Lead-Induced Anemia: Dose-Response Relationships and Evidence for a Threshold

JOEL SCHWARTZ, PHD, PHILIP J. LANDRIGAN MD, MSC, EDWARD L. BAKER, JR., MD, MPH, WALTER A. ORENSTEIN, MD, AND IAN H. VON LINDERN, PE, PHD

Abstract: We conducted a cross-sectional epidemiologic study to assess the association between blood lead level and hematocrit in 579 one to five year-old children living near a primary lead smelter in 1974. Blood lead levels ranged from 0.53 to 7.91 μmol/L (11 to 164 μg/dl). To predict hematocrit as a function of blood lead level and age, we derived non-linear regression models and fit percentile curves. We used logistic regression to predict the probability of hematocrit values less than 35 per cent. We found a strong non-linear, dose-response relationship between blood lead level and hematocrit. This relationship was influenced by age, but (in this age group) not by sex; the effect was strongest in youngest children. In one year-olds, the age group most severely affected, the risk of an hematocrit value below 35 percent was 2 percent above background at blood lead levels between 0.97 and 1.88 μmol/L (20 and 39 μg/dl), 18 percent above background at lead levels of 1.93 to 2.85 μmol/L (40 to 59 μg/dl), and 40 percent above background at lead levels of 2.9 μmol/L (60 μg/dl) and greater; background was defined as a blood lead level below 1.88 μmol/L (20 μg/dl). This effect appeared independent of iron deficiency. These findings suggest that blood lead levels close to the currently recommended limit value of 1.21 μmol/L (25 μg/dl) are associated with dose-related depression of hematocrit in young children. (*Am J Public Health* 1990; 80:165–168.)

Introduction

Lead-induced anemia is produced principally by two mechanisms: impairment in heme biosynthesis, and increased rate of red blood cell destruction.[1]

Lead-induced anemia has been reported to occur in children at a blood lead level of 1.93 μmol/L (40 μg/dl).[2]* However, no clear dose-response relationships between blood lead level and hematocrit have been established. Further, almost no data are available to assess whether this relationship extends downward to blood lead levels below 1.93 μmol/L (40 μg/dl), to ascertain the fraction of children with lead-induced anemia at various blood lead levels, or to determine whether there exists a threshold, below which the association is no longer evident.

To assess dose-response relationships between blood lead level and hematocrit, we examined data obtained in 1974 during an epidemiologic study of lead exposure in children living near a lead smelter.[3]

Methods

A cross-sectional prevalence study of lead exposure in children living near a lead ore smelter in Kellogg, Idaho, conducted in August 1974, found blood lead levels of 1.93 μmol/L (40 μg/dl) and above in 285 (41.9 percent) of 919 children. Within 1.6 km of the smelter, 170 (98.8 percent) of 172 children had blood lead levels above 1.93 μmol/L (40 μg/dl), the highest being 7.91 μmol/L (164 μg/dl). Blood lead levels were positively associated with exposures to airborne lead (correlation coefficient, $r = 0.72$; $p < 0.0001$) as well as with exposures to lead in soil ($r = 0.5$; $p < 0.0001$).[4]

Blood samples (drawn in lead-free vacuum tubes) were analyzed for hematocrit by centrifugation and for erythrocyte protoporphyrin (EP) by the method of Granick, *et al.*[5] Samples were analyzed for lead by modified Delves' cup atomic absorption spectrophotometry.[6] These methods have previously been described in detail.[3]

A total of 1,058 children, ages 1 to 9 years, were identified for whom data on both blood lead and hematocrit were available. In the present analysis, we focus on the 579 children in the age group 1 to 5 years, since children in this age range appear most sensitive to the hematotoxic effects of lead.

Anemia has been defined variously, with the lower bound of the normal range of hematocrit values in young children varying from 33 to 35 per cent.[7–10] We defined anemia as an hematocrit value less than 35 percent. To assess the relation between blood lead level and hematocrit in children using this definition, we fit logistic regressions, which predict the probability of anemia at different age, sex and blood lead levels.[11]

Initial examination of a raw scatter plot of hematocrit versus blood lead level showed a non-linear dose-response relationship. There was little variation in hematocrit at low blood lead levels and a negative relation with lead at higher levels.

