MEMORANDUM

TO: Dr. Donald Lynam, Director, Air Conservation, Ethyl Corporation, Ethyl Tower, 451 Florida, Baton Rouge, LA 70801

FROM: Ralph A. Bradley, Statistical Consultant, 1221 Hickory Hill Dr., Watkinsville, GA 30677

SUBJECT: Review of exchange of correspondence between Royall, Ware, and Schwartz regarding DuPont's analysis of NHANES II blood lead - blood pressure data.

DATE: March 7, 1986

My comments on the exchange of correspondence regarding DuPont's analyses of NHANES II blood lead - blood pressure data are given below. The time constraints that were imposed because of late distribution of the material to be reviewed were severe. Accordingly, it was not possible to attempt resolution of the many inconsistencies apparent when various analyses and reanalyses were considered.

Summary

1. The DuPont model seems to be an appropriate one. Any relationship between blood lead and blood pressure (diastolic or systolic) should arise as a within-individual effect - it is the individual's blood lead that should (or should not) affect the individual's blood pressure.

2. The analyses by Pirkle et al (American Journal of Epidemiology, 121, 246-258, 1985) were done using SURREGR, the program that utilizes sample design weights in regression analyses. Schwartz in his various new analyses insists on use of this program and the weights, although how the sample survey weights are relevant to a within-person investigation of blood lead - blood pressure relationships is unclear and likely wrong.

3. In the exchange of correspondence, Schwartz does not address the issues raised by the DuPont analyses in any direct way. He invariably changes covariates, age groups, districts for psu's, etc., and raises new issues, for example, measurement errors in measuring blood pressure, new models (Cox model), and so on. He also does not respond by using models suggested by Royall.

4. Models for standard regression analysis assume that independent variables (such as blood lead, serum zinc, etc.) are measured without error. The usual argument for proceeding when this assumption is violated is to consider results conditional on the observed values of the covariates. This is not pleasing and research is in progress on modified techniques led by Wayne Fuller at Iowa State University. Schwartz uses an Iowa State program called SUPER CARP to account for variation in blood lead but apparently not for variation in other independent variables. No adequate technical explanation is given and changes in results of analyses seems counter-intuitive. (Schwartz memo of 10-2-85 to Weil.)

5. There are many unresolved issues in data analysis. Attempts at Ethyl Corporation, admittedly done hurriedly in view of time constraints, fail to check results given in Pirkle et al cited above and discrepancies are both large and crucial to the significance of blood lead in predicting blood pressure. Grant, in a letter to Pfieffer and Pierrard (1-7-86) at DuPont, noted that no workshop or other meetings to resolve inconsistencies in analyses had been judged necessary. Royall (letter to Weil, 10-31-85) states "much remains to be clarified about the various analyses which have been presented." Ware (7-29-85 comments on DuPont's analyses) states "some inconsistencies in the analyses remain to be explained."

6. A data base (NHANES II) is again being used for purposes not intended. The DuPont analyses attempt to account for concurrent downward trends with time (confounded with the sequencing of data collection by sites or psu's) in both blood pressure and blood lead that cannot be attributed to a within-person relationship and which should not dominate estimation of the regression coefficient for log blood lead as it appears to do in the Pirkle et al analyses.

7. Each set of analysts has doubtless found some editing of the data necessary to eliminate gross errors or outliers. A few data points can make a difference. Analyses should be compared on a standardized data set. An Ethyl Corporation test showed that removal of one datum point changed the regression coefficient for log blood lead by 11%!

8. Inconsistencies and controversy among analysts can only be resolved by some method of collaboration or review. An independent and neutral review panel should be set up, say under the auspices of the American Statistical Association or the National Research Council, to check analyses and interpretations and provide an authoritative report.

Detailed Comments

The following sections address the exchange of correspondence in sequence. The views of the reviewer are given and actual analyses have not been checked. Gross errors may have occurred in some analyses. Data sets may be sufficiently different to affect results. Choices of independent variables or covariates differ.

