Final Progress Report

Occupational Lead Exposure: Risk to the Aging Worker (OH03891-03)

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Abstract

This study investigated neuropsychiatric changes associated with lead exposure. Persons with past and current exposure to lead were compared to a demographically similar non-exposed control group. That is, between 1981 and 1984, lead-exposed and non-exposed workers were evaluated as part of an epidemiological study of lead conducted at the University of Pittsburgh. Lead-exposed workers were members of District 10, United Steel Workers of America, and worked at three industrial plants in Eastern Pennsylvania (approximately 200 miles from Pittsburgh) that manufactured lead batteries for automobiles and motorcycles (one of the three plants is still in operation). At the initial testing, subjects were randomly selected from company lists: the lead-exposed workers had a mean age of 35 (range 21-60) and blood lead levels averaged 40 μg/dl, with peak blood levels around 90 μg/dl. Demographically similar non-exposed blue-collar workers were also seen for the initial study (mean age = 35). For the current study we attempted to recruit as many subjects as possible who were initially tested approximately 20 years ago and to repeat the neuropsychological test battery. In addition, information was collected on current and past psychiatric history, and current blood lead levels (BLL) were obtained. Finally, bone concentration of lead was determined with x-ray fluorescence (XRF) – a procedure that was not available 20 years ago.

We were able to contact 169 of the subjects who had been evaluated 20 years earlier. We originally estimated we would be able to locate 212 subjects. Of the 169 subjects who were located, 141 (83.4%) traveled to Pittsburgh (more than a three hour drive with an overnight stay) for the assessment. Of the 141 subjects who completed the entire testing, 89 were lead-exposed workers and 52 were controls. We saw our final subject two months ago. At this date, we have begun preliminary analysis of the data. Because prior research suggested that mobilization of lead stores from bone increases with advancing age, we have assessed the relationship between bone lead and blood lead level for subjects across age groups. At the time of the current assessment the average blood lead level was 10.93 ug/dL and tibia bone lead concentrations ranged from -12.58 to 223.33. Correlations between blood lead and bone lead were highest in the middle and oldest age bands (.49 and .75, respectively). Hierarchical regression analyses demonstrated that the interaction of bone lead and age significantly predicted current blood lead levels. The results support the hypothesis that lead stored in bone is a significant source of blood lead later in life and suggest that older workers with past occupational exposure may face a particular risk for recirculation of lead in blood with advancing age. Preliminary analyses are also currently being done to examine the change in neuropsychological function. Lead workers have poorer scores on the majority of neuropsychological tests. In addition, a comparison between the initial neuropsychological testing and the current testing shows that bone lead levels are related to neuropsychological decline. That is, workers with higher levels of bone lead show significantly more impairment on measures of problem solving, spatial reasoning and overall cognitive function, even after controlling for confounding variables (e.g., education, medical risk factors) and baseline neuropsychological performance. These findings suggest that lead exposure may pose a significant risk factor for cognitive decline in later years.

Significant Findings

Results of this study will have several important implications. This study will provide detailed information concerning the relationship of prior exposure to lead and cognitive and psychiatric function in aging workers. No other study to date has integrated these factors. We collected measures of cumulative and current lead exposure in a large group of older workers with long-term exposure to lead. We will be able to address the hypothesis that persons with higher cumulative exposure (i.e., as shown with XRF) will have higher blood lead levels due to remobilization of lead in later life – a hypothesis that is currently supported by the data analysis. This research will also allow us to determine if cumulative bone lead levels are related to poorer cognitive performance in later life. Preliminary analysis show that certain cognitive functions, particularly those involving higher level problem solving, reasoning, and visuospatial analysis seem to be particularly susceptible to the long-term effects of lead exposure. That is, scores on those cognitive functions were significantly related to bone lead levels after controlling for initial test scores and other medical risk factors. Our initial study aim also included assessment of psychiatric status – Axis I and Axis II diagnoses - and this data is currently being analyzed.