Rather than fitting this relationship directly in a non-linear parametric regression, which imposes an explicit functional form on the data, we employed non-linear smoothing techniques developed for robust graphical analysis.[12,13]

Results

The smoothed plot of the data follows a logistic-shaped curve (Figure 1), which is relatively flat at blood lead levels below 0.97 μmol/L, becomes increasingly steep as blood lead levels rise, and, at very high lead levels, flattens again. This curve can be represented by the logistic function:

$$Hct = A/(1 + EXP(B_o + B_1*lead + B_2*age)) + C \quad (1)$$

Address reprint requests to Philip J. Landrigan, MD, Division of Environmental and Occupational Medicine, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, Box 1057, New York, NY 10029–6574. Dr. Schwartz is with the US Environmental Protection Agency, Washington, DC; Dr. Baker is Deputy Director, National Institute for Occupational Safety and Health, Centers for Disease Control, Atlanta, Georgia; Dr. Orenstein is Director, Division of Immunization, Center for Prevention Services, CDC, Atlanta; Dr. von Lindern is with TerraGraphics Environmental Engineering, Moscow, Idaho. This paper, submitted to the Journal January 3, 1989, was revised and accepted for publication November 13, 1989.

*1 μmol/L = 20.72 mg/dl blood lead.

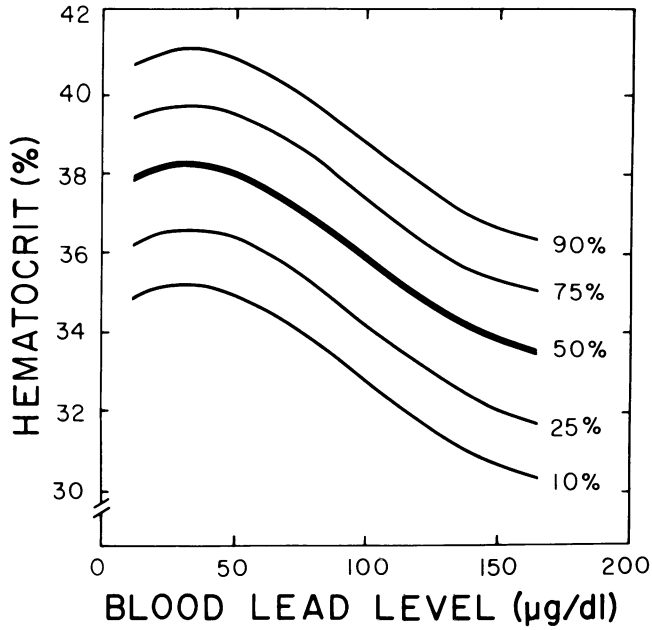

FIGURE 1—Percentile Curves for Hematocrit versus Blood Lead Level in 1–5 Year Old Children, Northern Idaho, 1974

The logistic regression analysis showed a strong association between elevation of blood lead level and the probability of anemia (regression coefficient = 0.3083; (SE = 0.0061). Year of age was also a significant predictor of low hematocrit (coefficient = −0.3831; SE 0.1134). In this age group, sex was not a predictor of anemia. The predicted probability of anemia in relation to blood lead level is plotted graphically for each year of age in Figure 2.

To illustrate the fit of the predicted curve to the actual data, Figure 3 shows both the predicted curve and actual points for the mean proportion of children with anemia for each interval of 0.48 µmol/L (10 µg/dl) in blood lead level after controlling for age. The highest point represents the mean for the five children with blood lead levels greater than 5.79 µmol/L (120 µg/dl).

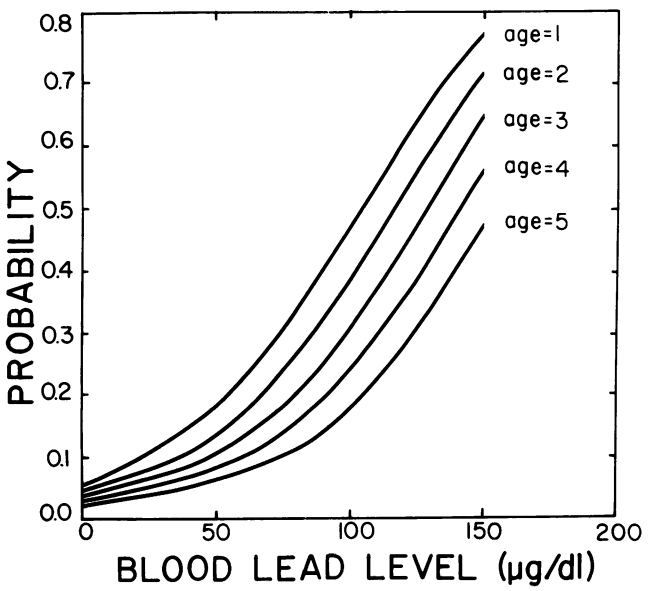

FIGURE 2—Predicted Probability of Hematocrit <35% by Age and Blood Lead Level in 1–5 Year Old Children, Northern Idaho, 1974

