

# Blood lead in the 21st Century: The sub-microgram challenge

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**Abstract:** In the US the dominant sources of lead through much of the 20th Century (eg, vehicular emissions, plumbing, household paint) have been significantly diminished. The reductions in adult and pediatric average blood lead levels in the US have been extraordinary. Progress continues: the US Environmental Protection Agency recently developed a new air standard for lead. In the 21st Century, the average blood lead level in a society may be seen as a marker of the status of their public's health. However, the threat of lead exposure remains a significant public health problem among subpopulation groups in the US and in many less developed countries. This paper examines some of the specific issues involved in the reduction of blood lead in a post-industrial era. These involve the control of the remaining exogenous primary sources, both general (eg, industrial emissions) and specific (eg, at-risk occupations), exogenous secondary sources (eg, contaminated urban soils, legacy lead-based paints), an endogenous source (ie, cumulative body lead burden) and emergent sources.

**Keywords:** environmental contaminants, public health, environmental policy, blood lead

## Introduction

The average level of lead (Pb) in blood may be seen by society as evidence of its commitment to its own health. Thus the concentration of a particular metal in our collective blood informs the condition of our society.

We present in Table 1 a chronology of the progression of human blood lead level (BLL) through time. Different societies have entered the stages at different points in time. The traditional industrial powerhouses (eg, the US, Europe, Japan) are in late Stage 3 and early Stage 4. Such emerging economies as China appear to be in Stages 2 and 3. Even within a society, some lead-related activities may not be indicative of a society's Stage. Likewise the BLL of sectors of a society, because of socioeconomic status or racial issues, may reflect a different Stage than that of the society as a whole.

In this paper, we examine some of the specific issues involved in the transition from a late industrial to a post-industrial society in the US. These issues include exogenous primary sources, both general (eg, fuel burning) and specific (eg, at-risk occupations); exogenous secondary sources (eg, contaminated urban soils, legacy lead-based paints), an endogenous source, or the bone-lead burden remaining from Stage 3, and emergent sources related to global trade and pollution from Stage 2 societies.

## Hematologic considerations

The major hematologic effect of lead is iron-deficient microcytic, hypochromic anemia. Anemia is among the most common signs of lead toxicity observed in children.

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**Table 1** Stages in the succession of societal blood lead level

Stage condition	Time frame	Typical BLL	Health effects
Stage 1 Primitive	to ~500 BCE	<<1 µg/dL, world	none
Low population. Extraction of metals from ores on a small scale late in this stage			
Stage 2 Industrial	500 BCE–1970s	>10 µg/dL, US.	acute and chronic
Extraction of silver from galena (PbS) by Greeks and Romans marks first large-scale release of Pb to the environment. Increasing releases from industrial revolution (1750 onward), culminating in 20th Century with leaded gasoline and lead-based paints.			
Stage 3 Late-Industrial	1970s–2000	1–5 µg/dL, US.	developmental
Clean Air Act, phase-out of leaded gasoline, actions on lead-based paint, pipes, and solder. Dramatic drop in US BLL.			
Stage 4 Post-Industrial	2000–	<1 µg/dL possible goal	none?
Remediation or sequestration of secondary sources in soil, old building paints, plumbing. Increased control over remaining primary sources, eg, piston aviation fuel, incineration, and coal and gasoline combustion, and substitution for Pb in industrial products, eg, batteries, plasticizers.			

**Notes:** Data from: Settle and Patterson<sup>1</sup>; National Research Council<sup>2</sup>; Davidson and Rabinowitz<sup>3</sup>; Needleman<sup>4</sup>; Warren<sup>5</sup>; Reuer and Weiss.<sup>6</sup>

Lead inhibits the production of protophobilinogen synthase by the precursor  $\delta$ -aminolevulinic acid dehydratase (ALAD). The ALAD enzyme is a zinc-dependent protein that catalyzes heme synthesis to form monopyrrole protophobilinogen, a precursor of heme. The heme synthesis process ends with the insertion of positively charged iron ( $\text{Fe}^{2+}$ ) into negatively charged protoporphyrin. Lead interferes with the binding of iron and protoporphyrin, resulting in high circulating levels of zinc protoporphyrin (ZPP). Studies have focused on the bio-kinetics of lead and ALAD gene expression in an effort to identify genetic biomarkers of risk among children.

