University of Pittsburgh

GRADUATE SCHOOL OF PUBLIC HEALTH
Center for Environmental Epidemiology

October 26, 1984

David E. Weil, Ph.D.
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U.S. Environmental Protection Agency
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, NC 27711

Dear David:

When I received your letter of October 11 regarding the Schwartz memo, I sent a copy of the material to Dr. Lewis Kuller, an Associate Director of our Center, and Chairman of our Department of Epidemiology. Dr. Kuller is our resident expert in cardiovascular disease, particularly hypertension. I did not have a chance to talk to Dr. Kuller before coming to RTP on October 17 and of course he did not have the benefit of the presentation. When I returned to my office today, I found that he had reviewed the material. His comments are attached. I am inclined to take Dr. Kuller's comments very seriously and don't feel much would be changed if he had gone to RTP.

My specific knowledge involves mainly lead in it's occupational settings. Enclosed is a copy of a very recent paper by Dr. Clark Cooper which updates an early study he conducted on battery and lead smelter workers. I have also discussed this by phone with Dr. Cooper. My general impression from reading the paper and from Dr. Cooper's comments is that lead definitely produces kidney damage and renal induced hypertension but is not clearly related to either coronary heart disease or stroke. On the basis of this I would question the extrapolation to stroke and heart attack.

I have also discussed this problem with Dr. David Parkinson who is Chief of Occupational Medicine in our medical school. He is just completing a study of about 500 workers with long exposure to lead from a battery plant along with a control group. Dr. Parkinson feels there is no difference in blood pressure levels between these two groups of workers. You may wish to contact Dr. Parkinson directly about this. His phone number is (412) 624-0127.

As for my personal observations, I am impressed by the thoroughness of the data analysis by Dr. Pirkle and his co-workers. The contribution of blood lead appears to be very small, however, adding about 1½ percentage points to R^2. While almost everything known about the HANES II participants was controlled for, I feel lead could still be a surogate for some socio-economic variable not controlled for or poorly measured. I'm also concerned by the fact that only about 60 percent of the population selected actually responded. Dr. Pirkle has sent me some information on non-response. Clearly non-respondents were not a random sample and I feel there may be a possibility of selection along the lines of Berkson's Fallacy.

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Other problems I see are: 1) Carrying out health examinations and recording results is not quite the same as designing an epidemiologic study to answer a question and I am uncertain about the scientific content in such a procedure. 2) There is no temporial relationship suggested by the HANES data. 3) There is not much consistency in observations with regard to blood lead and hypertension as evidenced by the recent paper by Pocock, et al. 4) There is no biologic reason why the relationship would hold for males and not for females. 5) If the 1976 paper by Beevers, et al, were important, it should have been followed by a flurry of papers comparing blood leads in normotensives and hypertensives. 6) There was apparently no relationship between alcohol consumption and blood pressure in this data set but the relationship is fairly well accepted.

As I understood the presentation on October 17, changes in blood lead levels from 30 to 7 would result in a change of about 5 mm in diastolic blood pressure. This is about twice as large as any change yet achieved in large scale intervention programs and, if true, could revolutionize our efforts in the field of public health.

My general impression is that we have a very good hypothesis here and should set about trying to test it. However, I don't think that the information available from HANES II provides the kind of incremental knowledge needed for input to national regulatory policy.

Sincerely yours,

Philip E. Enterline, Ph.D.
Director
Center for Environmental Epidemiology

PE/am
Enclosures

cc: Dr. Bernard Goldstein

REVIEW OF:

Schwartz Memorandum concerning:

The Relationship Between Blood Lead Levels and Its Cardiovascular Risk Implications

by

James L. Pirkle, M.D.,Ph.D.
Joel Schwartz, Ph.D.
J. Richard Landis, Ph.D.
William R. Harlan, M.D.

SUBMITTED BY:

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October 25, 1984

REVIEW OF: Joel Schwartz Memorandum

BY: Lewis Kuller, M.D., Dr. P.H.

