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THE RELATIONSHIP BETWEEN BLOOD LEAD AND BLOOD PRESSURE

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Prepared by
Dr. Irva Hertz-Picciotto, Ph.D.
Dr. Janet Croft, Ph.D.
Department of Epidemiology
University of North Carolina
Chapel Hill, NC 27599-7400

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Introduction

Excessive exposure to lead, a neurotoxin, is associated with impairment of the kidney and multiple organ systems [USEPA, 1986]. There is considerable public health interest in the possible toxic effects of environmental lead exposure on the cardiovascular system with additional concern regarding the role of chronic low-level lead exposures in the pathogenesis of hypertension, a leading risk factor for cardiovascular disease morbidity and mortality [USEPA, 1989].

This report summarizes recent epidemiologic studies of blood lead (PbB) and blood pressure level in general populations and occupational subgroups. Though not intended to be 100% comprehensive, this report does review most major recent papers. The primary objectives of this review are to evaluate the evidence on whether blood lead is related to blood pressure, to critique this literature in light of methodological questions, to interpret the value of the current body of research for the purpose of occupational risk assessment, and to make recommendations highlighting critical areas for further investigation and suggesting in-depth approaches that might lead to more definitive results.

I. Summary of the Evidence

In 1976, Beevers et al. reported higher blood lead levels among 135 hypertensives (74 men, 61 women) compared to age- and sex-matched normotensive controls selected from a population survey in Renfrew, Scotland. In this study population, blood lead levels $\geq$41.4 μg/dl were observed in 8.1% of hypertensives (diastolic $\geq$100 mm Hg) and 1.5% of normotensives (diastolic <90 mm Hg). The mean difference in blood lead levels comparing hypertensives to normotensives was 3.5 μg/dl among males, and 3.1 μg/dl among females. In a matched analysis, hypertensive subjects were more likely to have higher blood lead concentrations than their normotensive counterparts; this finding was statistically significant among males, but not among females. Since publication of this study, interest in this issue has grown. The literature can be divided into population-

based studies, summarized in Table 1 and described in section I.A., and occupational cohort studies, summarized in Table 2 and described in section I.B. One of the population-based studies and two of the occupational studies were included longitudinal data, i.e., repeated measurements on the same study subjects. These longitudinal analyses are described in greater detail in section I.C.

I.A. *Population-based studies*

Table 1 summarizes methods and results from seven recent reports that examined the relationship of blood lead to blood pressure from six relatively large population-based surveys. These six surveys were conducted in four countries: Great Britain, Canada, Denmark, and the United States, and study size ranged from 861 to 7,371, though one publication on a subset of the U.S. 1976-1980 National Health and Nutrition Examination Survey (NHANES II) included only the 564 white males. All seven reports examined the blood lead-blood pressure relationship among men, and four examined the relationship among women as well in: the U.S. [Harlan et al., 1985], Wales [Elwood et al., 1988], Canada [Neri et al., 1988], and Denmark [Grandjean et al., 1989]. One report from the NHANES II included both blacks and whites [Harlan et al., 1985].

In general, the surveys covered adults only: two focused on the 40-59 year age range. One NHANES II report evaluated persons aged 12-74 years. Methodology for blood pressure measurement varied between studies. The British Regional Heart Study [Pocock et al. 1984], the Glostrup Population Study [Hollnagel 1980], and the NHANES II used an average of 2 or more readings, while in the other surveys either one reading was used (Canadian Health Survey) or the report did not specify. The NHANES II and Canadian Health Survey reported that they excluded treated hypertensives and that the appropriate cuff size was used for different sized individuals. All studies analyzed blood pressure as a continuous variable, and several also dichotomized this variable at cutpoints of 90 or 100 mm Hg for diastolic blood pressures (DBP) [Pocock et al. 1984, Harlan et al.

1985, Neri et al. 1988], or 160 mm Hg for systolic blood pressures (SBP) [Elwood et al. 1988], or both [Grandjean et al. 1989].

All but one study reported using atomic absorption spectroscopy for determination of blood lead level. Pocock et al. [1984] categorized PbB in the British survey into groups ranging from <12 μg/dl to over 37 μg/dl, but most of the surveys used PbB as a continuous variable and transformed it to a log scale for regression purposes; the surveys in Wales [Elwood et al. 1988] and the Canada Health Survey [Neri et al. 1988] used both categories and continuous scaling. Most studies adjusted for confounders such as age, body mass index (BMI), alcohol use, and some blood biochemistries. Exceptions were the two analyses of population based surveys from Wales [Elwood et al., 1988]: one did not appear to adjust for any covariates, and the other adjusted only for age. The argument given for not adjusting for other covariates was that since the observed effect was low, adjustment for alcohol would simply reduce it further.

Results of these studies suggest small positive associations. In the British Regional Heart Study [Pocock et al. 1984], there was a weak but significant ($p<.01$) increase in systolic blood pressure with increasing log blood lead level, after adjustment for age, town, body mass, alcohol, social class, and observer. In the lowest category of PbB (<12 μg/dl), SBP had a mean of about 144 mm Hg, compared with an estimated mean of slightly over 146.5 mm Hg for those with PbB >37.3 μg/dl, who represented 1% of the study population [Pocock et al., 1984]. A greater prevalence of hypertension (diastolic > 100 mm Hg) was observed in those with PbB above 37.3 μg/dl vs. those below: 15% vs. 9% ($p=.07$). Similar results were obtained defining hypertension as SBP > 160 mm Hg (30% versus 21%, $p=.08$).

The relation of blood lead to blood pressure in the NHANES II population has been discussed in several reports [Pirkle et al 1985; Harlan et al 1985, 1988; Gartside et al 1988; EPA 1990]. Among white men, ages 40-59, both diastolic (n=564) and systolic (n=543) blood pressures increased with log blood lead level ($p<.05$) [Pirkle et al., 1985]. In

this analysis, an increase from 12 μg/dl to 32 μg/dl is associated with an increase of about 4 mm Hg DBP or 8 mm Hg SBP. In the NHANES II biracial population aged 12-74, adjusted systolic and diastolic blood pressure increased with log blood lead level in men ($p<.05$) but not in women [Harlan et al., 1985]. However, in both men and women ages 21-55, blood lead level was higher among those with DBP $\geq$ 90 mm Hg than among normotensives [Harlan et al 1985]. These results are shown in Table 3. For either men or women aged 56-74, PbB did not differ among three groups: normotensives, those with elevated diastolic, and those with isolated systolic hypertension (normal diastolic and elevated systolic). Thus, the PbB - blood pressure association was most notable in the younger age groups. A further analysis of blood lead and blood pressure using the NHANES survey was conducted by Gartside (1988), however this analysis does not utilize individual data. Ecologic analyses generally have lower statistical power, and since the reported effects are generally of small magnitude, such approaches are not likely to be effective. Further analyses of the NHANES II data are reported by the EPA (Air Quality Criteria for Lead: Supplement to the 1986 Addendum, 1990) in which geographic location was controlled. The relationship was slightly attenuated, but still significant.

In the two population surveys in Wales, the evidence for a relationship of log blood lead to either systolic or diastolic blood pressure [Elwood et al., 1988] was weak. As mentioned above, in only one of the surveys was adjustment for age conducted, and in neither survey were any other potential confounders taken into account. In the Welsh Heart Program (see Table 1), an increase from 6 to 26 μg/dl PbB (this was the 95% central range of the data from another Welsh survey) was associated with a nonsignificant (at the $p=.05$ level) 1.9 mm Hg rise in DBP for males and 0.8 mm Hg for females, for an average of 1.3 mm Hg.