The ALAD gene is located in chromosome 9q34. Eight human ALAD gene variants have been described. One polymorphism yields two alleles, designated ALAD-1 and ALAD-2. ALAD-1 homozygotes produce the least electronegative enzyme; ALAD 1–2 heterozygotes produce an intermediate electronegative enzyme; ALAD-2 heterozygotes produce the most electronegative enzyme. This means that ALAD-2 proteins bind to positively charged lead ions more tightly than ALAD-1 homozygotes and heterozygotes.

Originally, it was hypothesized that carriers of the ALAD-2 allele who are exposed to lead carry that lead in the blood longer, and therefore are more likely to express acute manifestation after exposure.<sup>7</sup> However, others found that the mechanisms by which ALAD genotype may modify the compartmentalization and movement of lead are more complex.<sup>8–11</sup> Polymorphisms of the vitamin D receptor (VDR) gene have been studied for their contribution to the kinetics of lead.<sup>10</sup> VDR polymorphisms determine calcitriol hormone expression and bone mineral density (BMD). Dietary calcium and iron intake, alcohol use and smoking also affect BMD. Iron and calcium deficiencies are both associated with higher uptake of lead ions, especially in children. Ferritin, the iron transport

protein, binds as well to lead as it does to calcium. Children that are already iron-deficient and calcium-deficient have increased circulating ferritin proteins that can bind more lead ions. In addition, patients with hemochromatosis (a disease of iron overload) have been shown to have higher circulating lead levels.

## Health effects of lead exposure

### Children

Lead exposure is implicated in a broad clinical spectrum of disease, including hematological, renal, cardiovascular, neurological, developmental, and behavioral disorders. By the end of the 20th Century a strong body of scientific evidence showed that children's ability to learn, memorize, behave normally, and concentrate was adversely affected by chronic low-level lead exposure, or BLL  $\leq 10$  µg/dL.<sup>12–19</sup> Neurotoxic lead effects are particularly deleterious to developing central nervous systems in children.<sup>19–21</sup> CNS damage during the perinatal period from maternal lead body burden is also well documented.<sup>20</sup> Covariants such as phenotype,<sup>7–11</sup> nutritional status, and social, economic, and cultural factors may alleviate or exacerbate these effects.<sup>13,22–24</sup>

The Centers for Disease Control and Prevention (CDC) still defines the blood lead intervention threshold in children to be  $\geq 10$  µg/dL.<sup>25,26</sup> However, a 2007 report by the Agency for Toxic Substances and Disease Registry<sup>27</sup> summarized the large body of more recent evidence for adverse health effects at lower BLL thresholds. Even BLL as high as 5 µg/dL may adversely affect a child's cognitive development<sup>28–31</sup> and physical maturation.<sup>32</sup> The risk of adverse effects from lead exposure is also higher amongst population subgroups, including ethnic minorities, low-income groups and those clustered in geographic lead pools. Bernard and McGeehin's<sup>33</sup> analysis of data collected as part of the Third National Health and

Nutrition Examination Survey (NHANES-III) revealed that 23% and 15% of Mexican-American and non-Hispanic white children, respectively, displayed blood lead levels between 5 and 10  $\mu\text{g}/\text{dL}$ . Nearly one-third (32%) of non-Hispanic black children had blood lead levels within that range.

