RDS

AIRLEAD - BLOOD LEAD MODELS

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The relationship between air lead and blood lead has received considerable attention by researchers because of the possible health hazard of airborne lead from the burning of leaded gasoline. Several models[1,2], for the relationship have been proposed, but not generally accepted by the scientific community because of unrealistic underlying assumptions and inadequate data used in parameter estimation.

Data that can be used in building models are generally from two different sources, lead chamber studies[3,4], and epidemiological studies[5,6,7]. The lead chamber studies are important for an understanding of the basic phenomenon but cannot be used to predict blood lead from air lead levels in the environment, because city residents may not have the same exposure levels as lead chamber residents although the lead chamber and average ambient air concentrations may be equal. It was decided, therefore, to build models of blood lead response to both controlled and natural environmental airborne lead. An attempt was made to incorporate into the models several realistic assumptions.

MODEL I: Abrupt air lead change (controlled environment)

Male and McCaughran[6] (1972) present a simple compartment model for the rate of change of blood lead with time for individuals subjected to abrupt change in air lead concentrations in controlled environment experiments.

$$\frac{dL_B}{dt} = A - \beta\mu$$

where:

L_B is the blood lead concentration (g/100 ml blood)

A is the average intake rate of lead into the blood from all sources (µg/100 ml blood/day).

$\beta\mu$ is the average removal rate of lead from the blood by all mechanisms (µg/100 ml blood/day).

Solving this equation and reparameterizing yielded the following model for the average blood level ($\mu(t)$) at time t.

$$\mu(t) = \begin{cases} Hn & \text{for } t<t_o \\ He - (He-Hn)\ \exp\left\{-\frac{Ae}{He}(t-t_o)\right\} & \text{for } t_o \leq t \leq t_f \\ Hn + (He-Hn)\ \exp\left\{-\frac{An}{Hn}(t-t_f)\right\}\left[1 - \exp\left\{-\frac{Ae}{He}(t_f - t_o)\right\}\right] & \text{for } t>t_f \end{cases}$$

and $\lim_{t\to\infty}\mu(t) = He$

where:

An is the average pre-experimental intake rate of lead into the blood

Ae is the average experimental intake rate of lead into the blood

Hn is the pre-experimental blood lead level

He is the asymptotic (equilibrium) lead level for blood under experimental conditions

The fact that the blood lead levels of city dwellers, exposed to reasonably constant concentration of air lead, do not rise continuously over their lives argues strongly for an equilibrium blood level. The data collected in the Albany study[4] also show that blood leads had or were in the process of reaching an equilibrium level.

The parameters of the model were estimated from the Albany study[4] data. The blood lead concentrations of nine individuals living in an average of 10.9μg/m^3 air lead and ten individuals living in an average of 3.2μg/m^3 were used. Individuals were selected that had a sufficient number of observations to provide valid estimates of the parameters. The data and fitted model for several subjects of the study are shown as an example in Fig. 1,2,&3. The data show that several subjects had not reached equilibrium conditions when the experiment was terminated. Values of the equilibrium level (He) and the pre-experiment level (Hn) estimated from the data are given in Table 1.

MODEL II: Steadystate Air Lead-Blood Lead Models

Several attempts have been made to obtain a relationship between ambient air lead and blood lead[1,2,5,6]. In several papers[1,6] the data were treated statistically by fitting a straight line to the $\log_{10}$ transformed air lead (L_A) and blood lead (L_B) concentration values. The basic model in these treatments was;

$$\log_{10} L_B = C + b \log_{10} L_A \qquad c, b \text{ are constants}$$

or exponentiating both sides of the equation;

$$L_B = (10)^c L_A^{\,b} = dL_A^{\,b} \qquad \text{where } d = (10)^c$$

This model implies:

i when air lead is zero blood lead is zero.

ii the rate of change of blood lead with changing air lead is

$$\frac{dL_B}{dL_A} = dbL_A^{\,b-1}$$

which shows that the rate of change in blood lead is proportional to a power of air lead when $b > 1$ and inversely proportional to a power of the blood lead if $b < 1$ and constant if $b = 1$.

iii no maximum blood lead value is approached as the air lead gets extremely concentrated.

Implication i is not true since lead is known to reach the blood from dietary sources. No data are available to validate implications ii and iii.

Knelson, J.H. et. al. (1972)[2] attempted to model the blood lead-air lead relationship using the Albany study[4] data. The model was of the form

$$L_B = m + b \log_{10}(BB) \qquad m, b \text{ constants}$$

where $BB = L \cdot V \cdot R \cdot D \cdot 10^{-3}$

L = air lead concentration

V = pulmonary retention

R = lead fraction retained

D = days of exposure

The variables V and R were assigned the arbitrary values of $15m^3$ and 37% respectively. Several problems arise with models of this kind;

i The model can only be used over the range of air leads in the study since the model predicts unreal values of blood lead at small air lead values ($L_B \rightarrow -\infty$ as $L_A \rightarrow 0$).

ii The variables V and R are parameters and must be estimated and cannot be assigned arbitrary values.

The two models so far presented have ignored an important piece of scientific information; that blood lead concentration is greater than zero in the absence of air lead due to dietary sources. The only justification for the log-log model is that when air lead-blood lead data are plotted they appear slightly curvilinear and a log transform is applied to linearize the data so that simple linear regression may be employed. This is done for statistical convenience.

