

The Future Challenge of Lead Toxicity

by Herbert L. Needleman*

Five decades ago, lead toxicity in childhood was thought in nonlethal cases to be without residual effect. This misconception was corrected in 1943 by Randolph Byers, who began the modern era of lead neurotoxicology by asserting that lead not only killed cells, but interfered with the normal development of central nervous system neurons. The human data from Byers forward is reviewed, with particular attention on methodological issues that have emerged. The papers on human neurotoxicology presented at the NIEHS lead conference held in Research Triangle Park, NC, in 1974 are examined to demonstrate the progress made over the last 15 years.

Seven methodological solecisms have clouded judgment over the question of lead toxicity at low dose: worship of the sacrament of $p=0.05$; inaccurate causal modeling; drawing conclusions from studies with inadequate power; positing phantom covariates; underestimating the importance of "small" effects; demanding proof of causality; and evaluating studies in isolation. The principles behind these errors are discussed. Lead exposure is associated with hyperactivity, and hyperactivity is a risk factor for antisocial behavior. The relationship between lead exposure and antisocial behavior is estimated. A plan for the effective removal of one major lead source, housing stock, is presented.

Introduction

Fourteen years ago, Bob Goyer organized and presided over one of the first conferences on low-level lead toxicity here in North Carolina. It is instructive, in attempting to forecast where the future will lead us in this field, to examine how far we have come in the past decade and a half. In this effort, I reviewed the seventh issue of *Environmental Health Perspectives* (1), which carried the proceedings of that meeting.

Let me begin a little earlier in time. Fifty years ago, it was generally believed in this country that if a child did not die from plumbism, he or she was left untouched. One of America's leading pediatricians in the 1930s said, "The neurologic manifestations of lead poisoning usually subside without serious consequences if the ingestion of lead is stopped and removal of lead from the circulation and its deposition in inert form in the bones can be hastened" (2). In 1943, Randolph Byers, Chief of Pediatric Neurology at the Boston Children's Hospital, followed up 20 children who had recovered from lead poisoning and found that 19 of the 20 children were learning or behavior disordered (3). He advanced the modern neurotoxicologic theory when he argued that lead's effects were not due simply to the killing of cells, but also interference with the normal development of the child's central nervous system.

In 1974, the Centers for Disease Control paper in *Environmental Health Perspectives* reported that the incidence of excess lead exposure was 4.8%; in blacks the rate was 7.6%. At that time, excess lead exposure was defined as a blood lead level $< 40 \mu\text{g/dL}$. Blood lead levels have declined in the 15 years since then, but the enormous amount of new data from animal and human studies has led to the

redefinition of low-level lead exposure. The prevalence levels of intoxicated children, to be discussed later, are much higher.

Three papers at the 1974 meeting dealt with human neuropsychological outcomes. Oliver David reported that blood lead levels were raised in children with idiopathic hyperactivity (4). Sig Pueschel found increased neurologic soft signs in children with high levels of lead in hair, compared with controls, but no difference in measures of intellectual function (5). Roy Albert (6) reported that elevated blood lead levels, but not tooth lead levels, were associated with inferior IQ scores. Ellen Silbergeld presented data indicating that dosing immature mice resulted in behavior resembling hyperactivity (7). Carson and colleagues found that lambs given lead during pregnancy were deficient on tasks of visual discrimination (8).

Shortly after that meeting, my colleagues and I reviewed the human data from a methodologic point of view and found that it had many serious flaws (9). We tried to design a study that directly confronted these design issues. We chose subjects in an unbiased fashion, classified them by dentine lead levels, controlled for a number of covariates, and found that lead impaired performance on psychometric intelligence, attention, auditory, and language function (Table 1). Most strikingly, teachers, who did not know the children's lead levels, found impaired performance in a dose-dependent function (Fig. 1). These findings were replicated by Lansdown et al. (10) and by Hatzakis (11), who controlled for a large number of covariates. A third generation of studies, using larger sample sizes, found IQ effects at lower levels of exposure (12-14).