### Adults

The CDC threshold for intervention in adults is a blood lead level  $\geq 25 \mu\text{g}/\text{dL}$ . The vast majority of cases are related to occupational exposure.<sup>34</sup> A growing body of evidence now links lifetime cumulative lead exposure, as well as current exposure, to chronic health disorders seen in older adults. A systematic review by Navas-Acien et al found that hypertension is one of the most consistent cardiovascular outcomes seen among lead-exposed subjects. There is an estimated increase of 0.6 to 1.25 mmHg associated with every two fold increase in blood lead levels (ie, from 5 to 10  $\mu\text{g}/\text{dL}$ ). Experimental, mechanistic and prospective studies support this relationship. The associations with cardiovascular and coronary heart disease, peripheral artery disease and stroke are less clear.<sup>35</sup>

Tsaih et al reported on the relationship between lead, diabetes, hypertension and renal function in 448 subjects that had been selected from the Normative Aging Study (NAS), and in which bone and blood lead were measured at baseline and follow-up. Age, basal metabolic index, alcohol consumption, smoking status, diabetes, hypertension and baseline serum creatinine were measured. Bone lead level predicted diabetes, hypertension, and progression of kidney disease. The association between bone lead (particularly tibial bone lead) and renal disease was stronger among diabetic subjects.<sup>36</sup>

Unlike the direct causal relationship between acute lead exposure (up to 70–80  $\mu\text{g}/\text{dL}$ ) and nephrotoxicity, the relationship between low-level chronic exposure and renal outcomes from cumulative stores has been less well understood. Recent epidemiologic evidence supports relationships between lead exposure and renal dysfunction in adults.<sup>37,38</sup> Peters et al studied hypertension status in 513 participants recruited from the NAS. They found a positive interaction between stress and bone lead on systolic blood pressure, after adjusting for age, body mass index, family history of high blood pressure, education, smoking, alcohol consumption, physical activity and nutritional factors.<sup>39</sup>

## Sources of lead exposure: Banned but not gone

Lead is a soft, malleable metal that has proven both magnificent and devastating to human societies through

the ages. The oldest lead artifact dates from approximately 3000 BCE. Although lead is a naturally occurring heavy metal (at levels of approximately 15–20  $\mu\text{g}/\text{g}$  in Earth's crust and uncontaminated soils), the roots of human exposures are almost exclusively man-made. Use of lead in ancient civilizations is well documented, as is lead exposure in archeological finds of human remains. The element lead itself is, of course, essentially indestructible; its compounds are variably toxic, bioavailable, and biodegradable. Humans can absorb lead through the gastrointestinal tract, by inhalation, or, for certain compounds, by absorption through the skin.

A reasonable benchmark for the wealthy societies in Europe, the US and elsewhere might be to achieve a typical BLL of  $< 1 \mu\text{g}/\text{dL}$  in their populations. The Healthy People 2010 national public health objectives, to reduce to zero the prevalence of elevated BLL in children (BLL  $\geq 10 \mu\text{g}/\text{dL}$ ) and in adults (BLL  $\geq 25 \mu\text{g}/\text{dL}$ ), fall well short of the unspoiled historic benchmark. This demonstrates continued societal tolerance for low-level chronic lead exposure. A recent meta-analysis of children's IQ scores and their blood lead concentrations showed that each incremental 1  $\mu\text{g}/\text{dL}$  increase in blood lead concentration resulted in a one-point decrease in IQ score (in school-aged children).<sup>30</sup> One research team has called for lowering the blood lead action level in children from 10 to 2  $\mu\text{g}/\text{dL}$ .<sup>40</sup>

In the late industrial Stage 3, US regulatory statutes and public awareness have had great impact in reducing adult and childhood blood lead levels. However, by post industrial Stage 4 it is critical to address the heritage of accumulated lead. It is important to understand the changing face of exposure and risk by tracing the current pathways by which lead reservoirs are maintained and recycled.

## Exogenous primary sources of lead

The major primary contemporary sources of lead emission in the US include leaded aviation fuel for piston-driven engines, manufacturing, and metal operations. The emission route of greatest concern is through the air, which is naturally dispersive, pervasive, and, unlike an oil spill, impossible to remediate. The new US Environmental Protection Agency airborne lead standard of 0.15  $\mu\text{g}/\text{m}^3$  represents a 90% decrease from the 1978 standard of 1.5  $\mu\text{g}/\text{m}^3$ .<sup>41</sup> From a public health perspective, although no level of lead exposure is considered absolutely safe, primary airborne lead emissions no longer represent the major challenge in decreasing BLLs.

