

DRAFT

Heavy Metal Pollution and Race as Factors in Hypertension and Heart Diseases

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Jonathan Kahn's report on FDA approval of BiDil, a drug targeted to hypertension in blacks (*Scientific American*, Aug. 2007, pp. 40-45) fails to consider abundant evidence linking both toxic chemicals and race to hypertension and heart disease. Recent studies linking toxins and health indicate three factors that could influence the effectiveness of BiDil and perhaps justify the approval of the drug primarily for blacks.

- **TOXINS:** Geographic differences in rates of cancer (Figure 1) reveal the importance of considering the possibility that pollution with lead or manganese can contribute to another disease like hypertension. Lead has long been identified as a source of hypertension along with other health and behavioral problems.¹ Geographic differences in rates of heart disease in counties reporting pollution with lead or manganese confirm earlier studies that these toxins have important biological effects.²
- **RACE AND POVERTY:** Race plays an important role because blacks tend to absorb more lead than whites exposed to pollution in the same community (Figure 2). Because poverty can have similar effects, new studies are needed to reconsider both racial and socio-economic differences in vulnerability to toxins.³ Moreover, county level data suggest there may be racial differences in vulnerability to hypertension and to other forms of heart disease (Table 2).
- **WATER CHEMISTRY:** Lead absorption is increased where compounds called silicofluorides (H_2SiF_6 or Na_2SiF_6) are added to U.S. public water supplies -- and this increase in harm from pollution is more pronounced among blacks than whites.⁴

¹ Needleman, H. (1992), *Human Lead Exposure* (Boca Raton: CRC Press).

² Masters, R, Hone, B, and Doshi, A. (1998). "Environmental Pollution, Neurotoxicity, and Criminal Violence," in J. Rose, ed., *Environmental Toxicology: Current Developments* (London: Gordon and Breach, 1998), pp. 13-48.

³ The studies linking lead and manganese pollution with increases in heart disease are based on geographic data (averages in all U.S. counties). Such evidence don't provide accurate evidence for individuals and specific health conditions: although overall rates of heart disease in counties with an above average Black population [637 per 100,000] are lower than in counties where Whites predominate [1255 per 100,000], nationally 227.2 per 100,000 individual blacks and only 184.4 per 100,000 whites suffer from heart failure (Kahn, *Sci. Amer.*, p.45). Because counties level data often reflects multiple factors and differ for hypertension and overall heart disease, individual case-control studies are essential when attributing hypertension or heart failure to environmental exposure.

⁴ Masters, R. and Coplan, M. (1999a), "Water Treatment with Silicofluorides and Lead Toxicity," *International Journal of Environmental Studies*, 56: 435-49 [on children's blood lead in Mass.]; Masters, R. and Coplan, M. (1999b) "A Dynamic, Multifactorial Model of Alcohol, Drug Abuse, and Crime:

In a national sample, all three effects (silicofluoride use, race, and their interaction) contribute to higher blood lead levels among children 3-5 and 5-17 (Figures 1a-b).

The reasons cited by Jonathan Kahn for ignoring race in the study of BiDil therefore ignore important recent scientific research. It has already been noted that racial and environmental factors differ depending on whether hypertension or other forms of heart disease are at issue. Approval of BiDil needs to be revisited for two additional reasons. First, among relevant differences between blacks and whites is differing vulnerability of lead absorption (probably due to differing rates of lactose intolerance and poor diet). Given the well-established connection of lead to hypertension, any drug intended to treat it needs to measure individual blood lead levels – and for this purpose, control for race is necessary. Second, since environmental pollution can expose children to lead in soil, air, or water as well as from chips in lead paint or from lead solder in old houses, tests in a single location could easily miss environmental factors that influence BiDil’s effectiveness.

The study of links between toxins and cancer have therefore been repeated for hypertension. Data show heart diseases are significantly higher in counties where the EPA’s Toxic Release Inventory reports pollution with either lead or manganese – and even worse where both are present (Figures 1a-b).

