

# **Applied Toxicology**

**NURS 735**

## **METALS**

### **•Lead**

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This module will focus on the toxicology of metals. A general overview of metal toxicity is presented throughout portions of your text, and in the initial slides of this presentation. Greater detail will be offered on specific metal toxicity through examples in this PowerPoint presentation (cadmium) and other resources (refer to Module 4 resources).

## Toxicity of Lead (Pb)

*“If we were to judge of the interest excited by any medical subject by the number of writings to which it has given birth, we could not but regard the poisoning by lead as the most important to be known of all those that have been treat of, up to the present time”*

*Orfila, 1817*

**In ancient Rome:**

- Pb pipes were used to convey water in the city
- Pb was added to sweeten wine

**Today, we continue to use Pb in ways that lead to human exposure and Pb is the most ubiquitous of known toxic metals.**

As indicated by the quote on this slide, the toxicity of the heavy metal lead (Pb) has long been recognized, however we continue to use it in many different ways. Although we have developed controls to prevent exposure to Pb from a few obvious sources, there are many more that need to be recognized and addressed.

**Can we reduce our exposure to Pb to a safe level?**

**Some think not, especially for children**

**Recent/Ongoing Routes of Exposure:**

- **Occupational**
  - Pb production and smelting**
  - Brass, Cu or Pb foundries**
  - Pb soldering**
  - Battery manufacturing**
  - Demolition of old structures**
  - Burning, scraping or sanding old paint**
  - Indoor firing ranges**
  - Ceramic glaze mixing**

One of the major questions facing toxicologists is whether we can control Pb exposure sufficiently to prevent adverse health effects? This list of examples of current sources of occupational exposure to Pb stem from past as well as current uses of this heavy metal

**Recent/Ongoing Routes of Exposure:**

- **General Population**
  - Paint in houses built before 1978**
  - Soil and air near factories which use Pb**
  - Drinking water from pipes with Pb solder**  
(especially if pH < 6.5)
  - Lead-soldered cans**
  - Folk medicine/cosmetics**
  - Gasoline exhaust emissions**

**Recent reductions in Pb exposure:**

- **Removal of Pb from gasoline**
- **Reduction in use of Pb-soldered cans for food**
  - 1940s dietary intake of Pb was 400-500 ug/day**
  - 1990s dietary intake of Pb is less than 20 ug/day**
- **Ban on the use of Pb in house paints**

Known sources of exposure also continue for the general population. Pb can leach from the solder used in plumbing in old homes or buildings, especially if the water is acidic and stands in the pipes for extended periods of time. In these situations it's good to let the water run for a while in the morning before drawing water for drinking in older homes. Environmental contamination with Pb from past activities remains a big problem, for Pb binds tightly to certain soil types and thus does not go away with time. As noted in this slide, there have been some very successful programs that have lead to significant Pb reductions in some environments.

