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To: Dr. David Weil
From: Drs. H. A. Tyroler and G. Heiss
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Subject: EPA PRESENTATION ON RELATIONSHIP OF BLOOD LEAD LEVELS TO HYPERTENSION

The materials presented were of considerable interest and potential importance. One very general concern we have is that in effect two separate concepts with different supporting evidence for each of them were combined into one paper. More specifically, one is the analysis of the prevalence study of the relationship between blood lead levels and blood pressure derived from a probability sample of the United States (NHANES II); the other is an extrapolation of the findings to estimates of the potential impact of this association on the morbidity and mortality related to blood pressure as derived from estimates from the Pooling Project and the Framingham Surveys. These two types of endeavor are so dissimilar in the assumptions involved and the rules of evidence pertaining to each, that we feel very strongly that a fundamental distinction should have been made between them. It would have been preferable to present these two issues as separate though clearly related publications. We would anticipate that considerable criticisms will be directed towards the implications and extrapolation, which may detract from the importance and the firmness of the conclusion regarding the associations between blood lead levels and blood pressure. Given this conviction on our part our evaluation and critique of the material is divided into two sections.

I. The association detected in the NHANES Survey data between blood lead levels and blood pressure. In general we believe the association as described and quantified satisfies many of the criteria for causally related variables. Among these, the magnitude of the association can be summarized as moderate to strong. Both the strength

of the association as estimated from weighted multiple linear regression and the magnitude of the variation in blood pressure across the observed range of blood lead levels were sizeable.

A second criterion, namely dose response, seems to have been satisfied and there appears to be a monitonically increasing function. The data as presented to us were not described in enough detail for us to decide whether this was linear or not but it would appear that there is at least a stepwise function of increasing blood pressure with increasing levels of blood lead. Further, systematic replicate analyses were performed testing for the presence of a threshhold below which associations were non detectable and no threshhold was found. These are extremely important findings since the analysis were being carried out on a probability sample of the U.S. with blood lead levels below the range of 30 micrograms per deciliter. This greatly expands our knowledge from the data based on much higher levels of lead as found in occupationally exposed populations.

A third point in the rules of evidence in support of this association to be "real" was that systematic inspection for confounding was carried out at great lengths. In fact, each of the covariates measured and available in this dataset was tested for its potential to introduce bias in the estimate of the blood lead blood pressure relationship and virtually without exception little or no change in the strength of the association was detected (except for race and sex on initial analysis and for that reason the analyses as presented were restricted to white males).

Despite the exhaustive treatment of the numerous measurements available in NHANES in testing for potential confounders, there were several conspicuous omissions. Measures of blood glucose, serum uric acid, and pulse rate were not available. These variables, have been found associated with blood pressure in other human population based studies and least in principle could be confounder factors. These reviewers were unaware of any known associations of these variables with blood lead levels and therefore it is unlikely that in fact important confounders were excluded. However, they and others that may be identified subsequently, will possibly be invoked as alternate explanations for the findings.

Fourth, at this point in our remembrance it is not clear whether or not tests were made for interactions. This is an important point. If none were actually carried out this is likely to be brought up in the criticism, i.e., is the association between blood lead and blood pressure the same across major subgroups of the population. For example, is the blood lead - blood pressure association the same in the lean versus the obese, since obesity per se is such a strong correlate of blood pressure in population studies.

Fifth, estimates of the validity and reliability of the measures. No specific __ data were available to us regarding the determination of blood lead, however, one can assume that carried out at CDC, appropriate laboratory quality control was maintained. The estimates of the measurements taken by NHANES have been well standardized and described.

Sixth, the modelling procedures used have been carried out with sophistication and exhaustive completeness. Each of the potential confounders has been tested for; however, there was less presentation of biologic rationale and assumptions regarding the processes by which lead putatively is association with blood pressure, to accompany the statistical modelling.