In the 2356 U.S. counties in which the Toxic Release Inventory (TRI) shows no pollution with either lead or manganese, there are 81.4 cases of cancer per 10,000 population. Compared to unpolluted counties, in the 305 counties where the EPA’s TRI reports manganese pollution, the rate is more than **doubled** (189.4 per 10,000) -- and in the 104 counties with lead pollution, cancer rates are **tripled** (260.5 per 10,000).

These effects pale by comparison to the increased cancer rates in the 1148 U.S. counties where the TRI reports both lead and manganese pollution. Where the public is exposed to this toxic cocktail, cancer rates are **ten times** those in unpolluted counties (853.12 per 10,000). Statistical analysis (Table 1) shows that these effects would occur by chance less than the standard measure of a “significant” association ($p = .05$).

Of course, other environmental or genetic factors are also involved in vulnerability to cancer. The statistical technique used to study the combined effects of numerous potential causes is called “multiple regression.” In this method, the

Linking Neuroscience and Behavior to Toxicology,” *Social Science Information*, 38:591-624 [data from children in NHANES III]; Masters, R.D., Coplan, M. J., Hone, B.T., and Dykes, J.E. (2000). "Association of Silicofluoride Treated Water with Elevated Blood Lead," *Neurotoxicology* 21: 101-1100 [analyzing venous blood lead samples of 131,422 children in New York state]; Masters, R.D. (2002). “MacLean’s Evolutionary Neuroethology: Environmental Pollution, Brain Chemistry, and Violent Crime,” Gerald A. Corey Jr. & Russell Gardner Jr., eds. *The Evolutionary Neuroethology of Paul MacLean* (Westport: Praeger), pp. 275-296 (Ch. 15) [data from children in NHANES III].

“standardized coefficient” is a measure of how much each contributing factor (listed in left-hand column) contributes to more heart disease. The “t-value” is another statistic” linked to contribution to higher rates of heart disease. Probability measures the chance these numbers are merely accidents; by convention, probability less than .05 is “significant” (since roughly 95 times out of 100 the factor is expected to help explain the disease).

Table 2a indicates whether higher levels of the “independent variable” (listed in left-hand column) is associated with additional heart disease, *taking into consideration the effects of the other factors listed*. When 12 variables are considered, including race, population size and density, education and income, and unemployment, lead pollution does **not** add significantly to the rate of heart disease, but manganese pollution is related to an increase of heart ailments.

Table 2b checks this effect by excluding all the factors in Table 2a that make no significant contribution to county rates of heart disease. The results are unchanged. Whereas the mere presence of either lead or manganese pollution is linked to higher rates of heart disease, the amount of manganese pollution significantly effects rates of the disease. As this is a more rigorous test than the graph in Figure 1, it seems hard to deny three important findings related to the Bidil treatment of heart disease.

