Background: Despite declines in blood lead levels during the past 20 years, lead exposure continues to be a public health concern. Studies have linked lead exposure with increased risk for diverse health outcomes. Few studies have evaluated the association of lead exposure and mortality in the general population.

Methods: To evaluate the association of lead exposure and mortality in the United States, we used the recently released mortality follow-up data for participants of the Second National Health and Nutrition Examination Survey, a national cross-sectional survey of the general population conducted from 1976 to 1980. Survey participants aged 30 to 74 years with blood lead measurements were followed up through December 31, 1992 (n=4292).

Results: After adjustment for potential confounders, individuals with baseline blood lead levels of 20 to 29 µg/dL (1.0-1.4 µmol/L) had 46% increased all-cause mortality (rate ratio [RR], 1.46; 95% confidence interval [CI], 1.14-1.86), 39% increased circulatory mortality (RR, 1.39; 95% CI, 1.01-1.91), and 68% increased cancer mortality (RR, 1.68; 95% CI, 1.02-2.78) compared with those with blood lead levels of less than 10 µg/dL (<0.5 µmol/L). All-cause mortality for those with blood lead levels of 10 to 19 µg/dL (0.5-0.9 µmol/L) was intermediately increased and not statistically significant (RR, 1.17; 95% CI, 0.90-1.52).

Conclusions: Individuals with blood lead levels of 20 to 29 µg/dL in 1976 to 1980 (15% of the US population at that time) experienced significantly increased all-cause, circulatory, and cardiovascular mortality from 1976 through 1992. Thus, we strongly encourage efforts to reduce lead exposure for occupationally exposed workers and the 1.7 million Americans with blood lead levels of at least 20 µg/dL (≥1.0 µmol/L).

Arch Intern Med. 2002;162:2443-2449

Despite the decline in blood lead levels during the past 20 years, lead continues to be a public health concern for individuals with past and present lead exposure. Based on the 2000 census and analysis of the Third National Health and Nutrition Examination Survey (NHANES III) data by Pirkle et al, we estimate that in the United States, at present 1.7 million people (0.6% of the population) have blood lead levels of at least 20 µg/dL (≥1.0 µmol/L). Even more Americans have a history of lead exposure. Based on the 2000 census and analysis of the Second National Health and Nutrition Examination Survey (NHANES II) data by Pirkle et al, we estimate that 29 million people (15% of the adult population older than 20 years) had blood lead levels of at least 20 µg/dL from 1976 to 1980. A substantial number of Americans, then, are currently exposed to lead or have a history of lead exposure.

The long-term consequences of lead exposure are not well understood. Results of epidemiological and toxicologic studies have associated lead exposure with a number of disorders and disease processes, including learning and behavior disorders, cardiovascular and kidney diseases, decreased fertility, and cancer. On an individual level, the effect of lead on these disorders and disease processes may be subtle and dependent on age and sex as well as diverse genetic, dietary, and environmental factors. On the population level, however, lead exposure may contribute an important fraction to the morbidity and mortality associated with these disease processes.

Several occupational studies have evaluated mortality in lead-exposed workers, but no clear association of lead and mortality has emerged from these studies. For example, in a cohort of 3832 lead-exposed workers, Gerhardsson et al found significantly increased all-cause mortality in the cohort as a whole com-
pared with the general population, but decreased all-
cause mortality in workers with the highest levels of lead
exposure. Similarly, Wong and Harris found significantly
increased all-cause mortality in a cohort of 4518
lead-exposed battery workers, but decreased all-cause
mortality in a cohort of 2300 lead-exposed smelter
workers. Thus, occupational studies do not indicate either a
dose-response relationship of industrial lead exposure and
mortality, or a consistent association of lead exposure and
mortality across cohorts.

