Unraveling the Chronic Toxicity of Lead: An Essential Priority for Environmental Health

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Although population exposure to lead has declined, chronic lead toxicity remains a major public health problem in the United States affecting millions of children and adults. Important gaps exist in knowledge of the pathophysiology of chronic lead intoxication. These gaps have impeded development of control strategies. To close current gaps in knowledge of chronic lead toxicity, we propose an integrated, multidisciplinary, marker-based research program. This program combines *a*) direct measurement of individual lead burden by ^{109}Cd X-ray fluorescence analysis of lead in bone, *b*) determination of ALA-D phenotype, an index of individual susceptibility to lead, and *c*) assessments of subclinical injury produced by lead in the kidneys, nervous system and, reproductive organs. Data from this research will provide answers to questions of great public health importance: *a*) Are current environmental and occupational standards adequate to prevent chronic lead intoxication? *b*) Is lead mobilized from the skeleton during pregnancy or lactation to cause fetal toxicity? *c*) Is lead mobilized from bone during menopause to cause neurotoxicity? *d*) What is the significance of genetic variation in determining susceptibility to lead? *e*) What is the contribution of lead to hypertension, renal disease, chronic neurodegenerative disease or declining sperm counts? *f*) Is chelation therapy effective in reducing body lead burden in persons with chronic overexposure to lead? — Environ Health Perspect 104(Suppl 1):141–146 (1996)

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Introduction

Chronic lead toxicity is a major public health problem in the United States (*1–3*). Although population blood lead levels have declined (*4*), chronic lower level exposure to lead remains widespread. Approximately 2 million preschool children are estimated to have blood lead levels above the federal guideline of 10 μg/dl, and 200,000 have levels above 25 μg/dl (*2*). More than 1.4 million adult workers have potential occupational lead exposure (*5*), and thousands have documented elevations in blood lead levels (*6–9*).

Lead is understood today to cause adverse effects at levels of exposure that produce no clinically detectable symptoms and that only a few years ago were thought to be safe (*1*). This recognition of subclinical toxicity first arose from studies in young children showing that chronic asymptomatic exposure to lead could cause irreversible injury to the nervous system (*10–14*). The underlying premise is that there exists a dose-related continuum of toxicity, in which the clinically apparent effects of lead, many of which have been known for millennia (*15*), have their asymptomatic subclinical analogs (*16*).

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Abbreviations used: KXRF, K shell x-ray fluorescence, ALAD, δ-aminolevulinic acid dehydratase; PCR, polymerase chain reaction; BUN, blood urea nitrogen; NAG, *N*-acetyl-β-glucosa-minidase; GGT, γ-glutamyltransferase; LDH, lactate dehydrogenase; β-2MG, β-2-microglobulin; RBP, retinol binding protein.

What Are the Gaps in Knowledge of Chronic Lead Toxicity?

Serious gaps exist in knowledge of the chronic, subclinical toxicity of lead and dose–response relationships are still largely uncertain. Little information is available on whether there exist threshold levels below which no toxic effects can be detected. The contribution of stored lead to lead toxicity remains primarily the subject of case report and conjecture. Specific gaps in knowledge include the following (*17–21*):

- What is the threat to human health of lead stored in bone? Under what circumstances is this lead released, and how much is released?
- Is lead mobilized from bone during pregnancy a threat to mother or baby? Can it cause fetal neurotoxicity *in utero*? Should certain high-risk women be evaluated for body lead burden prior to becoming pregnant? If their levels are high, should they be chelated? Is chelation effective in reducing body lead burdens in women with chronic overexposure? Is such lead a legacy of environmental injustice?
- Is lead mobilized from bone during menopause to cause adverse effects on the health of women, including neuropsychological dysfunction? How can this mobilization be prevented?
- What is the relationship between male reproductive impairment and chronic exposure to lead? Male reproductive impairment with reduction of sperm count has been observed in men heavily exposed to lead but has not been systematically studied in men with more modest exposures using more recently developed technologies for assessing reproductive dysfunction (*19,20*). It is not known whether the male reproductive impairment caused by lead is due to direct testicular toxicity or is mediated through neuroendocrine disruption (*16*). Also it is not known whether lead has played a role in the decline in sperm counts observed among men in industrialized nations.
- What is the contribution of lead to chronic neuropsychological dysfunction in adults (*18*)? What is the possible contribution of lead to chronic neurological degenerative diseases, such as dementias and movement disorders?