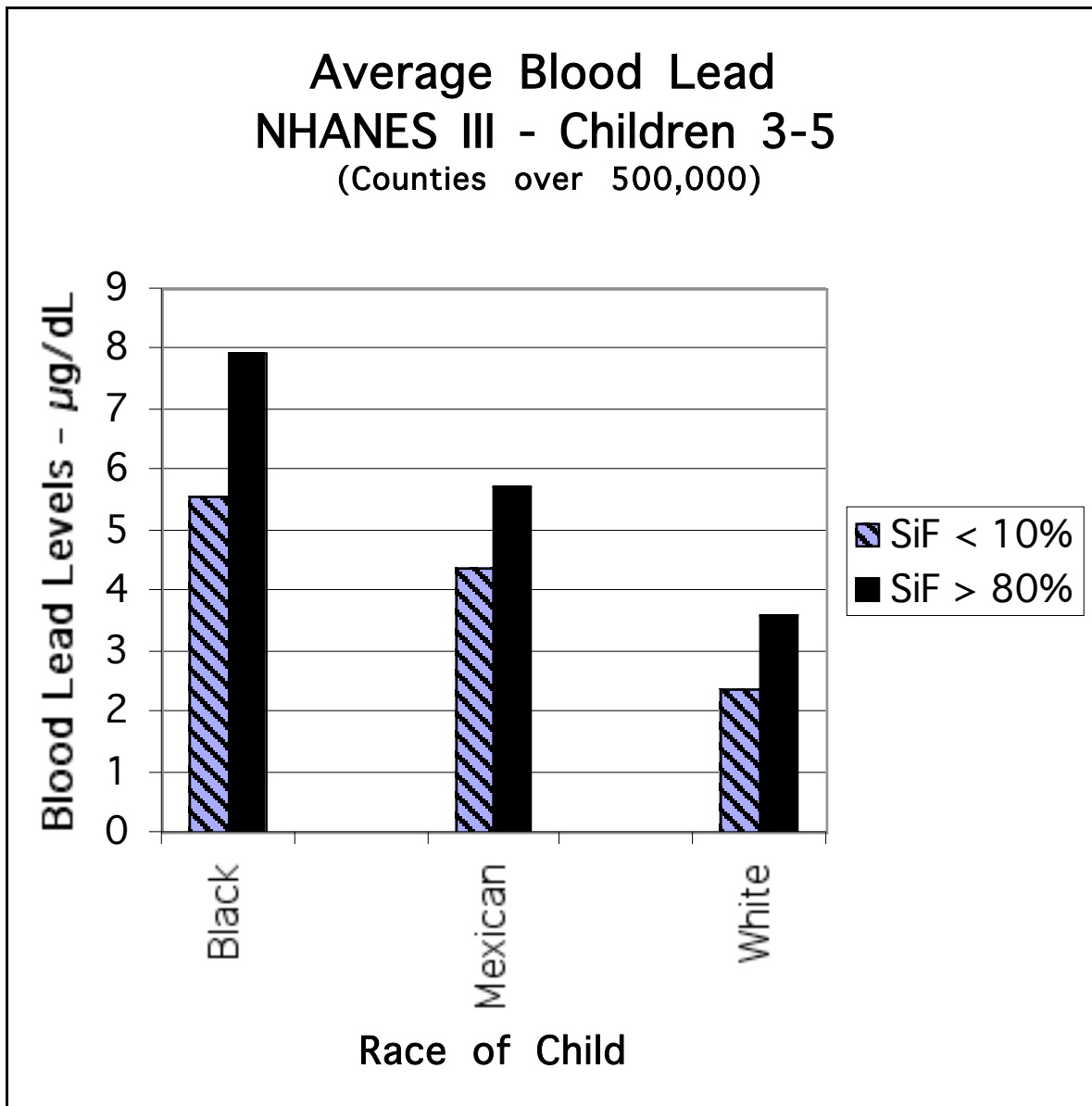
- First, toxic heavy metals have at least some effect increasing the risk of heart disease.
- Second, for many reasons, Blacks are more vulnerable than others to exposure to the toxins that have this effect.
- Third, treatment of public water with silicofluorides increases the absorption of toxins like lead and has other harmful effects on brain chemistry and behavior.

These findings suggest the need to take further factors, including exposure to heavy metal toxins and use of silicofluorides in water treatment as well as ethnicity, into account when considering the treatment regimes described above. Of these, given the research summarized in note 4 above, the easiest factor to eliminate is the treatment of public water supplies with either hydrofluorosilicic acid or sodium silicofluoride (and a return to sodium fluoride if water fluoridation is still considered essential despite the ubiquity of fluoridated tooth paste). In addition to the indirect effects on hypertension and heart disease documented above, preliminary evidence links these compounds with higher rates of asthma.

