UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 4, 1983

Dr. David Weil
Environmental Criteria
Assessment Office
US EPA
Research Triangle Park, N.C. 27711

Dear David,

I am enclosing the memo I have written that I would like the reveiw panel to read before the meeting on next Thursday. I have also enclosed a review by Dr. Dan Violette and Dr. Craig Miller which I would also like shared with the panel. The copy I am sending you is their first draft. They will send you their final draft separately on Friday. I am enclosing this copy as a backup in case the second one is inexplicably delayed.

Thank you very much. I will see you on Thursday.

Sincerely

Joel

Joel Schwartz, Ph.D

N33861

TEH 0532917

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 3, 1983

MEMORANDUM

SUBJECT: The Use of NHANES II to Investigate the Relationship between Gasoline Lead and Blood Lead

FROM: Joel Schwartz
Office of Policy Analysis
Joel

TO: David Weil
Environmental Criteria Assessment Office

You have asked for any additional comments on whether the NHANES II data set can be used to examine the relationship between gasoline lead and blood lead. This memo will focus on that issue, and I will subsequently provide a more detailed memo amplifying on our study. Since the issue of whether you can analyze the NHANES data and how you analyze it are inextricably mixed, and since it involves not merely theoretical issues but pragmatic ones including the strength of association, I will also discuss our analysis here.

Our basic contention is that while the NHANES II data are not optimal for studying this issue, nor most efficient, even an inefficient 10,00 person sample leaves the possibility of analyzing the relationship, if properly controlled, and if the strength of association is large enough. We believe it is possible to control for the imperfections in the sample for these purposes, and that the association is demonstrably strong enough to resolve the issue. We also believe that the question of how rigorous a test these analyses are put to must be viewed in context. This context requires examining the rigor to which the air lead/blood lead studies are subjected, and to which some of the medical effects studies are subjected, so that there is some consistency in the degree of statistical rigor required by the criteria document, and so the panel examining the NHANES study understands the degree of uncertainty the Agency has implicity indicated it is willing to accept.

Medical Data regressed analyzed

Issues of Sample Control

The principle objection raised to using the NHANES II data is that it was drawn sequentially in time, by two stands, each spending two to three months at a site, and moving to another location. Thus, the representation of different subgroups changed over time as the two sampling locations changed. While this is clearly a problem, the extent of the problem is a function of how the regression analysis controlled for this, and of the pragmatic issue of whether those subpopulation had different lead levels, or different responses to gasoline lead.

only if you have the correct model must have the right variables in model

By including dummy variables to account for level effect changes attributable to different demographic subgroups one can prevent changes in the mix of those groups from causing changes in blood lead which the regression might otherwise attribute to gaso-

In our multiple regression analysis we controlled for three age groups, three income groups, rural areas, cities, and large cities, whether city residents lived inside the center city or in suburbs, sex and race. Industry critics of the first analyses CDC did of the NHANES data had emphasized that since children and city residents have higher blood lead, it was important to control

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for changes in their representation. The above dummy variables appear to control for all the major demographic factors that have been associated with differences in blood lead levels. Income, race and outside center city (which correlates well with post 1950 housing), should provide indirect control over lead paint exposure. Food lead, as discussed in our paper, increased over the period, and therefore the gasoline variable will not pick up any drop in blood lead that should be attributed to decreased food lead.

vague

Interaction terms also play an important role in controlling for subpopulation changes. In addition to testing for and including, significant interactions between demographic dummies, we tested for the interaction between main effects and gasoline. This allows us to control for changes in the representation of groups that may have different responses to gasoline lead, and avoid biasing the gasoline coefficient. It is worth noting not merely that we controlled for this, but that the pragmatic results were telling. Rural gas was statistically insignificant, i.e. inhabitants of rural areas had the same change in blood lead as gas lead changed as urban residents did (Of course absolute rural levels were lower). Inside center city was likewise not significant, and for whites, children had the same rate of change as adults. This increase our confidence that changes in the sampling of NHANES over time do not invalidate our results. Finally it is worth mentioning that during the survey the two stands were always kept in different regions of the country, that in general each stand tested urban and rural residents of the county it was located in, and that they moved frequently enough, relative to the rate

why ?!

OK for inhalation but not for hand to mouth

not so

How do you know this??

of change of gasoline lead usage, that the sample was not as unrepresentative as some have implied, even before the use of dummy variables.

Another important control we examined was to include time and season as explanatory variables, to see if they could make gasoline lead insignificant. It is important to note first that there is

Not so?

no outside evidence that any other major source of lead was diminishing during this period. Food lead increased and lead paint exposure changed little. Thus there is no theoretical justification for including time, it was merely examined to validate or invalidate the association with gasoline. Including time puts gasoline's explanatory power to a strenuous test, since it must compete against another variable that is highly correlated with itself and blood lead. Gasoline can do this by differing from time in its fine structure. (Gasoline lead did not change constantly, among other things it has a strong seasonal component.) To further test its explanatory power, however, we included seasonal dummies which could compete with gasoline's short term behavior in explaining blood lead. In addition, we simultaneously examined the lag structure for gasoline by including variables for two different months gasoline lead usuage. Despite this, lagged gasoline lead was significant at better than the 97% confidence level (F=5.34). Moreover since we were testing the two gasoline variables jointly we should really compute a joint F test for them that would be even more significant.

CORRELATION

When season (which was insignificant) was dropped, the F value for lagged gasoline rose to 7.22. Thus even controlling for hypothetical changes over time and season as well as the main effects and interactions, gasoline was significant. These results are included in

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Appendix I including both the weigted OLS results and the Surregr results which adjust the variances for the stratified sampling by using an algorithm based on 32 pairs of psuedosampling units.

Finally, and perhaps most telling, we have inserted dummy variables for the sampling locations into the model to account for any variations in blood lead levels due to the specific sites themselves and not controlled for by the demographic dummies. The results of this regression leave the gasoline lead variable with a t statistic of 19 (before Surregr correction), and the coefficieint of lagged gasoline lead is essentially identical to the sum of the coefficients for current month gasoline (PBNAT) and one month lagged gasoline (GASLAG) in the earlier models. It also attributes 57% of the mean blood lead over the four year period to the mean gasoline lead usage. We used only one gasoline variable in this run because of the large size of the model. We also only used 48 variables for the 48 site locations NCHS has released. The remaining 16 locations have a population less than 100,000 and their location has not been released for reasons of confidentiality. We have represented them all by one additional dummy.

This result is also included in Appendix I and indicates that neither variation in subpopulation representation nor the choice or pattern of sites themselves interferes with using the NHANES II data to determine a relationship between gasoline lead and blood lead.

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Empirical Observations

The NHANES data cannot be examined in a vacuum, we must use our knowledge of the etiology of lead exposure, and theoretical models, along with statistics. This other knowledge bears directly on the ability to use the NHANES data. The absolute magnitude of the drop in average blood lead levels, 5-6 ug/dl, severely limits the number of variables that can be causally related to the drop for the simple reason that few factors contribute as much as 1 ug/dl to blood lead. The possibility of mispecification error is inherently limited, therefore.

The other principle factors that contribute large amounts of blood lead, and which are capable of changing, are food and paint.[1] As mentioned above, food lead intake did not decrease over the period. Paint lead is an unlikely explanatory variable for several reasons. First, paint is a more significant contributor to high blood levels than to low ones. This is because exposure to paint lead usually results in the absorption of enough lead to produce large increases in blood lead. However, the NHANES II drop in mean blood lead involved the entire distribution shifting. It was not due to effects primarily concentrated in the upper end of the distribution. Indeed, even low blood lead groups had significant declines in blood lead. Second, adult blood leads fell as well as children's blood lead, and adults generally do not eat paint. Third, the drop occurred in suburbs of central cities. These have a lower fraction of pre-1950 housing stock, and therefore inherently less exposure to lead paint, yet they showed the same drop and the same gas lead coefficient. Finally, lead paint removal

Not So

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[1]Soil lead due to years of buildup may contribute substantially, however the only change in this factor would be the change in most recent dustfall. This dustfall is principally due to gasoline, which contributes about 90% of emissions of lead to the air.

programs during this period reached only 50,000 of the 30 million housing units with lead paint. Since there do not seem to be any omitted variables that could have accounted for any significant fraction of the large magnitude change we saw in NHANES, we can be more confident about using the data for this type of analysis.