Without a complete understanding of the pathways taken by dietary and airborne lead a truly realistic model cannot be constructed but a curvilinear model which acknowledges dietary blood lead is scientifically more acceptable than the previously mentioned models.

The following assumptions are suggested for the construction of an air lead-blood lead model.

1. Blood lead concentration should increase as air lead concentration increases.

2. At zero air lead concentration the blood will contain lead from dietary sources.

3. At any particular air lead level an equilibrium between input of lead to the blood and removal of lead from the blood is finally reached.

4. As the air lead concentration gets large ($L_A \rightarrow \infty$) a maximum intake rate is reached since the intake mechanisms are finite.

5. The rate of change in lead intake decreases as the maximum rate of intake is approached.

Assumptions 3, 4, and 5 provide the curvilinear shape to the model and imply that a maximum blood concentration is approached as air lead concentrations become extremely large. Having an asymptotic blood concentration will have little effect on the model in the range of air leads encountered in ambient or in occupational situations.

These assumptions are implicit in the following model for the rate of change of blood lead concentration as a function of air lead concentration;

$$\frac{dL_B}{dL_A} = C(L_E - L_B), \quad L_A = 0 \Rightarrow L_B = L_D$$

C is a constant

L_E is the maximum (asymptotic) blood lead concentration (g/100 ml)

L_D is the blood lead concentration from dietary sources.

Solving the above differential equation yields the blood lead concentration model;

$$L_E - (L_E - L_D)e^{-C_2 L_A}$$

This model can be used to represent the blood lead-air lead concentration relationship for a particular individual or for the average relationship of a group of individuals.

Parameter Estimation

The data needed for parameter estimation for an individual is a set of air lead-blood lead concentration values obtained from an individual living for long periods of time at a variety of air lead concentrations. The individual should have a constant dietary lead intake and must live at each air lead concentration level long enough for the equilibrium blood lead value to be reached. The air lead concentrations should be measured by personal samples to obtain the most accurate measure of the mean daily air lead contribution to the individual's respiratory air. The wide range of air lead concentrations is necessary for estimating L_E accurately. If the estimated model

is only going to be used for predicting blood lead values at ambient environmental levels an accurate estimate of the asymptotic level (L_E) is not necessary since a 20 µg/100ml error in L_E for example will introduce no more than a 1 µg/100ml error in blood lead at 10 µg/M^3 air lead. Increased variability in blood lead values will result if the dietary lead varies and will lead to a decrease in the precision of the estimates.

If estimates of the average of a population are desired then data as indicated must be collected from a randomly selected group of individuals from the population of interest.

No data that fits the described criteria are available. The best data set for parameter estimation was found in a study by Williams M.K., King, E., and Walford, J. (1969). The data are from an industrial source, therefore the lead particles may be somewhat different than those found in the environment. The air lead was only measured during the working day and hence is an overestimate of the daily average air lead exposure. In any case the relative exposure between people is probably correct and the data are of sufficient range (8 µg/M^3 to 298 µg/M^3) to get reasonably good estimates of the parameters. The estimates are,

$$\hat{L}_E = 89.102 \text{ µg/100ml (asymptotic level)}$$
$$\hat{L}_D = 24.632 \text{ µg/100ml (dietary level)}$$
$$\hat{C}_2 = 0.006535$$

The proportion of variability accounted for by the model;

$$R^2 = 0.846.$$

The data with the estimated model are presented in figure 4.

An attempt was then made to find a set of data suitable for parameter estimation for the environmental air lead-blood lead relationship. The problem with all data sets investigated[1,5,6] is that the range of air lead concentrations is too small to obtain meaningful estimates of L_E. The individual variability in blood lead measurements over the small range of air lead values was so great the Azar et.al.[6], (1972) were not able to show a significant relationship with the log-log model using thirty subjects! The same problem occurred with the data from Tepper, L.B., and Levin, L.S. (1972)[5].

However, parameter estimates were obtained for women using Tepper, L.B., and Levin, L.S. (1972) and from the estimated equilbrium blood lead values (H_e) from Male, L. and McCaughran, D.A. (1972). The parameter estimates for the women are;

$\hat{L}_E$ = 54.65 µg/100ml (asymptotic level)

$\hat{L}_D$ = 15.75 µg/100ml (dietary level)

$\hat{C}_2$ = 0.017

Since only two air lead concentrations were used in the Albany study[4] and we had three parameters to estimate L_D was estimated separately from pre-exposure values and the other two parameters were obtained by nonlinear least squares. The estimates are;

$\hat{L}_E$ = 55.00 µg/100ml

$\hat{L}_D$ = 19.71 µg/100ml

$\hat{C}_2$ = 0.071

Figure 5 shows the data and the estimated models and the data and model of Goldsmith and Hexter[1].

