.5321	−1.61	1.40
CMAP amplitude (mV)									
Median motor	5	7	−12.25	6.01	1	−2.04	0.2906	−88.67	64.17
Deep peroneal motor	6	9	−1.38	1.02	2	−1.36	0.3076	−5.77	3.00
CNAP amplitude (μV)									
Sural sensory	3	5	−1.28	0.19	1	−6.88	0.0919	−3.63	1.08

Studies number of studies; *n* number of groups; *SE* standard error; *DF* denominator degrees of freedom; *LCL* 95% lower confidence limit; *UCL* 95% upper confidence limit

Table 3 shows the results of the mixed models used to estimate the slopes between the blood lead concentration and the nerve conduction measurements. For conduction velocity, the slopes for the median motor, median sensory, distal median sensory, ulnar motor, ulnar sensory, and deep peroneal motor nerves were statistically significantly less than zero, indicating a slowing in nerve conduction velocity as the blood lead concentration increases. The slopes for the median and ulnar motor distal latency were statistically significantly greater than zero, indicating an increase in latency as the blood lead concentration increases. There were no statistically significant relationships for the amplitudes.

Figures 1, 2, 3 show nerve conduction measurements as a function of blood lead concentration for the median, ulnar, and deep peroneal nerves, respectively.

Table 4 shows the lowest concentrations of blood lead at which a relationship could be detected. The values ranged from 33.0 μg/dl for the conduction velocity of the median sensory nerve to 64.0 μg/dl for the distal motor latency of the median nerve. The slopes in this table are calculated using the data at and below the lowest concentrations.

Discussion

Conduction velocity was reduced in motor and sensory nerves in the arm, and in a motor nerve in the leg. Distal latencies in the arm and leg increased. No changes in amplitude were detected. The number of studies measuring distal latency and amplitude were less than the number measuring velocity. Few studies measured amplitude. Some nerves were studied more often than other nerves. The median, ulnar, and deep peroneal nerves were investigated the most. No detected change does not necessarily mean no effect of lead. It may mean that the number of studies was too small to detect an effect.

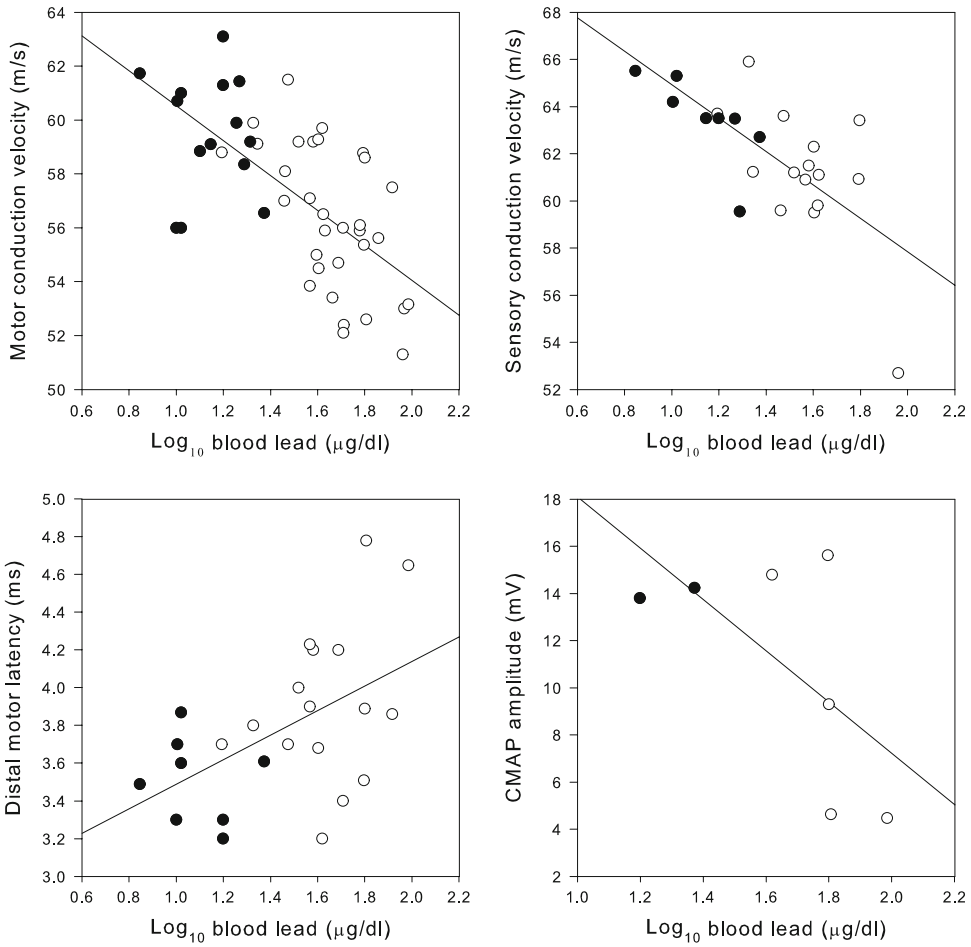

Fig. 1 Nerve conduction measurements as a function of blood lead concentration for the median nerve (contol groups *filled circle*, exposed groups *open circle*)