Another empirical fact supporting the use of the NHANES data is the large seasonal variations present in both gasoline lead and blood lead. Dr. Billick's data (from the New York, Chicago, and Louiville screening programs) also verifies that this seasonality has existed in blood lead for years before NHANES period. This provides an opportunity to test gasoline's explanatory power over two different scales, seasonal fluctuations and long term trends. Moreover, the causes of the increase in gasoline lead in the summer is a volume effect due to an increase in driving. The cause of the long term drop in gasoline lead was a regulatory program that effected density (grams per gallon). The fact that we can test the relationship between two different time trends caused by different factors makes the NHANES data more reliable than might otherwise be thought. And the fact that season's are statistically insignificant when gasoline is introduced, means that there is no statistically significant difference between the short term and long term blood lead to gasoline lead coefficients. The fact that these slopes are the same is an important verification of the procedure.

no, but outside activity does

It also speaks to mispecification. It is difficult to believe, for instance, that the amount of lead paint in housing oscillates seasonally. Moreover, in the summer children spend less to indoors, exposed to interior paint. While there is some lead paint on the exterior of housing, it is indoor lead paint that has been linked to undue lead exposure. In addition, much public housing has brick exteriors.

Additionally, the lag structure for gasoline provides some empirical guidance on the ability to use the NHANES II data. If gasoline lead is merely a proxy for time, or some artifact of the

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sampling path we would not expect an ~~examination of its~~ lag structure to yield something meaningful. In particular, current gas lead, one month lagged gas lead, two month lagged gas lead, etc., should all be equal proxies for missing time. In fact, the lag structure agrees well with what we would expect physically. Current and one month lagged gasoline lead are significant, with the one month lagged gasoline having the most significance and the highest coefficient. The latter lags fall off in significance and coefficient size. This agrees with the view that gasoline lead in dustfall through resuspension in the air and injection, is the major pathway between gasoline lead and air lead. This lag structure is not consistant with the view that gasoline lead is simply picking up a time trend caused by some unexplained change in an unknown other factor, independent of the fact that no one has been able to suggest a reasonable other possible cause for the fall in blood lead. It is also difficult to believe that the time pattern of the surveying could have produced this structure.

Finally, there are the confirmatory studies that put the use of NHANES in perspective. First, it should be noted that the lead isotope study in Italy removes any doubt that gasoline lead contributes large amounts of lead to blood. By changing the isotopic composition of the lead added to gasoline in the Turin area and looking at isotopic changes in blood lead, Fachetti and others discovered that gasoline contributed 6-8 ug/dl to adult blood lead. Moreover, blood lead in adults constantly re-equilibrates with large stores of lead in bones. Studies by Rabinowitz indicate that it takes more than four months for blood lead isotopic ratios to correctly reflect current exposure rather than historic isotope ratios stored in bone. Therefore Fachetti et el concluded that they may be underestimating the contribution from gasoline. Children equilibrate much faster since they have less bone lead stores. Unfortunately the Turin study had no baseline ratios on children. If one assumed children had the same baseline isotope ratio as adults this would suggest substantially higher contributions from gasoline. These results are in very good agreement with NHANES regression, which also predicted 8 ug/dl from gasoline. Of course Italy is not the U.S. (on the one hand in 1976-80 Italians used no unleaded gasoline, whereas about 34% of U.S. gas was unleaded then. ? On the other hand U.S. cars got only about half the mileage of Italian cars.) Is this correct? Nevertheless the conclusion that gasoline contributes significant amounts to blood lead, on the order of 5-10 ug seems reasonable to apply to the U.S as well as Italy.

In addition to evidence confirming the reasonableness and approximate magnitude of the general results, there is evidence that helps lay to rest concern over the way the NHANES survey moved around the country. For example, Rabinowitz and Needleman analyzed lead levels in the blood contained in the umbilical cords of 11,837 birth between April 1979 and April 1981 in Boston lying In hospital. When they correlated these with local gasoline lead emissions, and examined the lag structure, they found a significant correlation ($P<0.001$), with the one month lagged gasoline lead having the strongest relationship, as analysis of the NHANES data also indicated. They found 57% of the variance in blood lead explained by gasoline. There were no significant trends of smoking, education level, or alcohol consumption with blood lead levels. Water lead levels appeared to rise over the period.

The ICF report on the NHANES data also shows the results of regressions on the blood lead screening data in New York, Chicago, and Louisville, done separately for blacks and whites. Again gasoline lead is a significant explanatory variable explaining most of the drop in blood lead. Again season is insignificant in these cities, indicating that gasoline explains seasonal as well as long term trends. While these children are not a random sample of the population, approximately 20% of all black preschool children were screened each year, making it unlikely that variations in sampling produced these results. These three city studies confirm that even if you stay in one location, the strong relationship with gasoline holds. Thus the regression results are unlikely to be significantly affected by the way the sample was taken.

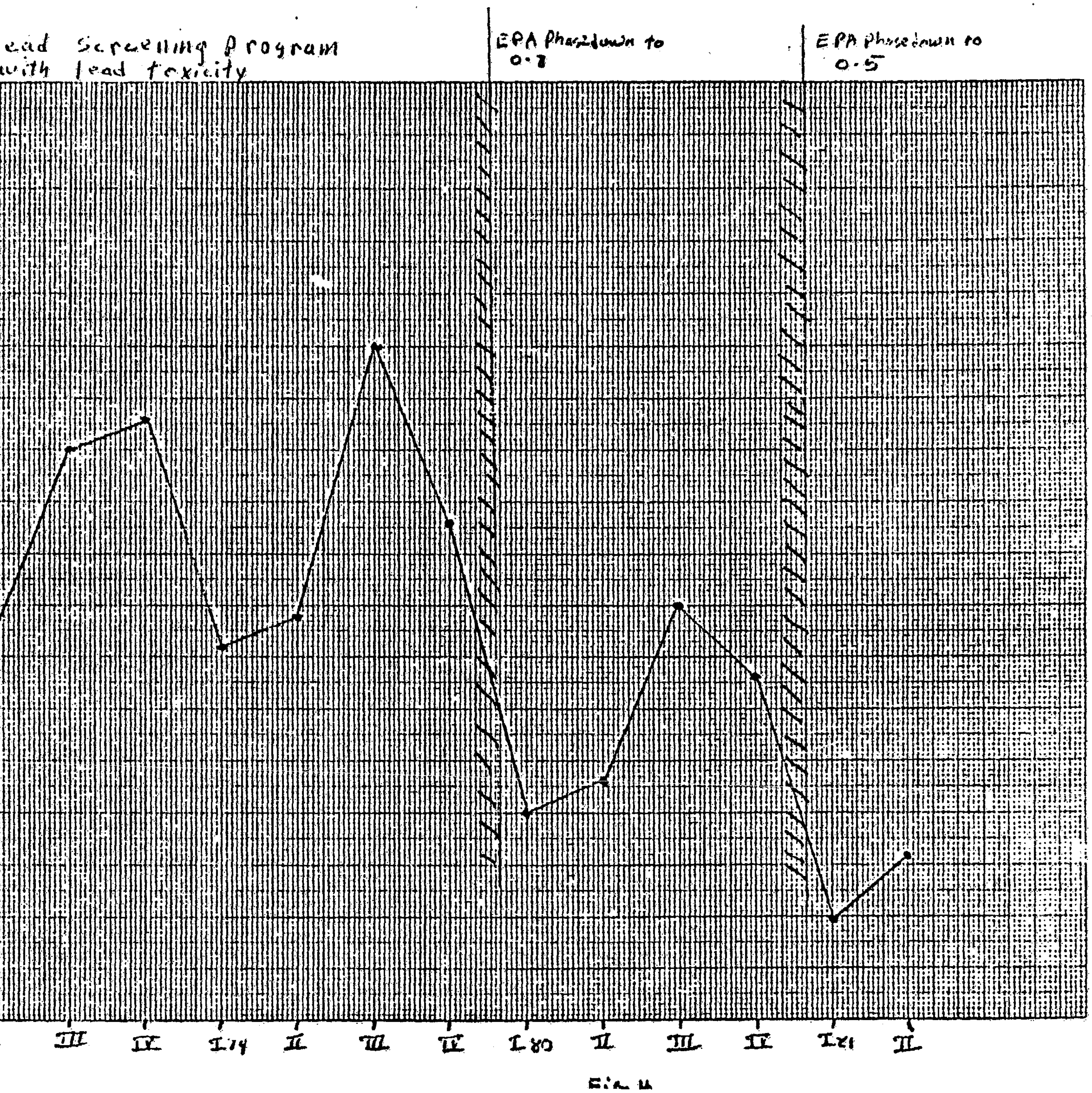
Similarly CDC tabulates summary statistics for those screening reported to them each quarter. There are major changes in the level of screening in each city over time, as well as in which ones reported, so this aggregated data is not very useful for regression purposes. However, there were two discontinuous changes in EPA's lead rules in late 1979 and late 1980. The enclosed graph shows the percent of children with lead toxicity nationwide, evidencing a clear sign that the two regulatory changes produced drops in the percent of toxic children. Therefore what happened in N.Y., Chicago and Louisville appeared to occur nationwide, and discontinuous changes in lead rules had perçeptable impact. The accompanying graph for Providence shows the results are not a function of variations in cities reporting.