DuPont Analyses

The DuPont comments are clear, straightforward, and, I think, convincing. They agree, as we suggested that any real relationship between log blood lead and blood pressure must be demonstrated on a per-individual basis and should exist within each location. It was noted in preliminary analyses that there was a downward trend in blood pressures over the four-year sampling time of NHANES II paralleling the recognized similar trend in blood lead for the same period. The concurrent trends then induce a blood lead - blood pressure correlation, spurious or real. Any analysis that does not take these concurrent trends into account will provide a measure of association that is affected by both between-location correlation and within-location correlation, if the latter exists. The various regression analyses of Pirkle et al and Harlan et al (Journal American Medical Association, 253, 530-534, 1985) were

redone with the models reconstructed as possible and most importantly with location or site or psu indicator variables added as additional independent variables. The effect of the addition of location variables is to obtain a regression coefficient for log blood lead in the prediction of blood pressure which is roughly an average of within-location relationships. In the reanalysis of the regressions of Pirkle et al, the only significant blood pressure - blood lead relationship to remain significant was for systolic pressure for males, ages 12-74. At the same time the magnitudes of the coefficients for log blood lead were substantially reduced. The coefficients for other significant independent variables (age, age squared, body mass, etc.) were hardly changed by inclusion of location indicators and this was interpreted to mean that their effects on blood pressure were probably real. Similar results are exhibited in reanalyses of regression models of Harlan et al, with location variables added. The clear conclusion was drawn by DuPont that the apparent relationship of blood lead and blood pressure claimed in both references was spurious, did not exist on a within-location basis, and was induced by the concurrent time trends. The conclusion is strengthened by the fact that regression coefficients for other variables associated with blood pressure were virtually unaffected by inclusion of the location indicator variables.

It is noted that a time variable, perhaps date of examination, might have been used instead of the location or site variables. DuPont argues that the location variables are better because other differences in location effects are accounted for also.

The DuPont approach is the one used by the consultant and Ethyl Corporation in regard to the effect of gasoline lead use on blood lead. We showed that the use of location indicator variables essentially removed all association of gasoline lead use and blood lead. The argument was not effective then and should have been. There were two difficulties, an inherent belief that gasoline lead must be the source for blood lead and a lack of any within-location data to relate blood lead to gasoline lead exposusre. We believe that the convincing factor in the DuPont argument is that the blood lead - blood pressure association should remain on a within-location basis if real, and essentially it did not.

Any relationship between blood lead and blood pressure is essentially an individual thing. It is the blood lead of the individual that may or may not affect the individual's blood pressure. Surely all would agree with this notion. But other factors also affect the individual's blood pressure, obesity, genetic makeup (family history of high blood pressure), personal habits (smoking, etc., perhaps) and so on. There may be external factors also affecting the individual such as nature of employment (pressure of work situation), family problems, etc. Some of the personal factors and the external ones may be location related but it does not seem that they should be attributed to lead except as they affect that individual's blood lead measured directly. I think that DuPont tried to accept this philosophy as they did their analyses.