## **AD(M)E**

- **Absorption**

**Gastrointestinal: Adults absorb 5-15%, retain about 5% of absorbed dose**

**Children absorb about 40% and retain about 32% of absorbed dose**

**Pulmonary: About 90% of Pb particles in outdoor air are small enough to enter the alveoli.**

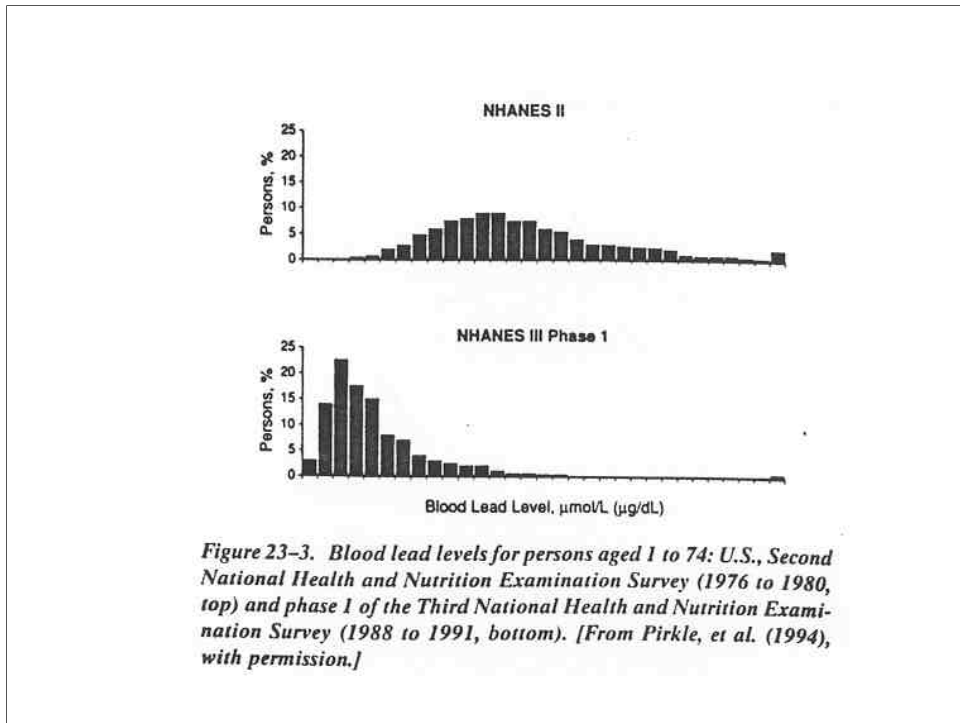
- **Tissue Distribution**

**Blood Pb: More than 90% of Pb in blood is in the red blood cells. Blood Pb concentrations are used to measure recent exposure to Pb**

The absorption of Pb from the GI tract is much greater in children than in adults, which is one of the reasons that children are more susceptible to Pb poisoning than adults. The greater absorption is due, at least in part, to the fact that Pb crosses the intestinal cells through Ca uptake systems which are upregulated in children to support bone growth.

Airborne Pb is/was also an important source of Pb, particularly when gasoline contained Pb additives. Since Pb is primarily associated with air particles < 10 microns in diameter, airborne Pb enters the alveoli of the lung where absorption into the blood stream is high.

Because Pb that enters the blood stream readily enters and remains in the red blood cells, blood Pb levels are an important biomarker of Pb exposure.



*Figure 23-3. Blood lead levels for persons aged 1 to 74: U.S., Second National Health and Nutrition Examination Survey (1976 to 1980, top) and phase I of the Third National Health and Nutrition Examination Survey (1988 to 1991, bottom). [From Pirkle, et al. (1994), with permission.]*

A comparison of results for blood Pb levels in the US population from national health surveys conducted by CDC ten years apart is shown in this figure. Note that blood Pb level distribution in the population was much lower in the late 1980's. This decline is attributed to reduction in sources of Pb exposure, most important of which was removing Pb from gasoline.

### **Sensitivity of Children to Pb**

**Even though blood Pb levels are decreasing in the general population, still 35% of inner city children have blood Pb concentrations above 10 : g/dl (recommended by CDC to prevent impairment of cognitive and behavioral development.**

**Due to:**

- **Higher exposure from Pb-based paint in homes and urban dust due to childhood behaviors**
- **Higher rate of intestinal absorption in children and nutritional deficiencies in iron and calcium which enhance Pb absorption**

Many children in the US are still at risk of health effects from Pb exposure. In general inner city children have high body burdens of Pb because they have higher exposures to Pb containing paint in the older city homes and differences in their behaviors compared to adults (e.g. they will chew on painted surfaces, and ingest dust as they crawl on the floor and put their hands in their mouths). Nutritionally deficient children will also absorb a great percentage of an ingested dose of Pb.

# AD(M)E

## Tissue Distribution

**Bone - Largest and kinetically the slowest pool**

**$t_{1/2} = >20$  yr.**

**Contributes to maintaining blood Pb levels**

**Mobilization of Pb from bone occurs:**

- **During pregnancy and lactation which can increase fetal exposure**
- **After menopause with onset of osteoporosis which can increase exposure to soft tissues**

In addition to accumulating in red blood cells, Pb also accumulates in bone. Since the half-life of Pb in bone is long (i.e. it leaves bone very slowly), it can accumulate to high concentrations and remain high for long periods of time. The slow release of Pb from bone into blood can continue to keep blood Pb concentrations elevated for a long period of time after exposure to Pb stops. In humans, there is always a slow steady release of Pb from bone stores, but this release can be accelerated by physiological states that increase the mobilization of calcium from bone (e.g. pregnancy and lactation or osteoporosis).

# **AD(M)E**

## **Tissue Distribution**

**Soft tissues - Liver, kidney, brain**

**Pb in CNS concentrates in gray matter and  
specific nuclei**

**Highest concentration in hippocampus > cerebellum >  
cerebral cortex and medulla**

**Pb crosses the placenta. Cord blood Pb and fetal  
tissue concentrations correlate with maternal  
blood Pb concentrations**

Pb stores in soft tissues such as liver and kidney turn over more rapidly than Pb in bone. Consistent with its neurotoxic effects, Pb has been shown to accumulate differentially in brain tissue .