Ignores Pre-auto old Cars

Again a study by the Illinois Institute for Environmental Quality of the city of Morton Grove, an upper middle class suburb (population 28,000) west of Chicago, consisting primarily of post 1950 housing found that children living within 200 feet of a major roadway had a statistically significant ($p<0.01$) higher mean blood lead than children living more than 200 feet from a major roadway. For children living within those boundaries all their lives, the difference in mean blood leads was about 5.6 ug/dl. It is also interesting to note that in 1974-75, when gas lead emissions were very high, most of these white upper income children (living in homes expected to be free of lead paint) had blood lead levels over 20 ug/dl range. By the NHANES period similar children had significantly lower lead levels, and gasoline lead usuage was also down significantly.

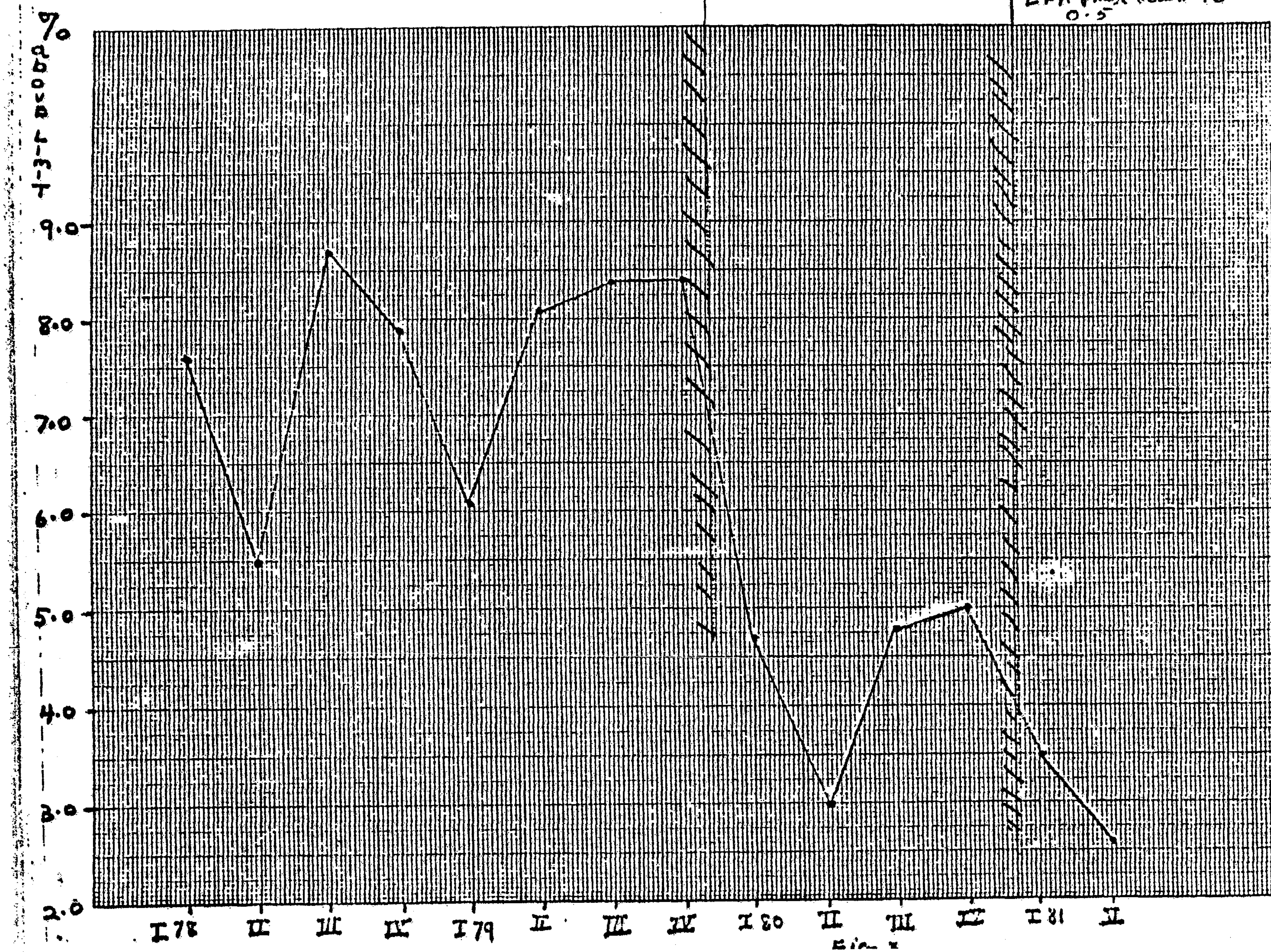
Consistency

As mentioned before, it is important for the criteria document to apply consistent statistical standards across the body of data it examines. We recognize that uncertainty is inherent in evaluating



ead Screening Program
with lead toxicity
EPA Phasedown to
0.8
EPA Phasedown to
0.5
III
IV
I 79
II
III
IV
I 80
II
III
IV
I 81
II

Providence, R.I.



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data on the effects of a pollutant, and judgements must be made on what is our best estimate based on available data. Since industry representatives on the workgroup have suggested subjecting the NHANES analyses to extremely rigorous examination, it is fruitful to examine how other data already included in the criteria document have met these tests.

SOP in quick investigation

Medical Data

Medical data is clearly of a different nature that epidemiological data, since it examines detectable biological changes. Nevertheless, in order to get an ambient standard EPA must frequently know how much of an effect occurs, and at exactly what lead levels. Questions of population representativeness and sample size are clearly relevant here since different groups respond differently, and because even homogeneous populations have distibutions of responses to environmental stress, and small samples may misrepresent the size of the response.

The health effects section of the criteria document nevertheless relies on studies that frequently involve small and non representative samples. This is for the excellent reason that those are frequently the only studies we have, and the agency cannot ignore the results. Nevertheless this procedure cannot be ignored in evaluating the use of dose response studies using the NHANES II data. One example of this approach is a section of chapter twelve (P24 and 25) discussing the affects of lead on inhibition of an enzyme (PY5N). Papers are cited that studied 9 adult male workers, and 21 children, among others in drawing conclusions about the degree of inhibition. Obviously larger samples more representative of the U.S. population would have been desirable but clearly conclusions are capable of being drawn from the existing studies.

Air lead/Blood lead studies

Clearly these studies are more relevant since they deal not with medical effects but blood level response to environmental exposure as the NHANES regressions did. They include (Chapter 11) Griffen's study of 14 adult male prisoners exposed to lead aerosols in chambers, Rabinowitz's study of 5 adult males volunteers similarly exposed, and Kehoe's study of 12 subjects living in the vicinity of a lead smelter. From these and other similar studies of small nonrepresentative populations, EPA derived air lead to blood lead ratio's which were used in 1978 to set the ambient standard. They also receive prominence in the draft revised criteria document. A graphic representation of their results is included (Figure 13-2). The real question that the panel should consider is whether regressions between gasoline lead (90% of air lead emissions) and blood lead, using the NHANES data, has anything to contribute to the knowledge of the relationship between air emissions and blood lead levels, and whether the three studies cited above have been put to the same stringency of examination.