To conclude, the findings above indicate the need to include routine screening of children and adults exposed to pollution for bodily levels of lead, manganese, and other toxins – and where advisable, chelation to remove these toxins before they compromise health (as well as early childhood development, educational achievement, and behavior). Steps to reduce exposure and absorption of heavy metals from the environment could, furthermore, play a role in preventive health care – thereby contributing to lowering the cost of health care in the United States. Since Americans now pay over \$7,000 per person per year for health care – higher than any other industrialized society – while our

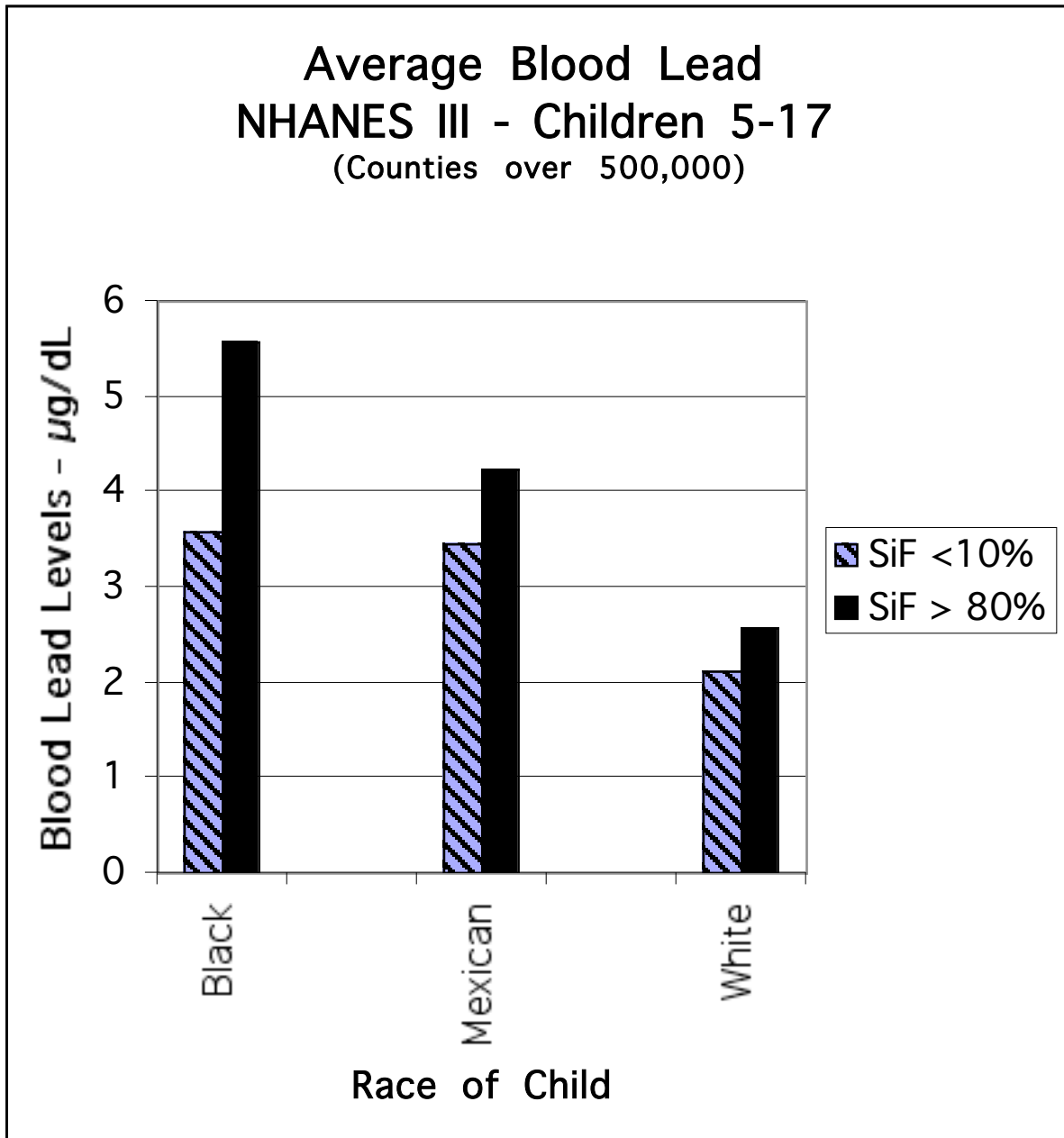
longevity rates 19th in the 30 OECD nations, cost-effective preventive medicine should become a number 1 priority.

