MODELS FOR THE RELATIONSHIP BETWEEN BLOOD LEAD AND AIR LEAD

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ABSTRACT

A "lead exposure" model is proposed for the relationship between blood lead and air lead. Unlike the commonly-used log-log model, this model describes blood lead as a function of both air lead exposure and lead intake from sources other than the air (ie, food, water, etc). The blood lead-air lead relationship at low air lead levels is also studied. It is shown that the mathematical characteristics of the log-log model can result in an overestimate of the effect of air lead on blood lead at air lead levels less than 1 to 2 $\mu g/m^3$. The lead exposure model is shown to give a good description of data collected in studies in which subjects' air lead levels were measured by personal monitor.

1. Introduction

The determination of the relationship between blood lead and air lead is a crucial step in determining the effects of airborne lead and in the setting of an air quality standard for lead. To be useful a model for the blood lead-air lead relationship should take into account that there are several sources of lead exposure (eg, air, food, water, etc). This fact indicates that at zero air lead the model should not predict a zero blood lead value. The commonly used log-log model (1) does not take these considerations into account. The purpose of this paper is to describe a "lead exposure" model which incorporates these important biological considerations. The availability of the lead exposure model also enables one to evaluate the ability of the log-log model to accurately describe the effect of air lead levels $\leq$ 1-2 $\mu g/m^3$ on blood lead levels.

2. Data on Individual Blood Lead Levels and Air Lead Exposures Are Essential

Models cannot be adequately compared without accurate information on blood lead levels and air lead exposures of several individual subjects. It is generally agreed that personal monitors give the best measure of an individual's exposure to airborne lead. The studies of Azar, et al (2, 3) and Williams, et al (4) are the only studies in which personal samplers have been used to obtain the air lead data. The data collected in these studies will be used to evaluate the models discussed.

The Azar Study (2, 3) is probably the best study of the relationship between air lead and blood lead conducted to date.

Twenty-four hour air lead exposures were obtained for each of 150 male subjects (five groups of 30 subjects each) for a 2-4 week period through the use of personal samples. These exposures ranged from 0.2 to 9.1 μg Pb/M^3. Two to eight (2-8) blood samples were obtained on each subject and each sample was analyzed in duplicate. Two of the groups studied were taxi cab drivers in Philadelphia and Los Angeles. The participants in the Starke, Fla., Barksdale, Wis., and Los Angeles office workers studies were employees of E. I. du Pont de Nemours & Company. With a few exceptions, the subjects in these three groups had no occupational exposure to lead. Azar et al (2, 3) give a detailed discussion of these studies.

In the Williams Study (4) blood lead and air lead data were collected from 10 control subjects and 19 subjects who had occupational exposure to lead. A work exposure (on duty) was obtained by personal monitor for each subject. The air lead measurements represent the mean of 10 samples collected daily for a two-week period. The blood lead measurements are the mean of 5 daily samples collected during the second week of the air sampling period. The total air lead exposure was computed for these subjects using a weighted average of the measured 40-hour per week "on-duty" exposure and an assumed constant "off-duty" exposure of 0.5 $\mu g/m^3$ (ie, total exposure = 0.24 on-duty + 0.76 off-duty). Because the off-duty exposures were not available for the William's subjects this study was used to provide a check on the model rather than to develop the model.

3. The Model Should Take All Sources of Lead Exposure Into Account

As noted earlier Azar, et al (2, 3) presented blood lead levels and personal monitor air lead levels obtained from five study groups (30 subjects/group) involving a total of 149 subjects (one moonshiner subject was deleted from the analysis). The analysis reported by Azar et al (2,3) indicated that there were significant ($p < .01$) differences in the blood lead levels of the different groups even after the effect of air lead had been taken into account. The following six coefficient model was found to give the best fit (residual standard deviation = 0.1119 log units) to the data.

$$\text{Log Blood Pb} = a_i + 0.153 \log \text{Air Pb} \qquad (1)$$

Group	a
Philadelphia Cab Drivers	1.27
Starke, FL	1.21
Barksdale, WI	1.13
Los Angeles Cab Drivers	1.25
Los Angeles Office Workers	1.20

Azar, et al (2, 3) also reported the following average relationship.

$$\text{Log Blood Pb} = 1.2257 + 0.153 \log \text{Air Pb} \qquad (2)$$

This model, which passes through the average log blood lead concentration of the 149 subjects, describes the average blood lead-air lead relationship for this group of subjects.