One question that has been frequently raised is the direction of the causal arrow. Do children with neuropsychologic impairment eat more paint? Forward studies from birth were needed to solve this question. John Scanlon (15) had shown that lead crossed the placenta and could be measured in the umbilical cord blood. We capitalized on these findings and in 1980 were funded to conduct a forward study of lead

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Table 1. Comparison of test outcomes between students with high- and low-lead levels.^a

| Test | Mean score | | <i>p</i> -Value |
|---------------------------|----------------|-----------------|-----------------|
| | Low-lead group | High-lead group | |
| Full scale IQ | 106.6 | 102.1 | 0.03 |
| Verbal IQ | 103.9 | 99.3 | 0.03 |
| Performance IQ | 108.7 | 104.9 | 0.08 |
| Seashore Rhythm Test, Sum | 21.6 | 19.4 | 0.002 |
| Token Test, Sum | 24.8 | 23.6 | 0.09 |
| Sentence Repetition Test | 12.6 | 11.3 | 0.04 |

^aAnalysis of covariance; *n* = 2146.

during pregnancy. David Bellinger reports in these proceedings of the effects of prenatal lead exposure on psychometric outcome (16), and Kim Dietrich presents similar data from Cincinnati (17). It is clear that lead exposure is a cause, rather than a marker, of intellectual deficit.

Some Issues in Judgment

In 1986, David Bellinger and I (18) reviewed some errors in judgment we encountered in many studies that contributed to the controversy over low level lead effects. We summarized these under seven headings: *a*) worship of $p < 0.05$; *b*) positing phantom covariates; *c*) inaccurate causal modeling; *d*) drawing conclusions from studies of inadequate power; *e*) underestimating the importance of "small" effects; *f*) demanding proof of causality; and *g*) measuring studies in isolation. The use of an arbitrary statistical significance level to sort out causal from accidental associations has no basis in logic and is beginning to fall into deserved desuetude. In the field of lead effects, however, it continues to be raised to argue against the causal relationship between lead and intellectual deficit (19).

Some observers (19), noting that adjusting for covariates tends to reduce the size of the main effect coefficient, have argued that had the proper covariate (unnamed) been measured, the coefficient would approach zero. Some variates such as early temperament or school placement measured in lead studies may be independent variables, or they may be effects of lead. They may be both. To control for them would necessarily reduce the variance properly assigned to lead.

Many studies (20,21) have reported null findings for lead when the sample size and the number of covariates evaluated make the probability of finding a small effect less than 0.5. For small effects in the range of $r = 0.14$, samples of over 500 are required. No null study should be taken seriously without a well-grounded power analysis.

The demonstrated effect size (difference between means of exposed and unexposed groups) in many studies is about 4 to 6 points. Some critics have interpreted this as inconsequential. We have shown (22) that a shift of this magnitude predicts a 4-fold increase in the rate of severely impaired children (IQ < 80). In addition, shifting the curve truncates the distribution at the upper end of the range. This means that 5% of children will be prevented from achieving superior function as a result of lead exposure (Fig. 2).

Critics of the low lead-IQ association assert that causality has not been proven. In this regard they resemble spokesmen for the tobacco industry. Epidemiologists, recognizing David Humes's comments on the limitations of causal demonstration (23), are content to pile up, datum by datum, inference by inference, the body of evidence. They hope by this painful process to draw a coherent picture of nature from which lawfulness can be inferred.

Most reviews of lead and children's IQ are narrative summaries that treat each paper in isolation. Following up on Joel Schwartz's original meta-analysis (24), we extended the review to 13 informative reports. Table 1 summarizes the data, shows the sample sizes, effect sizes, power, and using Fisher's method of aggregating data, calculates a joint *p*-value for all studies. The probability that the collective *p*-values occurred by chance under the null hypothesis was less than 3 in a trillion (Table 2).

Academic and Social Costs of Silent Lead Exposure

Most attention has been focused on psychometric intelligence and lead. I want to speculate briefly about the real social costs of this exposure. We have followed these children into their 19th year of life. When they were in the fifth grade, David Bellinger showed that the incidence of grade reten-