This report is based on an apparent association between the blood lead levels and blood pressure, both systolic and diastolic, found by the merging of the HANES blood pressure data and the measurement of blood lead in this same population. The data is restricted to white men ages 40-59. Apparently the positive relationship between blood lead levels and blood pressure was not noted for women. No data or discussion is provided of the relationship between blood lead levels and blood pressure in blacks nor in other age groups but apparently the relationship was consistent for men. This point however, must be clarified.

The authors presume that this relationship between blood lead and blood pressure is causal and then attempt to estimate the economic impact of reducing the lead in gasoline and its effect on blood pressure. There are three essentially critical questions in this particular problem. 1) Is the relationship between the blood lead levels and blood pressure causal or a confounder that is related to some other variable which is correlated with both the blood lead and the blood pressure? 2) Given the fact that higher blood lead levels are associated with higher blood pressures and that this may be causal, what is the attributable risk of increased blood pressure due to elevated blood lead levels as compared to other risk factors for blood pressure especially obesity, alcohol intake, sodium potassium and calcium intake, and perhaps certain measures of environmental stress; and 3) What is the impact of reducing the blood lead levels on the blood pressure; what will this do to the risks of heart disease and stroke and other hypertensive related diseases; and what is the economic and health related impacts of such a change?

The authors suggest that prior studies are consistent with the observation that blood lead levels are related to blood pressure. On the contrary, however, the literature is quite confusing. The two papers on the studies in rats that they provide suggest that there was an increase in blood pressure when the rats were fed 100 ppm of lead in the water but no change when the dose of lead was increased to 500 ppm, nor was there any relationship between increased lead in the water and blood pressure among female rats. The experimental study in rats comparing the effects of various alpha and beta agonists on blood pressure in lead-fed and non-lead-fed rats is somewhat confounded by the fact that the rats fed the lead had higher blood pressures than the control rats. A better study certainly would have compared rats with similar blood pressures, that is increased blood pressure due to lead as composed to increasing in the blood pressure due to some other factor such as sodium and then compared the effects of alpha and beta agonists.

The study presented - of the relationship between hard and soft water, lead leached from the lead pipes in the soft water areas, blood lead levels and blood pressure in England is well-known. However, it is unclear in that study whether the relationship is with the soft water, which is correlated with the lead and obviously, with other factors, especially calcium and magnesium or other trace metals, or to the effects of lead itself. It would be important to evaluate the data relating soft and hard water in the U.S. from the same HANES data set to blood pressure. Studies of blood pressure levels in lead workers are very inconsistent.

The data from the HANES study relating blood pressure and blood lead levels must be viewed very cautiously. First, only two regression analyses are provided. In both of these regression analyses, it is clear that there are many factors which are apparently independently related to blood pressures. These include such factors as vitamin C, potassium, obesity, riboflavin, albumin in the blood, level of hemoglobin,

calcium as reported in other studies, amount of oleic acid which is probably a measure of either total fat intake or mono-unsaturates vs. poly-unsaturate intake of fat. Other investigators have apparently demonstrated that high intake of polyunsaturated fats are associated with lower levels of blood pressure. The complex inter-relationship of these environmental and dietary factors to blood pressures as well as the socio-economic correlates of blood pressure such as race, education level, and geographic area of the country, certain other markers of social class, the possible relationship to environmental stress and the known genetic correlates, all make one suspicious of any single relationship with blood pressure.