FIGURE 1a



For NHANES III Children 3-5, mean blood lead is significantly associated with silicofluoride use (DF 3, F 17.14, $p < .0001$) and race (DF 2, F 19.35, $p < .0001$). Interaction effect between race and fluoridation status: DF 6, F ;3.333, $p < .0029$. Not shown here are effects of local poverty income ratio (DF 1, F 66.55, $p < .0001$), probably a factor in lead absorption due to calcium deficiencies associated with inadequate diet. Source: reanalysis of data from Masters, "MacLean's Evolutionary Neuroethology: Environmental Pollution, Brain Chemistry, and Violent Crime," p. 286.

FIGURE 1b



“SiF” = use of either silicofluoride in local water treatment. Significance, for ages 5-17: silicofluoride use (DF 3, F 57.67, $p < .0001$), race (DF2, 28.68, $p < .0001$). Interaction between race and fluoridation status is again highly significant (DF 6, F 11.17, $p < .0001$). Not shown here are effects of local poverty income ratio ($p < .0001$), probably a factor in lead absorption due to calcium deficiencies associated with inadequate diet. Source: reanalysis of data from Masters, “MacLean’s Evolutionary Neuroethology: Environmental Pollution, Brain Chemistry, and Violent Crime,” p. 286.

FIGURE 2

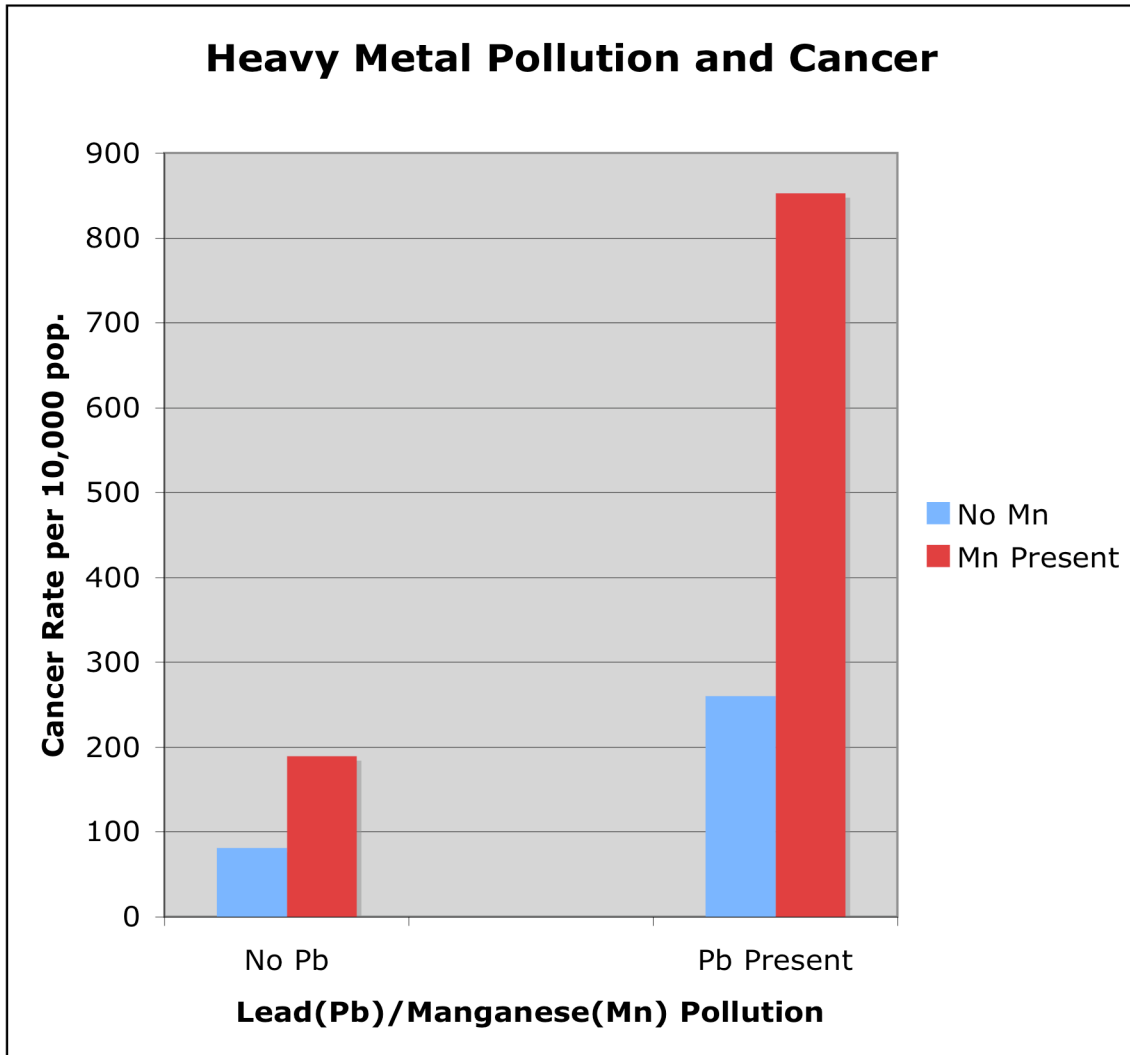


Table 1:
Rate of All Forms of Cancer per 10,000 population

	<u>No Manganese TRI</u>	<u>Manganese TRI</u>	<u>Total</u>
<u>No Lead TRI</u>	81.4 (2356)	189.43 (305)	93.8 (2661)
<u>Lead TRI</u>	260.5 (204)	853.1 (246)	584.5 (450)
<u>Total</u>	100.7 (2560)	453.0 (551)	108.6 (3111)

Parentheses: number of counties. Probabilities:

