IIA.D.10

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

August 26, 1985

Dr. Richard Royall
Dept. of Biostatistics
School of Hygiene and Public Health
Johns Hopkins University
615 N. Wolfe St.
Baltimore, MD 21205

Dear Richard:

Thank you for your letter of August 21, which contains your evaluation of Joel Schwartz' work and the DuPont comments on it. I must say that I am disappointed that Joel has apparently not yet adequately addressed the specific points about which you are concerned, but I am quite confident that he will do so when he reads your letter. I am sending a copy of it to him today, along with a request that he do what he can to respond to answer your questions.

For your information, I have enclosed the following material:

1.) A memo from Joel containing additional analyses in response to the DuPont comments. (IIA.C.4)

2.) The evaluation of Joel's work and the DuPont comments on it by Jim Ware. (IIA.E.23)

3.) The letter from me to Joel asking for his help in allaying your concern. (RG-8)

Why don't we hold off on submitting an invoice for your time until after you have had a chance to evaluate Joel's response to your letter? (I will forward it to you as soon as I receive it.) If it becomes apparent that you will exceed the number of days we allotted in your contract (5 working days), please let me know so that we can make the appropriate adjustments.

Looking forward to resolving this issue soon, I remain

Sincerely yours,

David E. Weil, Ph.D.
Project Manager

ECAO-CD-81-2
AG-8

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office (MD-52)
Research Triangle Park, North Carolina 27711

DATE: August 26, 1985

SUBJECT: Response to DuPont comments on blood lead-blood pressure relationship.

FROM: David E. Weil, Ph.D.
Project manager, Air Quality Criteria Document for Lead

TO: Joel Schwartz
OPA (PM-220)

Thank you for responding to the comments submitted by DuPont at the CASAC meeting on the Lead Criteria Document. All of the materiaL that both you and Dick Landis sent to me was forwarded to Richard Royall and Jim Ware for their review. Attached, you will find copies of their evalautions of both the DuPont comments and your responses to them.

As you can see, Jim Ware has concluded that you and your co-workers have adequately addressed the DuPont criticisms. Apparently, he has no problems with the conclusions you have reached. On the other hand, Richard Royall raises several questions that he feels have not yet been answered, and that must be answered before he is satisfied that the DuPont comments have been laid to rest.

Would it be possible for you to answer Richard's questions in writing in a memo to me? I realize that some of his concerns may only be addressed by performing additional computer runs; you may wish to discuss them with him on the telephone before undertaking any major effort. In fact, a telephone call to Richard before you do any more analyses may be just the thing to save us all a lot of work and time.

Thank you for your continued help and cooperation in this matter, Joel. If your free time or the expense of computer time becomes a limiting factor in clearing up these lingering questions, I'm sure that Lester would be happy to document the importance of your input to his preparation of the addendum to the Lead Criteria Document. Please let me know immediately if you will have any trouble responding to Richard's letter by, say, the end of September.

ECAO-CD-81-2
IIA.C.4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

AUG 21 1985

To: David Weil
ECAO

From: Joel Schwartz
OPA

Subject: Additional Analysis in Response to Dupont

I am enclosing two additional analyses that I have done on the blood pressure relationship.

The first analysis relates to the statement I made in my previous submission that the noise in measureing blood pressure and blood lead reduced the significance and coefficient of lead, and made it more sensitive to disturbance by variables such as date and location, that are measured without error, and correlate better with the true lead values than with the measurement error. I have done some additional analyses to address that issue.