Despite this significant decrease in airborne lead levels, workers in the primary lead-impacted industries or activities (eg, recycling) remain at risk from lead exposure.

The families of such workers also may be at risk from lead transferred to the home or automobile from the workplace. Even as the US enters Stage 4, many of the workers responsible for this transition remain occupationally at-risk of lead exposure. Sources of occupational lead exposure include the mining and smelting industries, refineries, construction and remodeling, auto mechanics, plumbing, soldering and pottery-making. Occupationally acquired lead may be transported to the household setting in work clothes and shoes. Particulate emissions from industries, such as local smelters or demolition, remain as sources of human lead exposure.<sup>42–45</sup>

Other primary sources in Stage 3 include lead plumbing pipes and solder; lead-based paints; lead solder in the food industry (eg, cans); and lead in a variety of consumer products, such as cosmetics, pharmaceuticals, crayons, inks, etc. Most of these sources are closely regulated, or eliminated by industry consent. Nonetheless, legacy issues remain (paint, plumbing) to produce secondary sources, and misuse of lead in consumer products re-emerges with global trade.

Of special pediatric interest are such lead-containing products as glazed pottery,<sup>46</sup> imported candy,<sup>47</sup> and culture-bound traditional remedies for illness.<sup>48</sup> Lead used in products targeting children, including candy and toys, pose particular threats to children's health. Despite a 2007 joint agreement between the US Consumer Product Safety Commission and China's consumer regulatory agency to ban lead paint on products destined for the US, products tainted with lead continue to pose a health hazard for children worldwide.

## Exogenous secondary sources of lead

The major pervasive 20th Century sources of environmental lead in the US were leaded gasoline, lead-based paint and lead plumbing materials. These materials remain as secondary sources, and their removal or sequestration are a major target of societies intent on reaching Stage 4.

### Lead-based paint

Lead-based house paint was widely used in the US in the first half of the 20th Century. Basic lead carbonate ("Dutch process") and other lead salts were present at levels of "tens of percent".<sup>49,50</sup> With growing concerns about children's health in the 1970's,<sup>51,52</sup> lead was finally banned from household paint in the US.<sup>53,54</sup> The Residential Lead-Based Paint Hazard Reduction Act of 1992,<sup>55</sup> also known as Title X, was enacted to protect families from exposure to lead from paint, dust, and soil, in recognition of the need for strategies to address the legacy of lead-based paint in older homes. Section 1018

of this law directed the US Department of Housing and Urban Development (HUD) and the US Environmental Protection Agency (EPA) to require the disclosure of known information on lead-based paint and lead-based paint hazards before the sale or lease of most housing built before 1978. A 1998–2000 national survey estimated that about 38 million homes contain lead-based paint.<sup>56</sup> Lead particles readily settle in household dust and can be a toxic source.<sup>57,58</sup>

Residual lead-based paint presents numerous challenges in Stage 4. Older urban housing with lead-based paint typically faces one of several fates. *Degradation* occurs when the house or neighborhood value relegates the building to a substandard, low-rent condition. Under such circumstances, lead-based paint will be mobilized due to lack of upkeep, ie, sequestration by painting over. *Renovation* can lead to mobilization unless proper care is taken during the project. *Demolition* typically leads to mobilization and dispersal. *Paint removal/remediation* is expensive, and, if not performed by professionals, also dispersive.

### Lead in urban soil

The addition of tetra-ethyl lead to gasoline as an anti-knock agent began in the 1920's and resulted in massive roadside and airborne emission of a variety of reactive lead-halogen compounds. These dispersed into and reacted with urban soils. Lead additives in gasoline were gradually phased out in the US over a 24-year period ending in 1996.<sup>59</sup> The first EPA reduction standard was published in 1973.<sup>53</sup> By 1975 most cars and light trucks were manufactured with catalytic converters that required lead-free fuel. Lead-containing fuel continues to be sold for piston aircraft, and classic and racing cars.