The sensitivity of a nerve to lead exposure is best reflected in the slopes relating blood lead and nerve conduction measurements, the larger the magnitude of the slope, the more sensitive a nerve is to lead exposure. The magnitude of a slope would not be expected to change as the sample size increases or as the precision of the measurements increases, although its precision would improve. Comparisons must be restricted to nerve conduction measurements with the same units, e.g., slopes for velocity cannot be compared to slopes for latency or amplitude.

The lowest concentration at which a relationship can be detected gives an estimate of the concentration of blood lead at which the relationship becomes consistently statistically significant. It is dependent on the number and precision of the nerve conduction measurements, as well as at what blood lead concentrations measurements were made. More measurements at lower concentrations may produce a lower estimate. It is not an estimate of a threshold for lead to have an effect.

The meta-analysis reported here is in part an update of the analysis done by Davis and Svendsgaard (1990). In Table 1 of their paper they presented nerve conduction velocities in m/s by study, group, and nerve. The differences between the exposed and control groups were expressed as percent differences. In Table 2 of their paper they expressed effect size as the exposed group mean minus the control group mean divided by the pooled standard deviation. They found statistically significant decreases between the control and exposed groups in the nerve conduction velocities of the median and ulnar, motor and sensory nerves. In Fig. 4 of their paper, they categorized the effect sizes based on duration of exposure (<6, 6–12, and >12 years) and blood lead concentrations (<25, 25–40, and >40 µg/dl), and plotted the weighted average effect sizes. The effect sizes were weighted by the reciprocal of their squared standard errors. The effect sizes were averaged across nerves. They found that the average effect size became more negative as the duration of exposure increased, but that the average effect size became less negative as the blood lead concentration increased and was positive in the highest blood lead category, indicating an increase in the nerve conduction velocity of the exposed groups.

In the present analysis, the relationships between blood lead and nerve conduction velocity measurements were not paradoxical. Means from the control and exposed were