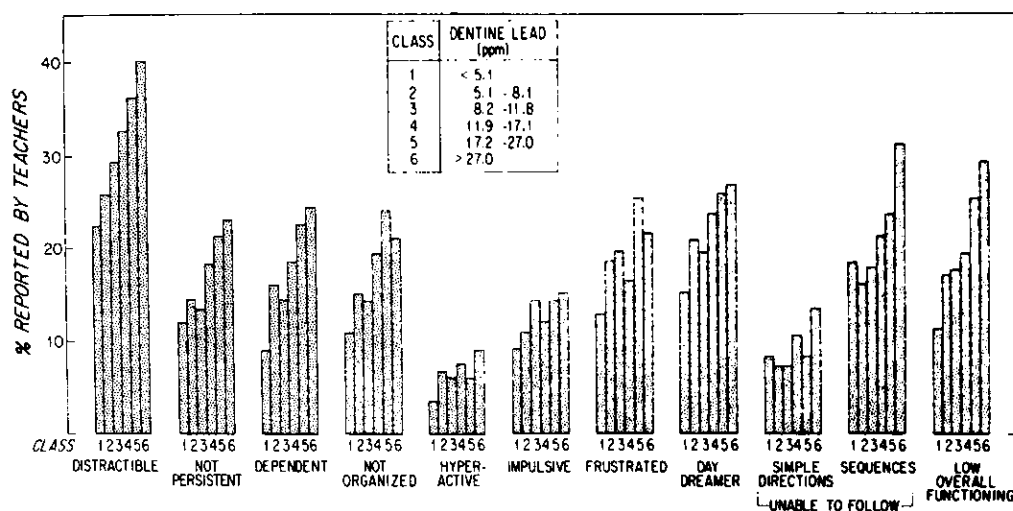


FIGURE 1. Teachers' ratings of classroom behavior in relation to dentine lead level. The height of each bar represents the percentage of negative reports for each lead group.

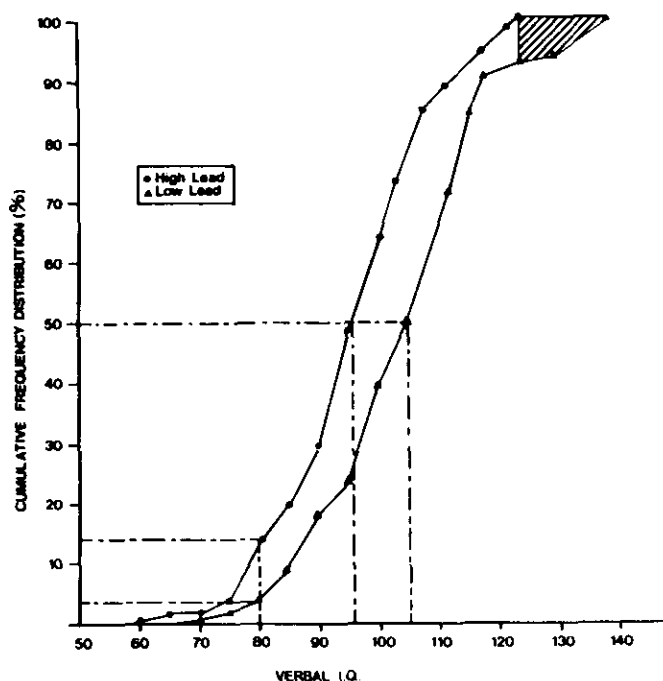


FIGURE 2. Cumulative frequency distribution of verbal IQ scores in high and low lead subjects. A shift in the median score of 6 points is associated with a 4-fold increase in the risk of IQ below 80.

tion was significantly higher in the high lead group and that the attention of lead subjects tended to be disturbed by their lead exposure (25). We have found and retested 132 of the children we first studied when they were first graders. The relative risk for not graduating from high school, associated with lead, is 4.8. In their adult years, these subjects have

Table 2. Meta-analysis, studies of the lead IQ relationship.

| Reference | Year | n | Effect size | Power small effect | p (I) | -2 Loge p |
|----------------------------|------|-----|-------------|--------------------|---------|-----------|
| Perino et al. (29) | 1974 | 80 | 0.6 | 0.2 | 0.025 | 7.38 |
| Needleman et al. (9) | 1979 | 73 | 0.35 | 0.47 | 0.015 | 8.4 |
| Yule et al. (30) | 1981 | 82 | 0.573 | 0.42 | 0.021 | 7.73 |
| Winneke et al. (31) | 1982 | 26 | 0.26 | 0.18 | 0.15 | 3.7 |
| Smith et al. (19) | 1983 | 185 | 0.17 | 0.7 | 0.12 | 4.24 |
| Winneke et al. (32) | 1983 | 115 | 0.351 | 0.25 | 0.4 | 1.83 |
| Harvey et al. (21) | 1984 | 48 | | 0 | | |
| Shapiro and Maracek (33) | 1984 | 193 | 0.46 | 0.48 | 0.025 | 7.38 |
| Lansdown et al. (34) | 1986 | 162 | 0.07 | 0.48 | 0.66 | 0.83 |
| Hansen et al. (14) | 1987 | 82 | 0.5 | 0.34 | 0.0005 | 15.2 |
| Hawk et al. (35) | 1986 | 75 | 0.64 | 0.25 | 0.0004 | 15.64 |
| Schroeder et al. (36) | 1985 | 104 | 0.5 | 0.33 | 0.005 | 10.6 |
| Fulton et al. (12) | 1987 | 501 | 0.4 | 0.52 | 0.003 | 11.6 |
| Hatzakis et al. (13) | 1987 | 509 | 0.4 | 0.52 | 0.00065 | 14.6 |
| $\Sigma x = 109.13$ | | | | | | |
| $p = 2.97 \times 10^{-12}$ | | | | | | |