Uncontrolled confounding and selection bias further
complicate the picture, making interpretation of the
occupational studies difficult. Lead-exposed workers may
be different in many ways from the general population
besides the lead exposure. Lead-exposed workers as a

group may be more physically fit, and they may have dif-
f erent diets and smoking patterns than individuals in the
general population. The occupational studies generally
do not present these types of data, so assessment of these
effects as confounders or sources of selection bias is dif-
ficult. 12-13,15,16,18,20

Few studies have been conducted on lead and mort-
ality in nonoccupationally lead-exposed individu-
als.21,22 McDonald and Potter conducted a follow-up
study of 454 children who were hospitalized for lead poi-
noning between 1923 and 1966. They found signifi-
cantly increased all-cause mortality and significantly in-
creased cardiovascular and cerebrovascular deaths. Moller
and Kristensen conducted a population-based survey of
1052 men and women born in 1936 and living in Copen-
haven, Denmark. The authors found that, after ad-
justment for potential confounders, blood lead levels were
a significant predictor of all-cause mortality.

Similar studies of the general population of the
United States are lacking. To evaluate the relation of lead
exposure and mortality in the general population of the
United States, we used the recently released mortality fol-
low-up for participants of the NHANES II, which was con-
ducted from 1976 to 1980.23,24

The NHANES II was designed to provide a comprehensive eval-
uation of the health and nutritional status of free-living, nonin-
stitutionalized individuals aged 6 months to 74 years in the
United States. A total of 20322 people were interviewed and
examined for the survey. The interview included a detailed medi-
cal history and an assessment of sociodemographic factors (eg,
smoking, income, and education). Examination included a labo-
atory evaluation of hematologic and biochemical variables such
as blood lead levels. Measurements of blood lead levels are avail-
able for 10049 individuals (49.4% of the total study population).
The plan and operation of the NHANES II and the methods for
determining blood lead levels have been described previ-
ously. 23,25

Recently, the National Center for Health Statistics (Hy-
attsville, Md) released mortality follow-up data for those indi-
viduals aged 30 to 74 years at baseline in the NHANES II
(n=9252). The National Death Index and the Social Security
Administration were used to ascertain vital status as of Decem-
ber 31, 1992. Two individuals could not be followed up for vi-
tal status owing to incomplete information and were excluded
from the analysis (n=9250). If no record of death was avail-
able, individuals were assumed to be alive for the purpose of

analyses. During the course of follow-up, 2145 individuals died
(crude mortality rate, 23.2%).24

Baseline measurements of blood lead levels were avail-
able for 4292 individuals aged 30 to 74 years (46.4% of the mor-
tality follow-up). As the purpose of this study was to examine
the potential risks associated with lower levels of lead expo-
sure, individuals with lead levels of at least 30 µg/dL (≥1.4
µmol/L) were excluded from the analysis (n=102). We chose
this cut point because 30 µg/dL is the standard of the Occupa-
tional Safety and Health Administration for monitoring of lead-
exposed workers. Of the remaining 4190 individuals, 929 died
during follow-up (crude mortality rate, 22.2%).

To allow for the complex, multistage survey design, all
analyses were conducted using SUDAAN software (Research
Triangle Institute, Research Triangle, NC). We chose to weight
each individual equally in the analysis, as the weights pro-
vided with the NHANES II data were designed to be used for
individuals aged 6 months to 74 years. We analyzed the sub-
group of individuals aged 30 to 74 years with mortality fol-
low-up and blood lead levels of less than 30 µg/dL. Weights
specifically appropriate for this group were not available. We
also chose not to use the weights because we present exten-
sive subgroup analyses in this report, and the weights were not
designed for this.

Survival analysis was conducted using the proportional haz-
ards models available in SUDAAN (PROC SURVIVAL; Re-
search Triangle Institute). Covariates for the analysis were se-
lected on the basis of well-established factors that are known
to be associated with lead.26 We considered the following 2 sets
of models: age- and sex-adjusted (using age as a quadratic) mod-
els and multivariate-adjusted models. The multivariate model
contained the following covariates: age, sex, race (white vs Af-
rican American and other nonwhite), education (report of any
vs no college education), income (represented as a 5-level vari-
able), smoking (represented as lifetime nonsmoking, cur-
rently smoking <1 pack/d, currently smoking ≥1 pack/d, and
former smoking), body mass index (BMI, calculated as weight
in kilograms divided by the square of height in meters), exer-
cise (report of moderate or frequent exercise), and location (ur-
ban, rural, or suburban). Lifetime nonsmoking was defined as
smoking less than 5 packs of cigarettes ever. Education and a
5-level representation of income were included in the model
to control as thoroughly as possible for socioeconomic status.
A small number of individuals did not report their incomes,
so a missing category was created (n=152 [3.6%]). In analyses
of the association of lead level and mortality, lead level was in-
corporated in the model as a 3-level categorical variable (<10
µg/dL, ≤0.5 µmol/L, 10-19 µg/dL [0.5-0.9 µmol/L], and 20-29
µg/dL [1.0-1.4 µmol/L]). The final regression models con-
verged, so overparameterization was not a concern.