- What is the relationship between lead dose (both acute and chronic) and renal dysfunction? Does a threshold exist for this damage? What is the earliest damage that occurs, and at what level of exposure does it occur? Are currently available biological markers adequate for tracing such damage (*17*)?
- What is the relationship between lead and hypertension? Is there a threshold? Is it a renal or a vascular phenomenon, and are there differences in susceptibility between racial groups? Does lead, perhaps lead mobilized from skeletal stores, constitute a potentially preventable cause of pregnancy-induced hypertension? What is the contribution of lead to patterns of hypertension in the United States?
- What is the significance to lead toxicity of genetically determined polymorphism in enzymes susceptible to inhibition by lead (*21*)?
- Are current occupational and environmental standards sufficiently stringent to protect against lead toxicity?

What Obstacles Have Impeded Research on Chronic Lead Toxicity?

The fundamental impediment to the study of chronic lead toxicity has been a lack, until relatively recently, of well-validated biologic markers (*22*), specifically *a*) the absence of a reliable biologic indicator of cumulative lead dose or body lead burden; *b*) the absence of biologic markers of individual genetic susceptibility; and *c*) the availability of only a limited array of well-validated biologic markers of subclinical toxicity.

A Research Strategy to Understand the Chronic Toxicity of Lead

The central thesis of this review is that critical public health questions concerning the chronic toxicity of lead can be answered and the above obstacles overcome, through systematic application in clinical and epidemiologic studies of an integrated, marker-based strategy. We argue that support for such a strategy continue to be a high priority for research in environmental health in the United States because of the continuing wide extent of the problem of lead toxicity. The principal elements of the strategy are

- Assessment of cumulative lead absorption and lead mobilization through measurement of body lead burden using ^{109}Cd-based K shell X-ray fluorescence (KXRF) analysis of lead in bone (*23*);
- Evaluation of the molecular genetic basis of individual variation in susceptibility to lead through examination of genetic polymorphism in the enzyme δ-aminolevulinic acid dehydratase (ALAD) (*21*).
- Detection of subclinical toxic effects on kidney function and hypertension through application of biochemical indices of renal function and vascular reactivity (*17*);
- Assessment of subclinical toxic effects on the central and peripheral nervous system by application of validated test instruments, including computerized and manual assessment batteries, standardized nerve conduction velocity measurements, measurements of evoked potentials, assessment of postural stability, and assessments of autonomic function.
- Assessment of reproductive effects by application of newly developed parameters for assessing sperm function and endocrine status.

The strength of this strategy is in its simultaneous use of three classes of biologic markers: exposure, toxic outcome, and susceptibility (*22*).

Measurement of the Body Burden of Lead

The cornerstone of the strategy proposed here is the direct, noninvasive measurement of the body lead burden through measurement of lead in bone (*23*).

The lead body burden represents the difference between cumulative lifetime absorption of lead from all sources and total excretion (*24*). Lead is not distributed homogeneously in the human body. Experimental studies have shown instead that it is dispersed among several physiologically distinct compartments that differ from one another in size and accessibility (*25*). These compartments and their interrelations can be portrayed by metabolic models that describe the absorption, distribution, deposition, accumulation, and excretion of lead both qualitatively and quantitatively. Such models have been proposed by several authors, for example, by Marcus et al. (*26–28*), O'Flaherty (*29*), and Leggett (*30*). A reasonable portrayal of the functional anatomy of the body lead burden is provided by the model of Rabinowitz and coworkers (*31*). This model is based on stable isotope and metabolic balance studies. It proposes that the lead burden be described in terms of three dynamically interrelated compartments.

Lead in Blood. Lead in blood comprises about 1% of the body lead burden in the Rabinowitz model (*31*). Because it is conveniently accessible and is the fraction of the body burden that correlates most closely with recent environmental exposures, it is the component measured most frequently. A large percentage of the lead in blood is found in the erythrocytes. The half-life of lead in blood is 36 ± 5 days.

Soft Tissue Lead. Compartment 2 in the Rabinowitz model is composed principally of soft tissue lead (*31*). The contact between lead and soft tissues such as the kidneys and nervous system is responsible for most of lead's toxicity.

