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Dear David:

Enclosed please find my review of the various analyses of the association between blood lead concentrations and blood pressure level in the NHANES sample. Please call me at (617) 732-1056 if you have any questions.

Sincerely,

James H. Ware
Assoc. Professor

COMMENTS ON

# ANALYSES BY THE DUPONT CORPORATION, J. SCHWARTZ, AND J. R. LANDIS RELATIVE TO BLOOD LEAD AND BLOOD PRESSURE RELATIONSHIPS IN THE NHANES DATA

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## SUMMARY

Comments on the recent corrigenda to the Lead Criteria Document submitted by the Du Pont Corporation challenge the finding by Harlan et al. (1985) and Pirkle et al. (1985) of an association between blood lead concentration and blood pressure among men participating in the NHANES survey, noting that the analyses failed to control for temporal trends and for geographic covariation of blood lead and blood pressure. The issues raised in these comments merit consideration and have been addressed in the analyses submitted by Du Pont, Joel Schwartz, and J. Richard Landis. These analyses show that the association is not explained by known confounding variables and that adjustment for time of examination or for examination site reduces but does not eliminate the association. Some inconsistencies in the analyses remain to be explained. Given the lower sensitivity of the within-site analysis, these results are consistent with the earlier finding of an association between blood lead concentration and blood pressure level among male participants in NHANES.

This commentary draws on seven documents discussing the relationship between blood lead concentrations and blood pressure

levels of male participants in the NHANES survey. The first of these are two published papers (Harlan et al. 1985, Pirkle et al. 1985). The third is a set of corrigenda to the lead criteria document (Docket No. ECAO-CD-81-2) made public on April 8, 1985. The fourth is a set of external comments on those corrigenda submitted by the Du Pont Corporation on May 9, 1985. The last three are a memorandum submitted to CASAC by Joel Schwartz at the meeting of May 13-15, a subsequent memorandum sent to the reviewers through David Weil, and an unpublished article by Richard Landis, also written after the CASAC meeting. These last three documents address the issues raised by Du Pont.

Harlan et al. (1985) reported a statistically significant positive association between blood lead concentrations and both systolic and diastolic blood pressure levels among males age 12 to 74 participating in the NHANES survey. A further analysis by Pirkle et al. (1985) found a somewhat stronger positive association among males aged 40 to 59. Both analyses relied upon multiple regression models, with blood pressure level as the dependent variable and the logarithm of blood lead concentration as the primary independent variable. The investigators showed that the size and statistical significance of the regression coefficients for blood lead were insensitive to adjustment for an extensive set of demographic, nutrition, and health variables. Du Pont acknowledged the association between blood lead

concentration and blood pressure, but suggested that it may have arisen either from temporal trends in both blood lead and blood pressure levels during the period of the NHANES examinations or from other sources of geographic covariation in blood lead and blood pressure over the 64 examination sites in the NHANES survey. Du Pont, Mr. Schwartz, and Dr. Landis have submitted additional analyses addressing this issue. Subsequent paragraphs discuss the validity of the Du Pont critique and the implications of these additional analyses.

In this reviewer's opinion, the issue raised by Du Pont deserves serious consideration. Comparisons between populations, or between subpopulations divided geographically, are often called ecologic analyses and are known to be vulnerable to certain kinds of bias. One potential sources of bias in such analyses is geographic variation in demographic, ethnic, or nutritional factors that induces an association between blood lead concentration and blood pressure level. A second possibility is coincident temporal trends in blood lead and blood pressure, which would be expressed as covariation between sites because sites were visited sequentially. More generally, however, blood lead and blood pressure may covary geographically for reasons that are not well understood but which may not reflect a causal relationship. An analysis of the association between blood lead and blood pressure values within sampling sites would not be confounded by

geographic covariation and would provide a new perspective on the original findings. Because much of the total variability in blood lead concentration is between-site variation, however, analyses of within-site variability will be less sensitive than than those which consider all variation in blood lead values. In particular, within-site analyses do not utilize seasonal, urban-rural, and other potentially informative differences between sites.

Demographic variables do not appear to be a source of confounding in these analyses. Schwartz considered a variety of different demographic variables, and found that they had very little effect on the size or the significance level of regression coefficients for blood lead. He also investigated the issue of coincident temporal trends. Blood lead concentrations decreased over time in the NHANES survey, in part because of reductions in gasoline lead, but also because of predictable urban-rural and geographic differences in blood lead concentrations among NHANES sites. Blood pressure levels may also have been falling during this period (although Schwartz suggests that they were not). Such a trend could have arisen from national trends in health consciousness along with the specific effects of the National High Blood Pressure Program, as well as any effects of declines in blood lead concentrations. To eliminate bias due to such trends, Schwartz examined the effect of including date as a covariate in each multiple regression model. This maneuver will eliminate the

association between blood lead and blood pressure due to linear trends in the two measures over time, but will not eliminate seasonal covariation in the two variables or geographic covariation that it is not colinear with time. In his memo to CASAC for the May 13-15 meeting, Schwartz reported that the regression coefficients for blood lead remained significant at the 0.02 level in these models. (There is an inconsistency between the text and Table VIII of this report. I have taken the value quoted in the text.) These analyses show that the association is not explained by linear trends over time. Residual confounding from seasonal covariation of blood lead and blood pressure values or from other sources of geographic covariation in blood pressure and blood lead is still a possibility in these models.