Similar results were reported by Neri et al [1984] for the Canada Health Survey: the predicted mean difference in DBP comparing a PbB of 47 μg/dl PbB to a level of 0 μg/dl fell in the range 1.4 to 3.0, the precise value depending on the treatment of PbB in

the analysis (e.g., whether blood pressure was modeled as a linear function of PbB or a logarithmic function of (PbB + 0.01) and whether adjustment was made for hemoglobin and zinc. The relative risk of being on hypertensive medication was 1.4 (.06, 31), and of being hypertensive but not on medication, 1.2 (1.0, 1.5). Apparently there were very few individuals taking anti-hypertensive medication.

The study from Glostrup, Denmark reported both cross-sectional and longitudinal analyses [Grandjean et al 1989]. The longitudinal analysis is discussed in a separate section below. The cross-sectional analysis showed an association primarily with systolic blood pressure: at age 40, a doubling of PbB gave rise to a significant ($p<.05$) increase of 2.6 mm Hg for males and 3.1 for females. Control for confounders (hemoglobin and alcohol) attenuated these measures to nonsignificant increases in the range of of 1.1 to 2.0.

In short, a small increase in blood pressure was associated with increases in blood lead in all of the population-based studies. In spite of different model choices and/or cutpoints for categorizing PbB, increases from PbB levels below 12 μg/dl to levels higher than 25 μg/dl were consistently accompanied by blood pressure increases in the range of 1.2 to 4 mm Hg DBP and 1.4 to 8 mm Hg SBP. These small increases remained significant after adjusting for numerous (and differing) covariates in the British Regional Heart Study, the Canadian Health Survey, and the NHANES II data; the fact that the findings, though not large, were, nevertheless, statistically significant implies that they were unlikely to have been a result of random sampling variability. In the Caerphilly survey in Wales [Elwood et al 1988] and in the Glostrup, Denmark population [Grandjean et al 1989], the regression of diastolic blood pressure on log PbB predicted nonsignificant blood pressure increases that do not substantially differ from the results that were significant in other studies.

I.B. *Occupational subgroups*

Adults absorb lead through inhalation of lead dust and fumes and through the ingestion of lead dust from fingers, food, and cigarettes [NIOSH, 1983]. Of adult U.S. men who were examined in NHANES II and had blood lead levels over 30 μg/dl, 92% worked in occupations associated with potential occupational exposure to lead [NIOSH, 1983]. These included secondary lead smelting, cutting of steel, recovery of scrap metal, the manufacturing of batteries, lead pigment, and lead-soldered stained glass, and exposures in car repair shops [NCHS, 1984]. Among men with potential occupational exposures to lead, 5.8% had blood lead levels greater than 30 μg/dl in contrast to 1.2% of male workers without potential occupational lead exposure [NIOSH, 1983].

Table 2 summarizes the methods and results from six studies of the relationship of blood lead to blood pressure level in occupational subgroups. These include: two groups of workers exposed to lead during smelting and manufacturing; policemen and bus drivers with exposures primarily from vehicular exhaust; a small group of civil servants with no known occupational lead exposure; and a cohort of lead foundry workers. Sample sizes ranged from 89 to 431. Two of the studies included small numbers of women working in lead smelters (n=4) [Kirkby and Gyntelberg, 1985] and as bus drivers (n=27) [Sharp et al., 1988]. Ages ranged from 18 to 65 years.

The referent group for lead smelter workers employed 9-45 years in Denmark was a sample obtained from participants in a population-based survey and who were matched with the lead-exposed group on age, sex, occupational status, and duration of employment [Kirkby and Gyntelberg, 1985]. For the lead-exposed workers employed at least one year in three battery plants in eastern Pennsylvania, a referent group of workers from a truck side-frame manufacturing plant was chosen who had no known neurotoxic exposures to lead, arsenic, or solvents [Parkinson et al., 1987]. Internal comparisons were made for bus drivers in San Francisco, California [Sharp et al., 1988], civil servants in Paris, France [Orssaud et al., 1985], and two studies using longitudinal information on each worker: a

four year follow-up of Boston policemen [Weiss et al., 1986], and a six year follow-up of foundry workers [Neri et al, 1988].

In terms of methodology for blood pressure measurement, three studies used an average of two or more measurements [Parkinson et al. 1987, Weiss et al. 1986, Sharp et al. 1988] and two excluded hypertensives [Parkinson et al. 1987, Sharp et al 1988]; the other studies did not report these details. In all of the occupational studies reviewed, blood lead determination was obtained with atomic absorption spectroscopy. For linear regression analyses, blood lead values were transformed to the logarithm in all studies except that of the foundry workers, where this relation was examined and found not to fit the data. Two of the studies, those of the policemen [Weiss et al. 1986] and the foundry workers [Neri et al. 1988], were longitudinal in nature and are discussed separately below.

The range for exposure varied considerably. Over 23% of the Boston policemen examined 1969-1975 had blood lead levels of at least 30 μg/dl. Blood lead levels in the 1980s among San Francisco bus drivers assumed to be exposed to vehicular exhaust were relatively low and ranged between 2 and 15 μg/dl. In those studies using external control groups, mean lead levels among the lead-exposed subgroups were considerably higher than in their respective referent groups (lead smelters: 51 vs 11 μg/dl [Kirkby & Gyntelberg 1985]; battery plant workers: 40 vs 7 μg/dl [Parkinson et al. 1987]).

Results from three studies [Kirkby & Gyntelberg 1985, Sharp et al. 1988, Neri et al. 1988] showed significant or suggestive associations of lead exposure with diastolic blood pressure; all three showed a weaker, nonsignificant, but still positive association with SBP. Two- to five-fold increases in lead concentrations were associated with increases in DBP in four of five studies and with increases in SBP (from 0.9 mm Hg to 8 or more mm Hg) in five of six studies. The diastolic increases ranged from 0.9 mm Hg to 4 or more mm Hg; the systolic increases ranged from 0.9 mm Hg to 8 or more mm Hg. Two studies showed strong significant associations with systolic blood pressure; only one of these

examined diastolic, and found a very weak association [Weiss et al. 1986]. This latter study was longitudinal and is discussed below. Parkinson et al. [1987] utilized four different measures of lead exposure: employment in a battery plant vs. manufacturing plant without lead exposure; current PbB; current zinc protoporphyrin; and time-weighted average cumulative PbB (based on historical measures of PbB). None of these measures of exposure was associated with either systolic or diastolic blood pressure.

Lead smelter workers had higher systolic (not significant) and significantly higher diastolic blood pressures than matched workers chosen from a population-based survey [Kirkby & Gyntelberg 1987]. Ischemic electrocardiographic changes were also significantly more common among the smelter workers. Additionally, the blood pressure among smelter workers with electrocardiographic changes was 23 mm Hg (systolic) and 11 mm Hg (diastolic) higher than among referents with such changes. The two studies that used categories for the PbB levels also noted a dose-response [Weiss et al. 1987, Orssaud et al. 1985]. Of course, those using continuous PbB in a regression were testing for a dose-response, by definition.