Translation of Findings

Our preliminary findings indicate that older workers with a history of lead exposure have remobilization of lead stores as they age. This migration of stored lead into the blood stream in older workers poses a potential hazard for older lead-exposed workers. In addition, bone lead levels are predictive of cognitive decline over a 20 year span. These data have important theoretical and occupational health implications in assessing relative risk for development of neuropsychiatric disease/disorder in older workers. While permissible exposure limits for lead have been reduced over the past decades, data from other studies and from this project lend support to the belief that lead exposure should be minimized as much as possible in the workplace. Moreover, physicians should be made aware that older workers with past exposure to lead may be at risk for elevated blood lead levels in later years and a screening may be recommended for such workers. We currently have a draft paper of this data and one of the goals of the paper to make primary care physicians aware of this possible source of elevated blood lead levels in older workers.

The demonstration of an association between bone lead levels and central nervous system disorder in later life would have practical applications as well. Over 1 million workers continue to be employed in lead-handling trades. The application of more sophisticated epidemiological designs and more sensitive measures of outcome and exposure to the question of low level neurotoxicity have demonstrated neurotoxic effects of lead at lower and lower internal doses. Thirty years ago, lead toxicity was thought to occur at blood lead levels of $60 \mu g/dl$. The current definition of lead toxicity is $10 \mu g/dl$. It is now well established that children with moderately elevated blood lead levels, but no signs or symptoms, have lower IQ scores, poorer attention, impaired language function and more antisocial behavior, and these impairments do not seem to recede over time. Many workplaces still involve lead handling and lead exposure.

Does lead exposure increase their risk for early onset mental decline? This study will provide data to directly address this issue.

Scientific Report

Between 1981 and 1984, 288 lead-exposed workers and 182 non-exposed controls were evaluated as part of an epidemiological study of lead carried out at the University of Pittsburgh (MH36221). Lead-exposed workers were members of District 10, (District Local 3733) United Steelworkers of America, and worked at three industrial plants in Eastern Pennsylvania that manufactured lead batteries for automobiles and motorcycles. Only workers with no previous exposure to neurotoxins, except lead, were recruited into the lead-exposed group. The controls were employed in a heavy industrial plant in Eastern Pennsylvania that manufactured auto and truck chassis. All were native English-speaking males. Subjects were randomly selected from company lists. The PI was involved in analyzing part of this data set. At that time, the workers had a mean age of 35 (range 21-60). Today, these workers are age 40 and over. We were able to contact 169 of the subjects who had been evaluated 20 years earlier. We originally estimated we would be able to locate 212 subjects. Of the 169 subjects who were located, 141 (83.4%) traveled to Pittsburgh (more than a three hour drive with an overnight stay) for the assessment. Of the 141 subjects who completed the entire testing, 89 were lead-exposed workers and 52 were controls.

The Specific Aims are those that we initially described in application. The four major aims and four hypotheses were:

Specific aims:
1) Administer a battery of cognitive tests to assess neuropsychological function and information processing capacity.
2) Use X-ray fluorescence (XRF) to estimate cumulative lead exposure.
3) Measure blood lead levels (BLL) to quantify current circulating lead.
4) Gather information on psychiatric function, health and alcohol medication use.

Hypotheses to be tested:
1) Exposed subjects will have poorer neuropsychological test scores and more psychiatric dysfunction.
2) Exposed subjects will show steeper performance declines across the age range compared to controls.
3) Exposure will be predictive of performance, with a dose-response pattern.
4) Higher bone lead concentration will co-vary with current blood lead levels.

Alcohol was quantified in the previous study and we quantify current and past drinking history for the present assessment. Workers were also screened for psychiatric and substance abuse histories at the initial testing, as well as serious head injury, neurologic, renal and hepatic disease. At the present testing, the medical history gathers information on disease state since the prior assessment, as well as medication use. We also obtain information on smoking and assess current blood pressure. Subjects

are asked to refrain from drinking alcoholic beverages in the 48 hours prior to the testing.

