

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 correspondence regarding DuPont's analysis of NHANES II blood lead - blood pressure data as requested in your letter of February 22, 1986

DATE: March 2, 1986

As you know I have very little time to effect the requested review and accordingly I shall meet your deadline by examining the material provided sequentially in judged order of importance and perhaps with only limited consolidation of comments at the end. It does appear that the task is rather more formidable than you suggested in our follow-up telephone call in regard to the letter and material noted above. In all of this, it is necessary to end up with the comment of Royall (10-31-85 letter) wherein he says "much remains to be clarified about the various analyses which have been presented" although he gives up on pressing for clarification and rather weakly expresses satisfaction. He does not resolve the stated contrast of conclusions between the new Schwartz analyses (as well as earlier ones) and the DuPont analyses.

Let me refer next to my comments on the DuPont analyses in my memorandum to you of January 7, 1986. I refer particularly to the first paragraph of (i) on page 2. 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 make-up (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.

Let me turn to the undated Schwartz response to the DuPont analyses addressed to Weil that you dated 6-26-85. I do not believe that they are generally very well founded or pertinent and I do not believe that either Royall or Ware showed much understanding. 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 it 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 now seems to admit that there are trends in blood lead over time and seasonally (see page 4 of his 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 complaint 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 causal 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 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. Does Schwartz insist on not understanding this point? Do we have any simple plots of this kind that are convincing?

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 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 significance. 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 very relevant. The next analyses use 8 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. 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 .05-level and could flop one way or the other depending on other variables included or excluded. In his analyses (some unreadable on my copy) 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 this data.

Let me turn next to the Ware comments of July 29, 1985. 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. 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 on 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. He is very probably influenced by the Landis results that he has also seen at this time.

Royall (report of August 20, 1985) properly specifies three possible regression models for regressing the logarithm of blood pressure on the logarithm of blood lead (except that the subscript j is omitted in (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. All models permit selectivity of other covariates. 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); this is rather similar to the Schwartz argument, but more clearly expressed, and 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 (2) would give more confidence to model (1); similarly, model (4), showing little variation in regression coefficients for 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 these 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 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 not fault the Royall comments in this August 20 set of comments.

Schwartz responded to Ware (memo to Weil, your stamped date, 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 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.

As I turn to the new Landis analyses using the Mantel-Haenszel model, I find that I was only sent alternate pages of his document. 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 blood lead and blood pressure is still significant, probably just at the .05 level. Some comments suggest that Landis does not understand the points about components in the correlation. He does note 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 more about the Landis analysis without the whole paper and time for review. I do not think that it is a major part of the controversy. Attached to the paper was yet another 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 responded to Royall in an undated memo to Weil

(your stamp, 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. variables and 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 is satisfied but notes that much remains to be clarified.

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 to try to resolve this, it has not been done unless in some new DuPont rebuttal that has not yet been received. One would think that there would be some new DuPont input for the next hearing; we should watch for this. 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.