poorer reading scores, are clumsier, have more evidence of depression, and tend to have a higher rate of hard drug use. With regard to the last observation, is Nation's report that rats, which ordinarily find alcohol aversive, when given lead, will significantly increase their intake of alcohol (26). Under funding from NIEHS, we will study the effects of lead exposure on school outcome, attention deficit disorder, and social adaptation.

Lead is associated with increased risk for attention deficit disorder (ADD). The attributable risk is 0.5. ADD is a risk factor for antisocial behavior. The attributable risk for antisocial behavior, given ADD, is 0.58. If one multiplies the lower boundaries of the attributable risk estimates for the two associations, we obtain a first-order estimate of the joint probability of delinquency given lead exposure. It may be that 20% of delinquency is lead-associated. This is a relationship we are examining at this time.

Primary Prevention: A Modest Proposal

Enormous progress has been made into the scientific understanding of the neurobiology and epidemiology of lead exposure. After an intense fight, joined on both sides by a number of people in this audience, an air standard was written, and over the past decade, 90% of the lead added to gasoline has been removed. This is a public health triumph. Blood leads in newborns have dropped in parallel fashion. But what of the most important hazardous source: old housing? Little or nothing has been accomplished here. The responsibility for this must be borne by slum landlords, banks who will not give home improvement loans and, most bitterly, by the agency with responsibility for housing the poor: HUD.

HUD—the biggest slum landlord—has been a regressive force in housing abatement. This was clearly testified in a GAO document, "HUD fails its duty to prevent lead paint poisoning" (27). Having recently abandoned their assertion that lead paint is not a danger to children, HUD has adopted a new model: they are treating lead as if it were asbestos. HUD has contracted with the National Institute for Building Sciences (NIBS) to develop guidelines for housing abatement. The draft NIBS document calls for abatement measures that will raise the cost of deleading 3- or 4-fold. This is because, on the basis of the slimmest evidence, they are recommending extraordinary measures, e.g., window replacement, to reduce dust lead levels to the lowest possible levels. The writers of the document have ignored the combined experience of existing lead control programs. These show that traditional paint removal, with good cleanup, can lower children's blood lead levels. If one is puzzled by the distance between the scientific progress made over the past 15 years and the absence of response in lead paint removal, one has to look first at HUD and its contractors.

The Agency for Toxic Substances and Disease Registry Report to Congress states that there are 20 million homes with lead-painted surfaces (28). There are 2 million homes that are deteriorated and in which children live. These are the twentieth century equivalent of pest houses or open sewers.

The children in these houses are at greatest risk for brain damage. Fifty-five percent of poor black children have elevated blood lead levels. I believe this is one of the greatest single threats to the polity.

The presence of lead in homes, is, at the same time, an enormous opportunity. If one were to map the prevalence of excess lead burden and map the prevalence of housing shortages and map the prevalence of unemployment, these maps would be isomorphic. It should be possible to rationalize this disequilibrium. Why not train unemployed persons in safe (and inexpensive) deleading, pay them, and allow them to purchase equity in these houses? Current estimates are that a home costs \$5000 to delead. To delead 2 million homes would cost \$10 billion. If 30,000 individuals were employed at \$20,000 per year, with a 5% annual increase, this would cost \$7.8 billion dollars and leave \$2.2 billion for training, materials and insurance. Of this sum, approximately \$1.5 billion would be returned in taxes. Money paid in salaries would be spent in the neighborhoods where the workers were employed, and there multiplied. If this sounds Utopian, one needs to be reminded that the current requests for appropriations for new prison construction is \$11.6 billion.