In short, the results of studies on occupational cohorts are mixed, but overall, these studies seem to suggest a small positive association between PbB and blood pressure. Five out of six studies that examined SBP found small increases. The magnitudes of these increases range from just less than a mm Hg comparing 3.6 μg/dl to 10.8 μg/dl (the 5th and 95th percentiles among bus drivers, Sharp et al, 1988) to 8 mm Hg comparing <12.4 μg/dl to >24.8 μg/dl (the low and high ranges among civil servants, Orssaud et al 1985). Other studies found intermediate increases [Kirkby & Gyntelberg 1985, Weiss et al 1986, Neri et al 1988], and only one study found an inverse association [Parkinson et al 1987]. Among the studies that also examined diastolic blood pressure, Parkinson et al [1987] again found a weak inverse association, Weiss et al [1986] found a positive association that was much weaker than the association with SBP, and three studies found much

stronger positive associations than with SBP [Sharp et al 1988, Kirkby & Gyntelberg 1985, and Neri et al 1988].

I.C. *Longitudinal studies*

We use the term longitudinal to denote studies that utilized repeated measurements on the same subjects. Three such studies were reviewed: two based on occupational cohorts involving foundry workers [Neri et al. 1988] and policemen [Weiss et al. 1986]; the other population based, from Denmark [Grandjean et al. 1989]. The population-based study examined the change in blood pressure between age 40 and 45 as a function of PbB at age 40 years. Results for both men and women showed sizeable associations (e.g., a doubling of PbB produced increases of 3.0 and 2.3 mm Hg SBP for men and women, respectively) that were markedly attenuated (reduced by about 25 to 50%) after controlling for covariates measured at age 45 years. The covariates responsible for this change in results were alcohol and hemoglobin.

A great advantage of this study was the complete control of age through the restriction of subjects to having been born in 1936. It is also unique in that the effect of a prior lead measurement from a population-based sample was evaluated. Comparing the result of these regressions with those that utilized only the cross-sectional Glostrup data [also reported by Grandjean et al. 1989], the magnitude of the association is greater using PbB at age 40 years to predict blood pressure at age 45.

This report found that controlling for alcohol consumption had a large impact in attenuating the PbB-blood pressure associations. On the other hand, the lead content of alcoholic beverages consumed in Denmark can be high [Grandjean et al. 1981], suggesting that control for alcohol may constitute "overadjustment" (see discussion of Confounding below). In a further analysis, restricted to those drinking less than 7 units of alcohol per week, the lead:hemoglobin ratio was used as the exposure variable. Men showed a

significant decrease in DBP (4.7 mm Hg for a doubling of PbB), while women showed a nonsignificant but suggestive increase (2.3 mm Hg).

The report on foundry workers was apprently preliminary and unfortunately provided inadequate information on data collection and laboratory methods. What information was reported suggested that the blood pressure measurements were subject to strong digit preference. Nevertheless, there was an abundance of measurements of PbB, enough to conduct separate regressions on 288 individuals, each covering data for 6 years. These analyses showed a clear positive linear trend of BP with blood lead concentration that was stronger for diastolic than for systolic BP. The mean diastolic regression coefficient was .298 mm Hg per μg/dl PbB, or nearly 3 mm Hg for every ten μg/dl of blood lead. Neri et al. [1988] also found that the data among workers with substantial fluctuations in their lead values did not support the use of a logarithmic transformation of PbB. The data were available to look at the time lagging, i.e., to see whether earlier PbB measurements constituted a better predictor for BP, but such an analysis was not reported.

The third longitudinal study [Weiss et al. 1986] examined a small group of policemen (70-72 depending on the analysis performed) whose blood pressure was measured in three consecutive years after baseline PbB values were determined. Autoregressive statistical techniques were used to evaluate consecutive annual changes in blood pressure within individuals. These showed PbB levels >30 at baseline predicted increases in SBP but not in DBP. Bootstrap methods showed these results to be rather robust. Unfortunately, serial measurements were available for blood pressure but not for the exposure variable, lead.

II. Critique of the Literature

Methodological issues regarding the studies of lead and blood pressure fall into three major categories: measurement of outcome, measurement of exposure and statistical issues.

II.A. *Measurement and Analysis of Blood Pressure*

1. Blood Pressure Variability

Blood pressure is subject to many sources of intra-individual variation involving responsivity to physical and social environmental factors during measurement, as well as physiologic responses to the measurement situation [Reeves et al. 1986, Tyroler 1988]. Other sources of measurement variatibility include differences in instrumentation (random zero vs.mercury sphygmomanometers, cuff sizes, instrument variation) and observers (including terminal digit preference and expectation biases) [Patterson 1984, Rutan et al. 1989]. Blood pressure is also highly labile, i.e., there is a tendency during a given time period for a blood pressure level to be alternatively under or over a value that is clinically defined as hypertension [Rutan et al., 1989]. Multiple blood pressure readings during both the examination and over a period of months are usually required for diagnostic as well as therapeutic purposes [Joint National Committee, 1984; Tyroler, 1986]. Use of an average of multiple blood pressure measurements in the statistical analyses was reported for the British Regional Heart Study, NHANES II, Glostrup Population Study and occupational cohorts of bus drivers, policemen and battery plant workers. In all of these studies except that of battery manufacturing workers, a positive association between blood lead and blood pressure measurements was observed. Many studies did not report on whether multiple measurements were made.

2. Antihypertensive treatment

An important misclassification issue concerns whether or not treated hypertensives should be excluded from analyses when blood pressure is the outcome measure since those

on treatment may exhibit more normal ranges of blood pressure yet may make up a sizable proportion of individuals whose blood pressure level was related to lead exposure. Exclusion of these individuals would reduce the power but should not bias the results. Inclusion of these individuals would result in bias towards the null if a continuous blood pressure measure were the outcome. With the outcome dichotomized, however, inclusion of these individuals as hypertensives should not bias results, unless hypertensive medications influenced measures of blood lead.

Among the population-based and occupational-based studies reviewed here, treated hypertensives were excluded from the analyses for battery plant workers and bus drivers. The Canada Health Survey stratified by antihypertensive treatment status and NHANES II analyses were conducted both including and excluding treated hypertensives. These two analyses gave essentially the same results [Harlan et al. 1985]. Based on the Canada Health Survey, Neri et al. [1988] compared those with elevated blood lead (>10 μg/dl) to those without: the relative risk for untreated hypertension was 1.2 (1.02, 1.5),* and for treated hypertension, it was 1.4 (0.6, 31.4). The wide confidence interval for the latter suggests very few treated hypertensives were in this study.

In a subgroup of 51 bus drivers who were being treated for hypertension, blood lead levels ranged from 2-24 μg/dl [Sharp et al. 1989]. Of these hypertensives, 33 were treated with diuretics only and 18 were treated with both beta blockers and diuretics. The regression coefficient for the relationship of log blood lead to diastolic blood pressure among bus drivers treated with both beta blockers and diuretics was larger than that of bus drivers treated with diuretics only, bus drivers with normotension or untreated hypertension, and men in both the NHANES II and British Regional Heart Study [Sharp et al. 1989]. As Sharp et al. [1989] point out, these results raise the

*Authors did not specify level of confidence for these intervals.

possibility that low-level chronic lead exposure, catecholamines, and treatment with beta blockers interact positively in their effects on diastolic blood pressure.

3. Cuff artifact

Chiang et al. (1969) has raised concern that an elevated blood pressure in an obese individual can be a cuff artifact related to large arm circumference or excess adipose tissue in heavier individuals. Body mass index (BMI) has an inverse relationship to blood lead in the U.S. population [Harlan, 1988]. Heavier individuals with low blood lead levels may have been misclassified as having higher blood pressures if a smaller than appropriate blood pressure cuff were used. Only the reports from NHANES II and the Canada Health Survey indicated that the appropriate blood pressure cuff size was assessed and used [Pirkle et al., 1985; Harlan et al., 1985; Coates et al., 1985]. Both of these surveys did report an association of PbB and blood pressure. Other studies do not report the proportion of obese individuals and hence the magnitude of bias in estimates of the lead - blood pressure association stemming from the use of incorrect cuff sizes cannot be estimated. However, controlling for body mass may eliminate much of this bias.