It is possible to take the measurement error into account when doing a regression analysis if you know what it is. Supercarp, an alternative survey regression package to Surregr, contains an errors in variables module to do precisely that. The NHANES data had over 1100 blind quality control samples run, and from them the measurement variance of blood lead can be obtained. This will still not correct for the measurement error in using blood lead as a proxy for soft tissue lead, but it will allow the analytical error to be incorporated in the estimates. The variance of the measurement error for the log of lead is given as 0.0208 in the discussion of this issue in Vital and Health Statistics, series 11, no 233, which reports on the lead analysis of NHANES. I have used this variance in supercarp to reestimate some of the regressions previously submitted. The four regression tables attached show our regressions for systolic and diastolic blood pressure, incorporating the measurement error in log blood lead. The first two are without date included, and the second two are with date included. As you see, the regression coefficient, with and without date, is larger than in the previous surregr runs(in my May presentation to CASAC) , and the the significance level is higher. Lead is more significant than date for both regressions. The t-statistic for diastolic blood pressure, with date in the model, went from 2.09 to 2.41 when the measurement error is included, and for systolic blood pressure, with date, it went from 2.62 to 2.89.

Dr. Landis sent you his Mantel-Haenzel calculation for diastolic blood pressure, including age, BMI, and lead. He did not bother to present similar results for systolic blood pressure. For completeness I wanted to, however I do not have

his software package. I have done the closest possible thing using canned software I have, which is to use the Cox proportional hazard model. This relatively distribution free model assumes in this case, that the probability of an individual's blood pressure being between y and y + dy, given it is greater than y, is proportional to an unspecified underlying distribution of genetic and other unmeasureable risk factors, times exp(B*X), where X are the risk factors being analyzed. The procedure analyses stratified data by calculating the log likelihood in each strata, and then summing over strata, which is exactly analagous to the Mantel-Haenzel procedure. Since it allows continuous covariates, I included the other covariates in addition to age and BMI, and used the 64 PSU's as the strata. I am also enclosing those results, which indicate that lead is significant even after controlling for PSU and the measured covariates.

REGRESSION COEFFICIENTS - DEPENDENT VARIABLE IS BP2DIA

VARIABLE	COEFFICIENT	STANDARD ERROR	T-STATISTIC
INTERCPT	8.9215230D+01	3.1480411D+01	2.8339919D+00
AGEYRS	8.5179156D-01	1.0894348D-01	7.8186558D+00
AGESQ	-8.0111895D-03	1.1681387D-03	-6.8580808D+00
BMI	7.2849918D-01	9.2730583D-02	7.8560833D+00
LOGZINC	-3.6633675D+01	8.8970814D+00	-4.1174936D+00
LOGVITC	1.1480018D+00	3.1589729D-01	3.6340982D+00
ALBSQ	4.3278731D-03	7.2320342D-04	5.9843094D+00
LSCHOL	3.5014183D+00	1.5948060D+00	2.1955136D+00
SMOKNUM	-5.6466130D-02	2.3875944D-02	-2.3649801D+00
CALCIUM	1.6846338D-06	8.3832945D-07	2.0095128D+00
DIETVITC	-9.9106581D-03	3.2752592D-03	-3.0259156D+00
ZINC	3.3071074D-01	9.4888104D-02	3.4852708D+00
HEMOGLOB	1.2372121D-01	2.8875438D-02	4.2846521D+00
TRICEPR	1.2142064D-02	5.3527929D-03	2.2683604D+00
FAMHYPER	2.2039796D+00	3.9217988D-01	5.6198182D+00
COFFEE	-2.3803678D-01	9.4315350D-02	-2.5238392D+00
HEIGHT	1.4564105D+01	3.2050318D+00	4.5441374D+00
HYPERMED	5.4619252D+00	8.4050559D-01	6.4983806D+00
RACE	2.6210951D+00	8.6263038D-01	3.0384915D+00
LL	3.6376986D+00	1.1602883D+00	3.1351680D+00