REFERENCES

1. Low Level Lead Toxicity and the Environmental Impact of Cadmium. *Environ. Health Perspect.* 7: 1-323 (1974).
2. McKhann, C. F. Lead poisoning in children: cerebral manifestations. *Arch. Neurol. Psychiatr.* 27: 294 (1932).
3. Byers, R. K., and Lord, E. E. Late effects of lead poisoning on mental development. *Am J. Dis. Child* 66: 471-483 (1943).
4. David, O. J. Association between lower level lead concentrations and hyperactivity in children. *Environ. Health Perspect.* 7: 17-25 (1974).
5. Pueschel, S. M. Neurological and psychomotor functions in children with an increased lead burden. *Environ. Health Perspect.* 7: 13-16 (1974).
6. Albert, R. E., Shore, R. E., Sayers, A. J., Grehlow, C., Kneip, T. J., Pasternack, A. J., Friedhoff, F., and Covan, F. *Follow-up of children overexposed to lead.* *Environ. Health Perspect.* 7: 227-232 (1974).
7. Silbergeld, E. K., and Goldberg, A. M. Hyperactivity: lead-induced behavior disorder. *Environ. Health Perspect.* 7: 227-232 (1974).
8. Carson, T. L., VanGelder, G. A., Karas, G. G., and Buck, W. B., Development of behavioral tests for the assessment of neurologic effects of lead in sheep. *Environ. Health Perspect.* 7: 233-237 (1974).
9. Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Mañer, C., and Barrett, P., Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *N. Engl. J. Med.* 300: 689-695 (1979).
10. Lansdown, R., Yule, W., Urbanowicz, M. A., and Miller, I. B. Blood lead, intelligence, attainment and behaviour in school children: overview of a pilot study. In: *Lead versus Health* (M. Rutter and R. R. Jones, Eds.), John Wiley and Sons, Chichester, 1983, pp. 267-296.
11. Hatzakis, A., Salaminos, F., Kokevi, A., Katsouyanni, K., Maravelias, K., Kalandidi, A., Kouselinis, A., and Stefasis, A. Blood lead and classroom behaviour of children in two communities with different degree of lead exposure: evidence of a dose-related effect? In: *Proceedings of the Fifth International Conference on Heavy Metals in the Environment*, Athens (T. D. Lekkas, Ed.), CEP Consultants, Edinburgh, 1985.
12. Fulton, M., Raab, G., Thomson, G., Laxen, D., Hunter, R., and Hepburn, W. Influence of blood lead on the ability and attainment of children in Edinburgh. *Lancet* i: 1221-1226 (1987).
13. Hatzakis, A., Kokkevi, A., Katsouyanni, K., Maravelias, K., Salaminos, J. F., Kalandidi, A., Koutselinis, A., Stefanis, K., and Trichopoulos, D. Psychometric intelligence and attentional performance deficits in lead-exposed children. In: *Proceedings of the Seventh International Conference on Heavy Metals in the Environment*, New Orleans (S. E. Lindberg and T. C. Hutchinson, Eds.), CEP Consultants, Edinburgh, 1987, pp. 204-209.
14. Hansen, O. N., Trillingsgard, A., Beese, I., Lyngbye, T., and Grandjean, P. A neuropsychological study of children with elevated dentine lead level: assessment of the effect of lead in different socioeconomic groups. In: *Proceedings of the Seventh International Conference on Heavy Metals in the Environment*, New Orleans (S. E. Lindberg and T. C. Hutchinson, Eds.), CEP Consultants, Edinburgh, 1987, p. 54.
15. Scanlon, J. Umbilical cord blood lead concentration: Relationship to urban or suburban residency during gestation. *J. Dis. Child.* 121: 325-326 (1971).
16. Bellinger, D., Leviton, A., and Sloman, J. Antecedents and correlates of improved cognitive performance in children exposed *in utero* to low levels of lead. *Environ. Health Perspect.* 89: 5-11 (1990).
17. Dietrich, K. N., Succop, P. A., Bornschein, R. L., Kraft, K. M., Berger, O., Hammond, P. B., and Buncher, C. R. Lead exposure and neurobehavioral development in later infancy. *Environ. Health Perspect.* 89: 13-19 (1990).
