

# Human Health Risk Assessment of Lead and Arsenic

Food Toxicology  
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## Learning Objectives

- Explore the use of lead and its impact on public health.
- Understand the toxicology of lead in humans.
- Review the neurotoxicity of lead and its impact on child development.
- Survey the public health approaches to mitigating lead exposure.
- Explore human exposure to arsenic.
- Understand the toxicology of As.
- Survey food-water As regulations.
- Review the Bangladesh As crisis.

## History of Lead Poisoning

- Observations in ancient literature
  - In the second century BCE, the Greek physician Dioscorides noted that lead makes the "mind give way."
- Byproduct of silver smelting
- Fall of the Roman Empire?
  - Lead spice
  - Leaded wine

## Lead Paint

- White lead - basic lead carbonate,  $2\text{PbCO}_3 \cdot \text{Pb}(\text{OH})_2$
- One of the oldest pigments known
- Pica; household dust

## Leaded Gasoline

- 1921-1986
- Anti-knock additive
- *The Secret History of Lead*

## Progressively Lower Population BLL

- Phase-out of leaded gasoline
- Environmental health success
- Current mean BLL ~ 2-3  $\mu\text{g}/\text{dL}$

## Chronology of Childhood Lead Poisoning

- 1880s
  - 1892 Lead poisoning in children first described as distinct entity in Queensland, Australia
- 1900s
  - \*1904 Lead paint identified as source of childhood poisoning by J.L. Gibson
  - \*\*1904 Lead paint for interior use was banned in Belgium, France and Austria
- 1920s
  - \*\*1927 Public Health Panel reviews potential toxicity of leaded gasoline
- 1940s
  - 1943 Byers and Lord identify school problems in lead-poisoned children
  - 1944 Outbreak of lead encephalopathy due to burning battery casings

## Chronology of Childhood Lead Poisoning

- 1950
  - 1951 394 pediatric deaths due to lead poisoning in NY, Cincinnati, St. Louis and Baltimore
  - 1955 Companies voluntarily reduce lead, interior paint 1%
  - 1956 City of Baltimore attempts primary prevention
- 1970
  - \*\*1970 US Surgeon General recognizes lead poisoning as a potential health problem
  - \*\*1971 Widespread screening begins. Leaded gas phase-out begins. Lead Paint Poisoning Prevention Act

## Chronology of Childhood Lead Poisoning

- 1973 Lead Paint Poisoning Prevention Act Amendment-HUD must eliminate lead hazards in pre-1950 federally subsidized housing units
- \*\*1974 JW Sayre reports that lead concentration of dust on children's hands indicate that for those living in contaminated surroundings, normal hand to mouth activities can transfer dangerous amounts of lead into their bodies
- 1977 Lead paint is defined as being 0.06% by weight
- 1978 Lead paint regulated for use in residential units
- \*\*1979 Needleman shows detrimental effects of low-level Pb exposure

## Chronology of Childhood Lead Poisoning

- 1980
  - \*\*1980 CDC conducts the NHANES II study; prevalence of children between one and five years with BLL's greater than 10 µg/dl was found to be **88.2 %** (1976 -1980)
  - 1982 NHANES II demonstrates widespread lead exposure
  - \*\*1986 Lead banned as a gasoline additive
  - \*\*1986 Congress bans use of lead containing materials in public water supply systems
  - 1988 Lead Contamination Control Act-SDWA amendment

## Chronology of Childhood Lead Poisoning

- 1990
  - \*\*1990 Alliance to End Childhood Lead Poisoning formed 1991 Universal screening recommended by CDC 1991 CDC conducts NHANES III Part 1; prevalence of children between one and five years with blood lead levels greater than 10 µg/dl found to be **8.9%**, a 77.8% decrease from NHANES II
  - \*\*1991 CDC recommends universal screening and lowers level of concern to 10 µg/dl

## Chronology of Childhood Lead Poisoning

- 1992 Title X Lead Poisoning Prevention Act
- \*\*1994 CDC conducts NHANES III Part 2; prevalence of children with blood lead levels greater than 10 µg/dl found to be **4.4%**, a 21.7% decrease from NHANES III Part 1
- 1994 April 1994, US Congress mandated EPA health-based standards due
- 1996 HUD proposes dust-lead soil-lead standards

## Chronology of Childhood Lead Poisoning

- 1998 Final Rule Section 406 (b) of the TSCA - Pre-Renovation Rule; tenants/owners must receive lead hazard information prior to any lead abatement/remediation work being performed
- 1998 Section 403 of the TSCA - Proposed Rule concerning the identification of lead paint hazards sets clearance standards for soil and dust lead

- 2000
  - \*\*2003 Canfield (NEJM) shows 7.4 point decline in IQ was associated with blood lead values up to 10 ug/dl;

- each further increase of 10 ug/dl associated with a 4.6 point decrease.
- 2004 Proposals for CDC 2-5 ug/dl action levels for blood lead

## Children <6 yo BLL by State, 1998

### Lead Exposure

### Absorption

- The absorption and biologic fate of lead once it enters the human body depend on a variety of factors
  - Physiologic characteristics of the exposed person, including nutritional status, health, and age
  - Children and pregnant women, for example, can absorb up to 70% of ingested lead, whereas adults typically absorb up to 20%
  - Chemical form

### Distribution

- Absorbed lead that is not excreted is exchanged primarily among three compartments: blood; soft tissue (liver, kidneys, lungs, brain, spleen, muscles, and heart); and mineralizing tissues (bones and teeth), which typically contain the vast majority of the lead body burden.