4. Use of continuous versus dichotomous blood pressure

Blood pressure is a continuously distributed characteristic in a population. There is no clinical, pathophysiologic, or empirical evidence for a threshold value for blood pressure that distinguishes hypertensives from individuals with normal blood pressure [Tyroler, 1986]. Cutpoints and definitions of hypertension in population studies are arbitrary and often based on customary levels for management of individual patients or for comparisons with other studies. Each of the three population-based studies in Table 1 that examined blood pressure as both a dichotomous variable and as a continuous outcome chose a different arbitrary cutpoint based solely on diastolic level [Pocock et al., 1984; Harlan et al., 1985; Neri et al., 1988]. Use of a dichotomous outcome variable in each study resulted in findings and statistical significance levels similar to those obtained using the continuous systolic and diastolic variables as outcomes.

II.B. *Measurement of Lead Exposure*

1. Internal Dose

The use of blood lead, as opposed to some measure of exposure external to the body, is a major strength of the studies of lead and blood pressure conducted to date. In this regard, the above-reviewed studies of lead incorporate internal dose in a manner not often seen in environmental epidemiology, though the particular target tissue for an effect of lead on blood pressure has not been established. Subclinical nephrotoxicity has not been ruled out and effects on renin-angiotensin activity or vascular responsiveness mediated by the sympathetic nervous system have also been postulated [Sharp 1987]. In the absence of a known relevant target, the use of lead in the blood is reasonable, under the assumption that a monotonic function of PbB reaches the relevant target tissue. Although most PbB is bound to proteins in the cell membranes, total lead in blood is highly predictive of plasma lead [EPA 1986]. This relationship is not linear: free lead increases more rapidly at higher levels of PbB than at lower levels [EPA 1986]. Additionally, much of the bound lead is relatively dissociable. None of the published studies on blood pressure attempted to measure free lead.

2. Relevant time period for exposure

All but three of the studies reviewed for this report used concurrent measures of both PbB and blood pressure. The time frame of exposure that is most relevant to blood pressure measurements is, however, not obvious. The lability of blood pressure and its responsiveness as an outcome relative to risk factors such as body mass suggest that lifetime lead exposure may not be appropriate. On the other hand, the half-life of lead in blood is only 30 days, which may be too short a time span for the relevant effect. Zinc protoporphyrin improves slightly on PbB in that it continues to accumulate even when PbB reaches a plateau and declines more slowly than blood lead, even after exposure ceases. It is, however, less specific, reflecting iron deficiency anemia rather than elevated PbB.

II.C. *Statistical Issues*

1. Choice of scale for PbB

All studies that examined PbB on a continuous scale conducted regressions on the logarithmic transformation, with the exception of the analysis of foundry workers. This transformation is used because it usually normalizes the skewed distribution of exposure. Sharp et al. [1988] used the logarithmic transformation in their study of bus drivers, but noted that this transformation imposes a structure on the data that may not be appropriate. In particular, using linear regression, the structure dictates that a doubling of exposure is associated with the same increase or decrease in blood pressure regardless of whether PbB changes from 5 to 10 μg/dl or from 20 to 40 μg/dl.

The study of foundry workers examined workers with substantial fluctuations in their lead values and found no support for a linear dependence of blood pressure on the log of the PbB. No other authors have reported an examination of this issue.

A further issue relates to the range of exposures. The use of log(PbB) rather than log(PbB+c) where c is a constant is problematic in that a value of zero for PbB yields an impossible ($-\infty$) value for log PbB. The transformation without a constant term thus introduces a further instability into the regression model. Data analysis to determine the most stabilizing choice of c is needed, in order to estimate a baseline blood pressure that corresponds to those with virtually no PbB. In populations with lower PbB levels, this issue becomes more critical.

2. Analysis of Influential Observations

Two of the occupational studies [Sharp et al. 1988, Weiss et al. 1986] evaluated the problem of influential observations. (An influential observation is a subject with extreme values for one or more variables. The extreme values could be errors in measurement or coding, or could represent true values. Such subjects sometimes exert an inappropriately strong influence on regression coefficients.) Among bus drivers, removal of such

coding, or could represent true values. Such subjects sometimes exert an inappropriately strong influence on regression coefficients.) Among bus drivers, removal of such observations resulted in stronger associations [Sharp et al. 1988]. The outliers were individuals with low PbB concentrations but extreme blood pressure values, potentially related to genetic predisposition, a variable that is frequently unmeasured in these studies. Among policemen, exclusion of influential observations improved the relation between blood pressure and other covariates, but did not alter the blood lead-blood pressure association [Weiss et al. 1986].

3. Confounding

Many major determinants of BP are also often associated with lead. These include age, body mass, social class, and many correlates of social class including ethnicity and nutrition. Table 4 lists correlates of elevated blood lead from the NHANES II data. Age, gender and ethnicity are controlled in virtually all studies reviewed, either in the analysis or the design. The control of other factors, however, varies among studies, and it is not always clear which factors are, in fact, confounders.

In particular, most of the published studies that conducted multivariate analyses [e.g., among population-based studies, Harlan et al. 1985, 1988; Pirkle et al. 1985; Pocock et al. 1984; Neri et al. 1988] did not report which of the covariates actually alter the magnitude of the lead-BP association. Also, whereas in some studies, controlling for other determinants of blood pressure attenuates the strength of the association, in at least one study [Pocock et al. 1984] the association appears stronger after such control. When different studies control for different factors, it is difficult to reconcile apparently discordant results without more specification of the actual confounders in each study.

Furthermore, the appropriateness of controlling for certain covariates has not been examined critically. The assumption behind the use of statistical methods to "control" for confounding is that the third variable is simultaneously associated with exposure and is an independent predictor of the outcome. Here, independence refers to causal activity on

a completely separate biological pathway. If we consider alcohol, the evidence as to whether it meets the critera for a confounder are not clearcut. First, in some circumstances, the lead content of alcohol due to storage conditions is not inconsequential [Grandjean et al. 1981] and hence alcohol consumption can be a surrogate for lead exposure. Under this scenario, statistical adjustment for alcohol consumption would give the wrong, i.e., a biased, answer. Second, whether alcohol influences the absorption, metabolism in the liver, or excretion ob Pb via the kidney has not been fully investigated; any such metabolic effects would imply that the separate pathway assumption is violated. Alcohol could thus act on the causal pathway, or be an effect modifier, or both. Under such scenarios, statistical control for alcohol would again be unjustified, and would lead to incorrect answers.

Even if alcohol fits the definition of a confounder, the adjustment for it can be counterproductive. Self reports are the basis for alcohol consumption data. The validity of such self-reports cannot be blindly accepted. Misclassification stemming from inaccurate self-reports could be differential or nondifferential, in either case introducing bias. Misclassification rates and degrees to which they are differential are also likely to differ by culture (e.g., the "stigma" associated with drinking varies by country, by region within countries, and by social class). Misclassification of a potential confounder implies that control of confounding will be incomplete, leaving some residual confounding [Savitz & Baron 1989].

Alcohol is not the only covariate for which adjustment may not be appropriate. Parkinson et al. (1987) controlled for education and income. Income was strongly and significantly associated with current PbB and with zinc protoporphyrin. It is not clear that low income itself is a causal factor in elevated blood pressure, rather than the accompanying exposures that workers with low job status and low income receive, one of which is lead.