Schwartz Response to DuPont

Let me turn to the Schwartz response to the DuPont analyses addressed to Weil, dated 6-26-85. I do not believe that they are generally very well founded or pertinent. The first point made by Schwartz is that the use of 63 (not 64 as stated by Schwartz) indicator variables for location is excessive when only 2260 observations were available; I do not see that this is excessive and many degrees of freedom are still available for tests in regression analyses. The notion that one in 35 observations is wasted has no real merit. It was not a waste! Schwartz admits that is now difficult to maintain a significant correlation and then goes on to develop what I think is a spurious argument to explain why. It is difficult to maintain a significant correlation because the correlation over locations part has been removed! Schwartz agrees that there are trends in blood lead over time and seasonally (see page 4 of this memorandum) but is silent on possible blood pressure trends over time (I believe that he has denied this in some writing). An admission on the second trend would seem to agree to a DuPont type of analysis. I cannot assess the argument about 32 strata and pseudo-sampling units. It seems irrelevant and site-indicator variables still do the job. This may be the answer to his complaining that only a few of the site indicators are significant. To assess which site indicators are significant depends on how they were put in the model and this can be done in many ways. Any site indicator set will give the same overall test for site effects collectively but individual indicators will have different coefficients in the regression model. Special site contrasts can be used for site indicators; if the main effect of sites is a time-trend with, say, linear and quadratic components, then contrasts roughly measuring these components will likely be significant and other site indicators will not. I see nothing in the argument that only a few of the site variables were significant and therefore their use was a bad idea. Schwartz says that, at most, location stands for some omitted casual variable, the most obvious being lead, and challenges critics to say what it is. This seems to show that Schwartz does not understand that, if blood pressure is plotted against blood lead, the apparent trend for individuals within sites can go one way (or not exist) while there is a marked trend for the site blood pressure mean versus site log blood lead mean. This phenomenon is well known to good applied statisticians and is the point of the whole DuPont analysis; again, surely it is the within-site trend or correlation that is relevant to the effect of blood-lead on blood-pressure argument.

The Schwartz argument about measurement error and misspecification of variables is strange and difficult to handle. It seems to involve misconceptions and is not clear. It has not been addressed by Ware and Royall. Schwartz seems to be saying that the effects of locations are relatively clean and noise-free in comparison with the excessive variabilities of both blood lead and blood pressure measurements, somewhat contradictory of the notion that location or site variables are not very significant anyway. If there are no site effects, any attempt to measure them only measures noise anyway! The arguments on page 4 don't make sense. If b is the estimated regression coefficient for log blood lead in the prediction of blood pressure,

in the presence of other covariates or not, regression analysis assumes that the predictor variables are without error, b is estimated as a linear function of blood pressure measurements and it is divided by the proper estimate of standard deviation of b to obtain a t-statistic and a test of significance for the hypothesis that b is estimating a regression coefficient for blood lead that is zero, i.e., b measures noise. The linear function for b depends on values of the independent variables, including blood lead, and so does the estimate of the standard deviation of b. Schwartz seems to be concerned that taking out site effects reduces b more than it reduces the standard deviation of b and hence makes it more difficult to obtain signifinance. This is simply not so unless the situation is as described above, where there is a site means correlation that should be taken out of b.

Let me turn to the Schwartz reanalyses. He objects to the use of site indicators and starts with region indicators. If regions were roughly sampled proportionately in time or had similar time and seasonal effects as the whole data set, it is not surprising that he obtained similar results to analyses that did not include region or site variables. These analyses do not seem relevant. The next analyses use eight sampling strata per region so 32 strata are now indicated, since it was claimed that two sites were in each such stratum and were very much alike. But were they sampled at the same time? If not, then they may have been quite different. Somehow Schwartz now has 32 instead of 31 indicator variables in his model and one has to wonder why the model was not singular with all sorts of analysis problems. Finally, Schwartz has all the site indicators with the proper 63 of them and finds significance for blood lead in predicting blood ~~lead~~ pressure. This is contradictory to the DuPont analyses except that Schwartz now has an expanded set of independent variables, some of which were not used by DuPont. At this stage significance is near the 0.05-level and could flop one way or the other depending on other variables included or excluded. In his analyses Schwartz uses a backward elimination technique intended to eliminate independent variables not contributing to prediction of blood pressure. A substantial number of site variables are now eliminated but certainly not all. I believe that all site variables should be left in on the argument that the experiment was designed that way. There is an analogy with the simple randomized block design of field plot experimentation where blocking is sometimes not very effective but block effects are still removed from experimental error. Also, as noted above, the main effects of sites might be time components and then one would need to look at the appropriate site contrasts that roughly measure the pertinent components. The only possibly convincing Schwartz argument is that he still apparently found significance with all site indicators present with his chosen set of additional covariates or independent variables in conflict with DuPont. I cannot rationalize this without a very detailed check on all analyses except for the comments above. There may be errors in analyses, there may be differences in the data sets after editing, maybe SURREGR does something, etc. There is the point that the test for blood lead effect has a lot of degrees of freedom for error and hence may detect real but very small effects or, since many tests are made, may be significant by chance in these data.