Preliminary Results:
Correlation between BLL and XRF in Lead Workers: As bone ages, stored lead may be remobilized into the blood stream. Post-menopausal women have been found to have significantly higher blood lead levels, suggesting a remobilization of lead from bone through involutional osteoporosis. A more recent study of a large cohort of elderly women with no current exposure found relatively low blood lead levels (mean = 5.26 μg/dl) but an inverse relationship to cognitive test scores. Although the circulating blood lead levels were low, they were hypothesized to be a surrogate marker for past cumulative exposure. That is, current blood lead levels were higher in those persons with higher past environmental exposure. Given the wide age range of subjects in the current study we divided subjects into three age bands (40-49; 50-59 and 60+). Correlations were computed between blood lead levels and XRF. In the younger age bands, the correlations were small and insignificant ($r = .25$). However, in the older age bands (none of these subjects were currently working), the correlations were higher, with the highest correlation found for the oldest age band ($r = .735$, $p < .01$). Hierarchical regression analyses demonstrated that the interaction of bone lead and age significantly predicted current blood lead levels. The current finding of a strong association between blood lead levels and XRF in this older, occupationally exposed cohort suggests that in these workers lead is being mobilized from bone with the onset of bone loss in age. Thus, older workers with moderately high past exposures may face an additional neurotoxic hazard due to lead re-mobilization long after exposure. A paper related to these data is in preparation.

Cumulative Lead Exposure and Neuropsychological Function: For the current assessment, lead exposed subjects and non-exposed controls do not differ in age, but overall education is slightly higher for controls. In the present evaluation, 60% of lead-exposed workers had not worked with lead for over a year, while 40% were currently working at the time of their assessment or worked within the past year. The Pittsburgh Occupational Exposures Test (POET) Battery was administered at the initial and follow-up assessment. The POET measures a range of cognitive skills (general intelligence, learning and memory, visuospatial, attention, perceptuomotor efficiency, and speed and dexterity) and has been shown to discriminate solvent-exposed persons from demographically similar controls. Included are subtests from the Wechsler Adult Intelligence Scale and the Wechsler Memory Scale, and the Halstead-Reitan Battery. A Multivariate analysis of variance (controlling for education) was done to compare lead exposed and non-exposed subjects. The lead-exposed subjects had significantly lower scores on the majority of cognitive tests. Statistically significant group differences were found for the cluster of visuospatial tests [$F(73,6) = 2.94$, $p < .04$], as well as Learning and Memory cluster and the Attention and Mental Flexibility cluster. Results of a hierarchical regression analysis on neuropsychological outcome variables were done for two neuropsychological tests from each cluster. Age and education were entered in the first model, followed by blood lead levels in the second model and XRF in the third model. Not surprisingly age and education accounted for a significant amount of the variance for most

tests. However, bone XRF accounted for a significant portion of the variance on the visuospatial measures, Trails B, Block Design and Picture Completion.

<u>Longitudianal Change in Neuropsychological Test Scores</u>: Preliminary analyses have begun assessing change over time in neuropsychological test scores. Scores on all of the POET tests for all subjects in the current data base were converted to z-scores. Initial test scores from 20 years ago (time 1 scores) were compared to test scores at the current testing (time 2 scores). Scores were clustered according to domains of functioning (e.g., visuospaital, mental flexibility, motor speed, etc) and an overall score for each domain was calculated. Linear regression analysis was conducted to look the relationship between XRF and performance at time 2, after taking into account education, medical variables, depression, income and controlling for baseline cognitive performance. The presence of higher levels of bone lead were significantly predictive of decline on tests in the visuospatial domain, mental flexibility and executive function, and overall cognitive status (adjusted R^2 = .60 and above). These results support the hypothesis that lead exposure may pose a significant risk for later decline in cognitive function. Our results are in line with findings from a group of researchers at Johns Hopkins. In that earlier study a large cohort study of former Tetraethyl lead workers and controls were evaluated approximately 16 years after their workplace exposure. Findings indicated elevated bone lead levels and dose- related deficits in visual memory, executive ability and manual dexterity in their lead-exposed subjects. Lead workers showed a greater decline in across time compared to controls. Our current data analysis is on-going and a draft paper is in the initial stages.

Inclusion of Gender and Minority Study Subjects
The aim of the current study is to estimate prevalence of neuropsychiatric disease in retired lead workers, so our sample is constrained by the demographics of this group. Because this was a follow-up assessment of workers in a previous study, testing was done on only those subjects. Therefore, no women or children were assessed in this project.

Related Publications
L. Morrow, H. Needleman, K. Metheny, C. McFarland & D. Sandstrom. Cumulative Lead Exposure and Neuropsychological Function. Paper presented to the International Neuropsychological Society Meeting, Toronto, 2002.

Materials Available for Other Investigators
Not applicable.

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