4. Effect modification

Two studies suggested a stronger effect among younger individuals: the population-based NHANES II [Harlan et al 1985] (see Table 3), and the report on Civil Servants in Paris [Orssaud et al 1985]. Since age ranges varied among studies, some investigators could not have examined this issue, e.g., the British [Pocock et al. 1984] and Danish [Grandjean et al. 1989] population surveys. Other researchers simply did not report on this possibility: associations were not reported within age categories and models were fit without age X PbB interactions.

Beevers et al. [1976] noted that the association between PbB and hypertension was stronger in men than in women. Since then, most studies that included women found associations among women were in the same direction, though sometimes of different magnitude, as among men. As seen in Table 3, even the age heterogeneity in NHANES II held for both sexes. An exception to the pattern of gender similarity is the study by Grandjean et al [1989], who observed heterogeneity of the lead-blood pressure association: in a cross-sectional analysis at age 40, men experienced a (nonsignificant) reduction in diastolic blood pressure as a function of PbB or of the lead:hemoglobin ratio. Women of the same age experienced an increase in DBP, using PbB as the predictor, that approached statistical significance, and using lead:hemoglobin ratio as the predictor, the regression was significant ($p<.01$). However, this heterogeneity was not observed at age 45 or using the age 40 lead value to predict blood pressure at age 45.

III. Causal Inference

A number of criteria have been used in epidemiology to evaluate the strength of evidence for a causal relation [Hill 1965]. These include consistency across multiple studies in different times and places; an appropriate temporal relation between exposure and the outcome; presence of a dose-response gradient; and biological plausibility and coherence.

III.A. *Consistency*

Evidence for an association between blood lead and blood pressure comes from both population-based studies [Pocock et al. 1984; Harlan et al. 1985, 1988; Pirkle et al. 1985; Elwood et al. 1988; Neri et al. 1988; Grandjean et al. 1989] and occupation-based studies [Kirkby & Gyntelberg 1985, Weiss et al. 1986, Sharp et al. 1988, Orssaud et al. 1985, Neri et al. 1988]. Likewise, evidence of no association can be found [Parkinson et al. 1987] The EPA [Air Quality Criteria for Lead: Supplement to the 1986 Addendum, 1990] concluded, nevertheless, that analyses of NHANES II and the British Regional Heart Study provided highly convincing evidence in that they demonstrated small but statistically significant associations between elevated or moderately elevated blood lead levels and blood pressure increases in adult men.

The body of evidence does show some inconsistency. In particular, some studies show a stronger association with DBP than with SBP [Kirkby & Gyntelberg 1985, Sharp et al. 1988, Elwood et al. 1988], whereas for others the reverse is true [Harlan et al. 1985, Pirkle et al. 1985, Weiss et al. 1986, Grandjean et al. 1989]. Findings also indicate heterogeneity with respect to age and gender, with stronger associations among men and younger persons in several studies.

In fact, the inconsistencies may be smaller than is initially apparent. When viewed not from the so-called "hypothesis-testing" mode, in which p-values determine which side of an either/or decision is favored, but rather from the vantage point of estimating the size of an effect that may or may not take the value zero, a more consistent pattern emerges. The magnitude of effect in population-based studies generally falls in the range of an increase of 1-8 mm Hg systolic blood pressure in those with PbB levels above 25 μg/dl compared to those with PbB levels below 12 μg/dl. Both "positive" (i.e., $p<.05$) and "negative" population-based studies yield similar effect sizes.

Differences in study results would not be surprising given the multitude of ways in which the exposure and response variable were treated in the analysis. Some used the log of the blood lead concentration [Tables 1 and 2], others categorized blood lead [Orssaud et al. 1985, Weiss et al. 1986], some did both [Pocock et al. 1984, Neri et al. 1988] and one study used blood lead as a continuous variable without the logarithmic transformation [Neri et al. 1988, analysis of foundry workers]. Among studies which used log blood lead and continuous blood pressure measurements, some report direct regression coefficients [Pirkle et al. 1985, Weiss et al. 1986, Sharp et al. 1988, Neri et al. 1988, Grandjean et al. 1989], others the standardized coefficients [Harlan et al. 1985, 1988; Parkinson et al. 1987], and still others partial correlation coefficients [Elwood et al. 1988]. In light of such widely variable methods, the consistency of the finding that small elevations in BP occur with higher blood lead values is all the more striking.

A further argument regarding the consistency of the body of data concerns the direction of effects. With few exceptions, the regressions from both population-based and occupational studies show some positive contribution of lead to blood pressure. Exceptions are the lead battery workers study [Parkinson et al. 1987], in which many of the coefficients for lead exposure are negative, and one of the analyses of the Glostrup study [Grandjean et al. 1989], in which diastolic blood pressure in men at age 40 is inversely related to PbB or the lead:hemoglobin ratio. The fact that more negative coefficients are not found suggests either a small effect that is difficult to detect as statistically significant, or a consistent true confounder that has not yet been identified or controlled. Given how many potential confounders have been evaluated in the literature, particularly in the numerous population-based studies, it is difficult to conjure such an unidentified risk factor for blood pressure, though one may exist. The problem here is one of developing a plausible and testable alternative hypothesis to that of a direct lead-blood pressure relationship.

III.B. *Temporality*

The temporality of exposure prior to the observation of the outcome is lacking in the cross-sectional surveys, and also in most of the occupational studies. As discussed above, the relevant time lag between exposure and manifestation of its effect on blood pressure is unknown. Though two longitudinal studies did find strong associations, neither is a particularly strong study, one because of its small sample size and lack of repeated PbB measurements [Weiss et al. 1986], the other because of its inadequate methodology [Neri et al. 1988]. The third longitudinal study was population based and provided evidence for an effect of PbB on blood pressure in men over a five year lag, but this result did not reach significance when adjusted for alcohol. The evidence among women was much weaker. Since current blood lead level may correlate strongly with past exposure, the determination of a critical time period for the relevant exposure may be both impossible and less relevant. However, the reduction of lead ought to be accompanied by reductions in blood pressure.

III.C. *Biologic Plausibility*

In addition to experimental studies of laboratory animals, observational studies of lead-exposed workers support the role of high-level lead exposure, in the range of 30 to 141 μg/dl PbB, as a nephrotoxin [EPA 1986, Sharp et al. 1987, Landrigan 1989]. Mortality follow-ups of lead-exposed workers show substantial excesses of death from chronic renal disease, cerebral hemorrhage, hypertensive vascular disease, and renal cancer [McMichael et al. 1982, Malcolm et al. 1982, Cooper et al. 1985, Selevan et al. 1985, EPA 1986]. Exposure levels were not always reported, though workers in the study by Cooper et al. [1985] had a mean PbB of 63 μg/dl and Selevan et al. [1985] defined high lead exposure departments as those with airborne values > 200 $\mu g/m^3$. A review of these mortality studies indicated that deaths from lead nephropathy tended to occur in workers with the

longest duration of lead exposure or in those with clinical lead poisoning [Selevan et al. 1985].