Lead: $p = .029$ ($F=4.75$); Manganese: $p = .0001$ ($F=14.83$); Lead&Manganese: $p = .035$ ($F=4.43$).

**Table 2a: Association of Environmental Factors and Race with Heart Disease
Multiple Regression – 12 Independent Variables**

Count: 3111 R: .17723 R-squared: .03141 Adj. R-squared: .02766 RMS Residual: .02147

Analysis of Variance Table

Source	DF	Sum Squares	Mean Square	F-test
REGRESSION	12	.0463	.00386	8.37231
RESIDUAL	3098	1.42777	.00046	p = .0001
TOTAL	3110	1.47408		

Beta Coefficient Table (BOLD = statistically significant)

Variable:	Standardized Coefficient	t-Value:	Probability:
% BLACK	-.08442	4.08782	.0001
% HISPANIC	-.01728	.90953	.3631
% HS GRAD	.058	2.1823	.0292
POPULATION	.0177	.83754	.4024
PC INCOME	-.08661	3.21843	.0013
PC INC BLACK	.01335	.71661	.4737
PC INC HISPANIC	-.02276	1.18123	.2376
%UNEMPLOYED	-.01483	.73754	.4608
LEAD POLLUTION*	.01466	.80544	.4206
Manganese POLLUTION*	.04257	2.36437	.0181
POP. DENSITY	.02788	1.38863	.165
%Age>65	.10277	5.17787	.0001

Table 2b: Multiple Regression: 5 Significant Variables plus Lead Pollution

Variable:	Standardized Coefficient:	t-Value:	Probability:
% BLACK	-.07731	3.91804	.0001
% HS GRADUATE	.06438	2.61375	.009
Per Capita INCOME	-.0725	3.08091	.0021
Lead Pollution	.01728	.96646	.3339 (<i>not sig.</i>)
Manganese Pollution	.04426	2.47276	.0135
%Age>65	.10995	5.85405	.0001

*POLLUTION: measured by pounds per year of lead or manganese recorded in Toxic Release Inventory. (Unlike Table 1, which is based on the *existence* of reported lead pollution, Table 2 measures the *amount* of lead or manganese pollution as a risk factor for heart disease.)