Discussion

The analysis of the Albany study[4] data points out the tremendous variability between individual response to increases in air lead exposure. The range in blood lead increase for the 3.2 μg/M³ exposure was 3.89 to 9.78 μg/100ml and 13.64 to 26.20 μg/100ml for the 10.9 μg/M³ exposure. This large variability can in part be explained by the variability in the dietary lead levels. The average increase when the model was fitted to the data on all subjects together was 8.71 for 3.2 μg/M³ exposure and 19.49 μg/100ml for the 10.9 μg/M³ exposure. These increases are considerably higher than any previously demonstrated. The use of this data to estimate the parameters in the air lead-blood lead model is of little consequence since there are only three air lead values in the study, pre-exposure, 3.2 μg/M³ and 10.9 μg/M³. Lead chamber studies using artificially produced lead particles have dubious applications to the ambient air-blood lead relationship in any case.

The air lead concentrations in Williams et. al. (1969) are an overestimation of the average daily air lead exposure concentrations since the samplers were only worn while at work. A conservative estimate of the average daily exposure would be to assume that one third of the day the individuals were exposed to the values reported in the study and the other 2/3

of the day the exposure was 0.0 $\mu g/M^3$. The only parameter estimate that changes is C_2, it now becomes $3C_2$. The predicted average blood concentrations will be overestimated since the individuals in the study were probably exposed to some air lead while not at work. The estimated average blood leads based on the model with parameters estimated from the Albany study[4], the Williams et.al. study[7] and the 7-City study[5] are given in Table 2.

The estimates of L_E and C_2 obtained from the 7-City study are imprecise. The problem is that to obtain good estimates of the parameter L_E, blood lead values at high air lead values (>50 $\mu g/M^3$) are needed, but since high air lead values never occur in the environment no good estimate of the asymptotic level can be obtained. The other problem with fitting models to environmental data is the large variability in blood lead values. It can be shown from the duplicate samples taken from a number of subjects in the 7-City study[7] that the variability in analytic error accounts for 79.6% of the total variability. The remaining variability comes from differences in actual exposure, dietary lead, smoking habits and physiological differences.

No extrapolation should be made from the Albany model to the environmental air lead situation. The lead particles are from a different source which may effect their intake rate. In addition, although an individual resides in a city with a particular average daily air lead concentration the real exposure

concentration is probably much lower. For this reason the type of data collected by Azar[6] et.al. is extremely valuable. It is unfortunate, however, that a larger sample was not obtained and a more realistic model used in the analysis.

It is felt that the model for the air lead-blood lead relationship presented is realistic and gives an adequate model for prediction when sufficiently large air lead values are available for parameter estimation. However, since the environmental air lead concentrations are small and the increase in blood lead concentration is so small that an increase cannot be detected with most data sets available, strictly empirical models such as a straight line with a non-zero intercept or a second degree function would give an adequate description of the relationship. The fact that in epidemological studies a small percentage of people have blood lead concentrations somewhat higher than the average indicates that they are exposed to lead from sources other than ambient air lead and the total removal of all lead from the air would not decrease their blood lead concentration more than a few micrograms per 100 mls. of blood.

References

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4. Coulston, F., Golberg, L., Griffin, T., Russell, C.: The Effects of Continuous Exposure to Airborne Lead. Exposure of Men to Particulate Lead. II at a level of 10.9 $\mu g/M^3$, IV at a level of 3.2 $\mu g/M^3$. Institute of Experimental Pathology and Toxicology. Albany Medical College. Albany, New York. Final Report, June 1972, February 1973.

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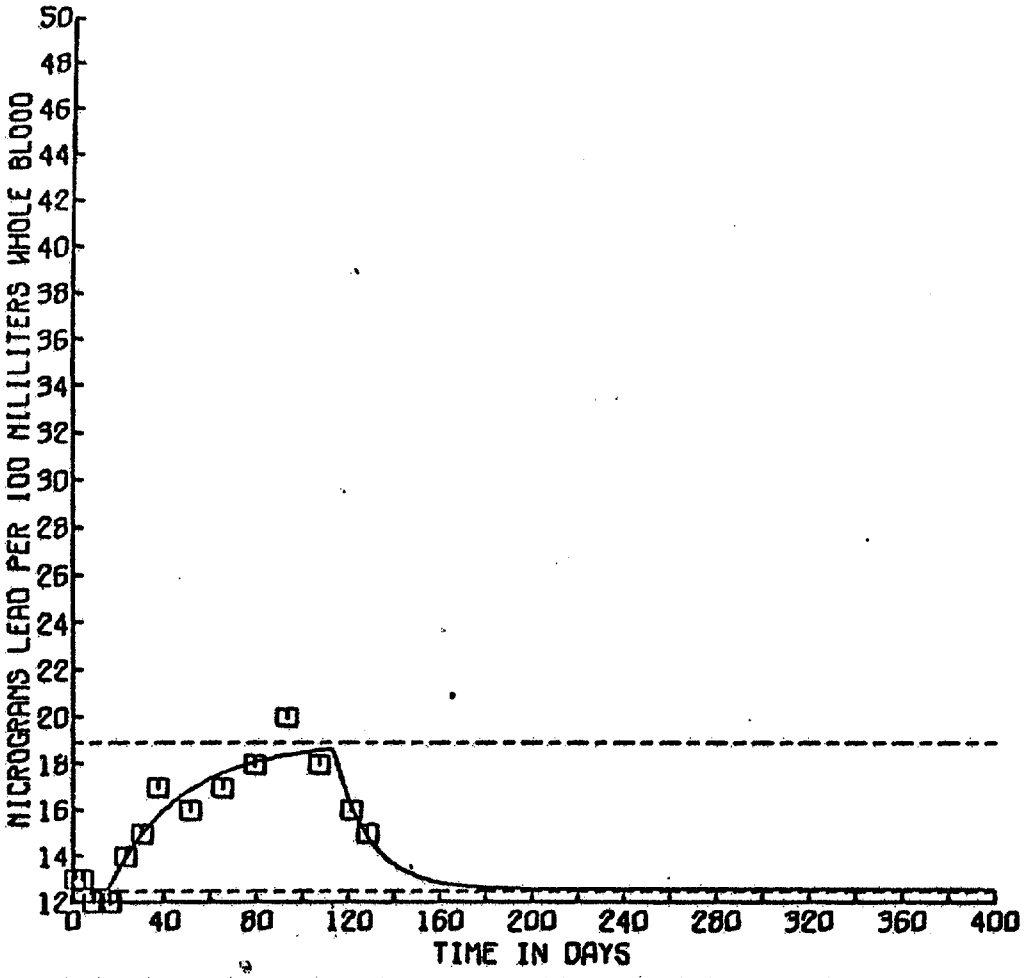
Figure 31