Pb also crosses the placenta and reaches developing a embryo. This transfer of Pb from a mother to her child makes the mobilization of Pb from bone that occurs in pregnant women very important. It means that a fetus can be exposed to Pb from it's mother even if the mother's exposure ceased many years ago.

**Table 23-5**  
**Lowest Observed Effect Levels for Lead-Related**  
**Health Effects**

EFFECT	BLOOD LEAD CONCENTRATION ( $\mu\text{g/dL}$ )	
	CHILDREN	ADULTS
Neurological		
Encephalopathy (overt)	80-100	100-12
Hearing deficit	20	
IQ deficits	10-15	-
<i>In-utero</i> effects	10-15	-
Peripheral neuropathy	40	40
Hematological		
Anemia	80-100	80-100
U-ALA	40	40
B-EPP	15	15
ALA inhibition	10	10
Py-5-N inhibition	10	-
Renal		
Nephropathy	40	
Vitamin D metabolism	<30	
Blood pressure (males)	-	30
Reproduction		40

Although there is still much to be learned, there are many health effects from Pb exposure that have been very well defined. Because blood Pb levels provide an excellent measure of Pb body burden, studies have been conducted to determine the dose response curves for Pb effects based on blood Pb levels.

This chart shows the level of exposure (blood Pb levels) at which specific effects are seen in children and adult populations. The effects are divided into 5 groups: Neurological effects, Hematological effects, Renal effects, Effects on blood pressure, and Reproductive effects. These will be reviewed in more detail in the following slides.

The numbers represent the low blood Pb concentrations at which these individual effects are usually first observed. The “ug/dl” unit used for blood Pb levels in this chart = ug of Pb per 100 ml of blood (1 dl = 100ml). This is the standard reporting unit for blood Pb values.

## **Toxic Effects of Pb in Children**

**Lead encephalopathy occurs at 80 : g/dl**

**Symptoms: Begin with lethargy, vomiting, irritability,  
loss of appetite and dizziness**

**Progress to ataxia, reduced level of  
consciousness, coma and death**

**Pathology involves edema of brain due to extravasation  
of fluid from capillaries, loss of neuronal cells  
and increase in glial cells**

**Recovery is accompanied by epilepsy, mental retardation  
optic neuropathy and blindness**

At high Pb exposures (blood Pb concentrations greater than 80 ug/dl), children exhibit the symptoms of encephalopathy outlined on this slide. If Pb exposure is not quickly reduced, children can die. If they do recover, they may well have permanent neurological damage. Fortunately the blood screening programs US cities catch most exposed children before encephalopathy develops, however this does still occur.

## **Toxic Effects of Pb in Children**

### **Nervous system effects:**

**Psychomotor, cognitive and behavioral functional alterations have been documented at lower Pb levels**

**Studies have reported a 2 to 4 point IQ deficit for each : g/dl increase in blood lead within the range of 5 - 35 : g/dl. There does not appear to be a threshold for this effect.**

Neurological effects still occur at blood Pb concentrations lower than 80 ug/dl. These psychomotor, cognitive and behavioral alterations have been very well studied and, unfortunately, there doesn't seem to be a threshold level below which there are no effects.

Although a 2 to 4 point IQ difference doesn't seem like a lot, a shift downwards in the total population IQ curve of even 5 points can significantly increase the number of people with sub-optimal IQ scores. In addition, studies have documented that the behavioral effects of Pb make it difficult for children to learn in school due to a decreased ability to concentrate.

### **Mechanism of Action of Pb on the Developing Nervous System**

#### **Morphological changes:**

**Modification of the “neuronal circuitry”**

**Pb appears to alter the timed programming of cell to cell connections in the developing brain**

**May occur through effects on the glial cells which help form proper connections**

Children are at high risk from even low Pb exposures because of the sensitivity of the developing nervous system, which takes place over a long period of time. The nervous system begins to develop in utero and continues its development throughout childhood. During this time the nerve cells are forming connections with each other that form the basis for learning and memory. The inability to make these connections most likely forms the basis for many of Pb's neurological effects. Pb may directly affect the nerve cells themselves or this heavy metal may alter the function of the glial cells which support the nerve cells.

### **Toxic Effects of Pb in Adults**

**Peripheral nervous system preferentially affected:**

**Peripheral neuropathy is classic manifestation of Pb toxicity at blood Pb levels above 40 : g/dl**

**“Footdrop” or “wristdrop ” due to segmental demyelination and axonal degeneration with Schwann cell degeneration.**

**Sensory nerves are less sensitive than motor nerves**

**CNS effects (changes in mood and affect) occur at higher blood levels than in children**

Although it is the central nervous system of children that is the most sensitive to Pb exposures, it is the peripheral nervous in adults that shows the greatest effects from Pb. People exposed to Pb as adults can develop peripheral neuropathy if their blood Pb concentrations get above 40 ug/dl.