Before this analysis can be accepted as even showing a potential causal relationship, further information is required. First, a tabulation showing the relationship between blood lead levels and blood pressure is missing. Clearly this analysis must have been done. It is important to look at this independent of the other variables to get some idea about the relationship of blood lead levels to blood pressure within each age, race, and sex group. This should be the primary available analysis and without such documentation, the further data set is of little value. This could be easily done using a simple analysis showing various levels of blood lead on one axis and levels of blood pressure on the other. It needs to be done, however, specifically for each age, race and sex group. Second, it would be extremely important to show similar types of both univariate and perhaps bivariate relationships between the blood lead levels and a variety of other risk factors. The fact that lead is an independent predictor of blood pressure in a regression analysis does not exclude the possibility of a relationship between lead and other environmental or dietary variables which may be related to blood pressure. It may well be that lead is serving as a surrogate for some marker related to dietary intake such as total calories, amount of sodium in the diet, fat, etc. All of these variables are interrelated with lower socio-economic class in which there

is a higher prevalence of obesity, greater caloric intake, apparently greater sodium intake, and less potassium, and probably less calcium intake. Lead intake or the association with environmental exposures to lead in the low socio-economic class may be serving as a surrogate marker for this constellation of risk factors. Many of these factors are poorly measured in the HANES analysis and it is possible that the blood lead levels are serving as a better surrogate marker than, let us say, sodium intake, some marker of obesity, some index of education, etc. On face value, the data is interesting but is far from causal and should not be used in its present format for any inference that the current blood lead levels are an important contributor to the distribution of blood pressure in the U.S.

The second question of importance is, given the possibility that there is some relationship to blood lead levels and blood pressure, what is the specific contribution of blood lead levels to the distribution of blood pressure in the population? As noted, there are numerous risk factors related to blood pressure. The presumption that changing the blood lead levels in any way will have a major impact on blood pressure is unacceptable.

The statistical analysis as presented to date is essentially a fairy tale unsupported or undocumented by any biologic or meaningful clinical observations. The absence of a relationship between the lead levels and blood pressure in the women is very worrisome. The authors pawn this off on the basis of the results in the rat experiments. There is, as far as I can tell, little or no evidence for any other environmental variable or dietary factor which preferentially causes an increase in blood pressure in men as compared to women, nor is there any evidence that the level of the blood pressure is a predictor of disease in men but not in women. Similarly, most of the risk factors that have been studied related to blood pressure appear to act in both blacks as well as whites. The strength of the association may be related to sex,

as well as genetic factors and race but certainly, absence of an association in women is quite worrisome. There is no documentation of the actual change in blood pressure with the change in units of blood lead levels and how these might be related to the distribution of blood pressure in the general population. There seems to be an inherent assumption that the blood pressures in the U.S. are declining, that is, the percentage with blood pressures greater than 90, and that this may have something to do with the changes in lead in gasoline. Quite on the contrary, the changes of blood pressure distribution in the U.S. appears to be primarily due to the treatment of hypertension, and the decline in blood pressures greater than 90 are because hypertensives are currently being treated with a variety of different drugs to lower their blood pressure. It is not completely clear from their analysis that those individuals on drug therapy or prior drug therapy for hypertension have been excluded, although I presume this is the case. No data is further provided on the consistency of the relationship in different geographic areas or in relationship to certain other social class markers which exist in the HANES set. They do, however, suggest that they have looked at multiple factors and that these do not account for the association between lead and blood pressure. A further question, of course, is whether the apparent elevated blood lead levels in people with increasing blood pressure as suggested, in the previous British study in Lancet are due to soft water and the leaching of lead from pipes or from the contribution of lead from gasoline. It is also important to consider the contribution of the lead from the food chain especially because of the possible association with caloric intake, obesity, and increasing blood pressure. Finally, I think it is important to look at the relationship between alcohol intake and cigarette smoking and blood lead levels independent of blood pressure to see whether these factors are in any way related to the blood lead levels.

There was also suggested evidence that the elevated blood lead levels are not due to changes in renal function in relationship to the blood pressure levels. The papers that have suggested this have looked at the serum creatinine levels and shown that the levels are not related to the blood lead levels. This of course, is a very crude estimate of small changes in renal function associated with the relatively modest increases in blood lead levels. This again, should be looked at carefully by some measurements of the lead excretion in the urine in relationship to the blood lead levels among the hypertensive and normotensive individuals.