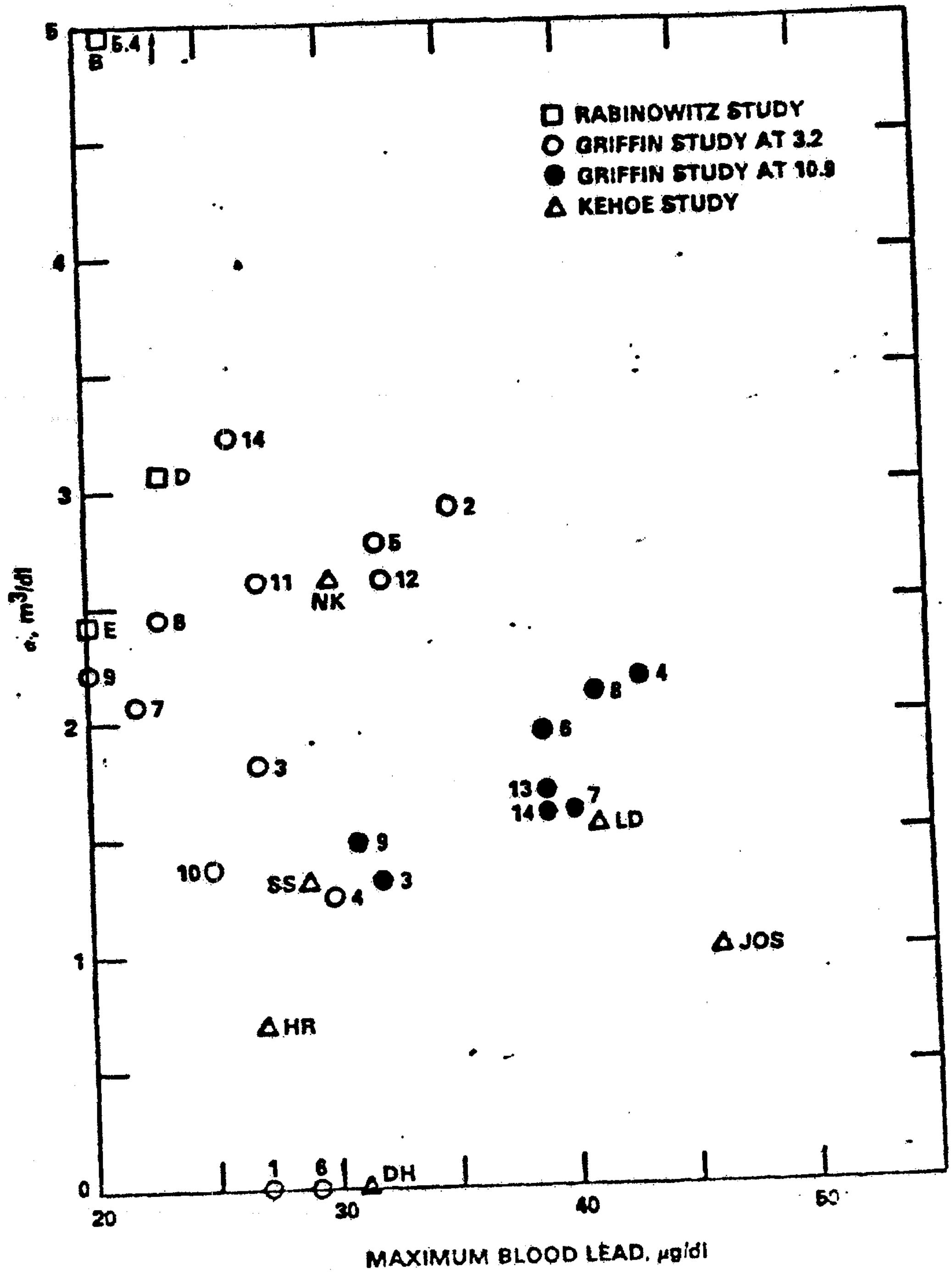

Figure 13-2. Blood lead vs. air lead slope as a function of maximum blood lead.

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Appendix 1
Multiple Regression Analyses of NHANES II Data

N.B. These show the weighted OLS results performed by Surregr, a software package designed to properly analyze stratified samples. While the coefficients are correct, these results overstate the F statistics because of oversampling of extreme groups. To correct this, Surregr next constructs 32 pairs of psuedosampling units and estimates the correct variances. An example of one of these second stage runs is included. All the results in our paper use these final runs, the first stage is displayed here to resolve questions that were raised abut whether we analyzed individual or grouped data.

1HYPOTHESIS TESTING RESULTS

0 8302 DENOMINATOR DEGREES OF FREEDOM

DEPENDENT EFFECT	F VALUE	DEGREES OF FREEDOM	PROBABILITY
LEAD			
TEST FOR OVERALL MODEL	173.02	17	0.0000
INDEPENDENT EFFECTS			
TIME	26.16	1	0.0000
TEEN	11.66	1	0.0006
TEENMALE	7.73	1	0.0054
KID	3.58	1	0.0586
KIDGAS	– 0.14	1	0.7054
ADLTMALE	73.64	1	0.0000
MALE	1.87	1	0.1718
RURAL	3.67	1	0.0556
RURALGAS	0.05	1	0.8280
SMALL	29.05	1	0.0000
INCOME1	42.46	1	0.0000
INCOME2	21.25	1	0.0000
WINTER	0.83	1	0.3619
SPRING	3.66	1	0.0556
FALL	1.06	1	0.3029
one month lag gas GASLAG	18.09	1	0.0000
Same month gas lead FENAT	6.64	1	0.0100

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1HYPOTHESIS TESTING RESULTS

0 8585 DENOMINATOR DEGREES OF FREEDOM

0DEPENDENT EFFECT	F VALUE	DEGREES OF FREEDOM	PROBABILITY
LEAD			
TEST FOR OVERALL MODEL	209.76	14	[illegible]
0INDEPENDENT EFFECTS			
TIME	31.32	1	[illegible]
TEEN	11.48	1	[illegible]
TEENMALE	7.73	1	[illegible]
KID	3.55	1	[illegible]
KIDGAS	0.16	1	[illegible]
ADLTMALE	73.80	1	[illegible]
MALE	1.82	1	[illegible]
RURAL	3.49	1	0.0616
RURALGAS	0.08	1	0.7807
SMALL	30.02	1	0.0000
INCOME1	41.51	1	0.0000
INCOME2	21.26	1	0.0000
GASLAG	50.19	1	0.0000
FBNAT	13.15	1	0.0000

1HYPOTHESIS TESTING RESULTS

0 8587 DENOMINATOR DEGREES OF FREEDOM

0DEPENDENT EFFECT	F VALUE	DEGREES OF FREEDOM	PROBABILITY
LEAD			
TEST FOR OVERALL MODEL	244.75	12	0.0000
0INDEPENDENT EFFECTS			
TIME	31.56	1	0.0000
TEEN	11.46	1	0.0007
TEENMALE	7.72	1	[illegible]
KID	[illegible]	1	[illegible]
ADLTMALE	[illegible]	1	0.0000
MALE	1.83	1	0.1763
RURAL	75.44	1	0.0000
SMALL	30.13	1	0.0000
INCOME1	41.57	1	0.0000
INCOME2	21.22	1	[illegible]
GASLAG	50.20	1	0.0000
FBNAT	[illegible]	1	[illegible]

HYPOTHESIS TESTING RESULTS

8966 DENOMINATOR DEGREES OF FREEDOM

DEPENDENT EFFECT	F VALUE	DEGREES OF FREEDOM	PROBABILITY
LEAD			
TEST FOR OVERALL MODEL	222.70	13	0.0000
INDEPENDENT EFFECTS			
TEEN	11.16	1	0.0008
TEENMALE	7.92	1	0.0049
KID	3.70	1	0.0545
KIDGAS	0.14	1	0.7065
ADLTMALE	73.81	1	0.0000
MALE	1.83	1	0.1765
RURAL	3.26	1	0.0712
RURALGAS	0.32	1	0.5691
SMALL	41.31	1	0.0000
INCOME1	48.30	1	0.0000
INCOME2	25.30	1	0.0000
GASLAG	69.74	1	0.0000
FBNAT	37.64	1	0.0000