Central nervous system (CNS) effects can occur in adults, however these occur at higher doses of Pb than in children.

## **Toxic Effects of Pb in Adults**

### **Hematological effects:**

- **Anemia occurs from shortened lifespan of red blood cells**
- **Inhibition of pyrimidine -5-nucleosidase leads to nucleotide accumulation which affects membrane stability of red blood cells**
- **Impairment of heme synthesis limits recovery of red blood cell populations**

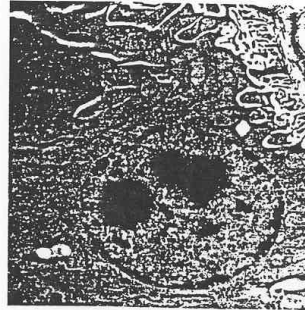
Effects of Pb on red blood cells can lead to anemia in adults at blood Pb concentrations of about 80 ug/dl. Other blood parameters affected by Pb exposure include decreased enzyme activities such as ALAD (aminolevulinic acid dehydratase) which is involved in the synthesis of heme molecules which are needed for hemoglobin and other heme containing proteins. When this enzyme is inhibited, its substrate, aminolevulinic acid (ALA), will increase and be excreted in the urine. Urinary ALA can be used as a marker of Pb exposure.

## Toxic Effects of Pb in Adults

**Renal Effects: Lead nephropathy is one of the oldest recognized effects of Pb exposure**

**Acute nephropathy (reversible) characterized by functional changes in proximal tubule cells: aminoaciduria , glucosuria, and ion transport**

**Also, see Pb inclusion bodies in nuclei of proximal tubule cells**



*Figure 23-5. Lead-induced inclusion bodies in nucleus of renal tubular lining cell.*

Effects of Pb on kidney function in adults is well known. Because Pb accumulates in kidney cells lining the proximal tubules, the ability of these cells to reabsorb filtered amino acids, glucose and ions such as Calcium and Phosphate is decreased and these are excreted in the urine at much higher levels than normal.

### **Toxic Effects of Pb in Adults**

**Chronic Pb nephropathy is not reversible**

**Renal tubules atrophy and interstitial fibrosis increases in severity.**

**Glomerular filtration rate decreases**

**Increased mortality from chronic interstitial nephropathy occurs at blood concentrations of > 60 : g/dl**

Like the effects of Cd on the kidney, the effects of Pb are not reversible. The destruction of the tubule cells and the increased fibrosis leads to decreased glomerular filtration which can be detected by increased serum creatinine concentrations and increased blood urea nitrogen levels.

### **Toxic Effects of Pb in Adults**

#### **Blood pressure effects:**

**Epi studies indicate positive association between blood Pb concentrations and systolic blood pressure**

**Appears to be a 1.5-3.0 mm Hg increase in systolic pressure for every doubling of blood lead in adult males. In females, the increase seems to be less than 1-2 mmHg.**

**Mechanism may be altered sensitivity of vascular smooth muscle, higher plasma renin activity and/or alterations in ion pumps involved in contractility of smooth muscle.**

Although the mechanism by which Pb increases blood pressure is not well established, Pb may play an important role in elevated blood pressure in the general population.

### **Toxic Effects of Pb in Adults**

#### **Reproductive Effects:**

**Overt Pb toxicity associated with sterility and neonatal deaths.**

**Reduction in sperm counts and motility at blood lead concentrations of 40 : g/dl**

#### **Carcinogenic Effects:**

**Classified as a 2B carcinogen by IARC**

**In lab rat, Pb causes renal adenocarcinoma**

**Studies with humans have been equivocal**

Although it has long been known that high Pb exposures can affect reproduction, it is only recently that the effects of lower Pb exposure on sperm counts and motility have been recognized. This is seen in occupationally exposed workers who are removed from their workplace exposure at blood Pb concentrations of 40 ug/dl.

Although Pb has been shown to cause renal tumors in rats, the carcinogenicity of Pb in humans has not been well established.

## Summary of Pb Toxicity

Lead (Pb) is a heavy metal that appears to cause adverse effects at all levels of exposure. Thus exposures should be kept as low as possible.

Children are particularly sensitive to Pb because intestinal absorption rates for Pb are higher in children and because the developing nervous system is exquisitely sensitive to Pb ions which cross the blood brain barrier and the placenta.

Adults are also sensitive to Pb. Target organs include the peripheral nervous system as well as the central nervous system, the kidney and the reproductive system.