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TEH 0412487

DUP050453539

REGRESSION COEFFICIENTS - DEPENDENT VARIABLE IS BP2DIA

VARIABLE	COEFFICIENT	STANDARD ERROR	T-S
INTERCPT	9.5163988D+01	3.1616604D+01	3.0099371D+00
AGEYRS	8.5682215D-01	1.0915849D-01	7.8493405D+00
AGESQ	-8.0768068D-03	1.1809449D-03	-6.8392749D+00
BMI	7.2047973D-01	9.1166482D-02	7.9029015D+00
LOGZINC	-3.6411404D+01	8.9400903D+00	-4.0728228D+00
LOGVITC	1.0862162D+00	3.1597251D-01	3.4376921D+00
ALBSQ	4.7185832D-03	7.6250304D-04	6.1882811D+00
LSCHOL	3.6037862D+00	1.6028364D+00	2.2483805D+00
SMOKNUM	-5.1476207D-02	2.3244385D-02	-2.2145653D+00
CALCIUM	1.7120795D-06	8.3251506D-07	2.0565148D+00
DIETVITC	-9.8029603D-03	3.2932479D-03	-2.9766846D+00
ZINC	3.2219450D-01	9.5867236D-02	3.3608407D+00
HEMOGLOB	1.2107548D-01	2.9677689D-02	4.0796803D+00
TRICEPR	1.3359908D-02	5.1479105D-03	2.5952099D+00
FAMHYPER	2.2754302D+00	3.8978703D-01	5.8376242D+00
COFFEE	-2.3139008D-01	9.2389141D-02	-2.5045159D+00
HEIGHT	1.3655142D+01	3.1395328D+00	4.3494184D+00
HYPERMED	5.4786618D+00	8.2362775D-01	6.6518665D+00
RACE	2.9850531D+00	9.5449333D-01	3.1273692D+00
LL	2.4028647D+00	9.9484602D-01	2.4153132D+00
DATE	-9.2529735D-02	3.9508605D-02	-2.3420147D+00

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REGRESSION COEFFICIENTS - DEPENDENT VARIABLE IS BP2SYS

VARIABLE	COEFFICIENT	STANDARD ERROR	T-STATISTIC
INTERCPT	6.3811359D+01	1.7701916D+01	3.6047712D+00
AGEYRS	-4.7275936D-01	1.6341380D-01	-2.8930198D+00
AGESQ	9.1906898D-03	1.7899688D-03	5.1345530D+00
BMI	1.2797492D+00	7.8843626D-02	1.6231486D+01
LOGZINC	-8.3776212D+00	2.5976941D+00	-3.2250222D+00
ALBSQ	8.4716657D-03	1.3558794D-03	6.2480968D+00
CALCIUM	2.6327408D-06	1.2264931D-06	2.1465598D+00
COFFEE	-3.8811590D-01	9.5377448D-02	-4.0692628D+00
FAMHYPER	3.3360347D+00	6.4388941D-01	5.1810678D+00
HEIGHT	1.8481922D+01	6.2587973D+00	2.9529510D+00
HYPERMED	8.6698445D+00	1.4178121D+00	6.1149462D+00
LL	6.0841298D+00	1.7029155D+00	3.5727726D+00

REGRESSION COEFFICIENTS - DEPENDENT VARIABLE IS BP2SYS

VARIABLE	COEFFICIENT	STANDARD ERROR	T-STATISTIC
INTERCPT	7.2652168D+01	1.8265141D+01	3.9776407D+00
AGEYRS	-4.6359129D-01	1.6511396D-01	-2.8077050D+00
AGESQ	9.0722704D-03	1.8029166D-03	5.0319968D+00
BMI	1.2863090D+00	7.8473872D-02	1.6391558D+01
LOGZINC	-9.0541824D+00	2.6682657D+00	-3.3932836D+00
ALBSQ	8.8186992D-03	1.3365090D-03	6.5983090D+00
CALCIUM	2.6541035D-06	1.2247476D-06	2.1670615D+00
COFFEE	-3.7908079D-01	9.3637368D-02	-4.0483922D+00
FAMHYPER	3.4125600D+00	6.3922527D-01	5.3385874D+00
HEIGHT	1.7634408D+01	6.1904162D+00	2.8486628D+00
HYPERMED	8.6833494D+00	1.4085296D+00	6.1648329D+00
LL	4.8919423D+00	1.6902485D+00	2.8942148D+00
DATE	-9.4914368D-02	4.5650034D-02	-2.0791741D+00