Ware Response to DuPont

Let me turn next to the Ware comments of July 29, 1985 submitted to Weil. The first several pages are nothing more than a review of existing papers. His paragraph starting on the middle of page 4 of his report seems pertinent and suggests an understanding of the principle on which the DuPont analyses were based. This paragraph is generally supportive of the DuPont approach. The following paragraph on page 5 is also pertinent and further agreeably defines the situation and discusses a Schwartz attempt to use date of sampling as a measure of time to take out a time effect. Ware correctly notes that this would not take out a seasonal effect. Ware criticizes the DuPont analyses in that he claims that use of site variables desirably takes out spurious ecological (?) correlation at the cost of losing any information contained in the geographic and temporal variation in blood lead. This does not seem correct or relevant to me! Ware then seems to buy the Schwartz argument about measurement error and difficulty in showing significance that I have discussed above. Ware worries about the discrepancies between DuPont and later Schwartz analyses and asks that both be asked to explore these discrepancies. Ware ends up, perhaps with some uneasiness, in accepting the notion that there is some real association between blood lead and blood pressure within sites, thus giving Schwartz the benefit of doubt where results disagree with DuPont.

Royall Response to DuPont

Royall (report of August 20, 1985 to Weil) specifies five possible regression models for regressing blood pressure on the logarithm of blood lead (except that the subscript j is omitted in his equation (2)). The first model leaves out site variables, the second includes them with a common within-site regression coefficient for log blood lead, and the third permits different dependencies on log blood lead within each site but has no site variables. The fourth model adds site variables to model (3) while the fifth model permits all regression coefficients, including those for other covariates, to change with sites. All models permit selectivity in choice of other covariates. The Pirkle-Schwartz analyses use model (1) and the DuPont analyses use model (2). Note that Royall is concerned in regard to model (2) that the within-site variation in log blood lead may be small and increase the standard error of b, the estimator of his beta (regression coefficient for log blood lead in the model). If this is so, it is a shortcoming of the data set and not an argument for model (1). Royall notes that b is still unbiased. Royall is right on page 2 when he states that little variation in estimates of the within-site regression coefficients in model (3) would give more confidence to model (1); similarly, model (4), showing little variation in regression coefficients for log blood lead, would give more confidence in model (2). Further complexity is introduced in model (5). Royall has no real comments on the last two models and states that he doesn't know which of models (2)-(5) was used by DuPont. I believe that DuPont used model (2) but admit that it is not entirely clear. Royall has the right concerns in this paper and asserts that a true relationship between log blood lead and blood pressure should show in a within-site measure. He states that he remains confused and that the responses of Schwartz to Weil and to Ware do not focus on the critical points. I do agree with the Royall comments in this August 20 set of comments.

Schwartz responded to Ware (memo to Weil, August 21,1985) by writing about measurement error in blood pressure and blood lead. He used some unknown program to take noise in blood lead into account. Presumably blood lead is now not assumed to be an independent variable measured without error but he apparently had no concern about noise in most of the other independent variables. I don't think that this was a very realistic attempt and my intuition would have led me to expect a reduced effect of log blood lead on blood pressure rather than an enhanced one.

The whole business of doing regression when the dependent variable, blood pressure, and the independent variables are all subject to variation is difficult. Basically such analyses are done conditional on the observed values of the independent variables and then the issue of Schwartz does not arise, although one may have discomfort. This is what has been done in every regression analysis on this problem to date. It is very difficult to examine what happens when the independent variables are subject to random variation; I doubt if there is an adequate technique except perhaps for use of partial multiple correlation theory, which has not been done.