SUBJECT 9 EXPOSED TO 3.2 MICROGRAMS LEAD PER CUBIC METER OF AIR

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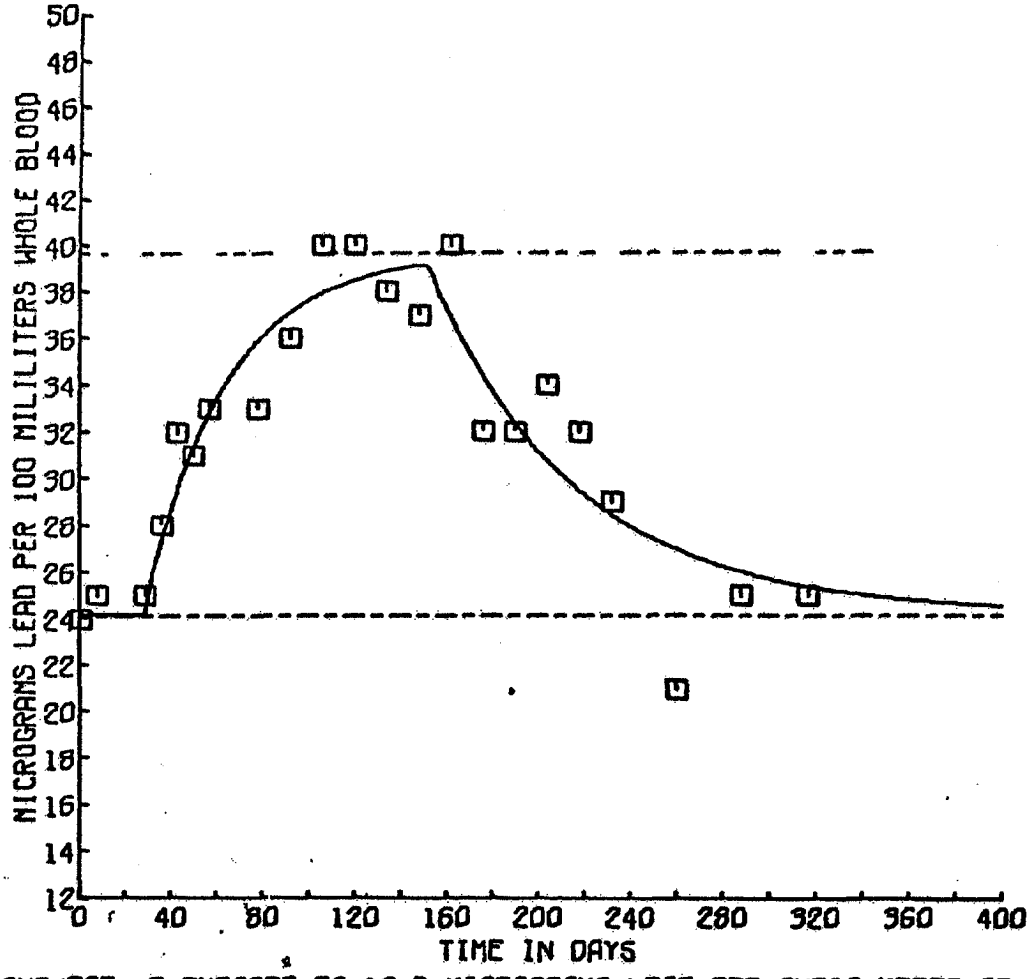
DUP050083460

