

## Exposure Assessment: Lead Neurotoxicity

### Is the Center for Disease Control's goal to reduce lead below 10 µg/dl blood in all children younger than 72 months by 2010, good enough?

Thomas F. Schrager, Ph.D.

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Blood lead threshold levels have been decidedly downward over the past forty years. While it may be possible that the bottom has been reached or that new research might at some point reverse the trend--something that does happen with other chemicals, although rarely--recent evidence suggests that the direction of the trend for lead will continue. In part this is due to better data at lower concentrations of lead, simply showing or confirming what has been suggested for a long time by insufficient data. And in part this is due to an appreciation and ability to test much more subtle effects of lead toxicity.

The results of the jury verdict in Rhode Island that held paint manufacturers responsible for lead paint that remains in homes and the toxic consequences of this situation, come at a time of growing understanding of the more subtle toxic effects of lead in the neurological development of children; that is, that (much) lower blood lead (BPb) than previously shown or considered, can be toxic and over a wider range of adverse affects. The rapid change in which significantly lower lead toxicity and the stakes involved has been recognized is reflected in the speed of change in acceptable threshold levels. The 1990 decision by the U.S. Department of Health and Human Services to eliminate all BPb > 25 µg/dl in children 6 months through 5 years of age by 2000 (Healthy People 2000) was followed in 1991 by a reduction in that 25 µg/dl threshold of concern to 10 µg/dl by the Centers for Disease Control (CDC 1991). By the late 1990's a new, Healthy People 2010 goal was set to eliminate all BPb  $\geq$  10 µg/dl (Myer et al 2003; US Dept HHS 2000).

By implementing these different thresholds and goals, the proportion of children at-risk (BPb  $\geq$  10 µg/dl) has been reduced during the past thirty years from approximately 88 percent to 2.2 percent (NHANES 2000), an obviously very significant accomplishment in public health efforts to eliminate child lead poisoning. Nevertheless, CDC estimates that the 2.2 percent figure translates into more than four hundred thousand children with BPb  $\geq$  10 µg/dl (NHANES 2000), and is a nationwide average; inner city and/or low socioeconomic areas often have much higher proportions of children with BPb exceeding 10 µg/dl, typically 8-10 percent of children and in some areas as high as twenty percent. Lead poisoning clearly remains a major problem in these areas, the very places that can least afford further compromise of intellectual functioning, due to negative socioeconomic circumstances and lack of early childhood stimulation.

Also, associations between BPb and intellectual functioning are typically based on population averages; neuropsychological testing of individuals, especially those with borderline intellectual functioning, shows widely varying impacts from individual to individual of even a few-point decrement in IQ (Dietrich 1993). And a few point decrement in intellectual functioning, among hundreds of thousands of children with borderline intellectual functioning to start with, can produce enormous economic and social impacts (Fulton et al 1987).

#### A 'Safe' Threshold for Lead Toxicity?

Further extending this trend, additional data and new analysis of existing data support a growing scientific consensus that a threshold for lead neurotoxicity in fetuses and young children does not exist (WHO 1995; CDC 2003); CDC stated in a consensus report that 'a threshold for harmful effects of lead remains unknown' (Myer et al 2003). And following the release of the comprehensive 'Third National Report on Exposure to Chemicals in Humans' (CDC 2005), Jim Pirkle, deputy director of CDC's Environmental Health Lab, stated unequivocally that a safe blood lead level in children simply does not exist.

The progressive reduction over time in the toxic threshold of lead ( a similar trend seen with most other chemicals) results from accumulation of data, improved understanding of target tissue injury, and more sophisticated tools and methodology to measure adverse toxic effects. The 'safe' threshold for lead has been revised downward six-fold during the past thirty years, from 60 µg/dl prior to 1971, 40 µg/dl until 1978, 30 µg/dl until 1985, and 25 µg/dl from

1985 until 1991 when the threshold was changed to the present < 10 µg/dl level (CDC 1975; CDC 1985; CDC 1991). Each reduction in threshold leads to greater focus on BPb toxicity at lower levels and, with that, more accumulated data at those lower levels, allowing verification of a reduced toxicity threshold.

Increasingly, the 10 µg/dl 'threshold' for lead is seen to reflect a 'threshold' of reliable data rather than a threshold of toxicity; that is, until recently insufficient data existed to verify lower toxicity, rather than sufficient data showing no toxicity at lower levels. This distinction is often the case and just as often is not made clear, leading to misinterpretation of data and toxicity. One resultant problem has been insufficient monitoring of children from infancy through five years of age or more—generally believed the critical window of significant and lasting neurological damage—so it has been difficult to know whether observed neurological effects at sub-10 µg/dl BPb concentrations actually reflected toxicity at those levels or simply reflected missed monitoring of periodic spikes of BPb above 10 µg/dl during the critical exposure period.

