UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

July 1, 1985

Dr. Richard Royall
Dept. of Biostatistics
Johns Hopkins University
615 N. Wolfe St.
Baltimore, MD 21205

Dear Dr. Royall:

As I trust you will recall from the CASAC meeting on the Lead Criteria Document, a number of important questions concerning the relationship between blood lead and blood pressure were raised by the Du Pont Corp. in their comments on the Corrigenda to the CD. It was decided at the meeting that the best way to answer those questions would be for Joel Schwartz to perform additional analyses which directly addressed the points raised by Du Pont, and to have you and Dr. Royall review both the comments and the responses.

Attached, you will find the following items:

1.) the Corrigenda to the Lead Criteria Document, which contains a discussion of the papers by Pirkle et al.(1985), Harlan et al. (1985), Pocock et al. (1984), etc...

2.) the comments on the Corrigenda from the Du Pont Corp.

3.) a response to the Du Pont comments prepared by Joel Schwartz.

We would very much appreciate it if you could find the time to review this material and provide us with a brief written opinion about whether or not Joel has adequately responded to the Du Pont concerns. I have made arrangements with our Contracts office to reimburse you for your efforts and someone should be contacting you shortly to "negotiate" your contract (I told them that 5 working days should be sufficient to complete this task). In case you have any questions, please feel free to call either myself [(919)541-4163] or Joel Schwartz [(202)382-2782].

If at all possible, we would like to receive your reply by the end of July. If the additional material from Dr. Dick Landis that Joel mentions in his cover memo arrives before then, we will send it along. Thank you again for your help and cooperation in this matter.

Sincerely,

David E. Weil,
Project Manager,
Lead Criteria Document

NOTE:
SEE IIA.D.5 FOR ATTACHMENTS

ECAO-CD-81-2
IV.A.D.5

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

July 1, 1985

Dr. James Ware
Dept. of Biostatistics
Harvard School of Public Health
677 Huntington Ave.
Boston, MA. 02115

Dear Dr. Ware:

As I trust you will recall from the CASAC meeting on the Lead Criteria Document, a number of important questions concerning the relationship between blood lead and blood pressure were raised by the Du Pont Corp. in their comments on the Corrigenda to the CD. It was decided at the meeting that the best way to answer those questions would be for Joel Schwartz to perform additional analyses which directly addressed the points raised by Du Pont, and to have you and Dr. Royall review both the comments and the responses.

Attached, you will find the following items:

1.) the Corrigenda to the Lead Criteria Document, which contains a discussion of the papers by Pirkle et al.(1985), Harlan et al. (1985), Pocock et al. (1984), etc...

2.) the comments on the Corrigenda from the Du Pont Corp.

3.) a response to the Du Pont comments prepared by Joel Schwartz.

We would very much appreciate it if you could find the time to review this material and provide us with a brief written opinion about whether or not Joel has adequately responded to the Du Pont concerns. I have made arrangements with our Contracts office to reimburse you for you efforts and someone should be contacting you shortly to "negotiate" your contract (I told them that 5 working days should be sufficient to complete this task). In case you have any questions, please feel free to call either myself [(919)541-4163] or Joel Schwartz [(202)382-7782].

If at all possible, we would like to receive your reply by the end of July. If the additional material from Dr. Dick Landis that Joel mentions in his cover memo arrives before then, we will send it along. Thank you again for your help and cooperation in this matter.

Sincerely,

David E. Weil,
Project Manager,
Lead Criteria Document

SUBJECT: Time trends and site effects in the NHANES blood lead-blood pressure relationship.

FROM: Joel Schwartz
U.S. Environmental Protection Agency

TO: James Ware
Clean Air Science Advisory Committee

I am enclosing the copy of the memo I submitted to CASAC this spring on the blood lead-blood pressure relationship as I promised you. It contains the discussion of the time trend analysis that I discussed. This memo will expand on my reasons for thinking that the time trend issue and site effect issue should be treated separately.

DOES A TIME TREND CONFOUND THE NHANES BLOOD PRESSURE ANALYSIS?

Before discussing the results of my analysis a few general points seem useful. While the United States has seen a long term trend of falling cardiovascular death rates over the last thirty years, the same is not true for blood pressure. The drop in cardiovascular deaths seems primarily due to the fall in mean serum cholesterol levels and smoking, the other two factors associated with CVD in the Framingham study. The average blood pressure in NHANES II and in the Framingham study (mostly 1950's data) was identical to within 0.1 mmHg. The NHANES I survey in the early 1970's had mean diastolic blood pressure levels of .61 mmHg above the NHANES II survey, but the NHES survey in the early 1960's showed the same levels as the NHANES II and Framingham studies. Thus the issue is not whether there has been a long term trend that the NHANES II blood lead levels correlated with, the issue is whether some other factor changed during that four year time period. Four years is a short time period for a secular trend in blood pressure to appear in, and the only factor that I know of that has been linked to blood pressure and might plausibly create a trend in the NHANES II data (other than lead) is the increased use of hypertensive medication for mild hypertension during the 1970's. Table 5, in the enclosed memo, shows the results excluding persons taking hypertension medication. They therefore cannot be confounded by that trend. It is interesting to note that gasoline lead use rose suddenly with the rapid rate of growth of gasoline demand, and premium leaded demand, in the late 1960's and early 1970's, and then fell with the introduction of leaded gasoline. This may account for the slightly higher blood pressures in NHANES I than either the prior or later surveys. In any case, the shortness of the time period and the absense of any historical data suggesting a blood pressure time trend makes the hypothesis of confounding of lead with an ommitted factor less likely, although obviously possible. The fact that no one has

suggested what that factor could be, and the extensiveness of our list of variables makes it less likely.