The log-log model (Eq. 1) was used in the Azar study so that the results could be compared with those of the log-log model published earlier by Goldsmith and Hexter (1). The different "intercept" coefficients (a_i) in Equation 1 account for the fact that there were significant differences between the blood lead levels of the five different groups of subjects.

A log-log model for the blood lead-air lead relationship has one important drawback. McCaughran (5) pointed out that the log-log model is not consistent with the biological background of the problem because it predicts either blood lead equal minus infinity at air lead = 0 (log-log form, Equations 1 and 2) or blood lead = 0 at air lead = 0 when the model was expressed in the exponential form (Equation 3).

$$\text{Blood Pb} = 10^{1.2257}\,(\text{Air Pb})^{0.153}$$

$$= 16.8(\text{Air Pb})^{0.153} \qquad (3)$$

This defect results from the fact that the log-log model does not properly account for other sources of lead exposure. The "lead exposure" model discussed in the following section does not have this serious limitation. It allows for the important consideration that, at an air lead concentration of zero, a subject's blood lead will reflect lead exposure from sources other than air. In fact, the US Environmental Protection Agency based its air quality standard for lead (6) on an assumed blood lead of 12 µg/dl in children at zero air lead.

3.1 Lead Exposure Model

An individual's blood lead level is a function of the person's total lead exposure. This fact together with the exponential nature of the relationship between blood lead and air lead suggests that the relationship between blood lead and total lead exposure can be described by the model

$$\text{Blood Pb} = A(\text{Air Pb} + b_1 \text{ Food Pb} + b_2 \text{ Water Pb} + \ldots)^K$$

where A, K, b_1, b_2, ... are coefficients to be estimated from the data. This model also has the desirable characteristic that it predicts Blood Pb = 0 when all sources of lead exposure = 0. This model will be referred to as the "lead exposure" model.

The lead exposure model could not be fitted to the Azar data directly because there were no data on lead exposure from sources other than air. A reasonable procedure in this situation is to represent lead exposure from other sources by a single Coefficient B which can vary from group to group.

$$B = (b_1 \text{ Food Pb} + b_2 \text{ Water Pb} + \ldots)$$

The resulting model developed by nonlinear least squares regression (7) is shown as Equation 4.

$$\text{Blood Pb} = 12.1\ (\text{Air Pb} + B_i)^K,\ K=0.2669 \qquad (4)$$

	Average Air Lead	B
Philadelphia Cab Drivers	2.62	6.00
Starke, FL	0.81	1.46
Barksdale, WI	1.01	0.44
Los Angeles Cab Drivers	6.10	6.26
Los Angeles Office Workers	3.06	2.23
		Avg = 3.28

This model fits the Azar data as closely as the log-log model reported in Equation 1 (residual standard deviation = 0.1128 log units).

The B coefficients vary from group to group. It was found that using a separate B coefficient for each group gave a significantly ($p < .01$) better fit to the data than a single B coefficient. It is noted that the log-log model (Eq. 1) also showed that there were significant group-to-group differences.

To develop an average blood lead-air lead relationship it is necessary to have lead exposures from each source in addition to air. It is reasonable in this study to use the average B coefficient since B reflects the sum of lead exposures from all sources other than air. The resulting model

$$\text{Blood Pb} = 12.1(\text{Air Pb} + 3.28)^{0.2669} \qquad (5)$$

will be used to describe the average blood lead-air lead relationship for the subjects in the Azar Study.

It is noted that there is a positive correlation between the B coefficient in Equation 4 and the average air lead level of the group. One should resist the temptation to express the B

coefficients as a function of air lead level. To do so would assign all the variation in blood lead to air lead and ignore the fact that the groups were found to have significantly ($p < .01$) different blood lead levels after the effect of air lead was taken into account. This indicates that the groups had different amounts of lead exposure from sources other than the ambient air.