A more comprehensive approach, proposed by Du Pont, is to control for site (primary sampling unit) by including 63 indicator variables for site in the multiple regression model. In this approach, the coefficient for blood lead is a weighted average of the 64 site-specific values for the NHANES sites. This analysis eliminates any spurious ecological correlation, but at the cost of losing any information contained in the geographic and temporal variation in blood lead concentrations. Thus, it tends to be less sensitive to true associations between blood lead and blood pressure. Mr. Schwartz addresses this issue very cogently in his response to the Du Pont critique, pointing out the loss of power

and noting that, because errors of measurement represent a larger fraction of the within-site variability in blood lead, the within-site regression coefficient for blood lead will have a larger bias toward zero due to errors in the independent variable than the regression coefficient based on total variability. Thus, within-site analyses will tend to produce smaller regression coefficients and larger significance levels, even when the true within-site and between-site coefficients are equal.

A review of the findings reported by Du Pont and Mr. Schwartz reveals some disagreements about the size of the adjusted regression coefficients. Both analyses report various models controlling for site and both find that the regression coefficients for blood lead are smaller in the adjusted than in the unadjusted analyses (Table 1). In the Du Pont analysis, none of these coefficients achieved statistical significance. Although standard errors are not provided, an indirect argument suggests that these adjusted coefficients are approximately 1.5 standard errors above 0, which would imply a two-sided P-value of between 0.20 and 0.10. Schwartz, however, reports coefficients of 1.39 ($P<.05$) and 3.23 ($P<.01$) for diastolic blood pressure (DBP) and systolic blood pressure (SBP), respectively, for males greater than 20 and 3.12 ($P<.05$) for DBP for men aged 40 to 59 after controlling for 64 sites. No results for SBP were reported for males aged 40 to 59, but Schwartz comments with good justification

that the results for SBP are consistently more highly significant than those for DBP. Thus, Schwartz obtains somewhat larger regression coefficients than the Du Pont analysis. A complete comparison of results reported by Schwartz and Du Pont for the same model shows some additional differences in results. In view of the importance of this issue, Mr. Schwartz and the Du Pont analyst should be asked to explore these differences.

In a related set of analyses, Landis employs a generalization of the Mantel-Haenszel method to test the hypothesis of no association between blood lead concentration and DBP after controlling for site, three age strata, and three categories of body mass index. He finds that the association is statistically significant at the 0.05 level.

For the moment, some uncertainty remains regarding the magnitude and statistical significance of the regression coefficients for blood lead after adjusting for site. The available results suggest, however, that the adjusted coefficients are somewhat smaller than the unadjusted coefficients and significant or nearly significant at the 0.05 level. Given the expected loss of sensitivity and increased bias toward zero of regression coefficients for blood lead in the analyses controlling for site, these results are reasonably consistent with previous analyses. In particular, a test for equality of the between-site and within-site regression coefficients would probably not achieve

statistical significance. Since the possibility of confounding of unknown origin is not a sufficient basis to completely discount the original analyses and because the within-site analyses show a marginally significant association between blood lead and blood pressure values, I interpret the available results as indicative of an association between blood lead concentration and blood pressure level among male participants in NHANES that is not explained by known confounding factors.

## REFERENCES

Harlan WR, Landis JR, Schmouder RL, Goldstein NG, Harlan LC. Blood lead and blood pressure: Relationship in the adolescent and adult U.S. population. J Amer Med Assoc 1985;253:530-534.

Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epid 1985;121:246-258.

Table 1

Coefficients for logarithm of blood lead concentration in models with and without site variables for all males and for males aged 40 to 59 years.

| | Unadjusted | Adjusted |
|---|---|---|
| All males | | |
| Du Pont (12-74) | | |
| Diastolic | 2.02 *** | 0.36 |
| Systolic | 3.43 *** | 1.95 |
| Schwartz (21-74) | | |
| Diastolic | 2.96 *** | 1.39 * |
| Systolic | 5.23 *** | 3.23 ** |
| Males Aged 40 to 59 | | |
| Du Pont | | |
| Diastolic | 4.01 ** | 1.93 |
| Systolic | 6.27 ** | 3.46 |
| Schwartz | | |
| Diastolic | 4.67 *** | 3.12 * |
| Systolic | 7.65 *** | -- |

* P<0.05, ** P<0.01, *** P<0.001