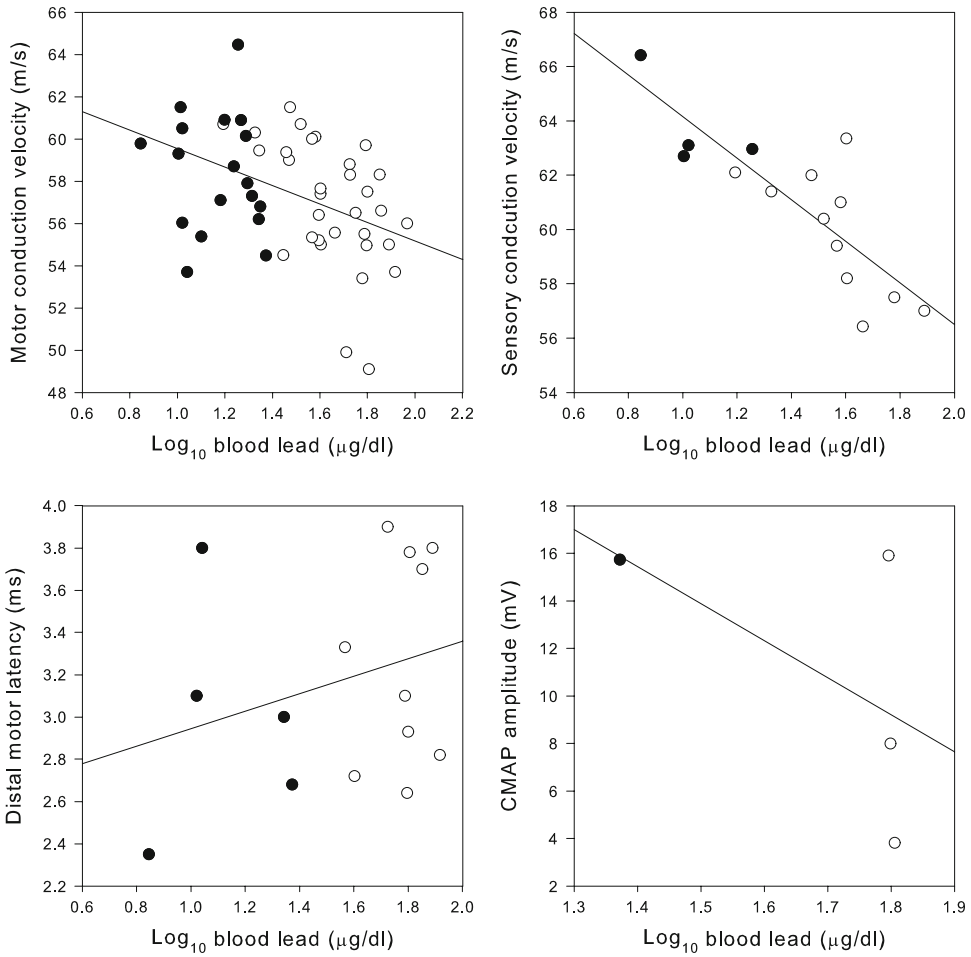

Fig. 2 Nerve conduction measurements as a function of blood lead concentration for the ulnar nerve (contol groups *filled circle*, exposed groups *open circle*)

used. Effect sizes were not used. No standardization or weighting was done. No averages were taken across nerves or across different types of measurements of an individual nerve, i.e., slow or fast fibers, distal or proximal locations. Any of these differences might account for our different results.

In case reports (Boothby et al. 1974; Campbell 1955; Herter 1895; Livesley and Sissons 1968; Preiskel 1958; Simpson et al. 1964), persons chronically exposed to lead and being treated for lead poisoning can have muscle weakness and wasting, and paralysis. The symptoms can improve after chelation therapy. It is usually thought that nerve rather than muscle tissue is affected. For example, Oh (1975) reported the case of a 50 year-old man who drank alcohol contaminated by lead. He was admitted to the hospital because of weight loss, anorexia, and muscle weakness. He complained about abdominal pain. An examination revealed moderate to mild muscle weakness and mild atrophy of the quadriceps. He was treated with calcium disodium edetate. At the time of discharge his muscle strength improved, but he was unable to walk. Prior to his second admission to the hospital, he began to drink again and was bedridden with quadriplegia. Examination revealed paralysis of the upper extremities and bilateral wrist drop. Marked to mild muscle weakness in the lower extremities was noted. Marked to mild muscle atrophy was noted in the upper and lower extremities. He was treated with calcium disodium edetate again. Seventeen months after the second admission, the muscle wasting, weakness, and atrophy were improved. Muscle biopsies, and nerve conduction, electromyography, and neuromuscular transmission studies were performed. It was concluded that the results were consistent with there being axonal degeneration rather than segmental demyelination.

In cats, Aub et al. (1925) found that muscles exposed to lead became more fatigued than control muscles. They observed that muscles paralyzed by lead exposure were the ones most used. In guinea pigs, exposure to lead was found to cause segmental demylination (Gombault 1880) and mixed axonal degeneration and demylination (Fullerton 1966). Segmental demylination has also been found in rats (Lampert and Schochet 1968; Ohnishi et al. 1977). Windebank and Dyck (1985) injected radioactive lead into rats and found it in the endoneurial space and the myelin