If there is an association of low level lead with hypertension, then a possible mechanism may be through nephrotoxic effects on the kidney, or by a direct action on vascular smooth muscle, as suggested by toxicologic studies in rats [Victery et al. 1982, EPA 1986, Sharp et al. 1987]. Prolonged low-dose lead exposures in rats reduce tissue concentrations of high-energy phosphates in the heart and this effect may result in reduced cardiac contractility [EPA 1986]. Furthermore, changes in the permeability of blood vessels and changes in the catecholamine content in the myocardium and blood vessels have also been observed in lead-exposed experimental animals [EPA 1986]. Results from animal studies suggest that lead may have a chronic effect on the renin-angiotensin system, alter vascular reactivity, and alter the mechanism that regulates intracellular calcium concentration, thus contributing to a possible abnormal vascular function in lead-induced hypertension [Sharp et al 1987, EPA 1990]. However, the relationship of low-level lead exposure with cardiovascular function in humans is unclear and results are inconsistent. A recent review of five studies that examined lead exposure in relation to renin-angiotensin activity in humans showed that chronic heavy lead exposure was associated with reductions in plasma renin activity while short-term low exposure was associated with increased activity [Sharp et al. 1987]. Suggestive data from one epidemiologic occupational study showed 20% of lead exposed workers to have ischemic electrocardiographic changes compared with 6% of occupationally unexposed referents [Kirkby & Gyntelberg 1987]. Further, among those with ischemic changes, lead exposed workers had dramatically elevated blood pressure as compared with those not occupationally exposed. Direct effects of lead on central, as opposed to peripheral nervous system function does not appear to have been considered, but has plausibility.

Whether epidemiologic studies showing nephrotoxicity at high exposures have relevance at lower exposures remains unknown. Nonetheless, data from experimental

studies on nonhuman animal species are supportive of numerous other mechanisms by which lead exposure may result in increased blood pressure.

III.D. *Dose Response*

Very few studies provided sufficient data to actually graph the observed blood pressure for different groups of blood lead levels. The four population-based surveys and one occupational cohort that did provide such data are plotted together to allow comparisons among the studies (Figure 1). The inter-study differences in blood pressure are largely due to major age differences. The overall picture appears not to suggest a dose-response effect, but this is not surprising since three of the five cohorts shown in the figure were from studies that did not observe a significant association. There does, however, appear to be some gradient up to the 25-30 μg/dl level in several of the studies, including the Welsh Heart Program women.

Orssaud et al. (1985) noted that the dose-response among civil servants in Paris is evident only up to a certain level of lead exposure. They further point to heterogeneity by age group and suggest that the influence of lead seen in younger groups is consistent with an effect of lead being flooded by stronger risk factors such as age. As noted above, several studies with significant findings observe a doubling of lead being associated with a rise of 1-2 mm Hg systolic blood pressure, and a smaller rise for diastolic blood pressure. Such regression analyses are, by definition, measuring and testing dose-response relations.

III.E. *Conclusion: Causal Inference*

There is a strong degree of consistency, particularly among the population-based studies, though certain inconsistencies persist which have not been explained. The evidence suggests a small dose-response through the range of PbB values from as low as 2 μg/dl up to about 30 or 40 μg/dl. Insufficient data have been collected and analyzed with respect to a temporal relation of lead exposure and elevations in blood pressure, though

the existing data is supportive. Experimental data in nonhuman species appear to support several mechanisms including effects on vascular reactivity and on the renin-angiotensin system.

At this stage, the body of epidemiologic literature relating lead exposure to blood pressure is suggestive, but in no way definitive. Given the population-based sampling of several studies, and the careful measurement of both lead and blood pressure in many, neither selection bias (nonrepresentative samples with respect to the Pb-blood pressure relation) nor information bias (errors in measurement of exposure or outcome) are plausible explanations that could serve as viable alternatives to that of a causal relation. Confounding bias, on the other hand, is conceivable. Nonetheless, the absence of a consistently uncontrolled, identifiable confounder leaves the research community without a testable explanation to contrast with the causal one. While not ruled out, the probability that confounding explains most of the findings would appear to be low.

IV. Value of Data for Occupational Risk Assessment

The last decade has seen a flurry of studies examining the relation between lead exposure, usually measured as PbB, and blood pressure. Though the results have been somewhat mixed, a suggestive pattern emerges, particularly from the reports on population-based samples. Several well-conducted studies in which the methodology of measuring both lead and blood pressure is of high quality have found small but statistically significant associations. Other studies not finding statistically significant results nevertheless observe effects of a similar magnitude. Unfortunately, epidemiology is often an inadequate tool for measuring small effects. For this reason, risk assessment frequently relies on animal models.

The suggestion in some reports (e.g., Parkinson et al. 1987) that the occupational literature shows overall less evidence of an effect than has been observed in population-based studies with lower exposures is somewhat misleading. Table 2 indicates that a

number of occupational groups with elevated blood lead values (in comparison with, e.g., NHANES data) show a blood lead-blood pressure association. Two of these occupational studies were longitudinal involving multiple measurements on the same individuals. On the other hand, where associations are observed, they appear to be strongest at PbB levels <25-30 μg/dl. Thus, the range of exposures is relevant.

The definitive answer is not available at this date, though even a small influence of blood lead on blood pressure would have rather large consequences for debilitating and fatal cardiovascular disease. Using the NHANES II data to estimate the lead-blood pressure association, and the MRFIT study to estimate the blood pressure-cardiovascular disease association, Schwartz [1991] has predicted that 24,000 cases of myocardial infarctions per year and over 100,000 cases of all cardiovascular disease would be eliminated if PbB levels were reduced by 50%. He points out that while this is a small proportion of the total population burden for cardiovascular disease, it is a substantial attributable risk for a single environmental chemical pollutant.

When data are strongly suggestive of an effect but do not provide a definitive answer, yet the outcome is common and has serious consequences, public health measures to reduce exposures may well be justified. Thus, prudence in policy and concern for the public welfare suggest that limitation of lead exposures, particularly in occupational settings where the overall decline in PbB for the population has not been felt, is rational and adviseable. A safe level cannot at this time be deduced from the available data.

V. Recommendations for Future Research

To resolve the question of whether PbB is causally related to increases in blood pressure and to determine the magnitude of this effect and the level at which the effect would be vanishingly small, future studies are needed that do not simply repeat the protocols of past studies. The recommendations listed below would be expected to resolve the critical issues that currently prevent meaningful inferences.

Future studies which conduct adjustment for confounding would be more informative if results included crude measures of association and the changes in magnitude of these measures that occur after consecutive adjustment for each covariate. Perhaps more important would be some presentation of data using stratification on covariates. Studies which use multivariate techniques need to report sufficient information for readers to distinguish which covariates actually do make a difference in the lead-BP relationship and which do not.

Further studies should evaluate lead content of alcohol consumed in the region of the study subjects. Instruments used for collecting alcohol consumption data also need to undergo extensive validation. Pharmacokinetic studies to evaluate alcohol's effect on absorption, metabolism, and excretion of lead are in order.

Physiologic studies are needed to clarify the mechanisms of lead effects on blood pressure, including investigations of possible alterations in vascular reactivity and in the renin-angiotensin system. In these studies and in epidemiologic investigations, closer attention to heterogeneity is mandatory, particularly for covariates such as age, gender, and alcohol. Stratification and other methods should be used for this purpose.

Also needed are careful analyses of outliers and influential observations, using, e.g., bootstrap methods. Influential points are not necessarily to be discarded, since susceptible subgroups may exist. Collection of data on family history as a surrogate for genetic predisposition to high blood pressure would be a useful addition to any future studies. Further analyses of treated hypertensives may be of interest, particularly for exploration of mechanisms.

Reporting of **both** dichotomized outcomes, preferably using a standard definition for hypertension **and** blood pressure on a continuous scale would facilitate comparisons among studies. The logarithmic transform for blood lead should not be blindly applied. The implicit structure imposed by such a transform should be evaluated carefully, and the impact of various constant terms, that is, c in $\log(PbB+c)$ requires close examination.