Our group used synchrotron-based X-ray absorption fine structure (XAFS) to identify and quantify the major Pb species in numerous soils and air samples in El Paso, TX.<sup>60</sup> Lead humate, and perhaps some similar sorbed forms of lead, is the dominant form of lead in contemporary El Paso soil and air. Lead humate is a stable, sorbed complex produced exclusively in the humus fraction of Pb-contaminated soils. Legacy lead from automobile exhaust, lead-based paint, and industry have reacted over time to yield lead-humate. This material is re-suspended into the local air, and enters houses where it may be available for accidental ingestion by toddlers. We found that the form of lead present in household dust wipes was similar to that found in soil lead, with some contribution from lead paint.<sup>61,62</sup>

Although humates are biologically active, the relative bioavailability of lead sorbed on soil is thought to be lower compared to other forms of lead. Casteel et al found that



the bioavailability of lead in soil and soil-like materials varied between 6% and 105%. Although soil chemistry is important in determination of bioavailability, speciation data are not yet adequate to predict bioavailability of lead in soil.<sup>63</sup>

### Lead plumbing

Lead contamination of water distribution systems includes lead pipes, lead solder on copper pipes, and plumbing fixtures.<sup>64</sup> Legislation has eliminated the installation of such pipes and solder; brass fixtures containing lead are no longer used in kitchens. Nonetheless, many such installations remain in service and drinking water is still a potential or actual source of ingested lead. Scaling formed on the inner surfaces of lead pipes and solder often prevents leaching of lead, a phenomenon similar to the painting over of lead-based paints. But the pH and chemistry of the water can result in lead leaching at unhealthy levels.

The removal of lead from municipal water distribution systems, the upgrading of plumbing in older houses, and the inexorable attrition of older housing through demolition are gradually decreasing the actual and potential transfer of lead to drinking water. Hastening this process should be a component of a society's Stage 4 lead strategy.

### Endogenous lead source – body lead burden

Lead exposure in industrialized countries such as the US tends toward low-dose, temporal or chronic exposure. Although technologies for measuring body lead burden have improved, technologies for discerning health effects have not advanced as much. Blood is a short-term reservoir for body lead burden. Blood lead measurement is the standard for pediatric and adult clinical surveillance,<sup>65</sup> although twenty-four-hour urine analyses provide useful clinical measures of heavy metals (eg, lead, cadmium), renal function (creatinine) and bone resorption (eg, calciuria, calciotropic hormones).<sup>66–68</sup>

Lead that is deposited in bone remains sequestered for considerably longer periods of time relative to lead found in the blood or soft tissue.<sup>69</sup> The cumulative dose of lead absorbed throughout the lifecycle in adults is reliably measured by K-shell X-ray fluorescence (KXRF) of the bone.<sup>70,71</sup> Lead that is stored in porous trabecular bone is thought to be more bio-available and may have a shorter half-life compared to dense cortical bone.<sup>37</sup> The prolonged half-life of lead in bone makes it a useful benchmark of chronic lead exposure that may not manifest in BLL.<sup>72</sup>

Cadmium-source KXRF is used to estimate cumulative lead exposure using both patellar and tibial bone.<sup>71</sup> Lead sequestered in the bone is measured as  $\mu\text{g/g}$  of mineralized bone. KXRF can provide a relatively unbiased estimate of bone lead levels, normalized to bone mineral content as micrograms of lead per gram of bone mineral.<sup>38,73–77</sup> The half-life of lead sequestered in bone can extend to 15 years. About 95% of the lead in the body of an adult, and up to 70% of the lead in the body of a child, is thought to be sequestered in the bones.<sup>78–80</sup>

Limitations of the KXRF technique are related to detection limits for lead and interpretation of results.<sup>70</sup> Lead levels measured by KXRF vary according to BMD. In turn, BMD may vary by age, ethnicity and other covariates. Changes in BMD occur throughout the lifespan in both men and women, such as in pregnancy, lactation or osteoporosis.<sup>77,81–83</sup> Progress has been made using age-adjusted mean bone mineral curves for areal and volumetric BMD for calculating standards among certain ethnic groups.<sup>84</sup>