Figure 2

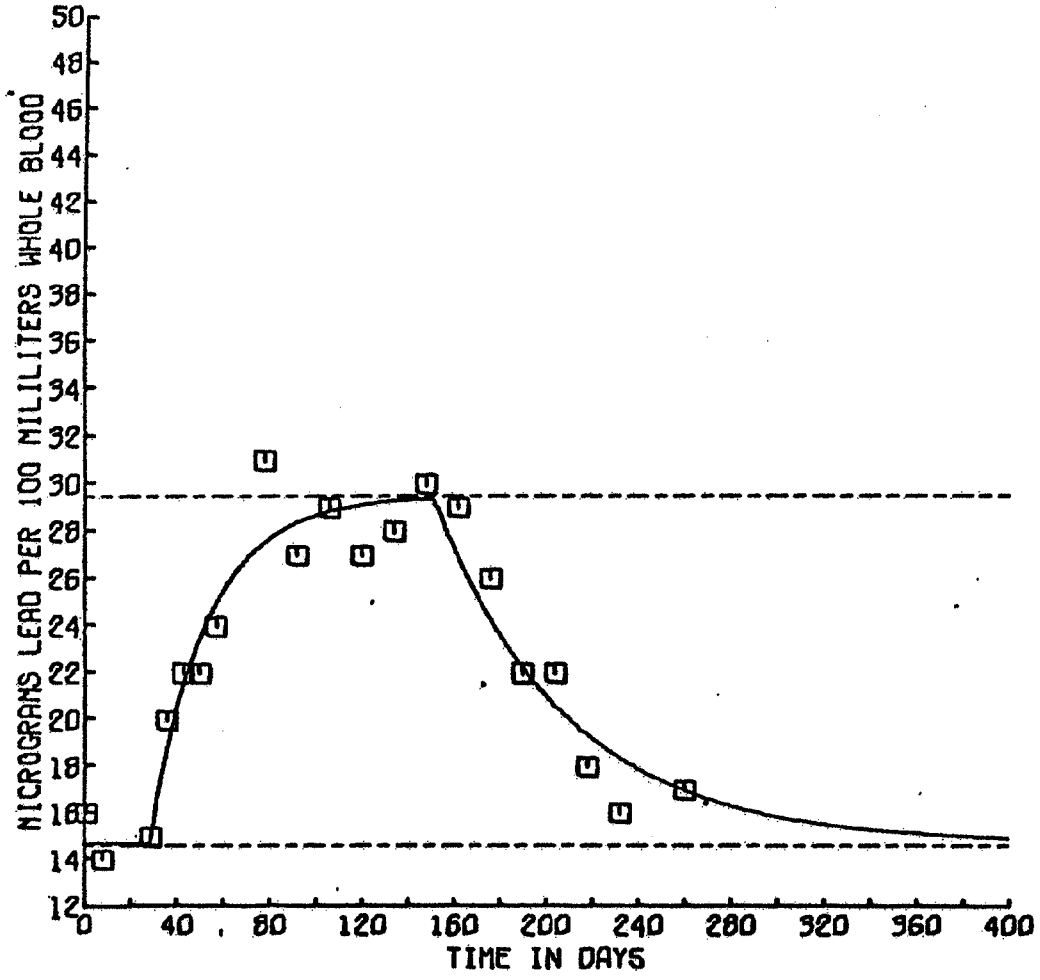


SUBJECT 7 EXPOSED TO 10.9 MICROGRAMS LEAD PER CUBIC METER OF AIR

TEH 0470644

DUP050083461

Figure 3