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PROPORTIONAL HAZARDS GENERAL LINEAR MODEL PROCEDURE

DEPENDENT VARIABLE: BP2SYS

2291 OBSERVATIONS
2291 UNCENSORED OBSERVATIONS
366 OBSERVATIONS DELETED DUE TO MISSING VALUES

-2 LOG LIKELIHOOD FOR MODEL CONTAINING NO VARIABLES=31149.66

MODEL CHI-SQUARE= 455.09 WITH 11 D.F. (SCORE STAT.) P=0.0 .
CONVERGENCE OBTAINED IN 5 ITERATIONS. R= 0.121.
MAX ABSOLUTE DERIVATIVE=0.2590D-04. -2 LOG L=30672.02.
MODEL CHI-SQUARE= 477.64 WITH 11 D.F. (-2 LOG L.R.) P=0.0 .

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
AGEYRS	0.01997275	0.00962326	4.31	0.0379	0.009
AGESQ	-0.00046098	0.00010384	19.71	0.0000	-0.024
BMI	-0.05707666	0.00536876	113.02	.	-0.060
LOGZINC	0.39398669	0.13238832	8.86	0.0029	0.015
ALBSQ	-0.00045827	0.00007860	33.99	0.0000	-0.032
CALCIUM	-0.00000015	0.00000007	4.19	0.0406	-0.008
COFFEE	0.02442041	0.00693851	12.39	0.0004	0.018
FAMHYPER	-0.15927341	0.04360349	13.34	0.0003	-0.019
HEIGHT	-0.81721235	0.30588945	7.14	0.0075	-0.013
HYPERMED	-0.38708687	0.06913807	31.35	0.0000	-0.031
LL	-0.26625981	0.05938370	20.10	0.0000	-0.024

without blocking

PROPORTIONAL HAZARDS GENERAL LINEAR MODEL PROCEDURE

DEPENDENT VARIABLE: HP2SYS

64 BLOCKS

2291 OBSERVATIONS
2291 UNCENSORED OBSERVATIONS
366 OBSERVATIONS DELETED DUE TO MISSING VALUES

-2 LOG LIKELIHOOD FOR MODEL CONTAINING NO VARIABLES=12821.14

MODEL CHI-SQUARE= 431.22 WITH 11 D.F. (SCORE STAT.) P=0.0 .
CONVERGENCE OBTAINED IN 5 ITERATIONS. R= 0.184.
MAX ABSOLUTE DERIVATIVE=0.3012D-03. -2 LOG L=12364.79.
MODEL CHI-SQUARE= 456.35 WITH 11 D.F. (-2 LOG L.R.) P=0.0 .

VARIABLE	BETA	STD. ERROR	CHI-SQUARE	P	R
AGEYRS	0.02946998	0.01045390	7.95	0.0048	0.022
AGESQ	-0.00056764	0.00011272	25.36	0.0000	-0.043
BMI	-0.06221312	0.00581151	114.60	.	-0.094
LOGZINC	0.40447939	0.14431253	7.86	0.0051	0.021
ALBSQ	-0.00053481	0.00008849	36.53	0.0000	-0.052
CALCIUM	-0.00000015	0.00000008	3.59	0.0582	-0.011
COFFEE	0.02430460	0.00748164	10.55	0.0012	0.026
FAMHYPER	-0.16874262	0.04650208	13.17	0.0003	-0.030
HEIGHT	-0.80404995	0.32877673	5.98	0.0145	-0.018
HYPERMED	-0.46827438	0.07591518	38.05	0.0000	-0.053
LL	-0.20559914	0.06855500	8.99	0.0027	-0.023

64 blocks