The association between body lead burden and social adjustment was first investigated using KXRF spectroscopy by following through adolescence 301 first grade boys, identified as being at risk for antisocial behavior. The boys with higher bone lead levels had a higher risk for attention impairment, delinquent behavior and academic failure.<sup>22,24</sup> Others have since found associations between bone lead level and low-income, minority status and immigrant status.<sup>85,86</sup>

Bone lead measurements are more predictive of renal function in older subjects, and in subjects with hypertension. Wu et al found an association between patellar (trabecular) bone lead and renal function in a sample recruited from the Normative Aging Study, but no association with ALAD genotype.<sup>87</sup> In their study of men also recruited from the Normative Aging Study, Kim et al found that bone lead is associated with age, but lead level remains more consistent in tibial bone than in patellar bone or in blood.<sup>74</sup>

### Emergent sources of lead

Because much of the world remains in Stages 2 and 3, the movement of people and products into the US and other Stage 4 nations will present continuing challenges throughout the 21st Century. Despite regulations, products with unacceptable levels of lead (eg, toys from China, candies and lead-glazed ceramics from Mexico) can be expected to arrive within the US through international trade. Even strong legislation, (eg, the European Restriction of Hazardous Substances (RoHS) Directive), cannot prevent sporadic importation of lead-tainted products. Similarly, immigrants from Stage 2 or 3 nations may unknowingly carry a locally acquired

endogenous bone lead burden that will be a potential source of blood lead for decades into the future.

Emergent sources can and will also appear from within a Stage 3 or 4 nation. For example, in the Washington D.C. area, changes in the chemical procedures for treating municipal water unexpectedly resulted in leaching of lead from old plumbing pipes.<sup>88</sup> This presented a serious health challenge to affected residents. Undoubtedly, other unanticipated lead “events” will mar the attainment of the sub-microgram Stage 4 goal.

## Discussion and conclusions

A roadmap to sub-microgram blood lead levels delineates the challenges our society will face to meet this goal in the 21st Century. Regulation of exogenous primary sources of lead is straightforward and effective. Control before release into the environment can be planned and is usually cost-effective. Control of exogenous secondary sources is more difficult due to dispersal of the targets. Lead in plumbing systems is widespread but not diffuse (the offending materials can be mechanically removed) and remediation by replacement is not a particularly hazardous process. Lead-based paints are widespread and diffuse, and removal is both difficult and hazardous. Abatement by proper maintenance is the cost-effective strategy, accompanied by proper regulation of demolition practices. Lead in soil is widespread and extremely diffuse. Removal and sequestration of lead-contaminated soils in hazardous waste dumps is a simple mechanical process requiring appropriate safety precautions. But the magnitude of this task and the expense involved is large. Perhaps a geometric analogy highlights the control of secondary sources. Lead plumbing can be thought of as a one-dimensional (linear) system composed of pure lead. Rip it out. Lead-based paint is a two-dimensional (planar) system with high lead content. Paint it over. Contaminated soil is a three-dimensional (volumetric) system of diffuse lead, at a level less than one percent. Shovel it.

The exogenous body lead burden, a legacy of 20th Century exposures, will persist well into the 21st Century in the US and most other countries. It will diminish by natural attrition; at present there is no bone-lead cleansing regimen. Research methodologies that discern health effects are limited to epidemiologic and genomic designs, and still rely much on animal models. The technology for tracking lead body burden is reliable for measuring both circulating lead and bone-sequestered lead, although KXRF is not clinically in use. It is important to consider that many of the covariants of lead exposure may also be seen as markers of the overall living conditions in a society.

Elimination of lead intake from exogenous sources is crucial in controlling future body lead burdens in our population. Primary prevention would appear to be the most important public policy strategy. Rapid and effective response to emerging lead sources is another essential part of the strategy to meet the one-microgram goal. Even if the one-microgram goal is possible technically, it remains to be seen whether it will be possible politically.

## Disclosures

The authors report no conflicts of interest in this work.

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