I mentioned in our conversation that we had used an interaction term to test for a change in the blood lead/blood pressure relationship in the second half of the NHANES II survey when the blood lead levels were falling much more quickly than in the first half. This is mentioned in the text of the memo, and the p -values are given in the copy of the overhead transparancies I used, which are also enclosed. I also used date of examination in several regression models. Table VII, in the memo shows Dr. Garside's model -- lead is significant and date is not. Table VIII shows my model, for both systolic and diastolicd blood pressure. Both lead and date are significant. Table X shows Dr. Gartside's latter model, lead is significant, but date is insignificant for systolic blood pressure. The last page of the overhead slides shows the same regression results for 25 age subgroups for diastolic blood pressure. Date was insignificant in every subgroup. Thus lead is significant in multiple model specifications when date is in the model, whereas date is often insignificant. In earlier analysis, seasons were considered (see the paper that I presented to the Canadian Royal Society, which Les Grant sent to you before the CASAC meeting. I am also enclosing a revised version) and were insignificant when lead was in the model, and did not effect its significance or magnitude. Note also that in the Harlan et al. paper in JAMA, they found that lead correlated with blood pressure in each of the four years of the NHANES II study.

I believe that these tests are more appropriate to determine whether a time trend in some unknown factor influencing blood pressure during the 4 years of the NHANES could have caused the correlation between blood lead and blood pressure. I do not think that the site variables should be used to test that problem. The reason is quite simple. Lead varied over time according to a complex pattern, depending on changes in demand for gasoline, changes in urbanization, etc. Using 64 dummy variables to represent psu stands does more than remove simple time trends, or even seasonal effects. It is very similar to the way a compact digital disc system works. A recorder for making compact discs samples the voltage produced by the microphone 50,000 times per second and records the mean level for that interval. Those levels contain enough of the information of the complex waveform produced by 100 instruments playing different notes with different harmonics, so that your ear is unable to distinguish the output form the real data. Likewise, 64 location dummies remove not merely the general time trend, but the very detailed specific nature of the time trend in lead levels, with its strong seasonal components, change in rate of fall, etc. If there were evidence of any other factor which effects blood pressure changing over that short period of time, and if such factor were ommitted, there might be reason for such a conservative approach. But given the absense of such unidentified factor, and the measurement errors in both lead and blood pressure I discussed before, I believe that such an

approach is unnecessarily conservative. The question of whether there are site effects that are truely geographic effects, and not proxies for time is a separate issue.

ARE THERE TRUE SITE EFFECTS THAT CONFOUND THE BLOOD LEAD BLOOD PRESSURE RELATIONSHIP?

There may be. The question is what is a site, what variables control for it, and how should the analysis be done. If the issure is factors such as urbanization, I dealt with that in the Royal Society paper, and my previous memo to you. In the Royal Society paper I considered family income (three levels), poverty index (percent of poverty level), region of the country, degree of urbanization (8 levels), residence inside central city, educational level, and race. These were considered in the stepwise regression both only with nutritional variables significant at the 0.15 level previously, and with all other variables. They were also considered without lead being a candidate for the regression, and in my memo to you they were forced into the regression. Clearly, there is no confounding with these variables.

If there are locational factors that are neither regional location nor urbanization, they are presumable idiosycratic to some of the locations sampled. In that case, stepwise regression, rather than inserting variables for evey site, seems apprpriate. However, the individual psu stands are no better than the strata as indicators of these locations. The New York metropolitan area had 4 psu's, 2 inside the political boundary of the city. Chicago and Los Angeles metropoolitan areas also were more than one PSU, and the meriden Connecticut psu sampled people from New Haven, Hartford, and the suburbs between. So psu's did not sample from only one city, and some cities were more than one psu. Even when a psu was basically one city it sampled people ffom center city, outer city, and suburbs. The degree of urbanization variable, which is coded individually, varies considerably inside a given psu. Strata are chosen within regions to contain places with similar demographic profile and size. There are two psu's within each strata. Since the strata are not as confounded with time as the psu's, they provide an excellent test of the hypothesis of significant location effects without the disadvantage of removing the true month to month variation of lead. The use of strata has less of an effect on the coefficient of lead than psu's because it allows the real seasonal changes in lead to remain. I have already argued that this seems appropriate. If one is worried about location effects, the strata regressions, and the stepwise psu regressions again indicate that this does not noticeably effect the lead coefficient.