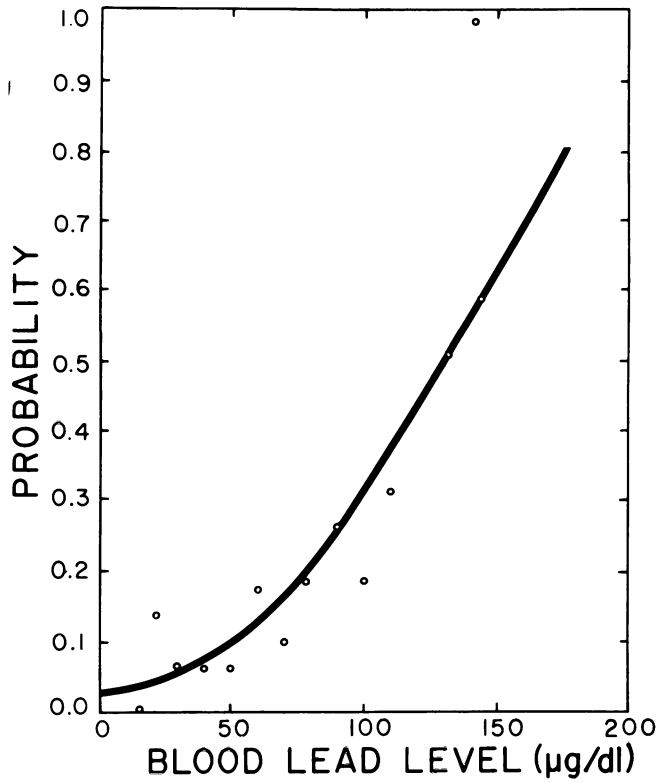

FIGURE 3—Mean Probability of Hematocrit <35% by Blood Lead Level, Northern Idaho, 1974 (This line is the fitted logistic curve for the probability of hematocrit <35% after adjusting, by regression, to the mean age)

Since Figure 2 suggests that the increased risk of depressed hematocrit begins at lower blood lead levels in one year-olds than in five year-olds, we calculated the mean proportion of children in each year of age with an hematocrit below 35 percent at various blood lead levels (Table 1). To compensate for the reduced sample size, we used increments of 0.97 µmol/L (20 µg/dl) in blood lead levels. While the sample size was too small to draw strong conclusions, the results were concordant with the regression analysis (Table 1). In one year-old children the probability of anemia was 0 percent at blood lead levels below 0.97 µmol/L (20 µg/dl), 2 percent at levels between 0.97 and 1.93 µmol/L (20 and 39 µg/dl), 18 percent at levels between 1.93 and 2.90 µmol/L (40 and 60 µg/dl), and 40 percent at blood lead levels above 2.90 µmol/L (60 µg/dl).

We also examined actual hematocrit values rather than proportion anemic. In Figure 1, the 20th, 25th, 75th, and 90th percentile curves reflect the broad variation in hematocrit levels due to age, iron deficiency and other factors. Percentile curves were estimated by confirming the homoscedasticity of the residuals from the smooth curve and then estimating their standard deviation from their interquartile range; percentiles were then calculated from the standard deviation. Table 2 presents the results of nonlinear regression of hematocrit on age and on blood lead level.

Figure 4 plots predicted hematocrit levels by age and blood lead level. Again, it shows the strong effect of age on hematocrit in young children, and demonstrates the interrelationship between age and blood lead level.

TABLE 1—Distribution of Population of Children with Anemia by Year of Age and Blood Lead Level, Northern Idaho—1974

Age (Yrs)	Blood Lead Level μmol/L*									
	0.–0.92		0.93–1.88		1.89–2.85		2.86 +		Total	
	# Anemic	Total	# Anemic	Total	# Anemic	Total	# Anemic	Total	# Anemic	Total
1	0	6	1	47	6	33	6	15	13	101
2	1	3	5	49	6	35	6	18	18	105
3	2	7	3	56	2	33	3	29	10	125
4	1	1	4	60	1	23	4	24	10	108
5	0	3	2	78	1	37	1	22	4	140
Total	4	20	15	290	16	161	20	108	55	579

*1 μmol/L = 20.72 μg dl whole blood lead level.