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CARY, N.C. 27511-8000

1 STATISTICAL ANALYSIS SYSTEM 20:46 THURSDAY, MARCH 3, 1983 1

0

0MODEL: MODEL01 SSE 209209.9 F RATIO 54.66

DFE 8542 PROB>F 0.0001

DEP VAR: LEAD MSE 24.491916 R-SQUARE 0.2673

0

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T RATIO	PROB>|T|	VARIABLE LABEL
INTERCEPT	1	2.414253	0.595597	4.0535	0.0001	
TEEN	1	0.097845	0.185788	0.5267	0.5984	
KID	1	2.948726	0.174653	16.8834	0.0001	
ADLTMALE	1	3.656996	0.219709	16.6447	0.0001	
MALE	1	1.121172	0.170369	6.5808	0.0001	
RURAL	1	-1.083656	0.386807	-2.8015	0.0051	
SMALL	1	-0.606628	0.396211	-1.5311	0.1258	
INCOME1	1	1.887866	0.163280	11.5622	0.0001	
INCOME2	1	0.889920	0.119018	7.4772	0.0001	
PBNAT1	1	2.075042	0.104640	19.8303	0.0001	one month lagged gasoline lead in million grams per day
CITY2	1	-0.953462	0.460041	-2.0726	0.0382	
CITY3	1	0.073215	0.695473	0.1053	0.9162	
CITY4	1	-0.523587	0.644479	-0.8124	0.4166	
CITY5	1	2.403546	0.589658	4.0762	0.0001	
CITY6	1	2.706952	0.665278	4.0689	0.0001	
CITY7	1	0.939055	0.472427	1.9877	0.0469	
CITY8	1	-0.593643	0.481660	-1.2325	0.2178	
CITY9	1	-0.163830	0.524241	-0.3125	0.7547	
CITY10	1	-0.041216	0.556119	-0.0741	0.9409	
CITY11	1	-0.891395	0.429897	-2.0735	0.0382	
CITY12	1	1.574945	0.342878	4.5933	0.0001	
CITY13	1	-0.143501	0.439475	-0.3265	0.7440	
CITY14	1	4.548707	0.466142	9.7582	0.0001	
CITY15	1	0.887415	0.606444	1.4633	0.1434	
CITY16	1	0.911101	0.508252	1.7926	0.0731	
CITY17	1	-0.570510	0.430307	-1.3258	0.1849	
CITY18	1	0.964078	0.637285	1.5128	0.1304	
CITY19	1	2.841471	0.555503	5.1151	0.0001	
CITY20	1	-1.921417	0.433118	-4.4362	0.0001	
CITY21	1	1.288683	0.623215	2.0678	0.0387	
CITY22	1	-1.767744	0.540179	-3.2725	0.0011	
CITY23	1	-0.774917	0.581860	-1.3318	0.1830	
CITY24	1	1.562597	0.398322	3.9230	0.0001	
CITY25	1	0.377149	0.660972	0.5706	0.5683	
CITY26	1	-1.133393	0.674583	-1.6801	0.0930	
CITY27	1	3.382883	0.631244	5.3591	0.0001	
CITY28	1	2.637064	0.727849	3.6231	0.0003	
CITY29	1	0.052393	0.678400	0.0772	0.9384	
CITY30	1	2.420480	0.503935	4.8032	0.0001	
CITY31	1	0.930684	0.614336	1.5149	0.1298	
CITY32	1	1.007609	0.600625	1.6776	0.0935	
CITY33	1	0.399083	0.617828	0.6459	0.5183	
CITY34	1	-0.247098	0.420854	-0.5871	0.5571	
CITY35	1	0.277434	0.425473	0.6521	0.5144	
CITY36	1	0.422788	0.469418	0.9007	0.3678	
CITY37	1	1.558622	0.563003	2.7684	0.0056	
CITY38	1	1.678821	0.681264	2.4643	0.0137	
CITY39	1	0.855217	0.574295	1.4892	0.1365	

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VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T RATIO	PROB>|T|	VARIABLE LABEL
CITY40	1	2.967630	0.489727	6.0598	0.0001	
CITY41	1	0.787219	0.516268	1.5248	0.1273	
CITY42	1	0.589933	1.048507	0.5626	0.5737	
CITY43	1	2.555036	0.455381	5.6108	0.0001	
CITY44	1	-0.450362	0.382247	-1.1782	0.2388	
CITY45	1	0.383373	0.452761	0.8467	0.3972	
CITY46	1	1.255387	0.497420	2.5238	0.0116	
CITY47	1	1.751771	0.387244	4.5237	0.0001	
CITY48	1	-0.794825	0.382457	-2.0782	0.0377	
CITY49	1	1.719334	0.437736	3.9278	0.0001	

0

Surregr results

Model Number 4
Dependent Variable: Lead
32 Denominator Degrees of Freedom

Independent Effect	Coefficient	F Value	Degrees of Freedom	Probability
INTERCEPT	3.74			
TEEN	-.63	8.04	1	0.0079
TEENMALE	1.54	19.20	1	0.0001
KID	3.11	93.94	1	0.0000
ADLTMALE	4.35	169.23	1	0.0000
MALE	.66	4.74	1	0.0369
RURAL	-1.45	14.91	1	0.0005
SMALL	-1.00	7.74	1	0.0090
INCOME1	1.21	16.50	1	0.0003
INCOME2	.59	16.14	1	0.0003
NGASPB	.74	4.54	1	0.0410
NGASPB(-1)	1.25	9.17	1	0.0048
TEST FOR OVERAL MODEL		168.26	11	0.0000

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TABLE 2

LEAD IN THE DIET

Fiscal Year	Estimated Lead in the Diet in Micrograms/Day Infants	Toddlers	Males Aged 15-20
1973			60.4
1974			90.2
1975	21	26	67.2
1976	21	30	71.1
1977	22	28	79.3
1978	25	35	95.1
1979	36	46	81.7
1980			82.9

Source: Bureau of Foods, FDA, "Compliance Program Report of Findings, Total Diet Studies." FY 73-FY 80.

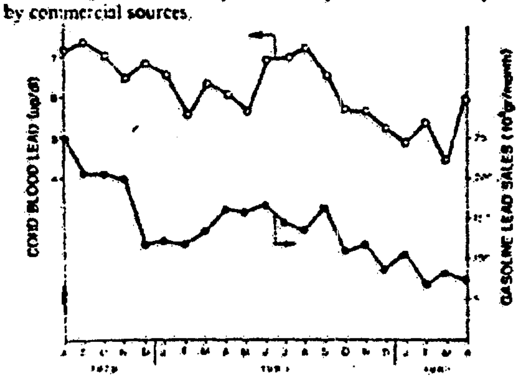
Note: Blanks indicate data not available.

Appendix II
Umbilical Cord Analysis; Correlation with Gasoline

PETROL LEAD SALES AND UMBILICAL CORD BLOOD LEAD LEVELS IN BOSTON, MASSACHUSETTS

SIR,—Practically all the airborne lead in American cities today comes from lead additives in petrol.[1] Airborne lead has been traced to human blood,[2] and raised levels of airborne lead have been associated with increased blood lead levels in many populations of urban dwellers, workers, and children.[3] Changes in blood lead over time in children correlate well with monthly changes in the consumption of leaded petrol.[4]

We report here on the positive correlation between levels of lead in umbilical cord blood and the use of leaded petrol in Massachusetts. Lead levels were measured for 11 837 births between April, 1979 and April, 1981 at the Boston Lying-In Hospital (now Brigham and Women's Hospital). Blood lead levels displayed both a definite downward trend with time and a seasonal pattern.[5] Local motorcar use (and petrol consumption) increases in the summer and use of lead additives has been changing recently in response to Federal standards. We have used pairwise product-moment correlations of the monthly cord lead (means of about 500 births each) and the monthly amounts of petrol lead sold as reported by commercial sources.



Monthly mean umbilical cord blood lead level (○) and total lead in all grades of gasoline sold in Massachusetts (●).

The figure displays the monthly values and the table shows the correlation coefficients calculated with a variety of lag-times between pairs of monthly gasoline lead sales and blood lead levels. Significant correlations were observed when gasoline lead sales in one month were matched with blood lead data for the same month, for the next month, and for the month after that. Although both variables were generally declining with time, lags of 3–12 months gave much poorer correlations. The best fitting linear correlation is blood level ($\mu g/dl$) = 2·95 + 2·[illegible]x, where x is the amount of lead in gasoline (in 10^6 g per month) sold in Massachusetts. 57% of the variance in mean blood lead levels is accounted for by this one variable. This may overestimate to some degree the slope of the true association, because exposure to outdoor air in Boston is higher in the summer from more open windows and time spent outdoors. So, attributing 57% of the variance solely to gasoline lead sales would not take into account the confounding seasonal changes in proximity of the pregnant women to automobile exhaust.