18. Needleman, H. L., and Bellinger, D. Type II fallacies in the study of childhood exposure to lead at low dose: a critical and quantitative review. In: *International Workshop on the Effect of Lead Exposure on Neurobehavioral Development* (M. Smith, A. Sors, and L. Grant, Eds.), Kluwer Academic Publishers, Edinburgh, Scotland, pp. 293-304.
19. Smith, M. Delves, T., Lansdown, R., Clayton, B., and Graham, P. The effects of lead exposure on urban children: the Institute of Child Health/Southampton Study. *Dev. Med. Child Neurol.* 25 (suppl. 47): 1-54 (1983).
20. Ernhart, C. B., Landa, B., and Wolf, A. W. Subclinical lead level and development deficit: re-analyses of data. *J. Learn Disab.* 18: 475-479 (1985).
21. Harvey, P. G., Hamlin, M. W., and Kumar, R. Blood lead, behaviour and intelligence test performance in preschool children. *Sci. Total Environ.* 40: 45-60 (1984).
22. Needleman, H. L., Leviton, A., and Bellinger, D. Lead-associated intellectual deficit. *N. Engl. J. Med.* 306: 367 (1982).
23. Hume, D. *Enquiry Concerning Human Understanding.* Clarendon Press, Oxford, 1894.
24. Schwartz, J., Pitches, H., Levin, R., Oshow, B., and Nichols, A. Z. Costs and Benefits of Reducing Lead in Gasoline: Final Regulatory Analysis. U.S. Environmental Protection Agency, Washington, DC, 1955.
25. Bellinger, D., Needleman, H. L., Bromfield, R., and Mintz, M. A follow-up study of the academic attainment and classroom behavior of children with elevated dentine lead levels. *Biol. Trace Element Res.* 6: 207-223 (1986).
26. Nation, R., Baker, D. M., Bratton, G. R., Fantasia, M. A., Andrews, K., and Womac, C. Ethanol self-administration in rats following exposure to dietary cadmium. *Neurotoxicol. Teratol.* 9: 339-344 (1987).
27. Comptroller General (GAO). HUD Not Fulfilling Responsibility to Eliminate Lead-based Paint Hazard in Federal Housing. Report no. 81-31. U.S. General Accounting Office, Washington, DC, 1980.
28. Agency for Toxic Substances and Disease Registry. The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress. US Department of Health and Human Services, Atlanta, GA, 1988.
29. Perino, J., and Ernhart, C. The relation of subclinical lead level to cognitive and sensory impairment in black preschoolers. *J. Learn Disabil.* 7: 26-30 (1974).
30. Yule, W., Lansdown, R., Millar, I., and Urbanowitz, M. The relationship between blood lead concentration, intelligence, and attainment in a school population: a pilot study. *Dev. Med. Child Neurol.* 23: 567 (1981).
31. Winneke, G., Kramer, G., and Brockhaus, A. Neuropsychological studies in children with elevated tooth lead concentration. 1. Pilot study. *Int. Arch. Occup. Environ. Health* 51: 1969-183 (1982).
32. Winneke, G., Kramer, G., Brockhaus, A., Ewers, U., Kujanaek, G., Lechner, H., and Janke, W., Neuropsychological studies in children with elevated tooth lead concentration. *Int. Arch. Occup. Environ. Health* 51: 231-252 (1983).
33. Shapiro, I. M., and Marecek, J. Dentine lead concentration as a predictor of neuropsychological functioning in inner-city children. *Biol. Trace Elem. Res.* 6: 69-78 (1974).

34. Lansdown, R., Yule, W., Urbanowitz, M. A., and Hunter, J. The relationship between blood-lead concentrations, intelligence, attainment and behavior in a school population: the second London study. *Int. Arch. Occup. Environ. Health* 57: 225-235 (1986).
35. Hawk, B. A., Schroeder, S. R., Robinson, G., Otto, D., Mushak, P., Kleinbaum, D., and Dawson, G. Relation of lead and social factors to IQ of low SES children. A partial replication. *Am. J. Mental Def.* 91: 178-183 (1986).
36. Schroeder, S. R., Hawk, B., Otto, D. A., Mushak, P., and Hicks, R. E. Separating the effects of lead and social factors on IQ. *Environ. Res.* 91: 178-183 (1985).