TABLE 2—Non-Linear Regression Model for Hematocrit versus Blood Lead Level, 1–5 Year-Old Children, Northern Idaho, 1974*

Effect	Parameter	Estimate	Standard Error	p-Value
Constant	A	39.54	0.79	0.0001
Constant	B_0	−3.112	0.446	0.0001
Blood Lead Level	B_1	0.0133	0.0041	0.0005
Age	B_2	−0.2016	0.0905	0.0129

*The parameters A, C, and B_0 all relate to the zero lead intercept and were not simultaneously significant. C was therefore deleted (reducing the error of sum squares) to give the model shown in this table.

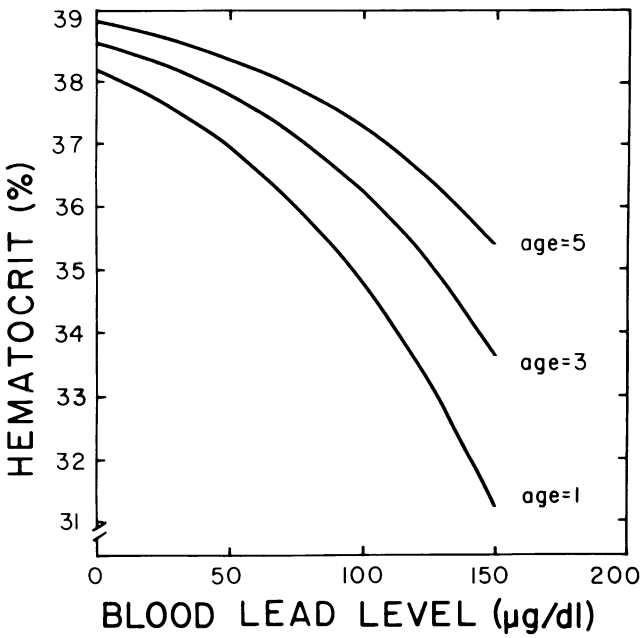

FIGURE 4—Predicted Hematocrit Value versus Blood Lead Level, by Age, in 1–5 Year Old Children, Northern Idaho, 1974

Discussion

The results of this study show a strongly negative, non-linear dose-response relationship between blood lead level and hematocrit in children, strongest in the youngest children. Although there is variability among children in the effect of lead on hematocrit, the data from this study suggest that lead-induced anemia is a biologically and clinically important consequence of lead absorption, even at low levels of exposure.

Iron deficiency may have accounted for some of the observed effect of lead on hematocrit since the effects of lead and iron deficiency on hematocrit have been shown to be strongly interactive.[14] Although data on the iron status of the children in our study were not obtained, the strong correlation between low socioeconomic status, elevated lead levels, and iron deficiency typically seen in urban populations did not exist in our study population. In our population, blood lead levels were determined principally by distance from the smelter and were not correlated with socioeconomic status,[3,4] hence lead exposure and iron deficiency were probably not correlated in these data.

The smoothed dose-response curve of hematocrit versus blood lead level (Figure 1) shows a slight, paradoxical increase in hematocrit at low blood lead levels, followed by a decrease, whose slope steepens until blood lead levels reach 4.83 μmol/L (100 μg/dl) and then subsequently flattens out again. The slight increase in hematocrit observed at the lowest blood lead levels may be artifactual. Since children with lowest blood lead levels came from a rural valley distant from the smelter town, with low family income and socioeconomic status, nutritional deficiency may have been more common there and account for the observed results. Alternatively, the effect may be due to differential partitioning of lead among the soft tissues of the body. At equilibrium, the fraction of lead stored in any body compartment will be proportional to the size of the compartment. At body burdens too low for lead to affect hemoglobin levels, higher hemoglobin levels could increase the fraction of lead stored in red blood cells thus causing the positive correlation seen here.

These data imply that there is no margin of safety between the threshold blood lead level at which lead begins to cause depression of hematocrit in young children and the blood lead level currently considered by the Centers for Disease Control to represent the upper limit of acceptability—1.21 μmol/L (25 μg/dl)[15] These findings complement other data showing deleterious effects of lead on heme synthesis of blood lead levels of 0.48 to 0.97 μmol/L (10–20 μg/dl), on vitamin D metabolism at blood lead levels below 1.21 μmol/L (25 μg/dl), on peripheral nerve conduction velocity at 0.97 to 1.45 μmol/L (20 to 30 μg/dl) and on cognitive function at 0.72 to 0.97 μmol/L (15 to 20 μg/dl).[16–22] Taken together, these findings suggest that the current recommendation on the acceptable upper limit for blood lead level in children requires reexamination.

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