We found no significant ($p > 0·3$) monthly fluctuations or trends in mean value of those maternal factors such as tobacco smoking, education, or alcohol consumption which we earlier demonstrated to be predictive of cord blood lead levels in this population. Tap water collected at the homes of 249 of the children at 1, 6, and 18 months showed a gradual rise in lead levels of about 25% per year, beginning at 5 µg/l in 1980, a low level.

These observations on the close concordance between blood lead and gasoline lead prompt us to recommend further reductions in allowable gasoline lead content to bring blood lead concentrations even closer to those prevailing in the pre-industrial era.

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1. Patterson C. Contaminated and natural lead environments of man. Arch Environ Hlth 1965; 11: 344.
2. Rabinowitz M, Wetherill G, Kopple J. Magnitude of lead intake from respiration by [illegible]. [illegible] 1977; 52: [illegible].
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[illegible] BETWEEN MONTHLY GASOLINE LEAD SALES [illegible] MEAN UMBILICAL CORD BLOOD LEAD LEVELS WITH VARYING MONTHS OF LAG

Lag (mo)	Pairs of months	r	P
0	2[illegible]	0·716	<0·001
1	21	0·758	<0·001
2	21	0·759	<0·001
3	21	0·651	<0·01
4	21	0·560	<0·05
5	2[illegible]	0·505	<0·05
7	18	0·238	>0·05
9	16	0·267	>0·05
11	14	0·611	<0·05
12	13	0·62[illegible]	<0·05

TRANSMISSION OF AGENT OF POST-TRANSFUSION NON-A, NON-B HEPATITIS BY CRYOPRECIPITATE PREPARED FROM PLASMA OF SYMPTOMLESS CHRONIC CARRIER

SIR,—Non-A, non-B (NANB) hepatitis after blood transfusion often differs clinically from that which develops following infusion of antihaemophilic factor (factor VIII concentrate).[1] Cross-challenge studies in chimpanzees suggest that these clinical differences may reflect the existence of two different agents.[2] To determine whether an agent responsible for many or most cases of blood transfusion associated NANB hepatitis in the United States[3] could also be transmitted by FVIII concentrate, which is purified from cryoprecipitate, we produced cryoprecipitate from plasma containing this agent.

The plasma used (inoculum I) was that of a symptomless patient who had acquired chronic NANB hepatitis after transfusions and whose blood had transmitted NANB hepatitis to man (via a broken capillary pipette) and to chimpanzees by experimental inoculation.[4] This inoculum had a NANB hepatitis infectivity titre of about 100 chimpanzee infectious doses per ml.

107 ml of inoculum I which had been stored continuously at −70°C was thawed until the plasma was liquid at 0°C. The cryoprecipitate was recovered by centrifugation at 4900 g (model RC 2B, Sorvall, Norwalk, Connecticut) for 20 min at 0°C. The yield of cryoprecipitate was 1·1 g. It was reconstituted in 10 ml of a solution of 10 mmol/l sodium citrate and 135 mmol/l sodium chloride at pH 7·0. The volume of the reconstituted cryoprecipitate was about one-tenth that of the starting plasma and contained 16 mg protein/ml.

2 ml of reconstituted cryoprecipitate was inoculated intravenously into a 14-month-old female chimpanzee weighing 8 kg. This chimpanzee had been born in a U.S. breeding colony, had had no prior exposure to sources of hepatitis, and had not been previously inoculated with any blood, plasma, or plasma derivatives. Acute hepatitis, defined by the detection of eosinophilic degeneration of hepatocytes and lymphocytic inflammation,[2,4] was

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4. Tabor E, Seeff LB, Gerety RJ. Chronic non-A, non-B hepatitis carrier state: transmissible agent documented in one patient over a six-year period. N Engl J Med 1980; 303: 1[illegible]–29.

Appendix III
Chicago, New York and Louisville Screening Data; Multiple Regression with Gasoline

TABLE 4
(Continued)

RESULTS FROM CDC SCREENING DATA

Dependent Variable: Chicago, Black, Percent Over 30, Logistic

Sum of Squared Residual =	903.7910
Standard Error of the Regression =	4.2947
Mean of Dependent Variable =	-5.9293
Standard Deviation =	5.3271
Log of Likelihood Function =	-155.0210
Number of Observations =	55.
Sum of Residuals =	-12.3123
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	0.6633

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	-2.06177	1.09922	-1.87566
SMSA Gas Lead	.200828E-01	.323946E-01	6.19942
Winter	- .802201E-01	1.08125	- .741917E-01
Spring	- .153203E-01	1.07987	- .141872E-01
Summer	.30173	1.07956	.27949
Fall	- .20619	1.08049	- .19083

Dependent Variable: Chicago, White, Percent Over 30, Logistic

Sum of Squared Residual =	236.7520
Standard Error of the Regression =	2.1981
Mean of Dependent Variable =	-5.4757
Standard Deviation =	2.5221
Log of Likelihood Function =	-118.1830
Number of Observations =	55.0000
Sum of Residuals =	-15.5591
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	0.9848

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	-2.901420	.611533	-4.74450
SMSA Gas Lead	.225653E-01	.370419E-01	6.09183
Winter	.964196E-01	.566928	.17007
Spring	.627358	.563742	.11128
Summer	- .626191E-01	.562615	- .11130
Fall	- .965362E-01	.562510	- .17078

TABLE 4

RESULTS FROM CDC SCREENING DATA

Dependent Variable: New York, Black, Percent Over 30, Logistic

Sum of Squared Residual =	1,565.410
Standard Error of the Regression =	6.994
Mean of Dependent Variable =	-14.631
Standard Deviation =	9.067
Log of Likelihood Function =	-130.098
Number of Observations =	40.
Sum of Residuals =	-25.960
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	0.704

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	-1.49686	2.03605	- .73518
SMSA Gas Lead	6.49250	2.33997	2.77461
Early Tri-State Gas Lead	.23089	.20763	1.11200
Later Tri-State Gas Lead	- .92929	.55681	-1.66896
Winter	- .23515	1.75445	- .13403
Spring	- .14904	1.75109	- .851138E-01
Summer	.31506	1.75327	.17970
Fall	.691338E-01	1.75120	.394780E-01

Dependent Variable: New York, White, Percent Over 30, Logistic

Sum of Squared Residual =	96.7623
Standard Error of the Regression =	1.7389
Mean of Dependent Variable =	-7.5064
Standard Deviation =	3.0394
Log of Likelihood Function =	-74.4251
Number of Observations =	40.
Sum of Residuals =	-15.3735
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	1.3655

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	-4.16557	1.03897	-4.00933
SMSA Gas Lead	5.09855	2.06430	2.46986
Early Tri-State Gas Lead	.59210	.18678	3.16996
Later Tri-State Gas Lead	- .21366	.49413	- .43240
Winter	- .155031E-01	.45508	.340670E-01
Spring	- .14977	.44233	- .338600E-01
Summer	.544287E-01	.45301	- .12015
Fall	.18870	.44248	.42645

TABLE 4
(Continued)

RESULTS FROM CDC SCREENING DATA

Dependent Variable: Louisville, Black, Percent Over 30, Logistic

Sum of Squared Residual =	328.7350
Standard Error of the Regression =	5.2340
Mean of Dependent Variable =	-7.3389
Standard Deviation =	5.7024
Log of Likelihood Function =	-51.6848
Number of Observations =	18.
Sum of Residuals =	-6.6824
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	1.6956

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	- 2.84155	1.46965	-1.93349
SMSA Gas Lead	33.79160	10.35040	3.26478
Winter	.853627E-01	1.32522	.644138E-01
Spring	.18590	1.32784	.140039E-01
Summer	.161720E-01	1.33636	.121016E-01
Fall	- .28748	1.33014	- .21613

Dependent Variable: Louisville, White, Percent Over 30, Logistic

Sum of Squared Residual =	97.94640
Standard Error of the Regression =	2.85696
Mean of Dependent Variable =	-6.17638
Standard Deviation =	3.04550
Log of Likelihood Function =	-40.78730
Number of Observations =	18.
Sum of Residuals =	-5.62555
Durbin-Watson Statistic (Adjusted for 1.GAPS) =	1.83940

Right Hand Variable	Estimated Coefficient	Standard Error	T-Statistic
Constant	- 3.07121	.918198	-3.34482
SMSA Gas Lead	33.22030	8.873070	3.37439
Winter	.753012E-01	.739037	.10189
Spring	.16809	.737968	.22778
Summer	.335372E-01	.741039	- .452570E-01
Fall	- .20986	.741126	- .28316