Skeletal Lead. Lead in the skeleton is the largest component of the body burden (*24*). This compartment contains about 95% of all lead in the human body in adults, and approximately 70% in children. Quantitative estimates of the biological half-life of lead in bone vary. Data suggest that the half-life may depends on bone type (i.e., cortical or trabecular) or even bone-site; the turnover of lead in trabecular bone appears to be substantially more rapid than that in cortical bone. Most estimates give a half-life of lead in bone that is measured in years or even decades. It should be noted that these estimates have shown a tendency to increase as new data from ongoing longitudinal studies of retired lead workers have become available.

Direct analysis of lead in the skeleton by XRF overcomes a major limitation that plagued previous research on chronic lead toxicity, namely, the lack of a sensitive and specific biologic marker of cumulative lead exposure (*23*).

Three methods have been developed to measure lead in bone *in vivo* (*32*). The method using ^{109}Cd-based fluorescence of the K shell X-rays of lead has been applied most widely because of its intrinsic methodological advantages, including a high degree of measurement accuracy that is robust against movement by the subject and independent of overlying tissue thickness (*33–37*).

Bone lead measurements complement, but do not replace, blood and plasma lead determinations. Most epidemiologic studies of populations chronically exposed to lead use bone and blood lead measurements in combination to assess past plus current exposure.

δ-Aminolevulinic Acid Dehydratase: A Marker of Susceptibility to Lead

Substantial interest surrounds the hypothesis that there exists a genetic basis for observed interindividual differences in susceptibility to lead (*21*). The hypothesis that genetic polymorphism in the home biosynthetic enzyme ALAD accounts, at least in part, for this variability has been generated by researchers at the Mount Sinai Medical Center (*38*).

Human ALAD has been shown by Petrucci and coworkers (*39*) to be a polymorphic enzyme with two common alleles, $ALAD^1$ and $ALAD^2$. This results in an enzyme system with three distinct isozyme phenotypes, designated ALAD 1-1, ALAD 1-2 and ALAD 2-2. These isozymes separate by starch gel electrophoresis. In an Italian population, the frequencies of the phenotypes were 1-1 (81%), 1-2 (17%) and 2-2 (2%), consistent with gene frequencies of 0.90 and 0.10 for the $ALAD^1$ and $ALAD^2$ alleles, respectively. Similar results were obtained in other European populations, whereas existence of the $ALAD^2$ allele was not observed in a large sample of Africans from Liberia (*40*).

The existence of this common polymorphism, coupled with the fact that ALAD is markedly inhibited by lead, suggests that there could be a physiologic relationship between the frequency of the $ALAD^2$ allele and lead poisoning. It was hypothesized that individuals with the $ALAD^2$ allele would be more susceptible to the detrimental effects of lead exposure if the $ALAD^2$ subunit bound lead more tightly than the $ALAD^1$ subunit (*38*).

To test this hypothesis, ALAD isozyme types were determined at the Mount Sinai Medical Center in 1277 blood samples obtained from the New York City blood lead screening program (*38*). The blood lead level and ALAD isozyme determinations were performed in double-blind fashion. The major finding was that the population homozygous or heterozygous for $ALAD^2$ had significantly higher mean blood lead levels than those homozygous for $ALAD^1$. These data support the hypothesis of a relation between the $ALAD^2$ allele and the accumulation of lead in blood. Similar data in other populations support an identical conclusion (*41,42*).

Determination of ALAD genotype can be accomplished accurately and inexpensively using a PCR method developed by Wetmur et al. (*43*). Population studies incorporating the ALAD biomarker have found significant correlations between ALAD phenotype, blood lead levels, and bone lead levels (*44*).

In the future, to understand further the chronic toxicity of lead, additional integrated marker-based studies will be needed that combine determination of ALAD phenotype with measures of lead body burden and subclinical toxic outcomes. Anemia, including anemia due to G6PD deficiency (*45*), has long been known to increase susceptibility to lead intoxication. Although the ALAD studies have been controlled for anemia, simultaneous analysis of ALAD and G6PD polymorphisms might be informative. In addition, studies should be undertaken to identify other polymorphic markers for increased lead susceptibility, such as the newly described erythrocyte metallothionein lead-binding protein (*46*).

Biochemical and Physiologic Markers to Assess Subclinical Lead Toxicity

Renal Toxicity

Chronic nephropathy, which may progress to kidney failure, is the classic manifestation of lead toxicity in the kidneys (*17,47,48*). It appears to result from long-term, relatively high-dose exposure to lead, but dose–response relationships have not been well defined.