We performed stratified analyses of the association of lead
levels and mortality. All models were sex and age adjusted. For
the analysis, continuous variables such as BMI and age were
dichotomized. In the age-stratified models (30-54 and
55+
years), age is represented as a covariate within the model to
control for age. Subgroups for analysis were chosen to present
as concise and meaningful an analysis as possible. Rather than
assessing between 5 subgroups of income, for example, reported
income was dichotomized.

We used codes of the International Classification of Dis-
ases, Ninth Revision (ICD-9) to provide cause-of-death infor-
mation. To examine whether the relation of lead level and death
varied by cause of death, we divided deaths into 3 categories
based on the ICD-9 code: circulatory (45.6% of deaths; ICD-9
codes 390-459), cancer (25.8% of deaths; ICD-9 codes 140-
240), and all other causes (all other ICD-9 codes).

Because the US lead standards are expressed in micro-
grams per deciliter, we report lead concentrations in the un-
}(REPRINTED) ARCH INTERN MED/VOL 162, NOV 25, 2002 WWW.ARCHINTERNMED.COM

©2002 American Medical Association. All rights reserved.
Table 1. Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Cohort (n = 4190)</th>
<th>Mortality During Follow-up (n = 929)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>54.1 ± 13.2</td>
<td>64.0 ± 8.6</td>
</tr>
<tr>
<td>Body mass index, mean ± SD†</td>
<td>26.1 ± 5.1</td>
<td>26.1 ± 5.2</td>
</tr>
<tr>
<td>Blood lead level, mean ± SD, µg/dL‡</td>
<td>14.0 ± 5.1</td>
<td>14.9 ± 5.3</td>
</tr>
<tr>
<td>Male</td>
<td>1950 (46.5)</td>
<td>542 (58.3)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3666 (87.5)</td>
<td>818 (88.1)</td>
</tr>
<tr>
<td>African American</td>
<td>438 (10.5)</td>
<td>98 (10.5)</td>
</tr>
<tr>
<td>Other nonwhite</td>
<td>86 (2.1)</td>
<td>13 (1.4)</td>
</tr>
<tr>
<td>Exercise</td>
<td>2466 (58.9)</td>
<td>488 (52.5)</td>
</tr>
<tr>
<td>College education</td>
<td>1024 (24.4)</td>
<td>156 (16.8)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1864 (44.5)</td>
<td>411 (44.2)</td>
</tr>
<tr>
<td>Suburban</td>
<td>698 (16.7)</td>
<td>163 (17.5)</td>
</tr>
<tr>
<td>Rural</td>
<td>1628 (38.9)</td>
<td>355 (38.2)</td>
</tr>
<tr>
<td>Lifetime nonsmoker</td>
<td>1809 (43.2)</td>
<td>320 (34.4)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1030 (24.6)</td>
<td>271 (29.2)</td>
</tr>
<tr>
<td>Currently smoke &lt;1 pack/d</td>
<td>474 (11.3)</td>
<td>112 (12.1)</td>
</tr>
<tr>
<td>Currently smoke ≥1 pack/d</td>
<td>877 (20.9)</td>
<td>226 (24.3)</td>
</tr>
<tr>
<td>Yearly income, $</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5000</td>
<td>680 (16.2)</td>
<td>233 (25.1)</td>
</tr>
<tr>
<td>5000-9999</td>
<td>1022 (24.4)</td>
<td>297 (32.0)</td>
</tr>
<tr>
<td>10000-19999</td>
<td>1332 (31.8)</td>
<td>257 (27.7)</td>
</tr>
<tr>
<td>≥20000</td>
<td>1004 (24.0)</td>
<td>111 (11.9)</td>
</tr>
<tr>
<td>Not reported</td>
<td>152 (3.6)</td>
<td>31 (3.3)</td>
</tr>
<tr>
<td>Lead level, µg/dL‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>818 (19.5)</td>
<td>130 (14.0)</td>
</tr>
<tr>
<td>10-19</td>
<td>2735 (65.3)</td>
<td>605 (65.1)</td>
</tr>
<tr>
<td>20-29</td>
<td>637 (15.2)</td>
<td>194 (20.9)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are given as number (percentage) of subjects. Percentages have been rounded and may not sum to 100.
†Calculated as weight in kilograms divided by the square of height in meters.
‡To convert to micromoles per liter, multiply by 0.0483.