Negative standardized coefficients mean that more of a factor *reduces* the observed rate of heart disease. The higher the value of the standardized coefficient and t-Value, the stronger the effect. Note that Blacks are significantly LESS likely than whites to have heart disease. This may explain the lack of significance of lead pollution in Tables 2a-b because Blacks are more likely to absorb lead from the environment than whites (see reference in note 1).

**Table 3a: Race, Lead Pollution, and Heart Disease per Capita
(Rates by County, U.S.)**

<u>Lead Pollution</u>	<u>%Blacks in County:</u>		Totals:
	<.0857	>.0857	
None	.01182 <i>1972</i>	.00598 <i>685</i>	.01031 <i>2657</i>
Present	.01749 <i>290</i>	.00806 <i>159</i>	.01415 <i>449</i>

Totals:	.01255 <i>2262</i>	.00637 <i>844</i>	.01087 <i>3106</i>

	Source:	Sum of Squares:	Mean Square:	F-test:	P value:
DichPb (A)	1	.00513	.00513	11.03658	.0009
Dich%Black (B)	1	.01994	.01994	42.91016	.0001
AB	1	.0011	.0011	2.36907	.1239
Error	3102	1.44172	.00046		

**Table 3b: Race, Lead Pollution, and Cardiovascular Disease per Capita
(Rates by County, U.S.)**

<u>Lead Pollution</u>	<u>%Black in County</u>		Totals:
	<.0857	>.0857	
None	.01175 <i>1972</i>	.00586 <i>685</i>	.01023 <i>2657</i>
Present	.01721 <i>290</i>	.00796 <i>159</i>	.01393 <i>449</i>
Totals:	.01245 <i>2262</i>	.00625 <i>844</i>	.01077 <i>3106</i>

	Source:	Sum of Squares:	Mean Square:	F-test:	P value:
DichPb (A)	1	.00487	.00487	10.50435	.0012
Dich%Black (B)	1	.0196	.0196	42.26385	.0001
AB	1	.00096	.00096	2.07134	.1502
Error	3102	1.43891	.00046		

**Table 3c: Race, Lead Polluton, and Hypertensive Heart Disease per Capita
(Rates by County, U.S.)**

	<u>%Blacks in County</u>		Totals:
	<.0857	>.0857	
<u>Lead Pollution</u>			
None	.00012 <i>1972</i>	.00016 <i>685</i>	.00013 <i>2657</i>
Present	.00009 <i>290</i>	.00016 <i>159</i>	.00011 <i>449</i>
Totals:	.00012 <i>2262</i>	.00016 <i>844</i>	.00013 <i>3106</i>

	Source:	Sum of Squares:	Mean Square:	F-test:	P value:
DichPb (A)	1	1.11199E-7	1.11199E-7	1.42608	.2325
Dich%Black (B)	1	1.11764E-6	1.11764E-6	14.33321	.0002
AB	1	5.55636E-8	5.55636E-8	.71258	.3987
Error	3102	.00024	7.79753E-8		

If probability is less than .05, the effect would happen by chance less than five times in 100 tests. The strength of the effect of manganese pollution on heart disease seems stronger both as measured by the higher likelihood that the statistics aren't an accident (p = .0001 means less than one chance in 10,000 of an error). The higher F statistic is consistent with this interpretation, which is strongly reinforced by the findings in Table 2a-b. These statistics seem to contradict the higher rates in counties with lead pollution without manganese pollution (260.5 per 10,000) than in counties with manganese pollution without lead pollution (189.4 per 10,000). The statistics in Tables 2a-b help explain this puzzle by indicating that counties with lead pollution seem to have higher rates of other risk factors for heart disease.