The evolution of lead nephropathy is usually silent. The central event appears to be the progressive destruction of tubular cells by lead and their replacement with fibrosis (*17*). Clinical manifestations of impairment, such as elevations in blood urea nitrogen (BUN) or serum creatinine, do not ordinarily become evident until 50 to 75% of the nephrons have been destroyed (*49*).

The most important research need in the study of lead nephropathy is a reliable early biologic indicator of the kidney damage induced by lead (*49*). Such a marker would permit better assessment of dose–response relationships in epidemiologic studies and might permit early identification of and intervention against evolving lead nephropathy (*50*).

Promising biomarkers of lead nephrotoxicity include the following assays of glomerular and tubular function:

- Glomerular Function. Isolated urinary excretion of high-molecular weight proteins, such as albumin, appears to be a reliable biologic marker of early glomerular dysfunction (*51*). Measurement of creatinine clearance remains, however, the "gold standard" for noninvasive assessment of glomerular function. Despite its relative difficulty of accomplishment, careful consideration should be given to its inclusion in longitudinal epidemiologic studies of progressive renal dysfunction in populations exposed to lead.
- Tubular Function. Lead-induced dysfunction of the proximal renal tubules is best assessed by measuring urinary excretion of a battery of low-molecular weight proteins (*52*). Suggested candidates include: *N*-acetyl-β-glucosaminidase (NAG), γ-glutamyltransferase (GGT), lactate dehydrogenase (LDH), β-2-microglobulin (β-2MG), and retinol binding protein (RBP).

A recent epidemiologic study of a population with occupational exposure to lead suggests that increased excretion of NAG may be especially sensitive to recent increases in the body lead burden, though not so much as to cumulative lead dose (*53*).

Additional prospective epidemiologic studies are needed that combine molecular markers of nephrotoxicity with markers of lead body burden and ALAD genotype. Only through longitudinal follow-up of exposed populations through such studies will the evolution of lead nephropathy be traced and its relation to body lead burden assessed. Also, it is only through such studies that the predictive validity of biomarkers of early renal impairment will be confirmed.

Male Reproductive Toxicity of Lead

Clinical and epidemiologic studies are needed to assess the possible chronic toxicity of lead to male fertility at lower levels of exposure using state-of-the-art biologic markers of sperm function, such as assays of cervical mucus penetration and hamster ovum penetration. These investigations need to correlate results with lead body burden as well as with ALAD phenotype. Also, need exists to determine through hormonal assays whether the male reproductive toxicity of lead is mediated solely by direct toxic effects on the testes, or whether there are also toxic effects on neuroendocrine function.

Studies are needed to assess the contribution of chronic lead intoxication to declining sperm counts. Perhaps to begin this assessment, secular trends in sperm count could be compared to trends in lead exposure. Also international comparison studies might be undertaken.

Neurologic Toxicity

Recent studies of peripheral neurotoxicity in asymptomatic adults exposed to lead have used electrophysiologic probes to determine whether lower level exposures cause covert abnormalities in function. With the development of increasingly sensitive methodologies and the incorporation of these methodologies into longitudinal studies, it has become possible to detect toxicity at progressively lower lead levels (*54*). Thus, in a prospective study of new entrants to the lead industry, slowing of ulnar nerve conduction velocity was reported at blood lead levels as low as 30 to 40 μg/dl (*55*).

In the central nervous system, the critical research question is whether lead causes asymptomatic impairment in function at doses insufficient to produce clinical encephalopathy (*10–14*). While extensive research into the subclinical neurobehavioral toxicity of lead has been undertaken in children (*10–14*), there is a striking lack of studies of chronic lead neurotoxicity in adults (*18*). In one of the earliest available investigations, a correlation was observed between lead exposure and diminished neuropsychologic performance in a group of asymptomatic workers, all of whom had blood lead levels below 70 μg/dl (*55*). The functions most severely impaired were those dependent on visual intelligence and visual–motor coordination. Also an increased prevalence of fatigue and short-term memory loss was seen in smelter workers exposed to lead; the prevalence of these abnormalities increased with blood lead levels (*56*).

Further clinical and epidemiologic studies that use sophisticated markers of neurotoxicity in combination with measures of lead body burden and ALAD genotype will be required to establish the nature and strength of the relationship in adults between chronic exposure to lead and decrements in central neurologic function.