RESULTS

Table 1 presents descriptive characteristics of the study cohort. The cohort represented men and women of diverse races, educational backgrounds, living locations, smoking histories, and incomes. The mean age of the cohort was 54 years, with a range of 30 to 74 years at baseline. The median blood lead level of the cohort was 13 µg/dL (0.6 µmol/L). During follow-up, 929 individuals (22.2%) died, with 424 (10.1%) dying of circulatory disease and 240 (5.7%) dying of cancer.

Table 2 presents a multivariate linear regression model for blood lead level. Age, sex, race, location, smoking, BMI, exercise, education, and income were included in the model. Collectively these variables are associated with 22.5% of the variance in blood lead levels. Male sex, increased age, urban location, exercise, increased smoking, and increased BMI were all positively associated with baseline blood lead levels, whereas white race, college education, and increased income were all negatively associated with blood lead levels.

Table 3 presents a multivariate proportional hazards model for mortality during follow-up. Blood lead level was not included in this model. Age, sex, race, location, smoking, BMI, exercise, education, and income were in the model. Male sex, increased age, increased smoking, decreased exercise, and decreased income were all positively associated with mortality, whereas BMI, education, race, and urban/suburban/rural location were not associated with mortality.

Table 4 presents the association of blood lead levels and mortality, adjusted for age and sex, for the cohort as a whole and subgroups of interest. In the cohort...
as a whole, blood lead levels of 20 to 29 µg/dL were associated with an age- and sex-adjusted increase of 74% (rate ratio [RR], 1.74; 95% confidence interval [CI], 1.40-2.16) in all-cause mortality, and blood lead levels of 10 to 19 µg/dL, with an age- and sex-adjusted increase of 24% (RR, 1.24; 95% CI, 0.97-1.57) in all-cause mortality compared with blood lead levels of less than 10 µg/dL. These associations were reasonably consistent across subgroups defined by sex, age, race, smoking, education, income, exercise level, and BMI.

Table 5 presents the association of blood lead level and mortality in the cohort as a whole, adjusted for multiple potential confounding variables (using the model presented in Table 3). After adjustment for multiple potential confounders (specifically age, sex, location, education, race, income, smoking, BMI, and exercise), blood lead levels of 20 to 29 µg/dL were associated with a 46% increased mortality (RR, 1.46; 95% CI, 1.14-1.86) and blood lead levels of 10 to 19 µg/dL, with a 17% increased mortality (RR, 1.17; 95% CI, 0.90-1.52) compared with blood lead levels of less than 10 µg/dL.

As shown in Table 5, the crude mortality RRs were higher than the age-/sex- and multivariate-adjusted RRs, and the age-/sex-adjusted RRs were higher than the multivariate-adjusted RRs. The difference between the age-/sex-adjusted and multivariate-adjusted RRs was almost completely attributable to introducing smoking into the regression model. Introducing location, education, race, income, BMI, and exercise into the age-/sex-adjusted model did not affect the age-/sex-adjusted RRs or the regression coefficients from which they were derived.

Table 5 also presents the association of blood lead level and mortality by cause of death, adjusted for multiple potential confounders. Subjects with blood lead levels of 20 to 29 µg/dL had significantly increased mortality due to circulatory disease (RR, 1.39; 95% CI, 1.01-1.91; P = .04) and cancer (RR, 1.68; 95% CI, 1.02-2.78; P = .03) compared with those with blood lead levels of less than 10 µg/dL. Collectively, mortality due to circulatory disease and cancer accounted for 71.4% of the mortality in this cohort.