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THE USEFULNESS OF THE NHANES II DATA FOR DISCERNING THE RELATIONSHIP BETWEEN GASOLINE LEAD USAGE AND BLOOD LEAD LEVELS IN AMERICANS AND A REVIEW OF ICF'S ANALYSIS USING THE NHANES II DATA

Prepared for:

Environmental Protection Agency
Office of Policy Analysis

March 1983

Contact:

Dr. Daniel Violette
Dr. Craig Miller

Our Ref: MEMO-SCHAR (100)

MEMORANDUM

The Usefulness of the NHANES II Data for Discerning The Relationship Between Lead in Gasoline and Blood Lead Levels in Americans and A Review of ICF'S Analysis Using the NHANES II Data

Date: March 4, 1983

To: Joel Schwartz, Office of Policy Analysis, U.S.EPA

From: Dr. Daniel Violette and Dr. Craig Miller

This communication is in response to your request that we review the use of the NHANES II data in the December 1982 report entitled "The Relationship Between Gasoline Lead Usage and Blood Lead Levels in Americans: A Statistical Analysis of the NHANES II Data" prepared by ICF, Inc. As you know, our firm is currently working with the Department of Biometrics at the University of Colorado on a project using the NHANES I and II data to examine potential relationships between hazardous air pollutants and health effects. In a previous project, Dr. Violette reviewed statistical studies relating air pollution to health effects for the National Commission on Air Quality. That latter work appeared in Environmental Policy: Air Quality, edited by G. S. Tolley and P. E. Graves, and published by Ballinger in 1981. Dr. Miller's experience includes managing a statistical project examining the relationship between soft water and heart disease. With this experience, as well our participation in many nonhealth related statistical projects, we feel qualified to comment on the ICF study.

The background documents provided to us depict a lively debate, although a good portion of the controversy appears to be fueled by misunderstandings of the statistical approaches used by the authors of the different papers. This is particularly apparent in the ICF comments (3) on the Ethyl Corporation Analysis (2) and the replies by Draper (5) and

Bradley (6). We feel that it is important to point out that Draper's very critical comments were confined to ICF's critique of Ethyl Corporation's analysis and were not directed at ICF's statistical analysis presented in either their October 1982 (4) or December 1982 (1) reports.

In general, we feel that the ICF use of the NHANES II data is appropriate; the analysis is sound statistically and the results provide useful and needed insights into the possible relationship between lead in gasoline and blood lead levels. As is true for any statistical study, improvements are possible, and we offer several suggestions in this regard. In the balance of this communication, we will address whether the NHANES II data can reasonably be used to study changes in blood lead levels over time, offer some general comments on the ICF analysis (1), and make a few comments on the Ethyl Corporation analysis (2) that we feel were not covered in previous critiques. We would enjoy preparing more detailed comments on the statistical analyses performed to date, but it was not possible to do so and meet the requested delivery time for this communication.

The first question concerns whether it is appropriate to use the NHANES II data to examine changes in blood lead levels over time. The NHANES II data was designed to be a cross-sectional—not a time-series study. The time trends that are available stem from the five-year duration of the sampling program. Over the five-year period, two sampling stations were used to obtain data at a number of locations, with each location being sampled once. The result is not a conventional set of time series data where there are observations on individuals at a single site in successive time periods. The data set contains information on individuals in different sites for the different time periods. This results in a "moving" sample over time. The general concern is that this data set does not constitute a representative random sample at each point in time and, therefore, could bias the statistical analysis.

After reviewing the data set and the comments by the different reviewers, it is our conclusion that it is perfectly appropriate to use the NHANES II data set as part of an effort to determine whether any trends in the data during the 1976 to 1980 time frame can be explained. However, use of an analysis based on this data to forecast trends for the nation must be done carefully and with full recognition of possible sampling biases. We are drawing a distinction between an analysis of what is going on within the data set (which is perfectly appropriate) and using the data to forecast national trends. The validity of any forecasts based on the data must be judgmentally determined. If a strong relationship between lead in gasoline and blood lead levels is found, then the implications of this finding for the nation should be explored and the information provided to policy makers with the appropriate caveats. This second use of the data, i.e., forecasting, must be based on sound judgment, but it is surely an appropriate use. This is particularly true if this data set is one of the few available for examining the relationship between gasoline lead and blood lead levels. This being the case, the useful information available from this data should not be ignored.

It is not appropriate to ignore the information from such a data set simply because it is not a representative random sample. Further, few data sets used in health studies are representative random samples in the strictest sense. The literature on health effects contains many examples where "natural experiments" were used. These analyses use data from several locations that have been subject to different environmental impacts. The choice of locations is not random, but stems from the availability of unique data. The data is analyzed statistically with controls for as many potential biases as possible, and judgmental extrapolations to a larger population are made. The use of the NHANES II data by ICF is just as appropriate, if the potential biases are controlled.

This conclusion seems to be shared by the different individuals who have been involved in the debate. Bradley (6) on pages 15 and 16 in reference to the NHANES II data states:

> If it were possible to devise a planned, controlled experiment to directly examine the effect of lead in automobile emissions on human blood lead, we would not need a sample of the U.S. population but rather homogenous groups of individuals falling into specified personal characteristic groups subjected to controlled exposure to automobile emissions. Such an experiment seems impossible, but the Ethyl Corporation's examination of individual records with variable exposure because of gasoline lead use may be as close as one can come to the desired experiment. <u>It is not necessary to have population estimates. It is only necessary to examine the relationship of blood lead to a measure of exposure after standardizing in so far as possible for other causes of variation.</u> (Emphasis added.)

The analysis by the Ethyl Corporation (2) states on page 21:

> ...there was a need to analyze the NHANES II data using techniques designed to reduce (or eliminate) the confounding of these variables, which is inherent in the experimental design of the NHANES II study. To accomplish this objective, we designed a linear regression model that was used to eliminate the effects on blood lead (dependent variable) of personal characteristics (independent variables)—age, sex, race and family income.

These statements by the parties that have participated in the debate indicate that use of the NHANES II data is appropriate as long as variables are incorporated to control for the potential biases that may occur due to the NHANES II sampling procedures. The objections that were raised by the Ethyl Corporation (2) and Bradley (6) were to the use of simple correllations between gasoline lead and blood lead levels that were used by Houk (7) and in other earlier analyses. They did not criticize the use of multivariate analysis of the NHANES II data, which can control for these potential biases. We fully agree with this interpretation.

<u>The ICF Analysis</u>

This section will briefly discuss the December 1982 ICF analysis. The discussion of potential sources of biases in the models (ICF, p. 5) is quite complete, and the methods used to control for these potential biases (ICF, p.6) represent good statistical practice. ICF controls for the changes in the locations and mix of persons sampled over the period of the NHANES II survey by incorporating a variety of subpopulation explanatory variables (such as age, income, urban, etc.). This is standard practice and might be fully adequate for controlling for the potential biases. However, a more extensive set of control variables could be used. In particular, 0-1 dummy variables for each site could be incorporated into the analysis. The incorporation of site dummy variables should not be restricted by the sample size, since on average, blood lead levels for 150 people were taken at each of the 64 locations. The incorporation of site dummy variables would capture the effects of variables specific to each location that may influence the blood lead levels of the individuals but were omitted from the equation. The dummies could be entered as additive terms, thereby allowing the intercept to vary for each site, or they could be entered as multiplicative interaction terms which would allow the coefficients on the independent variables (e.g., gasoline lead) to vary across sites. The use of site dummy variables should better control for potential biases due to the NHANES II sampling procedure.[1]

Although the ICF analysis is sound, there were several points we found confusing that had to be cleared up in conversation with the authors. In examining the presentation of the ICF results in Table 5, we were uncertain whether they had used the 10,000 plus observations on individuals or had aggregated the data and used the average blood lead values for each location as the dependent variable. The source of the confusion was the 32 degrees of freedom associated with each regression run presented in Table 5 and the lack of an explicit definition of the dependent variable used. With observations on thousands of individuals and only 15 independent variables in the equation, one would have expected a much larger number of degrees of freedom for the regression. The ICF authors explained that the use of the SURREGR program to adjust for the NHANES II stratified sampling

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[1] ICF has informed us that they are incorporating site dummy variables in their next analysis.

scheme accounted for the reduced degrees of freedom and that they had used the data on individuals. Incorporating an explanation of SURREGR in the report would allow for a better understanding of the analysis. We still are not quite sure if the 32 degrees of freedom listed in Table 5 constrains the number of variables that can be included in the regression equation or whether it is an independent constraint on SURREGR.