The rest of the Schwartz document to Weil is an alternative analysis to one done by Landis (discussed below). It gives an alternative to regression analysis based on a model of Cox. The results lead to additional confusion. The effect of blood lead was reduced fairly substantially when sites were included but remains significant. The other independent variables are changed again so that there is no very direct comparison with other analyses. We are given no clear indication of the direct effects of sites.

Landis Analyses

As I turn to the new Landis analyses using the Mantel-Haenszel model, I am familiar with the modelling but would need to review the methodology carefully to check this application. It appears that Landis only adjusted for age and body weight index and hence included fewer covariates than other analyses but he did somehow try to take sites into account. The claim is that correlation between log blood lead and blood pressure is still significant, probably just at the .05 level. He notes that both blood lead and blood pressure had striking declines over time. Landis was a coauthor of the Pirkle et al initial paper on this general subject. I can't say much about the Landis analysis without additional time for review. I do not think that it is a major part of the controversy. Attached to the paper was an undated Schwartz memo, this time to Ware, on time trends. He asserts quite strongly that there was not a trend on blood pressure during the NHANES II data collection period. He also gives a discussion on site effects based on some presentation to CASAC, but tables and graphs are missing.

Schwartz Response to Royall

Schwartz responded to Royall in a memo to Weil, October 2, 1985. He objected to all of the models because they did not address his noise or measurement error problem. He goes on to explain the measurement problem in more detail than before with respect to Royall's models (1) and (2). The other models of Royall are not addressed and the rest of the long response is a repetition of the arguments about use of site, region, etc. as variables. He appended copies of analyses using them and additional copies of efforts to incorporate measurement noise. I have commented above on all of this. I do not think that Royall's models are really addressed at all adequately. Royall seems satisfied that Schwartz' analysis with site variables in his earlier response to DuPont is now convincing and accepts the comment above the "conclusions" section as satisfactory, even though in conflict with the DuPont similar analyses. He states that he is satisfied but notes that much remains to be clarified.

Other Documents

You provided me with two other documents on which I shall not comment. The first is the Schwartz presentation to the Royal Society of Canada Commission on Lead and I have had to assume that this is the same story basically as presented in all of the EPA analyses. The second, Schwartz to Grant, October 23, 1985, gives some additional references and relates to the risk analysis and cardiovascular disease.

To sum up, I don't think that the point of the DuPont analysis on which I have elaborated is very well understood. Royall sort of half recognizes the problem but does not press in having his models addressed. I don't think that the Schwartz issues about noise in variables is very relevant nor that his new analyses are either. There is a substantial discrepancy between the DuPont analyses and the Schwartz similar analyses with site indicator variables. While there has been a plea to both analysts to try to resolve this, it has not been done, unless in some new DuPont rebuttal that has not yet been received. Any Ethyl input should be based on my comments noted in regard to the DuPont analyses and the notion of a possible within-site relationship between blood lead and blood pressure that may be quite different (or non-existent) than the relationship for the same variables based on site means. It would be nice to show plots of this if possible. There is some support for the DuPont position by reviewers as noted, but they do not follow up strongly and seem to accept the Schwartz analysis even though in unresolved conflict with the DuPont effort.

I hope that my comments are reasonably clear. This report could have been a bit more polished and better organized had more time been available. I am concerned that each new analysis changes other items - different covariates, different age classes, the data set, etc., so that it is impossible to make really direct checks or comparisons of analyses. I think that there are serious unresolved major discrepancies among analyses. Perhaps

these can only be resolved by impartial review by a committee selected by, say, The American Statistical Association or the National Research Council. Three of the models suggested by Royall have not been tried and they could provide insights. Full consideration of these models might be a charge to the suggested review committee.

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