Analysis by specific cancer-caused mortality indicates that blood lead level was associated with mortality due to lung cancer and nonlung cancers. After adjustment for multiple potential confounding variables (including smoking), individuals with blood lead levels of 20 to 29 µg/dL had 50% increased mortality due to nonlung cancers (RR, 1.50; 95% CI, 0.80-2.81) and 120% increased mortality due to lung cancer (RR, 2.20; 95% CI, 1.02-2.78; P = .03) compared with those with blood lead levels of less than 10 µg/dL. Those with blood lead levels of 10 to 19 µg/dL experienced increased mortality due to nonlung cancers (RR, 1.45; 95% CI, 0.76-2.76) and lung cancer (RR, 1.70; 95% CI, 0.60-4.81) as well, compared with those with blood lead levels of less than 10 µg/dL.

Close examination of Table 4 indicates that African American and other nonwhite subjects experienced increased mortality at lower blood lead levels than did white subjects. To explore this interaction, we evaluated a multivariate regression model for all-cause mor-
tality with interaction terms for race and blood lead level (using the same effects as previously described). The model indicates that even after adjustment for potential confounders, nonwhite subjects experienced significantly increased mortality at lower blood lead levels than did white subjects (P < .001 for the interaction). In African American subjects, blood lead levels of 10 to 19 µg/dL were associated with a 2.63-fold increase in multivariate adjusted all-cause mortality relative to blood lead levels of less than 10 µg/dL (RR, 2.63; 95% CI, 1.12-6.19; P = .02). In white subjects, blood lead levels of 10 to 19 µg/dL were associated with a 7% increase in multivariate adjusted all-cause mortality relative to blood lead levels of less than 10 µg/dL (RR, 1.07; 95% CI, 0.83-1.40).

These data also indicated an interaction between heavy smoking (≥1 pack/d) and blood lead level on mortality due to cancer (interaction, P = .07). Smoking was associated with higher cancer mortality in those with blood lead levels of 20 to 29 µg/dL compared with those with blood lead levels of less than 20 µg/dL. In those with blood lead levels of less than 20 µg/dL, smoking at least 1 pack/d was associated with a multivariate adjusted 2.70-fold increase in mortality due to cancer (RR, 2.70; 95% CI, 1.97-3.71) compared with those who currently smoked less or not at all. In those with blood lead levels of 20 to 29 µg/dL, smoking at least 1 pack/d was associated with an adjusted 4.67-fold increase in mortality due to cancer (RR, 4.67; 95% CI, 2.13-10.25) compared with those who currently smoked less or not at all. These data did not indicate a similar interaction of smoking and mortality due to circulatory disease.

COMMENT

These data indicate that blood lead level is an important predictor of mortality due to all causes, circulatory disease, and cancer. After adjustment for potential confounding variables (including age, sex, smoking, BMI, education, location, exercise, and income), individuals with baseline blood lead levels of 20 to 29 µg/dL experience 46% increased mortality due to all causes (RR, 1.46; 95% CI, 1.14-1.86; P = .003), 39% increased mortality due to circulatory disease (RR, 1.39; 95% CI, 1.01-1.91; P = .04), and 68% increased mortality due to cancer (RR, 1.68; 95% CI, 1.02-2.78; P = .04) relative to those with blood lead levels of less than 10 µg/dL. After adjustment for potential confounding variables, individuals with blood lead levels of 10 to 19 µg/dL experience 17% increased mortality due to all causes (RR, 1.17; 95% CI, 0.90-1.52), 10% increased mortality due to circulatory disease (RR, 1.10; 95% CI, 0.85-1.43), and 46% increased mortality due to cancer (RR, 1.46; 95% CI, 0.87-2.48) relative to those with blood lead levels of less than 10 µg/dL.

Stratified analysis by age, sex, race, smoking, education, rural/suburban/urban location, income, exercise, and BMI indicates that the association of blood lead level and all-cause mortality is reasonably consistent overall and across subgroups and argues against confounding by these variables as an explanation for these data. If the association of blood lead level and all-cause mortality is a product of confounding, the confounder would seem to be something other than a measured socioeconomic factor (eg, education, income, or race) or a measured lifestyle factor (eg, location of residence, smoking, or physical activity level).