It is important to recognize that the correlation between the B coefficients and air lead level has marginal statistical significance (two-tailed t test $p < .12$, one-tail t test $p < .06$) and is due entirely to the coefficients for the two groups of cab drivers. These two groups differ from the other three groups in many ways (eg, occupation, diet, socio-economic, ethnic), and it is not reasonable to attribute all of the observed variation to air lead differences. For example, the race distribution of the 30 Philadelphia cab drivers was 16 blacks and 14 whites. There were several Mexican-Americans among the Los Angeles cab drivers. Blood lead data collected on New York City children by the US Department of Health, Education, and Welfare show ethnic background (white, black, Hispanic) has a large effect on blood lead level (8).

3.2 Biological Considerations

It is important that any model for the relationship between blood lead and air lead be consistent with the biological background of the problem. The lead exposure (Equation 4) and log-log (Equation 1) models for the Azar data are shown

graphically in Figures 1 and 2. The family of curves reflect group differences which are related to lead exposure from sources other than air lead. Figures 1 and 2 differ in one major respect. The differences between the curves of the lead exposure model (Figure 1) are larger at low air lead levels than at high air lead levels. The opposite trend is present for the log-log model (Figure 2). One would expect nonair lead exposure to have a larger effect at low air lead levels than at high air lead levels. It is concluded, therefore, that the lead exposure model (Eq. 4, Figure 1)is more descriptive of the biological phenomenon being studied.

4. The Lead Exposure Model Gives a Good Description of the Williams Data

The Williams data (3) are occupational exposures and do not reflect the air lead exposures of the general population. It is of interest, however, to determine whether the lead exposure model developed above will give an adequate description of the Williams data. It is also appropriate to compare the resulting model with that developed for the Azar data.

Using nonlinear least squares regression (7) the lead exposure model for the Williams data was found to be

$$\log \text{Blood Pb} = 1.21 + 0.3779 \log (\text{Air Pb} + 1.65) \qquad (6)$$

$$\text{Blood Pb} = 16.1 (\text{Air Pb} + 1.65)^{K}, \; K=0.3779$$

This model had a residual standard deviation of 0.0675 log units. It is of interest to note that this model predicts

essentially the same blood lead levels as the following asymptotic model (Eq. 7) developed for these data by McCaughran (5).

$$\text{Blood Pb} = 89.1 - 64.5 \exp(-0.006535 (\text{on-duty air Pb})) \quad (7)$$

The similarity between the predictions of these two models are shown in the following table.

	Williams Data Predicted Blood Pb Level	
On-Duty Air Pb ($\mu g/m_3$)	Lead Exposure Equation 6	McCaughran Equation 7
10	29	28
50	42	44
100	55	55
200	71	71
300	79	82

The coefficients in Equation 6 have some similarities with those in the lead exposure model developed for the Azar data (Equation 4). The next step in the analysis was, therefore, to determine what differences existed between the two models. It was found that the proportionality constant A_i was different for the two data sets, however, there was no significant difference between the air lead exponent (K) in the two models. (Azar data, Eq. 4, K=0.2669; Williams data, Eq. 6, K=0.3779). The following model (Eq. 8) was obtained.

$$\text{Blood Pb} = A(\text{Air Pb} + B_i)^K, \quad K=0.3513 \qquad (8)$$

	A		B
Azar	10.0	Philadelphia Cab Drivers	6.24
Williams	17.9	Starke, FL	2.39
		Barksdale, WI	1.12
		Los Angeles Cab Drivers	5.59
		Los Angeles Office Workers	3.09
		Williams Data	0.93

The residual standard deviation for this model is 0.1068 log units. This value falls in between the comparable statistics for the fits to the two data sets separately (0.1128 and 0.0675). A residual analysis and an F-test of significance showed that assuming a common exponent had no significant effect on fit of the model.

It is of interest to note that the proportionality constant in the model for the Williams data of 17.9 is almost 80% larger than the proportionality constant in the model for the Azar data which is 10.0. This difference could be due to an analytical bias between the two data sets and/or an indication that the proportion of lead absorbed is larger for occupational exposures than for nonoccupational exposures.