Note: The more blacks in a county, the LOWER the rate of hypertension – but this does NOT refer to case-control data for black individuals (merely counties where the overall percent of blacks is over the national median). Controlling for percent blacks and overall per capita income in a county, black per capita income has no added significance: effect of race does not seem to be due to economic status of blacks. Presence of Manganese pollution is associated with higher rates of hypertension, with no effect of lead pollution. Apart from higher rates of hypertension where there is a higher rate of high school graduation and lower per capita income (effects contrary to conventional expectations concerning socio-economic status), other conventional socio-economic variables are not significant. Especially because neither % Hispanics nor Hispanic per capita income is significant, toxicity and genetics of African Americans need further study. Combined with a controlled study of DiBil, such research could provide valuable insight into hypertension and heart disease in the U.S.

Table 4a
Lead or Manganese Pollution and Heart disease
(Disease Rates per 100.000 in 3111 U.S. Counties)

<u>Lead TRI</u>	<u>Manganese TRI</u>		Totals:
	None	Present	
None	.01006 <i>2356</i>	.01219 <i>305</i>	.01031 <i>2661</i>
Present	.01015 <i>204</i>	.01742 <i>246</i>	.01413 <i>450</i>
Totals:	.01007 <i>2560</i>	.01453 <i>551</i>	.01086 <i>3111</i>

				ANOVA	
	Source:	Sum of Squares:	Mean Square:	F-test:	P value:
DichPb (A)	1	.00224	.00224	4.75206	.0293
DichMn (B)	1	.00698	.00698	14.83206	.0001
AB	1	.00208	.00208	4.43108	.0354
Error	3107	1.46134	.00047		

Note: each toxin has a significant effect increasing rates of heart disease, but presence of manganese pollution significantly increases the effect of lead pollution.

Table 3b
Lead or Manganese Pollution and Hypertension
(Disease Rates per 100.000 in 3111 U.S. Counties)

Lead TRI	Manganese TRI		Totals:
	None	Present	
None	.00013 2356	.00010 305	.00013 2661
Present	.00010 204	.00013 246	.00011 450
Totals:	.00013 2560	.00011 551	.00013 3111

ANOVA

Source:		Sum of Squares:	Mean Square:	F-test:	P value:
DichPb (A)	1	1.23701E-8	1.23701E-8	.15816	.6909
DichMn (B)	1	2.34657E-10	2.34657E-10	.003	.9563
AB	1	3.20400E-7	3.20400E-7	4.09643.0431	
Error	3107	.00024	7.82144E-8		

Note: no main effect; interaction effect ($p < .05$) occurs because, when only one of two toxins is present, rates are LOWER than no pollution; where both are present, rates are the same as where neither is present – and equal the national average. The contradiction between this data for the relationship between toxins and hypertension or heart disease calls for further study, especially given earlier data linking lead with hypertension. Adding counties with above average blacks (which have lower hypertension) increases the puzzle (which may be due to reporting rather than actual effects).

Table 4

Racial Differences by Type of Cardiac Disease

Average Rates per 100,000 for U.S. counties with above and below average % Blacks

	%Blacks <.0857< (n = 2262)	>.0857 (n = 844)
Hypertension Standard Deviation	12 (27)	16 (28)
Cardiovascular Disease	1245 (2439)	625 (1097)
Heart Disease	1255 (2436)	637 (1137)

While overall rates of heart disease are roughly twice as high in counties with less than the median % of blacks in the population, rates of hypertension are 1/3 higher in th 844 counties with above 8.6% Blacks. If nothing else, these data indicate the need for careful restudy of race, geography, and other socio-economic factors influencing hypertension and other heart diseases.