Lanphear et al (2005) conducted a pooled analysis of 1333 children from seven studies, which produced sufficient numbers of children whose BPb had been closely monitored during the critical early childhood period and whose BPb had not exceeded certain levels at any time. The Lanphear study found two such groups: those whose BPb did not exceed 10 µg/dl and those that did not exceed 7.5 µg/dl, allowing these two distinct BPb groups to be compared with those with BPb ranging from 10 µg/dl to 30 µg/dl from shortly after birth to five years of age. IQ was also measured during this time period. They found that increases of BPb from 2.4 to 10 µg/dl caused a much greater decrement in IQ score than increases in BPb from 10 to 20 µg/dl, or from 20 to 30 µg/dl. These results confirmed an earlier study by Canfield et al (2003), that tracked BPb from infancy through five years of age, with more than half having BPb that never reached or exceeded 10 µg/dl. Canfield found that BPb increases from 1 µg/dl to 10 µg/dl resulted in a decrement of 7.4 IQ points, compared to decrements of 4.6 IQ points for each additional 10 µg/dl increase in BPb above 10 µg/dl. A steeper dose response curve of BPb below, as opposed to above, 10 µg/dl, was also demonstrated in a study by Schwartz (1994).

A reanalysis of a Boston cohort by Bellinger and Needleman (2003), prompted by the Canfield results, found 48 children whose BPb had been closely monitored in early childhood and had never reached or exceeded 10 µg/dl, and they too found a steeper drop in IQ versus increases in BPb below 10 µg/dl, as compared to increases above that level. The Bellinger and Needleman reanalysis was also important because this cohort included many middle and upper middle income students. One of the questions about the steeper sub 10 µg/dl dose-adverse effect curves was whether the (detrimental) influence of other confounding factors, such as maternal IQ, stimulation of the home environment in early childhood or absence of other early educational opportunities, simply became more pronounced and apparent as the affects of very low BPb levels were reduced. Assuming such effect was solely due to BPb would create a seemingly disproportionate toxic effect of lead on IQ at those (very low) levels. The Bellinger and Needleman study, as well as other similar sub-10 µg/dl studies, suggests that these confounders were not the cause for the steeper dose response curve.

Rothenberg and Rothenberg (2005) extended these findings by applying a log linear model to these dose response relationships, rather than the usual linear model and found the log linear model fit the data better. The linear model emphasizes an absolute effect of BPb dose on toxicity, whereas a log linear model emphasizes a proportionate effect. For example, a linear model predicts that a 10 µg/dl increase in BPb (from 10 µg/dl to 20 µg/dl) exerts twice the toxicity as would a 5 µg/dl increase (from 5 µg/dl to 10 µg/dl), whereas the log linear model would predict a more proportionate increase in toxicity in each case.

The actual dose response curves fit the latter model much better than the former, and this has a number of implications. Such model not only predicts that a significant portion of low level lead toxicity occurs below 10 µg/dl, as reflected in the above studies, rather than above 10 µg/dl, but that the economic costs associated with intellectual, behavioral and other neurological deficits are more than twice previously calculated (Canfield 2003).

Lead neurotoxicity in young children affects not only intellectual development but other behavioral and social parameters, which can also greatly impact one's success in life and the social costs of managing these problems.

Needleman (2002) showed that bone lead (the lead reservoir) in young males was correlated with increased criminal behavior, anti social attitudes and other forms of juvenile delinquency. Dietrich et al (2001) showed similar effects on juvenile delinquency.

A study by Nevin (2000) shows a correlation between use of lead-based paint, as well as leaded gasoline, and both unwed pregnancy and criminality, including murder, as far back as the early 1900's. This study also showed a steeper dose relationship between BPb below 10 µg/dl and IQ deficits, compared to above 10 µg/dl, and showed a correlation between IQ deficits and social/behavioral problems, suggesting a significant effect of lead on social behavior at very low BPb.

Whereas lead toxicity is expressed and observed early, at the time of exposure, in causing apparently irreversible decrements in intellectual and social functioning, experiments by Basha et al (2005) (suggest latent neurotoxic effect from early, transient lead exposure. Rats dosed with lead during the first twenty days of life exhibited elevated BPb, characteristic of lead poisoning, which subsequently returned to normal post dosing. During the dosing period, APP mRNA also showed increased activity during the neonatal period of increased BPb, which also returned to normal. But in old age APP mRNA again became active, accompanied by excessive amounts of APP (B-amyloid precursor protein), the protein from which B-amyloid deposits are derived in the brain. These deposits are characteristics of brains in Alzheimer's patients. In older rats not dosed in early life but dosed for two months in old age, no such increase in APP m-RNA, APP or B-amyloid was found, suggesting that early lead exposure can not only produce permanent tissue damage with significant life long effects, but program alterations in gene expression which can cause significant effects later in life.

Beyond these neurotoxic effects lead is also implicated in cardiovascular disease, renal damage and dental caries. Taken together, these early, life long adverse effects of lead exposure, at likely very low levels, underlines the importance and implications of the Rhode Island jury verdict and repercussions it may have on communities throughout the country. Although the latest data remains to be verified, the trend is clearly in one direction and the consequences, both on the individual and on society are so great, that erring on the side of prevention seems the prudent course.

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