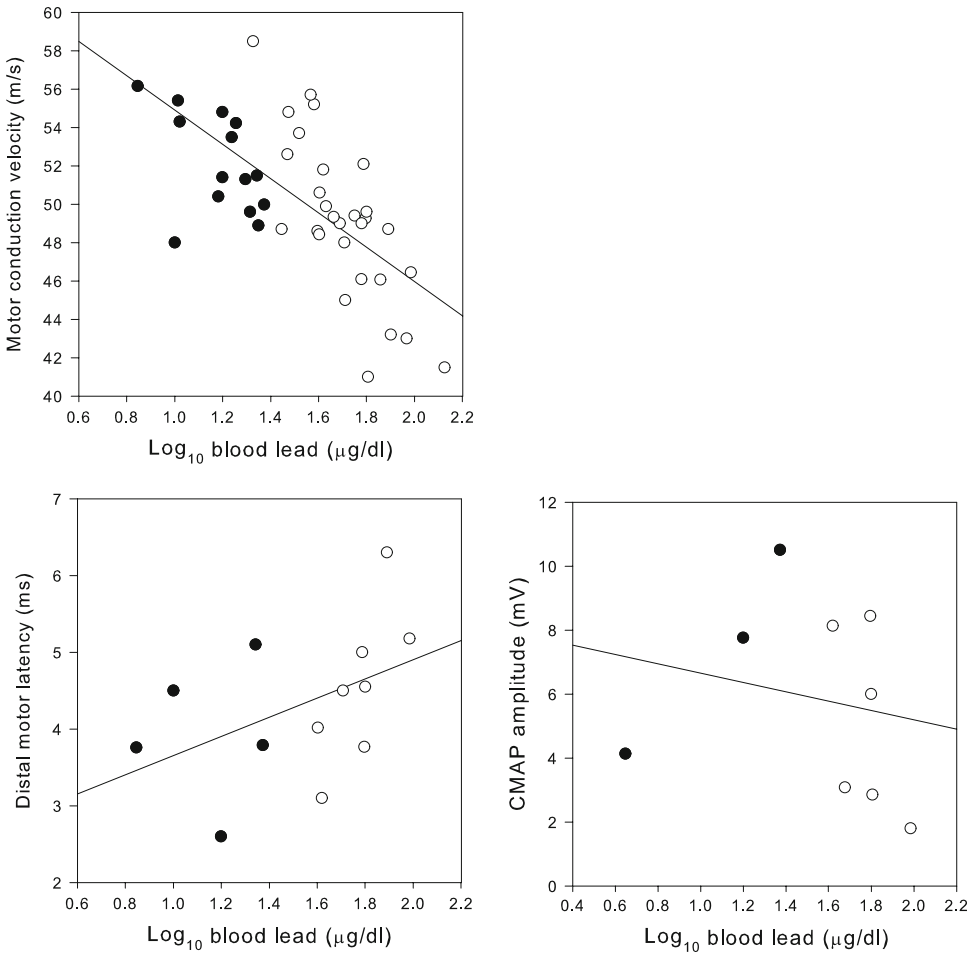

Fig. 3 Nerve conduction measurements as a function of blood lead concentration for the deep peroneal nerve (contol groups *filled circle*, exposed groups *open circle*)

Table 4 The lowest concentrations of blood lead at which a relationship could be detected

Variable nerve	Blood lead (μg/dl)	Studies	*n*	Slope	SE	DF	*t*	*p*	LCL	UCL
Conduction velocity (m/s)										
Median motor	39.4	28	46	−4.26	1.80	16	−2.36	0.0312	−8.07	−0.44
Median sensory	33.0	11	23	−6.66	2.43	10	−2.74	0.0210	−12.08	−1.23
Median sensory, distal	38.1	12	21	−8.03	2.08	7	−3.87	0.0061	−12.94	−3.12
Ulnar motor	60.0	26	50	−3.61	1.58	22	−2.28	0.0323	−6.88	−0.33
Ulnar sensory	40.1	7	15	−4.29	0.95	6	−4.52	0.0040	−6.61	−1.97
Deep peroneal motor	39.4	21	43	−6.46	2.48	20	−2.61	0.0167	−11.63	−1.30
Latency (ms)										
Median motor, distal	64.0	12	24	0.53	0.20	11	2.71	0.0202	0.10	0.96
Ulnar motor, distal	40.1	10	15	0.46	0.06	3	7.21	0.0055	0.25	0.66

Studies number of studies; *n* number of groups; *SE* standard error; *DF* denominator degrees of freedom; *LCL* 95% lower confidence limit; *UCL* 95% upper confidence limit

membrane of the peroneal nerve. In baboons, no morphological changes were found following injections with lead carbonate (Hopkins 1970).

In a study of 20 men who worked at a lead smelting and refining factory (Buchthal and Behse 1981), no evidence of axonal degeneration or abnormalities of the myelin sheath were found in the sural nerve. Their blood lead concentrations ranged from 70 to 144 μg/dl. The nerve conduction velocities of the men were slower in the median, superficial peroneal, and sural nerves. The motor latencies of the men were longer in the median and deep peroneal nerves. The amplitudes of their sensory nerve action potentials were

increased in the median and superficial peroneal nerves. The authors concluded that lead may prolong the rise time of the transmembrane potential at nodes of Ranvier.

Lead may have multiple sites and mechanisms of action in affecting nerve conduction. In addition to a direct action on nerve or muscle tissue, lead may affect nerve conduction indirectly. For example, lead exposure can result in damage to the kidneys (Loghman-Adham 1997), disorders of peripheral nerves are associated with chronic renal failure (Bolton 1980), and nerve conduction velocities improved in persons receiving kidney transplants (Oh et al. 1978). A recent review of epidemiological evidence indicated that lead can be nephrotoxic when below 5 μg/dl in blood (Ekong et al. 2006). Another possibility is the liver. Persons with acute hepatic porphyria can have symptoms similar to persons with lead poisoning, including abdominal pain, constipation, and motor neuropathy, as well as an increase in the production of δ-aminolevulinic acid (Bonkowsky and Schady 1982). Lead also increases the amount of δ-aminolevulinic acid by inhibiting δ-aminolevulinic acid dehydratase (Piomelli 1980). δ-aminolevulinic acid can bind to the receptors of γ-aminobutyric acid, an inhibitory neurotransmitter in the central nervous system (Müller and Snyder 1977).

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