5. Relationship Between Blood Lead and Air Lead at Low Air Lead Levels

Some scientists have expressed concern that the slope (change in blood lead/unit change in air lead) of the blood lead-air lead relationship may be larger at air lead levels $\leq 1.0\ \mu g/m^3$ than at air lead concentrations $> 1.0\ \mu g/m^3$. This concern has been based in large part on the predictions of the log-log model for the blood lead-air lead relationship

(Equations 2 and 3). The mathematical characteristics of the log-log model are such that at low air lead levels the model predicts that a small increase in air lead will produce a very large increase in blood lead. It is appropriate to question whether the log-log model gives an adequate description of the blood lead-air lead relationship at low levels.

As noted earlier the log-log model is not consistent with the biological background of the problem because it predicts blood lead equal minus infinity at air lead = 0 (log-log form, Equation 2) or blood lead = 0 at air lead = 0 when the model is expressed in the exponential form (Equation 3). The extreme behavior of the log-log model at low air lead levels is due to the mathematical characteristics of the log function. For example, the subjects in the Azar study (2, 3) have an air lead range of 0.2 to 9.1 $\mu g/m^3$. The air lead range of 0.2 to 1.0 $\mu g/m^3$ represents 100 (1.0-0.2)/(9.1-0.2) = 8.9% of the total range of the data; however, on the log scale the 0.2 to 1.0 $\mu g/m^3$ range represents 100 (log 1.0-log 0.2)/(log 9.1-log 0.2) = 36.3% of the range of the data. It is frequently difficult to determine whether one end of an observed relationship actually exhibits such extreme behavior unless the data contain very little random variation. Unfortunately, blood lead data do not have this characteristic.

The Azar study (2, 3) is uniquely useful in studying the effect of the mathematical form of the fitted model on the predicted change in blood lead at low air lead levels. As

noted earlier, the 149 subjects in this study had air lead exposures in the range of 0.2-9.1 $\mu g/m^3$. The effect of assumed model form was studied by fitting log-log (Equation 1) and "log-quadratic" models to the Azar data. The log-quadratic model (Equation 9)

$$\log \text{Blood Pb} = a_i + b\,(\text{Air Pb}) + c\,(\text{Air Pb})^2 \qquad (9)$$

is very similar to the model used by Yankel, et al (9) in the analysis of the Silver Valley Lead Study. This model has good data smoothing properties and can detect curvature in the dose-response relation if it exists.

The coefficients in the fitted log-log and log-quadratic model and the predicted blood lead-air lead slopes are summarized in Tables 1 and 2. The predicted blood lead-air lead slopes for the lead exposure model (Equation 4) are also included in Table 2. In each of the analyses described above group factor coefficients a_i were included in the model to account for the five different groups in the study. The group coefficients a_i were significantly different ($p < .01$) in all analyses. The a_i coefficients describe group differences in blood lead level which remain <u>after the effect of air lead has been taken into account</u>.

The log-log and log-quadratic-1 models (Table 2) were restricted to those 132 subjects with air lead levels $\leq 6.0\ \mu g/m^3$. The analysis was restricted to this air lead range because the fitted log-quadratic model developed from all the the subjects passed through a maximum at approximately

6.0 $\mu g/m^3$ (Table 1). The objective was to study the blood lead response of all groups at low air lead levels. It was felt that while the log-quadratic model did not give an adequate description of the total data set (ie, it passed through a maximum within the range of the data), it would give an adequate description of the lower end of the relationship. Using any air lead level lower than 6 $\mu g/m^3$ (eg, 5 $\mu g/m^3$) as an upper limit would have resulted in the deletion of almost all of the Los Angeles cab driver data. It is of interest to note that the quadratic coefficient was not statistically significant when the analysis was restricted to the subjects with air lead exposures $\leq$ 6.0 $\mu g/m^3$.

In Table 2 we see that both log-log and log-quadratic models fit the data equally well (ie, the goodness-of-fit statistics were identical for practical purposes); however, the models predicted considerably different blood lead changes at low air lead levels. The log-log slopes (change in blood lead/unit change in air lead) for air lead $\leq$ 1 $\mu g/m^3$ varied from 4.8 to 6.0, depending on the group of subjects, while the log-quadratic model predicted slopes of 2.0 to 2.6 in the same region. The lead exposure model slopes varied from 0.8 to 3.6. It is important to note that restricting the analysis to air lead levels $\leq$ 6.0 $\mu g/m^3$ had no effect on the predicted slopes of the log-quadratic model (ie, the slopes of the log-quadratic-1 (132 subjects, air lead $\leq$ 6.0 $\mu g/m^3$) and log-quadratic-2 (all 149 subjects) models are essentially equal, Table 2).