Instruments that could be included in such assessments will include both computer-administered and manually administered neuropsychological tests that assess a range of functional domains including memory, cognition, psychomotor abilities, attention, executive functioning, and mood. Many of these functions are covered by the Neurobehavioral Evaluation System (NES) developed by Letz et al. (*57*). Central neurologic function may also be assessed through measurement of somatosensory evoked potentials, visual evoked potentials, and brain stem auditory evoked potentials. Peripheral neurologic function can be assessed by *a*) nerve conduction velocity assessment, including assessment of the distribution of conduction velocities; *b*) hand strength dynanometry; and *c*) quantitative grip testing. Of these modalities, assessment of nerve conduction velocity is the traditional benchmark (Araki et al., unpublished data).

Autonomic neurologic dysfunction in persons chronically exposed to lead may be assessed using neurophysiological assays developed by Araki et al., such as assessment of R-R interval variability (*58*). Computerized assessment of balance and postural sway, as pioneered by Battacharya et al., provides an integrated measure of the peripheral and central neurotoxicity of lead (*59*).

Evaluation of the possible contribution of chronic lead intoxication to the etiology of chronic neurodegenerative disease will require case–control epidemiologic studies of patients with such illnesses as Parkinson's disease, dementia, and amyotrophic lateral sclerosis. These studies will need to incorporate direct measurement of bone lead by XRF as well as assessment of ALAD phenotype. The hypothesis that some fraction of these diseases is caused by environmental toxins, possibly including lead, needs to be tested (*60*).

Is Lead Mobilized from Bone a Source of Toxicity?

Lead can hypothetically be mobilized from the skeleton under any circumstance that increases bone mineral turnover. Potential examples include pregnancy, lactation, menopause, and hypermetabolic states including Paget's disease of bone and thyrotoxicosis (*61,62*). Mobilization of lead from bone has been observed after retirement among persons with many years of occupational exposure to lead (*63*).

Assessment of lead mobilization in an integrated marker-based research program requires serial measurement of bone lead concentration by XRF coupled with measurement of bone densitometry; the measurement of bone density provides an indication of total bone mass. The product of mineral density and bone lead concentration gives an index of the total amount of lead in bone. Determination of this index at various points in time in persons at risk of lead mobilization could provide a quantitative index of the extent of mobilization.

One population thought to be at particularly high risk of lead mobilization during pregnancy and lactation is young women in inner-city areas of the United States who may have had heavy exposure to lead during their childhood. Typically, the blood lead levels of these young women are normal when they reach reproductive age. Concern exists, however, that some of these women may have elevated concentrations of lead in bone that place them at risk of lead mobilization during pregnancy and lactation.

Another population at potential risk of lead mobilization during pregnancy and lactation consists of young women who lived during childhood in the vicinity of lead-emitting industrial facilities such as smelters. Previous studies have documented high levels of lead exposure among children living in such areas (*64*).

Lead mobilization during pregnancy is potentially very hazardous to the fetus. Lead passes across the placenta almost without hindrance. Blood lead levels in mother and fetus are usually identical.

In women undergoing menopause, concern exists that mobilization of lead from bone during bone demineralization may contribute to neuropsychological dysfunction (*61*). Assessment of this hypothesis may be undertaken through serial determination of lead in bone plus bone densitometry coupled with assessment of neuropsychological function in women before, during and after menopause.

Conclusion

Chronic lead toxicity is a major health problem in modern society, but is also a potentially preventable problem.

Lead exposure and toxicity today reflect the continuing use of lead in industry combined with the legacy of careless use in the past. Although lead consumption is less today than previously, approximately 400,000 metric tonnes of lead are still used each year in the United States (*66*) and this lead appears in a wide array of consumer products including batteries, solder, pipes, ammunition, roofing, and X-ray shielding (*1*). It may reliably be predicted that lead exposure and lead toxicity will continue to be problems for years to come. The American epidemic of lead toxicity is not yet over (*67*).

The integrated marker-based research program proposed here offers a feasible approach for understanding and controlling the current phase of the continuing epidemic of chronic lead toxicity (*65*). Information derived from a program such as this will provide good data for good public health decisions (*68*).

We suggest that because of the wide extent of the problem of lead exposure in American society, support for research into the chronic toxicity of lead should continue to represent a major priority in environmental public health. Even today there is much that we do not know about the toxicity of lead, and these gaps in knowledge are impeding our ability to control lead toxicity. We anticipate that the results of research into the chronic toxicity of lead will have substantial benefits for public health in the United States and the world, and that they will make an important contribution to the prevention of chronic lead toxicity.

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