

I. Abstract Summary

Summary of Study Results

The objective of this study was to determine the effects of exposure to organic (mainly tetraethyl lead) and inorganic lead on the central and peripheral nervous system in workers in the Antiknocks area of DuPont's Chambers Works plant. A total of 222 lead-exposed workers and 62 non-exposed controls were tested in March-June 1990.

Main Study Conclusions

1. Exposure to organic and inorganic lead was consistently associated with poorer performance on many of the neurobehavioral measures (see TAB J for a summary of the associations).
 2. All of the significant exposure-outcome associations clustered into three specific neurobehavioral functional domains: verbal memory, attention/concentration, and speed and accuracy of mental/motor executive functions (see TAB E for a description of these domains).
 3. Exposure to organic and inorganic lead was associated with reporting of more neuropsychiatric symptoms, as measured by the Minnesota Multiphasic Personality Inventory, the Present State Examination, and the Scandinavian Questionnaire 16 (see TAB J).
 4. No associations were found between organic and inorganic lead exposure and vibration threshold (a measure of peripheral nervous system damage) or olfactory function.
 5. The findings noted in numbers 1-4, above, were not significantly altered after controlling for important factors (confounding variables) known to affect performance on these tests (such as education or alcohol intake). Multiple linear regression was used to control for a group of five confounding variables (age, educational level or vocabulary score, smoking history, alcohol history, and race) in all analyses.
 6. Control for another potential confounding variable, exposure to other neurotoxins, both occupationally and avocationally, did not appear to alter the conclusions. Analyses with this variable are ongoing.
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Additional Important Comments

- While causal inferences can not be conclusively determined from a cross-sectional epidemiologic study, these results are suggestive that organic and inorganic lead adversely affects the central nervous system.

- The affected domains correspond to the neuroanatomic areas found to be targets of the toxicity of organic and inorganic lead in animals (hippocampus--verbal memory; limbic forebrain, frontal cortex and cerebellum--attention/concentration and speed and accuracy of mental/motor executive functions)

- The plots of some of the relations between the outcomes and the exposure and dose variables indicate that some of the associations are not interpretable at this time (e.g., are U-shaped, such that in workers with high exposure neurobehavioral function improves), despite significant findings from the regression models (TAB P). The two major competing explanations for these plots--that there is no association or that selection bias accounts for the results--would have to be sorted out in a prospective study.

- The interpretation of the U-shaped plots may be facilitated by these two further points:

- 1) Our understanding of the Antiknocks area is that thousands of workers have been employed there since its inception. This cross-sectional study of 222 current workers thus reflects the results from a cohort with much out-migration; selection bias may be a significant problem.

- 2) Many of the U-shaped associations became more linear and in an adverse direction after elimination of a group of workers with the highest exposure or internal dose values.

- It should be noted that our conclusions are based on exposure to inorganic and organic lead combined; only one of the 7 exposure and dose variables cumulates only organic lead. However, we feel that, because organic lead represents the majority of lead exposure in the area and because this species of lead is more lipophilic, the observed associations are more likely due to organic lead.

- Results from a prospective study would offer critical evidence to determine whether exposure to organic and inorganic lead is causally associated with brain dysfunction. Efforts to seek funds for this prospective study are currently underway.

Secondary Findings

1. A number of non-exposure covariates were strongly and consistently associated with outcome measures: increasing age was consistently associated with lower performance on most of the neurobehavioral tests; workers with less than 12 years of education performed worse on a number of the outcome measures; and the higher the vocabulary score (a measure of verbal intelligence) the better the performance on the neurobehavioral tests.

2. Cumulative smoking history and alcohol consumption show no consistent association with the neurobehavioral measures (i.e, both adverse and protective associations were found, depending on the outcome).

3. The exposed group versus control group comparisons revealed that organic and inorganic lead workers performed worse on several neurobehavioral tests. The exposed group also reported significantly more neuropsychiatric and physical symptoms than the control group. These results did not change appreciably when controlling for either education or vocabulary. These findings were considered most important when additional analyses documented a dose-effect relation.

4. The results of the analyses using 3 external exposure variables and 4 internal dose variables (urine, blood, and zinc protoporphyrin) showed adverse dose-response relations between exposure to organic and inorganic lead and several neurobehavioral outcomes. Organic and inorganic lead workers with higher exposures reported significantly more neuropsychiatric symptoms than less exposed workers. These results did not change appreciably when controlling for either education or vocabulary.

5. Based on the large number of regression models performed, by chance alone, 27 comparisons would be expected to be significant at $\alpha = 0.05$ ([8 exposure variables] x [2 methods for control of premorbid intellectual ability] x [34 outcome measures] x 0.05). Utilizing several different definitions of statistical significance, more outcomes were associated with the exposure and dose measures than would be expected by chance alone.