Fitted regression coefficients and their standard errors should be reported, as Greenland et al [1986] and Greenland [1991] have shown that standardized coefficients are biased.

More research using longitudinal data, i.e., serial collection of both PbB and blood pressure, would be essential in assessing the time lag of any effect. Finally, further studies are needed in which researchers evaluate whether reductions in lead exposure are accompanied by subsequent reductions in blood pressure. Such studies can also be used to evaluate the temporal relation.

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Table 1. Selected population-based studies
that investigated the relationship of blood lead levels to blood pressure level.

Methods	BRHS[1]	NHANES II[2]	NHANES II[3]	WHP[4]	CWHS[5]	CHS[6]	GPS[7]
Sample size	7,371 MM	564 MM	2,823 M 2,905 F (biracial)	865 M 856 F	1,136 M	2,193 (M & F)	451 M 410 F
Age of population	40-59	40-59	12-74	adults <65	49-63	25-64	40-45
Blood Pressure measurement:							
average of 2 or more readings	Yes	Yes	Yes	Unknown	Unknown	No	Yes
excl. treated hypertensives	Unknown	Yes	Yes	Unknown	Unknown	Yes	No
appropriate cuff size used	Unknown	Yes	Yes	Unknown	Unknown	Yes	No
Blood Lead measurement:							
flame microsampling atomic absorption spectroscopy	Yes	Yes	Yes	Yes	Yes	Unknown	Yes
Statistical adjustment:	Age BMI Alcohol Social class Observer Site	Age BMI Dietary factors Blood bio-chemistries	Age BMI Race Alcohol Dietary factors Blood bio-chemistries	Age	-	Age BMI Sex Zinc Hemoglobin	Age (by design) Alcohol Hemoglobin
Log blood lead in analyses	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[1]BRHS - British Regional Heart Study (1978-80) [Pocock et al., 1984]

NHANES - second National Health and Nutrition Examination Survey (1976-80):
[2][Pirkle et al., 1985] and [3][Harlan et al., 1985]

[4]WHP - Welsh Heart Programme (1985) [Elwood et al., 1988]

[5]CWHS - Caerphilly Collaborative Heart Disease Study, Wales, (1985) [Elwood et al., 1988]

[6]CHS - Canada Health Survey (1978-79) [Coates et al., 1985; Neri et al., 1988]

[7]GPS - Glostrup Population Study (1976-81) [Grandjean et al., 1989]

Table 1 (con't)

	BRHS[1]	NHANES II[2]	NHANES II[3]	WHP[4]	CWHS[5]	CHS[6]	GPS[7]
Results:							
Exposure defined (ug/dl)	≥37.3	continuous only	continuous only	continuous only	continuous only	≥10	continuous only
Outcome definition	DBP>100 mm Hg	continuous	DBP≥90 mm Hg	continuous	continuous	DBP>90 mm Hg	continuous
Hypertension comparing high vs low PbB	15% vs 9% (p=.07)		increase (p<.05)			RR=1.2 (1.0, 1.5)	
For a PbB increase (in ug/dl):	<12 to >37	14 to 30	12 to 32	6 to 26		0 to 47	any doubling
Predicted rise in SBP is:	2	7	8	0.7			1.1 to 2.3
Predicted rise in DBP is:		3	4	1.3		1.4 to 3.0	-1.6 to 1.7
Statistical significance	p<.01	p<.01	Men: p<.05 Women: ns	ns	ns	p=.04 to .24	ns

[1]BRHS - British Regional Heart Study (1978-80) [Pocock et al., 1984]
NHANES - second National Health and Nutrition Examination Survey (1976-80):
[2][Pirkle et al., 1985] and [3][Harlan et al., 1985]
[4]WHP - Welsh Heart Programme (1985) [Elwood et al., 1988]
[5]CWHS - Caerphilly Collaborative Heart Disease Study, Wales, (1985) [Elwood et al., 1988]
[6]CHS - Canada Health Survey (1978-79) [Coates et al., 1985; Neri et al., 1988]
[7]GPS - Glostrup Population Study (1976-81) [Grandjean et al., 1989]

Table 2. Selected occupation-based studies that investigated the relationship of blood lead levels to blood pressure level

Methods	Lead[1] Smelters	Battery[2] Plant	Police[3]	Bus[4] Drivers	Civil[5] Servants	Lead[6] foundry
Sample size	184 M, 7 F	270 MM	89 M	261 M, 27 F	431 M	288 M
Age of population	30-60	18-60		27-65	24-55	-
Reference group	population-based (92 M, 3 F)	manufacturing workers not exposed to lead (158 MM)	longitudinal comparison (each worker to himself)	internal comparison	internal comparison	longitudinal comparison (each worker to himself)
Blood Pressure measurement:						
average of 2 or more readings	No	Yes	Yes	Yes	nr	nr
excl. treated hypertensives	nr	Yes	nr	Yes*	nr	nr
appropriate cuff size used	nr	nr	nr	nr	nr	nr
Blood Lead measurement::						
flame microsampling atomic absorption spectroscopy	Yes	Yes	Yes	Yes	Yes	nr
Mean blood lead (μg/dl) ±SD or categories of exposure	Exposed: 51 ± 16 Referents: 11 ± 3	Exposed 40 ± 13 Referents: 7 ± 5	3 groups: <20 (40%) 20-29 (37%) ≥30 (23%)	median: 6.4 range: 2-15	7 groups: <12.4 to ≥37.3	nr
Definition of Pb exposure:	employment in smelter	-place of employm't -current PbB -current zpp** -TWA cumulative PbB	Low (<20) Medium (20-29) High (≥30	Log PbB	Log PbB	PbB (not log)
Statistical adjustment:	(matched on Age, Sex, Occ. status, Duration of employment)	Age, BMI, Education, Income, Alcohol, Smoking, Exercise	Age, BMI, Prior BP Smoking	Age, Race, Sex, BMI, Caffeine	Age, BMI, Alcohol	Age Weight Prior BP

Table 2 (con't)

	Lead[1] Smelters	Battery[2] Plant	Police[3]	Bus[4] Drivers	Civil[5] Servants	Lead[6] Foundry
Influence of outliers assessed:	No	No	Yes	Yes	Not applicable	No
Results:						
For a PbB increase (in ug/dl) of:	11 to 51 (means)	7 to 40 (means)	<20 to >30	3.6 to 10.8 (5th to 95th %ile)	<12.4 to >24.8	
Predicted rise in SBP is: (in mm Hg)	2 (ns)	-.05 (ns)	4.5 (p=.10)	0.9 (ns)	8 (p<.01)	.210 per ug/dl (ns)
Predicted rise in DBP is: (in mm Hg)	4 (p=.04)	-.03 (ns)	.88 (ns)	2.7 (p<.10)	Did not analyze	.298 per ug/dl (p<.01)
Other	Increased (20 vs 6) ischemic electro-cardiographic changes		Dose response for systolic		Dose response for systolic	
Notes:						
	Body weight & physical activity differed, not controlled in analysis	May have over-adjusted for correlates of lead exposure	Removal of influential points weakened SBP assoc, strengthened DBP	Removal of outlier strengthened SBP and DBP associations		Inadequate description of methods

[1]Lead-exposed workers employed 9-45 years in Denmark (1978) [Kirkby and Gyntelberg, 1985]

[2]Lead-exposed workers employed >1 year, eastern Pennsylvania (1982) [Parkinson et al., 1987]

[3]Policemen assumed to be exposed to automobile exhaust (1969-75), Boston, Massachussetts [Weiss et al., 1986]

[4]Bus drivers exposed to vehicular exhaust, San Francisco, California [Sharp et al., 1988]

[5]Paris civil servants with no occupational lead-exposure, Paris, France [Orssaud et al., 1985]

[6]Foundry workers in Canada (1979-85), [Neri et al., 1988]

* For analysis of treated hypertensive bus drivers, see Sharp et al., 1989.