Seventh, replication of findings. This level of the work constitutes one of the major weaknesses in drawing causal inferences, although a few references were cited regarding animal work and one or two confirmations of the findings in humans. A counter example of a very large population based study numbering some 7,000 examinees was cited which failed to confirm the blood lead - blood pressure association. It appears premature to draw causal inferences based on this limited body of confirmatory evidence; further, it would seem quite simple in principle to carry out human experimental studies, such as lead reduction experiments to test the inferences drawn from the observational work in humans.

II. The potential impact statements are based upon a series of assumptions which have not been made explicit. Among these are the following: a causal relationship has been assumed to explain the observed relationship between blood lead and blood pressure as mentioned above. Although this relationship is strong, consistent, of a dose response nature and non confounded in the NHANES dataset it is not clear that this is a general phenomenon nor is there human experimental evidence to confirm the assumption of

causality. There are further assumptions including modifiability, i.e., that reduction of blood lead will be feasible and that it will be attended by commensurate reduction in blood pressure. The latter assumption does not necessarily follow even if the associations described here were causal. It is not necessary that after the pathophysiologic process had been initiated that removal of the inciting cause will be followed by reduction in blood pressure. Irreversible pathophysiologic changes might have taken place leading to sustained hypertension even after removable of the provocative lead level which initiated the process.

Similarly, the assumption is made that the association in Framingham and Pooling Project between blood pressure levels and cardiovascular sequalae will provide an index of the consequences of lowering blood pressure. This assumption has <u>not</u> been fully realized quantitatively in clinical trials. Reduction of blood pressure is attended by reduction in pressure related cardiovascular sequalae, most conspicuously strokes, congestive failure and hypertensive heart disease. However, reduction of sustained elevated blood pressure in adulthood to lower levels of blood pressure does not result in cardiovascular experience of individuals who had achieved and sustained these lower levels of blood pressure spontaneously. Further, and most important, although there is an unequivocal relationship between elevated blood pressure and ischemic heart disease in observational studies, the collective clinical trials evidence is ambiguous regarding the effect of lowering blood pressure on ischemic heart disease risk. In most studies reported to date (and more particularly in the proper randomized blind trials) lowering of blood pressure is <u>not</u> attended by lowering of ischemic heart disease event rates in middle aged adults. Thus, one of the major assumptions in these extrapolations as it relates particularly to ischemic heart disease is not realistic.

In the section on extrapolations and implication the distinction is not made between reduction of risk after hypertension is established in contrast to the primary prevention of hypertension. The latter would be more likely in principle to yield the results upon which the extrapolations are based. There is, however, no human experimental data to confirm this assumption. For the primary prevention of hypertension an added difficulty would be that there would be necessarily lag time between reduction of lead in the environment and its benefits in humans, i.e., some period of time before the prevention of

hypertension would be achieved, and in turn followed by the reduction in cardiovascular events. How long such a lag period would be, whether it would be years or decades is not clear, but no lag time specification was built into the extrapolation. There is some epidemiologic - ecologic information which would argue against the assumptions as drawn in this paper, i.e., the long range time trends of hypertension related diseases. There has been a steady decline in stroke mortality for at least the past 35-40 years. The rate of this decline accelerated in approximately 1972 with the introduction of major high blood pressure control programs. However, the decline preceded by a long period the existence of effective community hypertension control programs. It was during this period of time that blood lead levels increased, and subsequently decreased in the period 1976-80. At an approximately concurrent time period of analysis, there is therefore no simple relationship between air and blood levels of lead and stroke mortality and hypertension.

On balance then, the demonstration of the association between blood lead levels and blood pressure has been rigorously and convincingly demonstrated in the NHANES II data set. Major methodologic sources of confounding and bias have been investigated and found absent. The relationship is robust and persists on multiple probes. It is a dose response relationship, and there is a plausible biologic explanation for the finding. There are, however, as identified above numerous reasons to regard the relationship as not yet demonstrated to be causal. Further, the extrapolations of potential community impact appeared to these reviewers to be gross overestimates for several reasons. Most important among them are those related to the failure of human experiments to reduce ischemic heart disease risk with pharmacologic control of high blood pressure, but also the inconsistency in time trend data and the failure to include time lag components in the extrapolations made.