This analysis points out that the mathematical form of the fitted model does have a great effect on the predicted effect of air lead on blood lead at low air lead levels. It is also clear that the best available data are not precise enough to distinguish between the two models. In such a situation one has to rely on biological considerations as a basis for deciding whether a given model is appropriate. Because of the data smoothing characteristics of the log-quadratic model and the concerns with the log-log model raised by McCaughran (5) one has to conclude that the log-log model does not give an adequate description at low air lead levels, and its use will result in a gross overestimate of the change in blood lead at low air lead levels.

6. Conclusion

In this paper it is proposed that the relationship between blood lead and air lead be studied through the use of a lead exposure model which relates an individual's blood lead level to his or hers total lead exposure. It has been shown that this model (Equation 4) is more descriptive of the biological phenomenon being studied than the log-log model originally proposed by Goldsmith and Hexter (1) and used by Azar et al (2, 3). This finding is of particular importance because the Azar Study and its log-log model (Equations 2 & 3) was one of three key studies used by the US Environmental Protection Agency in developing their air quality standard for lead (6).

The lead exposure model was found to give good descriptions of the best available data sets (2, 3, 4). The log-log model was also shown to overestimate the effect of low ($\leq$ 1 - 2 $\mu g/m^3$) air lead levels on blood lead. These results indicate that the lead exposure model should be used in future studies of the relationship between air lead and blood lead. In addition to using personal samplers to determine air lead exposure, these studies should also include the collection of lead exposure data on other sources such as food and water and duplicate blood lead measurements on two blood samples (spaced 2-7 days apart) from each subject.

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TABLE 1

BLOOD Pb-AIR Pb MODELS FOR AZAR DATA (1)
MODEL COEFFICIENTS AND GOODNESS-OF-FIT STATISTICS

Group	a_i Coefficients		
	Log-Log	Log-Quadratic-1	Log-Quadratic-2
Philadelphia Cab	1.26	1.16	1.18
Starke, FL	1.22	1.12	1.12
Barksdale, WI	1.15	1.04	1.03
Los Angeles Cab Drivers	1.23	1.08	1.16
Los Angeles Office Workers	1.19	1.08	1.11
Residual Std. Dev.	0.115	0.115	0.112
Adjusted R^2*	0.46	0.46	0.48
No. of Subjects	132	132	149
Air Pb Range ($\mu g/m^3$)	0.2-6.0	0.2-6.0	0.2-9.1

(1) Log-log: $\log \text{Blood Pb} = a_i + 0.1936 \log \text{Air Pb}$

Log-quadratic-1: $\log \text{Blood Pb} = a_i + 0.0761 \text{ Air Pb} - 0.00376 (\text{Air Pb})^2$

Log-quadratic-2: $\log \text{Blood Pb} = a_i + 0.0780 \text{ Air Pb} - 0.00677 (\text{Air Pb})^2$

The $(\text{air Pb})^2$ coefficient was statistically significant in the log-quadratic-2 model ($0.2 \leq$ air Pb $\leq 9.1 \mu g/m^3$) but not in the log-quadratic-1 model ($0.2 \leq$ air Pb $\leq 6.0 \mu g/m^3$).

* Fraction of the total variance explained by the model.