Stratified analysis indicates that African American and other nonwhite subjects have increased mortality at lower blood lead levels than white subjects (the interaction effect is statistically significant in a multivariate model, with P < .001). In the nonwhite subjects, those with baseline blood lead levels of 10 to 19 µg/dL experience a 2.63-fold increase in multivariate adjusted all-cause mortality compared with those with blood lead levels of less than 10 µg/dL (RR, 2.63; 95% CI, 1.12-6.19; P = .02). In white subjects, those with blood lead levels of 10 to 19 µg/dL experience only a 7% increase in multivariate adjusted all-cause mortality compared with those with blood lead levels of less than 10 µg/dL (RR, 1.07; 95% CI, 0.83-1.40).

It is unclear why nonwhite subjects experience increased mortality at lower blood lead levels than white subjects in these data. Several hypotheses could be advanced to explain this finding. Some unidentified factor could increase the sensitivity of African American subjects to the effects of lead exposure. Alternatively, a one-time cross-sectional blood lead level may describe different lead exposures in white and African American subjects. A one-time blood lead level may represent, on average, higher cumulative or past lead exposures in African American and other nonwhite subjects than the same blood lead level in white subjects. In African American subjects, then, mortality may increase at lower blood lead levels. In the NHANES II, no indices of cumulative lead exposure (such as bone lead levels) are included, so this hypothesis cannot be tested in these data. We have no way of correlating cumulative lead levels (the exposure of interest) with mortality. Instead, we are forced to rely on a one-time blood lead level as a biomarker for cumulative lead exposure. Thus, we recommend that future studies on lead and mortality (or more generally, morbidity) consider multiple blood lead levels over time or bone lead levels, so that cumulative and past lead exposures can be estimated. Such studies would have the advantage of mitigating methodological concerns about the interpretability of a single cross-sectional blood lead measurement as a biomarker for cumulative or past lead levels.

Several occupational studies have attempted to evaluate the association of lead exposure and mortality. However, no clear picture emerges from these studies because of conflicting data and limitations in study design. Typically, the occupational studies use standardized mortality rates and compare mortality in the occupational cohort to what is expected in the general population. Although frequently used, this approach is limited by the fact that industrial workers often differ from individuals in the general population in additional ways besides the occupational exposure. Industrial workers, for example, may be more physically fit and less likely to experience certain forms of mortality (eg, ischemic heart disease), a phenomenon known as the healthy-worker effect.27 Industrial workers may also have different lifestyle characteristics than the general population, such as different smoking habits. This finding may explain why investigators have found increased lung cancer mortal-
ity in some lead-exposed occupational cohorts and not others. Confounding coexposures such as arsenic, cadmium, and silica may also complicate the picture further. Lead in these cases may be a marker for exposure to several metals (such as arsenic and cadmium) that often co-occur with lead exposure. Thus, interpretation of the occupational literature is difficult.

Few studies have considered the association of nonoccupational lead exposure and mortality. Moller and Kristensen conducted a population-based survey of 1052 men and women born in 1936 and living in Copenhagen. After adjustment for tobacco use, cholesterol level, physical activity, and sex, they found a statistically significant association of total mortality and blood lead level.

Evidence is accumulating that lead exposure is associated with increased blood pressure, and ultimately circulatory disease. Some studies indicate that lead-fed animals have increased pressor responses and increased vascular reactivity to norepinephrine. Picomolar concentrations of lead have been shown to activate protein kinase C, a major regulator of vascular tone. Lead-fed rodents have increased blood pressure at doses that produce blood lead levels similar to those found in humans. Epidemiological studies on the association of blood lead levels and hypertension have presented conflicting findings. However, in a meta-analysis of 15 studies on blood lead levels and blood pressure in men, Schwartz concluded that a 5-µg/dl (0.2-µmol/L) increase in blood lead level (from 5-10 µg/dl [0.2-0.5 µmol/L]) is associated with an increase in systolic blood pressure of 1.25 mm Hg (95% CI, 0.87-1.63 mm Hg).