SUBJECT 9 EXPOSED TO 10.9 MICROGRAMS LEAD PER CUBIC METER OF AIR

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Figure 4

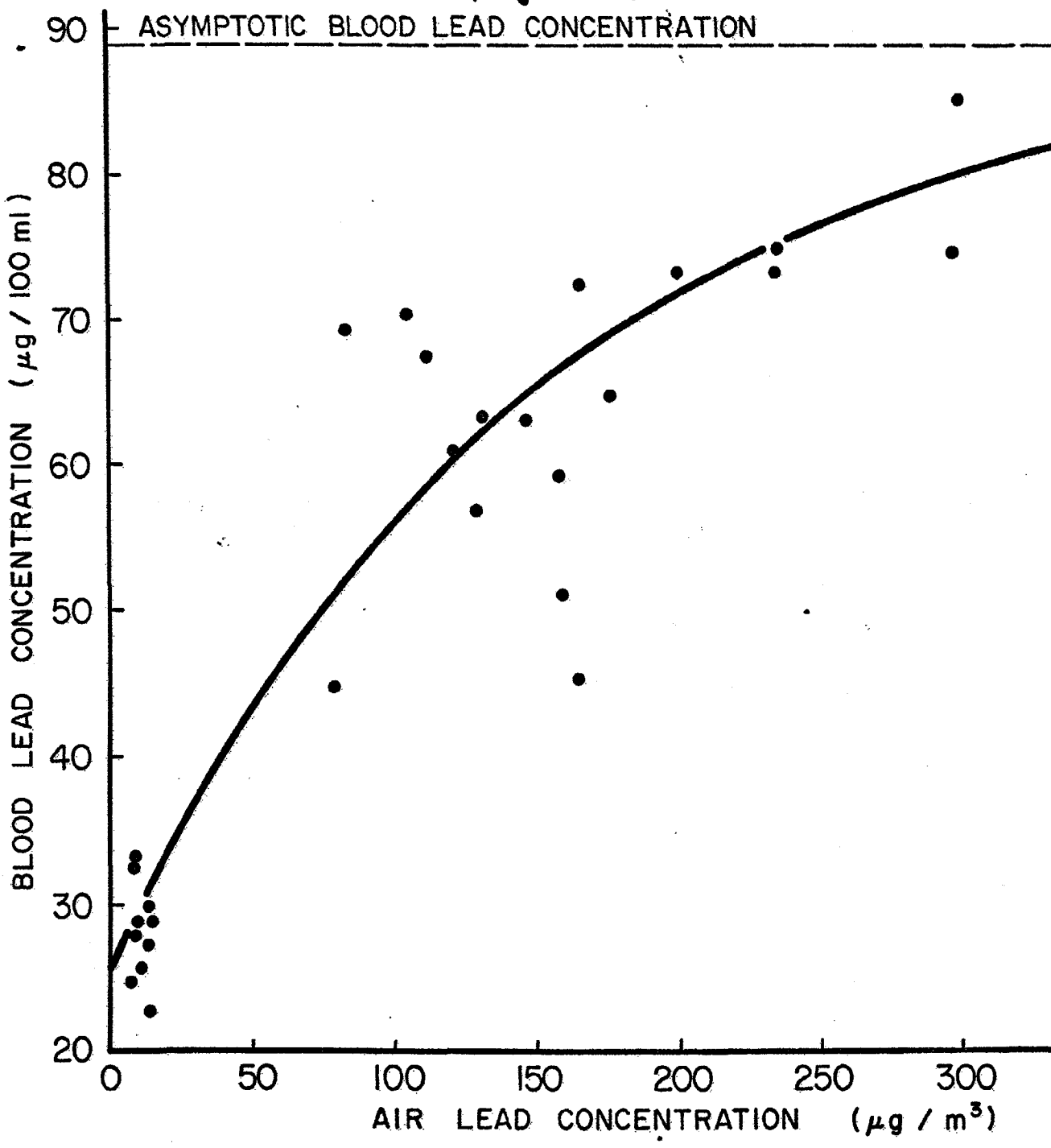
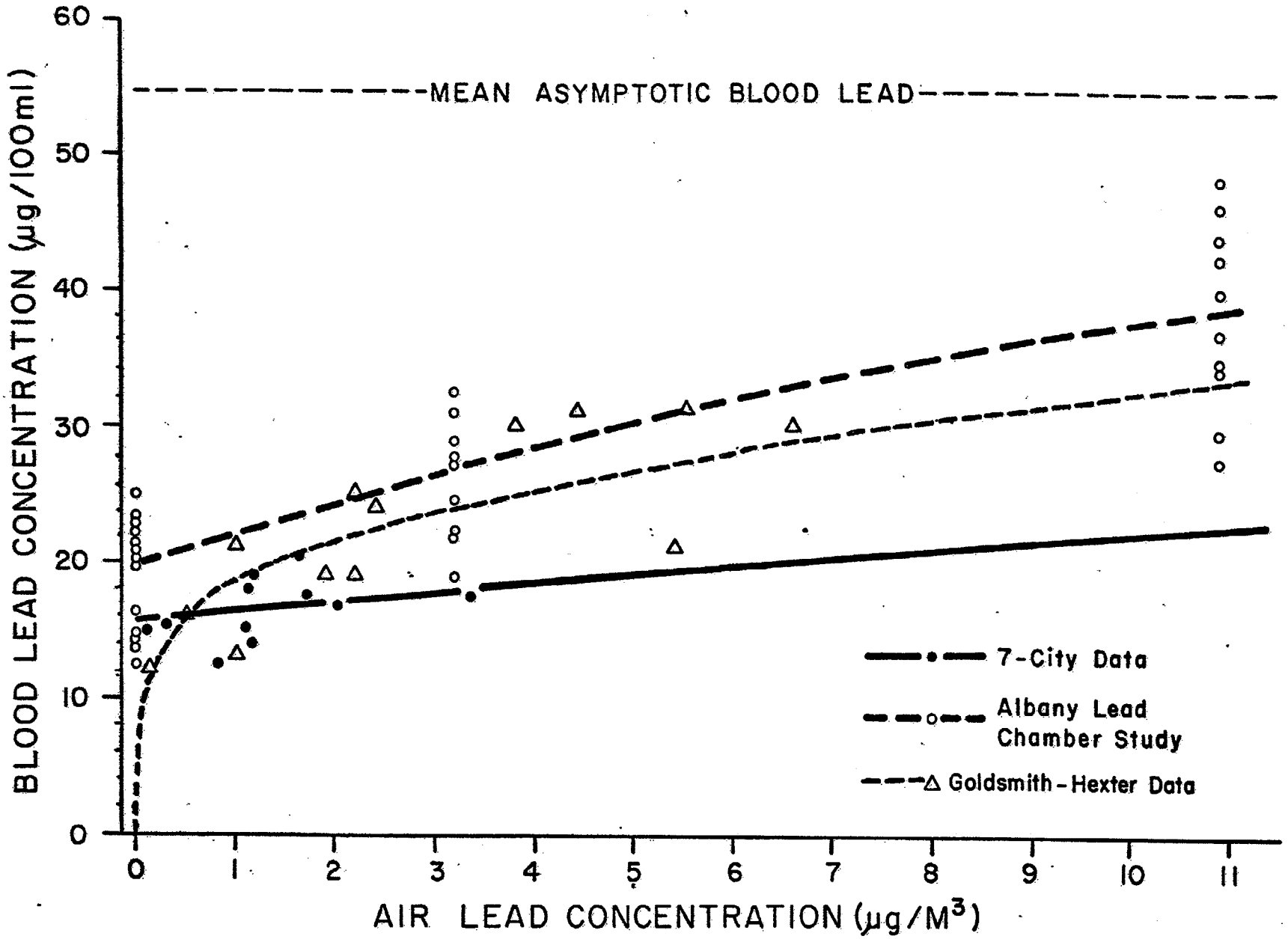