** zinc protoporphyrin

Table 3. Mean (SE) blood lead level by blood pressure category, sex, and age group, US population, 1976-80

Age group and BP category (mm Hg)	Mean Blood Lead, µg/dl (SE) Men	Women
Ages 21-55:		
DBP<90	16.9 (0.33)	11.5 (0.26)
DBP≥90	17.9 (0.49)	12.3 (0.38)
	(p<.05)	(p<.05)
Ages 56-74:		
SBP<160 and DBP<90	16.4 (0.28)	12.9 (0.34)
DBP≥90	16.9 (0.50)	12.9 (0.31)
SBP≥160 and DBP<90	16.5 (1.37)	13.1 (1.10)

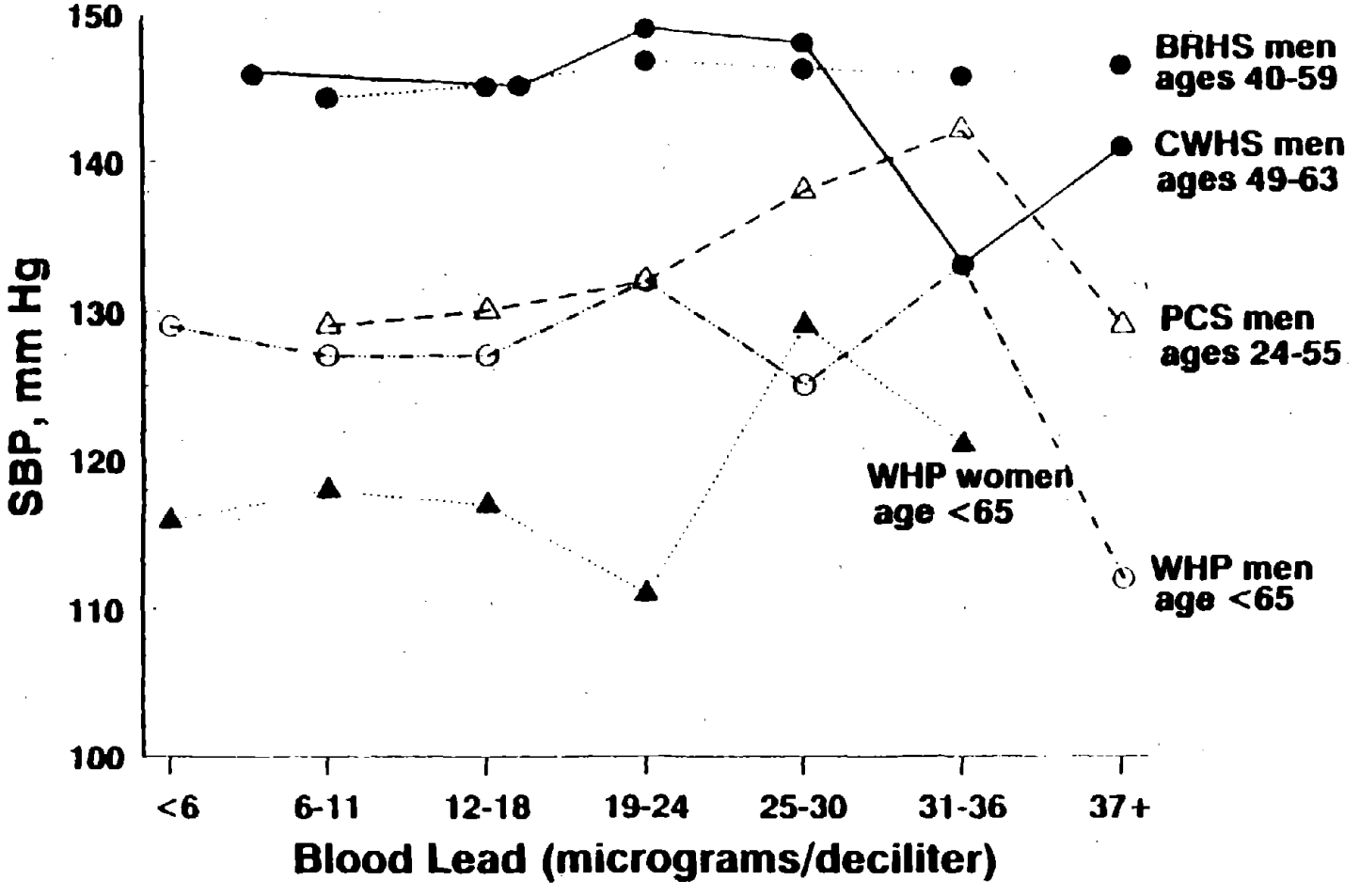
Source: NHANES II (1976-80) [Harlan et al., 1985]

Table 4. Correlates of elevated blood lead levels in the US population, ages 12-74 (1976-80)

Variables	Direction of the relationship
Age	direct (men); quadratic (women)
Population size	direct
Cigarette packs/year	direct
Alcohol consumption/week	direct
Body mass index	inverse
Black vs White	direct
SES (income - education)	inverse (men only)
Blood biochemistries:	
hemoglobin	direct
red blood cell count	direct (women only)
serum copper level	direct (men only)
Dietary intake:	
vitamin C	inverse
phosphorous	inverse (men only)
calcium	inverse
sodium	inverse (men only)
potassium	direct (women only)

Source: NHANES II (1976-80) [Harlan, 1988]

Systolic Blood Pressure by Blood Lead Level in Selected Surveys



BRHS - British Regional Heart Study (n=7,371), adjusted for age, town, BMI,alcohol, social class, BP observer (value estimated from published figure) [Pocock et al., 1984]

PCS- Paris Civil Servants (n=431), adjusted for age, BMI, alcohol [Orssaud et al., 1985]

WHP - Welsh Heart Programme (865 men and 856 women), age-standardized [Elwood et al., 1988]

CWHS - Caerphilly, Wales Heart Study (n=1,136), unadjusted [Elwood et al., 1988]

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15. Supplementary Notes

16. Abstract (Limit: 200 words) Epidemiologic studies on blood lead (7439921) and blood pressure in the general population and in occupationally exposed populations were reviewed. Six large population based surveys were conducted in Great Britain, Canada, Denmark, and the United States. In the population based studies, a small increase in blood pressure was associated with increases in blood lead. Increases in blood lead levels below 12 micrograms/deciliter (microg/dl) to levels higher than 25microg/dl were consistently accompanied by blood pressure increases in the range of 1.2 to 4mmHg diastolic blood pressure and 1.4 to 8mmHg systolic blood pressure. Occupational groups which have been studied due to their exposure to lead at the workplace include those in lead smelting, steel cutting, scrap metal recovery, battery manufacturing, lead pigment and lead soldered stained glass work, car repair, and police work. Although the results of the studies on occupational cohorts were mixed, they suggested a small positive association between blood lead and blood pressure. Methodologies used in the studies were critiqued. The authors recommend factors for future study.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Contract, Task-Order-91-39121, Epidemiology, Task-Order-91-39188, Lead-poisoning, Heavy-metals, Occupational-exposure, Blood-analysis, Foundry-workers, Environmental-exposure, Blood-pressure, Cardiovascular-system-disorders

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