The choice of blood lead level as a biomarker for lead exposure may be a reason for the inconsistent findings across epidemiological studies on lead and blood pressure. A recent prospective study by Cheng et al highlights this point. They found that bone lead level predicts the onset of hypertension, whereas blood lead level does not. If the effects of lead on hypertension accrue over time, a single cross-sectional blood lead level measurement (which would be heavily influenced by recent lead exposure) may not be expected to correlate very strongly with hypertension. Few studies have looked at the association of cumulative measures of lead exposure and blood pressure.

Evidence also suggests that lead exposure may increase susceptibility to cancer. Lead may exert diverse toxic effects on cells, disrupting the ability of cells to develop appropriate and precise responses to genotoxic environmental agents. By replacing zinc in zinc-finger loop proteins, lead is thought to alter the ability of some transcription factors to bind DNA and activate expression of genes that could be involved in a diversity of functions. By binding and depleting glutathione, a free radical scavenger and an antioxidant, lead may decrease the ability of cells to buffer the effects of certain genotoxins. Lead may interfere with the ability of DNA to repair itself after genotoxic insult. By binding histones, lead may decrease the protection these proteins give DNA, directly increasing the exposure of DNA to damaging agents.

Experimental studies on lead and cancer have generally evaluated lead alone, usually at relatively high doses of lead. The ability of lead to increase susceptibility to agents that cause cancer has been understudied. Some investigators have found that lead in vitro increases the mutagenicity of radiation and carcinogens. Roy and Rossman found that in transgenic hamster cells, lead increased the mutagenicity of UV-C and N-methyl-N′-nitro-N-nitrosoguanidine (a carcinogen) at doses at which lead is not otherwise mutagenic; this finding confirmed a similar report by Hartwig et al.

These data lend support to the hypothesis that lead increases susceptibility to genotoxins. We observed an interaction between heavy smoking and blood lead levels on cancer mortality (P = .07). One explanation for these findings is that lead increases the sensitivity of lung cell DNA to damage by the carcinogens in cigarette smoke, and/or lead decreases the ability of the DNA to repair itself after such damage.

**CONCLUSIONS**

These data indicate the importance of additional investigations into the long-term effects of inorganic lead, especially given the current Occupational Safety and Health Administration safety limits for lead. In this cohort, overall, cardiovascular, and cancer mortality increase at lead levels of 20 to 29 µg/dl, well below the current Occupational Safety and Health Administration action level of 50 µg/dl (2.4 µmol/L) for removing workers who are occupationally exposed to lead. We recommend additional studies on the associations of lead and mortality due to cardiovascular disease and cancer in the general population (studies have generally focused on occupational cohorts). We also recommend that future studies on lead evaluate it in combination with other agents to see whether lead increases the ability of these agents to cause disease.

We would like to comment on the range of lead levels represented in the NHANES II cohort. Conducted from 1976 to 1980, the median blood lead level in the NHANES II was 13 µg/dl for individuals aged 30 to 74 years. The median blood lead level in the NHANES III, conducted from 1988 to 1994, was 3 µg/dl (0.1 µmol/L) for this same age group. Thus, by today’s standards, the blood lead levels in the NHANES II are relatively high. However, it is important to remember that individuals presently 50 years or older experienced the more elevated lead exposures these blood lead levels represent and may be at increased risk for mortality because of these exposures.

Given the strength and consistency of the association of mortality and lead observed in these data, we are particularly concerned for workers who are occupationally exposed to lead, many of whom continue to have blood lead levels of at least 25 µg/dl (1.2 µmol/L), and the 1.7 million Americans with blood lead levels of at least 20 µg/dl. Thus, we strongly encourage programs of lead abatement and other efforts to reduce lead exposure. In light of these data and the literature on effects of lead levels of less than 30 µg/dl, we suggest that it may be prudent to reconsider the present occupational standards for blood lead levels.
Received for publication April 3, 2002.

This study was supported by a National Research Service Award from the National Institute of Environmental Health Sciences, Bethesda, Md (grant F30-ES05922-02), and grant ATPM TS288-14/14 from the Centers for Disease Control and Prevention, Atlanta, Ga, through the Association of Teachers of Preventive Medicine, Washington, DC.

Corresponding author and reprints: Mark Lustberg, PhD, Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, 660 W Redwood St, Baltimore, MD 21201 (e-mail: mlustber@umaryland.edu).

REFERENCES