Figure 5



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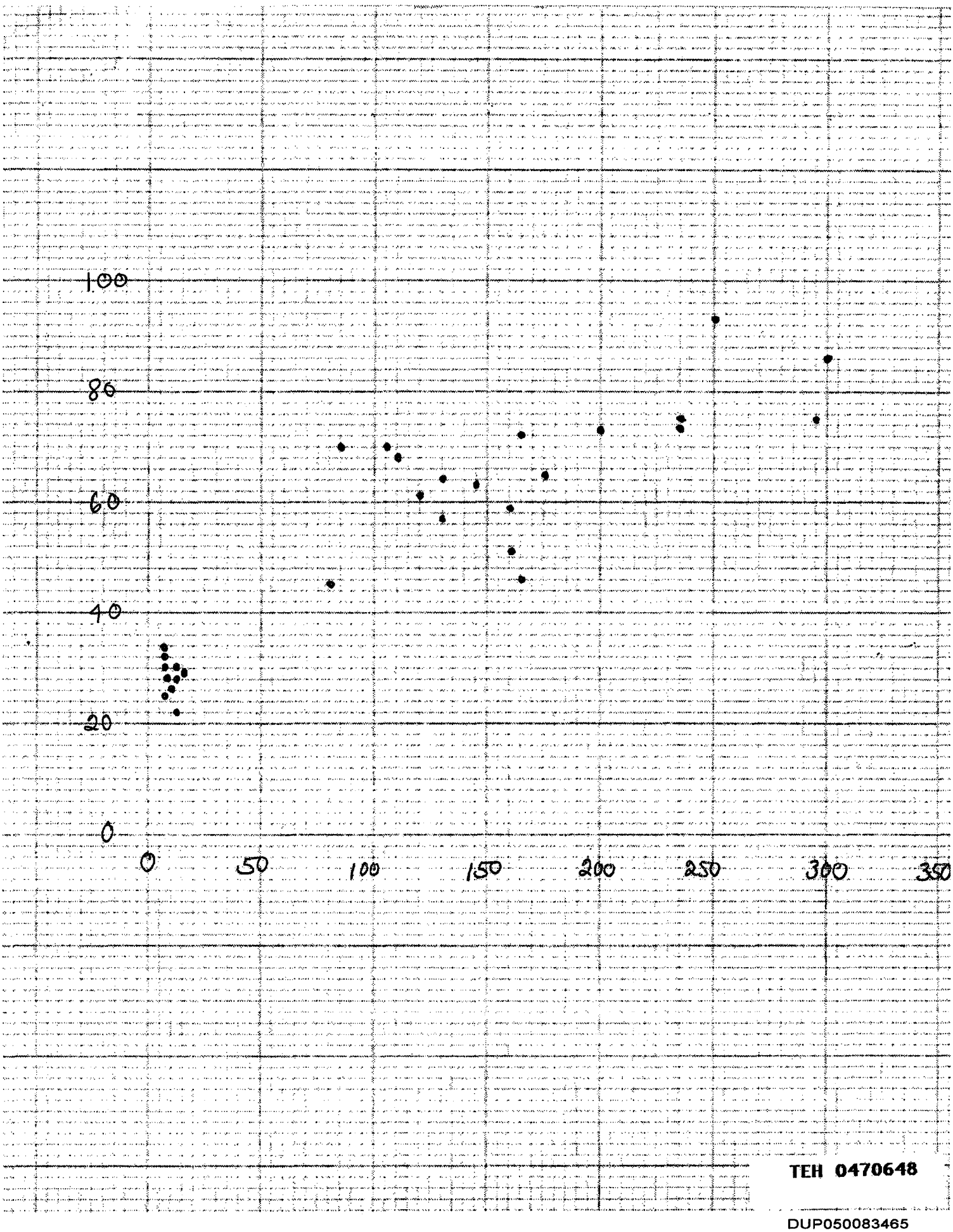

TEH 0470648

DUP050083465

MODELS FOR WILLIAMS DATA

Air Pb	mc Caughran	Sneer
1.0	25	22
10.0	29	28
100.0	55	45
300.0	79	82
500.0	86	99
1000.0	89	128

mc CAUGHRAN $B = 89.1 - 64.5\, e^{-0.6535 \times 10^{-2} Air\,Pb}$

SNEER $B = 16.1\left(.24A + .76(.5) + 1.65\right)^{0.3779}$

2.03

0	25	21
10	29	28
30	36	37
50	42	44
100	55	55
150	64	64
200	71	71
250	76	77
300	79	82

N = 29 K = 3 P = 0 M = 1 IFP = 1 GAMMA CRIT =
FF = .400+01 T = .200+01 E = .500-04 TAU = .100-02

(0) PARAMETERS .29000000+01 .35000000+00 .90000000+00

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(2) PARAMETERS .27939889+01 .37450759+00 .15429069+01