TABLE 2

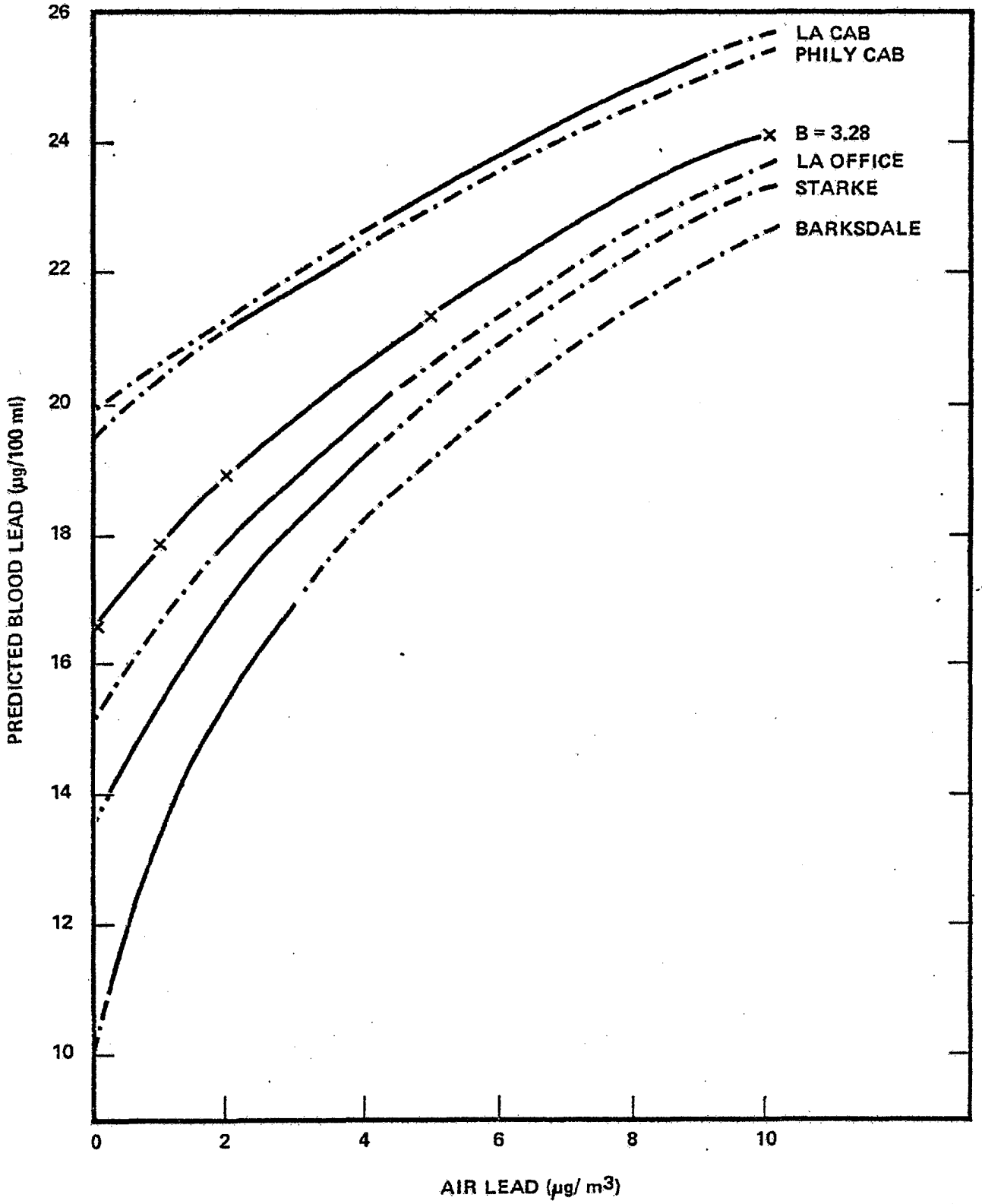
COMPARISON OF BLOOD Pb-AIR Pb MODELS FOR AZAR DATA AT LOW AIR LEAD LEVELS

Model	No. of Subjects(1)	Air Pb Range(2)	Predicted Blood Pb-Air Pb Slope: Phila. Cab	Starke	Barksdale	LA Cab	LA Off.
Log-Log	132	0.2-1.0	6.0	5.6	4.8	5.8	5.2
		0.2-2.0	4.1	3.8	3.2	3.9	3.6
Log-Quadratic-1	132	0.0-1.0	2.6	2.4	2.0	2.2	2.2
		0.0-2.0	2.7	2.5	2.0	2.2	2.2
Log-Quadratic-2	149	0.0-1.0	2.7	2.4	1.9	2.5	2.2
		0.0-2.0	2.6	2.3	1.8	2.4	2.2
Lead Exposure	149	0.0-1.0	0.8	2.0	3.6	0.8	1.6
		0.0-2.0	0.8	1.8	2.8	0.8	1.4

(1) Air Pb range of 132 subjects is 0.2-6.0 $\mu g/m^3$; air Pb range of 149 subjects is 0.2-9.1 $\mu g/m^3$.