A second suggestion is to better qualify the conclusions of the analysis, particularly as they appear in the Executive Summary. A reader becomes very wary when confronted with adamant and positive conclusions based on any statistical study. Qualifications are particularly necessary when presenting forecasts based on this data set. For example, it is assumed that all potential confounding factors in the sample have been removed, and this should be stated.

In conclusion, the ICF analysis is sound, and the results—with appropriate qualifications—should be considered as one piece of information useful for setting standards. Of course, more could have been done, but the analysis is typical in quality and approach of the statistical studies that appear in the published literature on health effects.

Comparison to the Ethyl Corporation Analysis

If the ICF analysis is sound and their finding of a stong positive relationship between the amount of lead in gasoline and measured blood lead levels reasonable, then what explains the difference in the results between the Ethyl Corporation's analysis and the ICF study? We believe the difference in the results can be at least partially explained by the different independent variables used by Ethyl to represent gasoline lead levels and the two-stage procedure they used. Both of these factors, in our view, bias the estimated relationship between lead in gasoline and blood lead levels in the direction of finding no relationship.

First, it is clear that the two-stage approach biases the estimated coefficients on gasoline lead levels towards zero. In the first step, Ethyl regresses site dummy variables, age level, race, sex and income (99 variables in all) against the mean blood lead levels. The residual variation (i.e., unexplained variation) from this first stage is then the independent variable in the second stage where variables related to lead in gasoline are included. This two-stage approach assumes that any common covariation between the second-stage gasoline lead variables and the independent variables in the first stage are attributable entirely to the first-stage variables in their explanation of the dependent variable (i.e., blood lead levels). If lead in gasoline is felt to be likely to influence the blood lead levels, them omitted variable bias will be introduced into the first stage regression. The severity of this bias will depend upon how closely the omitted gasoline lead variables are correlated with the variables included in the first stage regression. The result will always be a downward bias in the estimated coefficient in the second-stage regression. The extent of the bias will depend upon how closely the gasoline lead variables are correlated with the first stage variables. This determines how much of the variation in blood lead levels that could be due to variations in the lead in gasoline, is now falsely attributed to the first stage independent variables. Ethyl shows in Figures 3, 4 and 5 of their analysis that there is likely to be a strong correlation between lead in gasoline and the age level since both have declined over time.[2] Even if this were not the case, regressing the 99 variables against the blood lead levels would likely explain a fair

[2] There is another variable used by Ethyl in their first stage regression that might be correlated with the lead in gasoline variable. Rather than using a set of sixty-three 0-1 dummy variables to control for individual observations taken at the 64 different locations, Ethyl assigned the locations numbers from 1 through 64 and, apparently, used this variable in their regression (see page A-1 of reference 2). It is not clear how these numbers were assigned to the locations. If they were assigned according to the time the location was sampled, with the first location being 1 and the last being 64, then an obvious time trend is introduced into the first stage regression that will be positively correlated with any variables increasing over time and negatively correlated with any variables decreasing over time. Even if not ordered by time, it is not clear why one site should have a different weight (value) than another and an arbitrary weighting or trend is introduced as a variable in the regression.

portion of the variance, leaving a highly random residual to be explained in the second stage. As a result, Ethyl's statement on page A-3 of the appendix that "the correlation of the relationship between gasoline lead and blood lead should be strengthened when the effects of age, sex, race, and income level are removed" is incorrect.

Finally, the two independent variables used to proxy the amount of lead in gasoline in the second stage regression would appear to introduce sizable measurement errors. It is a mystery why Ethyl did not directly incorporate the data they had on the levels of lead in gasoline as an independent variable in the regression. Instead, Ethyl used population density and gasoline lead usage for the state divided by the area of the state as the independent variables. Population density is used "since gasoline lead usage would be expected to be highly correlated with population, therefore population density would roughly be interpreted as an indicator of the gasoline lead usage per unit area and thus represents the local air-lead concentration exposure." Of course, there are many potential problems with this proxy measure. Sites that are less dense but have poor public transit such as those in the South and West may have higher lead exposures than areas with a higher population density due to a higher consumption of gasoline. Further, the amount of lead in gasoline has declined considerably over the 1976 to 1980 NHANES II sampling period while the population density at a location will have remained essentially constant. As a result, two locations with the same population density would have very different exposures to lead in the atmosphere from gasoline consumption, if one were sampled early in the NHANES II period and the other sampled late. Using the population density as an independent variable cannot capture this change in lead content of gasoline over the sampling period and, therefore, is a poor proxy for exposure to lead from gasoline consumption.

The other gasoline lead variable (state gasoline lead use divided by state area) is meant to provide a variable to represent lead fallout entering the food chain. One need only consider that much of the food consumed in any region is not grown in state and the proportion of in-state food which is consumed locally will vary between states (e.g., California versus Arizona).

With the two-stage approach and the unusual proxy variables for lead in gasoline, it is not surprising to us that no significant relationship was found in the Ethyl analysis.

Final Comments

Any evaluation of the appropriateness of data and analyses for inclusion in a survey or summary document should take into account the body of research that has been accumulated. The appropriate criteria for inclusion concerns whether the study under consideration makes a positive contribution to the research, not whether the study is perfect in all respects. Obviously, it would have been desirable to have time series data for an unchanging set of locations but, with the incorporation of control variables in a multivariate regression analysis, the use of the NHANES II data is appropriate. We feel that the ICF analysis does make a positive contribution to the literature and should be included in any compilation of research on the relationship between lead in gasoline and blood lead levels. Of course, a policy decision is never made on just one statistical study, but is based on the weight of the evidence which incorporates both laboratory studies and epidemiological studies. The ICF study is one piece of information that should be considered.

As a final note, both Dr. Violette and Dr. Miller have reviewed many of the studies that were included in the document, "Air Quality Criteria for Particulate Matter and Sulfur Oxides--Volume IV, Health Effects." The appropriateness of the data set and the statistical analysis used in the ICF study are of a quality comparable to the epidemiological studies included in chapter 14 of the above Criteria Document and, in fact, are better than many of the studies included in that document.

REFERENCES

1) "The Relationship between Gasoline Lead Usage and Blood Lead Levels in Americans: A Statistical Analysis of the NHANES II Data," prepared for the Office of Policy and Resource Management, U. S. EPA by ICF, Inc., December 1982.

2) Ethyl Corporation's Comments following EPA's Public Hearing on Proposed Rule for Lead in Gasoline, Washington, D. C., September 7-8, 1982 - Submitted to EPA's Docket No. A-81-36, October 8, 1982.

3) "A Review of the Ethyl Corporation's Comments on EPA's Proposed Rule for Lead in Gasoline," prepared for the U. S. Environmental Protection Agency, Office of Policy and Resource Management, Office of Policy Analysis, by ICF Incorporated, November 1982.

4) "The Relationship between Gasoline Lead Emissions and Blood Poisoning in Americans," prepared for the Office of Policy and Resource Management, Office of Policy Analysis, by ICF Incorporated, October 1982.

5) "Comments on the Documents: Ethyl Corporation's Comments Following EPA's Public Hearing on Proposed Rule for Lead in Gasoline and Review of Ethyl Corporation's Comments by ICF," by Norman Draper for Ethyl Corporation, undated.

6) "A Discussion of Issues and Conclusions on Gasoline Lead Use and Human Blood Levels" by Ralph A. Bradley, for the Ethyl Corporation, undated.

(7) Statement by Dr. Vernon N. Houk, Acting Director, Center for Environmental Health, Center for Disease Control, before the Subcommittee on Environment, Energy and Natural Resources, Committee on Government Operations, U.S. House of Representatives, Washington, D.C., April 14 1982.

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1) "The Relationship between Gasoline Lead Usage and Blood Lead Levels in Americans: A Statistical Analysis of the NHANES II Data," prepared for the Office of Policy and Resource Management, U. S. EPA by ICF, Inc., December 1982.

2) Ethyl Corporation's Comments following EPA's Public Hearing on Proposed Rule for Lead in Gasoline, Washington, D. C., September 7-8, 1982 - Submitted to EPA's Docket No. A-81-36, October 8, 1982.

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6) "A Discussion of Issues and Conclusions on Gasoline Lead Use and Human Blood Levels" by Ralph A. Bradley, for the Ethyl Corporation, undated.