Finally, the question of whether the relationship between the blood lead levels and blood pressure levels have an impact on disease is, of course, of considerable importance as well as the economic impact. The authors have made exaggerated claims about the efficacy of reducing lead in gasoline in relationship to reduction of blood pressure and subsequent incidence and mortality from stroke and coronary artery disease. There is certainly strong evidence of a relationship between the level of blood pressure and the risk of myocardial infarction and sudden death, and other manifestations of coronary artery disease. The evidence, however, that lowering of the blood pressure even by reducing lead in the blood would also have a direct effect on reduction in risk of heart attack is not substantiated. This will depend, of course, on two factors: 1) The actual contribution to the blood pressure distribution by the increasing lead in the blood as compared to the other risk factors and, 2) the impact of reduction of blood pressure on the risk of disease. The answer to the first question, as far as I am concerned, is unknown. The answer to the second question is equivocal. Clinical trials generally have not demonstrated a substantial reduction in CHD mortality or incidence in association with reduction of blood pressure through drug therapy, at least among hypertensives. On the other hand, a downward shift of the

entire distribution of the blood pressure curves in the U.S. might have an effect and in fact, may have been a major factor in the reduction in CHD mortality in the U.S.

The situation with stroke is quite different. Clearly blood pressure is the major risk factor for stroke and any factor which will reduce the blood pressure levels would probably have an impact on stroke morbidity and mortality. Thus, even a modest change in the blood pressure in relationship to a reduction in blood lead levels could have an important effect on stroke mortality and morbidity. The stroke mortality and morbidity rates in the U.S. have been declining substantially, over 50% since 1960-68. Much of this decline is related to the treatment of hypertension but a substantial part of it occurred prior to the introduction of anti-hypertensive drug therapy and the impact of various environmental factors including blood lead should be considered. It would be quite perplexing however, to note that the decline in stroke mortality in the U.S. was probably occurring at a time when lead in gasoline was increasing because of the apparent greater use of gasoline and greater numbers of cars. The decline in stroke mortality being very substantial even from the end of the second world war through the 1968. Thus, any attempt to correlate changes in blood lead levels now and stroke mortality would clearly demonstrate a rather peculiar relationship, that is, a declining mortality in the fact of increasing lead in the U.S. and then a subsequent decrease in stroke mortality and apparent decrease in lead in the blood. The bottom line would be that there is no relationship between the amount of lead being used, probably the blood lead levels and either the changes in blood pressure in the U.S. or the stroke mortality.

Finally, it should be noted that this observation should not be dismissed as an interesting statistical artifact. Rather, the observation may have important implications. The problem is that the data as provided is both weak and far too premature for the exaggerated claims provided in the subsequent economic and health related analysis. Thus, the major recommendation at this time should be for a series of

carefully coordinated studies and evaluations to really look at the relationship between lead, blood pressure, and perhaps, cardiovascular disease and stroke, in order to either accept or disprove the causal associations suggested by this paper. Use of this data alone for policy decisions could be fraught with a substantial scientific incredulity if not shear folly. Studies that should be done include a much more detailed analysis of the data provided as suggested in the earlier discussion. Careful analysis of other data sets which include measurements of both blood pressure or blood lead or the addition of blood lead measurements to several on-going studies of blood pressure. Measurements of the effects of the blood lead levels and other determinants of hypertension especially obesity, of sodium, potassium and calcium intake should be done. Further experimental studies, perhaps using a different animal model than the rat to determine the relationship between blood lead and/or lead exposure and blood pressure, and more careful analysis of the HANES water data in relationship to hard and soft water and blood pressure levels are also needed. If the hypothesis is correct, then clearly individuals who have had a recent stroke, heart attack, etc., especially with hypertension, should have higher blood lead levels than controls or individuals with a heart attack without a prior history of hypertension. It should be reasonably simple to do these types of case-control studies and they would be of considerable interest and importance.

The economic analysis has some flaws in it but in general is quite interesting, although, again, based on some very specious biological and clinical associations.