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(3) PARAMETERS .27795703+01 .37796050+00 .16688045+01

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(4) PARAMETERS .27800896+01 .37791969+00 .16545662+01

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Williams Data

TEH 0470652

DUP050083469

N =, 29 K = 3 P = 0 M = 1
FF = .400+01 T = .200+01 E = .500-04 TAU = .100-02

① ② ③

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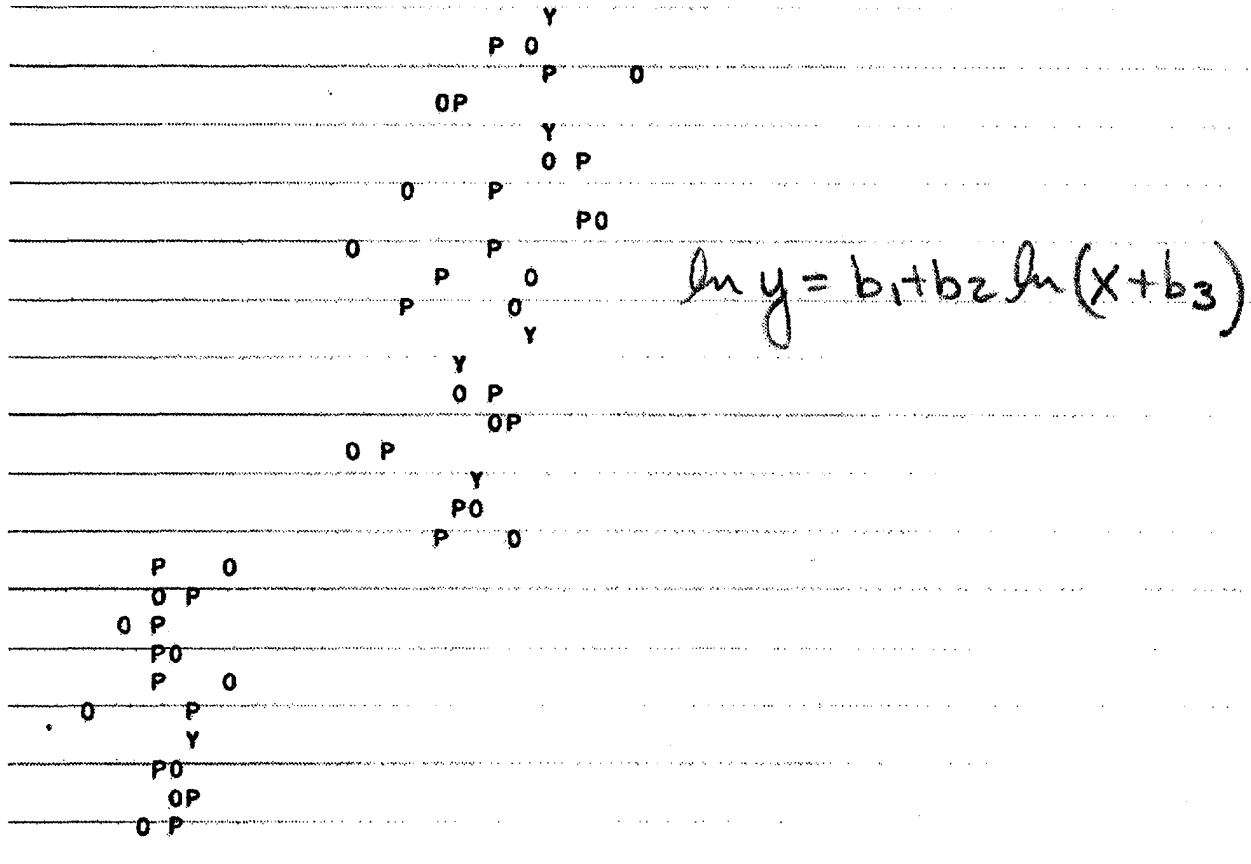
.31+01
+



$$\ln y = b_1 + b_2 \ln(x + b_3)$$

(4) PARAMETERS .27800896+01 .37791969+00 .16545662+01

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.43121405+01	.43988609+01	-.86720347-01
.39357395+01	.41730028+01	-.23726332+00
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.41108739+01	.40758388+01	.35035074-01
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.41682144+01	.42095609+01	-.41346490-01
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TEH 0470653

DUP050083470

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PHI	S E	LAMBDA	ESTIMATED PARTIALS USE
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PTP INVERSE

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2	-.27669530+01	.69323528+00	.20218649+02
3	-.81645957+02	.20218649+02	.61579134+03

PARAMETER CORRELATION MATRIX

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2	-.9969	1.0000	.9786
3	-.9870	.9786	1.0000

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B	ERROR	LOWER	UPPER	LOWER
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2	.12947027+00	.11897915+00	.63686023+00	-.70578478-01
3	.38587489+01	-.60629317+01	.93720640+01	-.11712532+02

NONLINEAR CONFIDENCE LIMITS

PHI CRITICAL = .91884670+00

PARA	LOWER B	LOWER PHI	UPPER B	UPPER PHI
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2	.34592453+00	.91914058+00	.40992286+00	.91884676+00
3	.12554183+01	.64223426+00	.41360154+01	.92710624+00

TEH 0470654

DUP050083471