(2) Air Pb range over which the blood Pb-air Pb slope was calculated.

LIST OF FIGURES



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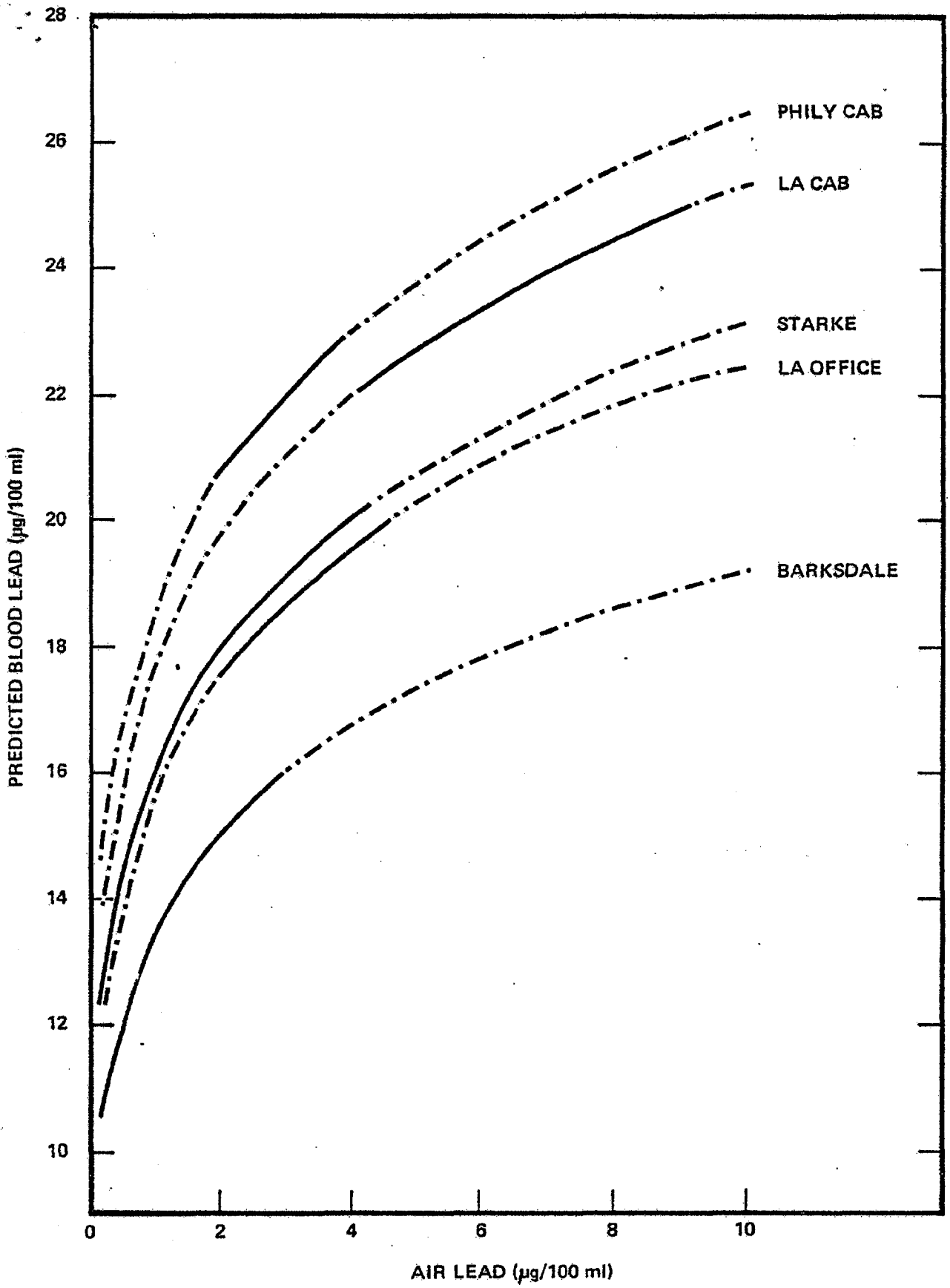

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