### Distribution – Soft Tissues

- Once in the bloodstream, Pb is primarily distributed among three compartments: blood, soft tissue, and mineralizing tissue.
  - The bones and teeth of adults contain more than 95% of the total Pb in the body
- Adults may ultimately retain only 1% of absorbed Pb, but children tend to retain more than adults
  - In infants from birth to 2 years, approximately 1/3 of the total amount of lead is retained.

### Distribution – Bones and Teeth

- Animal studies indicate that the liver, lungs, and kidneys have the greatest soft-tissue lead concentrations immediately after acute exposure (inhalation, oral, dermal, and intravenous routes)
- Autopsies of exposed workers revealed that lead had built up in these soft-tissue organs:  
liver > kidney > lungs > brain

- Selective brain accumulation in children and adults may occur in the hippocampus
- Soft tissues Pb  $T_{1/2} = 40$  da.

### Distribution – Bones and Teeth

- The body accumulates lead over a lifetime and normally releases it very slowly
- Most retained lead in the human body is ultimately deposited in bones.
  - The bones and teeth of adults contain about 94% of their total lead body burden
  - In children the figure is approximately 73%

### Excretion

- Most of the lead that is absorbed into the body is excreted either by the kidney (in urine) or through biliary clearance (ultimately, in the feces).

### Toxicity

- Primarily affects the peripheral and central nervous systems, renal function, blood cells, and the metabolism of vitamin D and calcium.
- Can also cause hypertension, reproductive toxicity, and developmental effects

### Toxicity

- In times of stress, the body can mobilize lead stores, increasing the level of lead in the blood
- Although the blood generally carries only a small fraction of the total lead body burden, it serves as the initial receptacle of absorbed lead and distributes lead throughout the body, making it available to other tissues (or for excretion).
  - The  $T_{1/2}$  of lead in adult human blood has been estimated to be from 28 days to 36 days
- Approximately 99% of the lead in blood is associated with red blood cells (erythrocytes); the remaining 1% resides in blood plasma
- BLL is the most widely used measure of lead exposure

### Lead Toxicity

### Mechanisms of Toxicity

- Proposed mechanisms for toxicity involve fundamental biochemical processes.
  - Ability to inhibit or mimic the actions of calcium (which can affect calcium-dependent or related processes)
  - Interaction with proteins (including those with sulfhydryl, amine, phosphate, and carboxyl groups)

### Neurologic Effects

- The nervous system is the most sensitive target of lead exposure.
  - Fetuses and young children are especially vulnerable to the neurologic effects of lead because their brains and nervous systems are still developing and the blood-brain barrier is incomplete.
  - There may be no lower threshold for some of the adverse neurologic effects of lead in children; some of these effects have been documented at exposure levels once thought to cause no harmful effects (<10 µg/dL) (CDC 1997)

### Neurologic Effects

- In children, acute exposure to very high levels of lead may produce encephalopathy and its attendant signs (e.g., hyperirritability, ataxia, convulsions, stupor, and coma or death)
- The BLLs associated with encephalopathy in children vary from study to study, but BLLs of 70–80 µg/dL or greater appear to indicate a serious risk
- There is a large body of evidence that associates decrement in intelligence quotient (IQ) performance and other neuropsychologic defects with lead exposure

### Neurologic Effects

- Some of the neurologic effects of lead in children may persist into adulthood
- One study, for example, correlated lead exposure with lower class standing (classroom performance); greater absenteeism; more reading disabilities; and deficits in vocabulary, fine motor skills, reaction time, and hand-eye coordination

in young adults more than  
10 years after childhood  
exposure  
(Needleman et al. 1990)

### Association of IQ and BLL

- “Conclusions: Blood lead concentrations, even those below 10  $\mu\text{g}/\text{dL}$ , are inversely associated with children’s IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations. These findings suggest that more U.S. children may be adversely affected by environmental lead than previously estimated.”

### *Intellectual Impairment in Children with Blood Lead Concentrations below 10 $\mu\text{g}/\text{dl}$*

- IQ declined by 7.4 points as lifetime average BLL increased from 1 to 10  $\mu\text{g}/\text{dl}$

### Transgenerational Effects of Lead

- Cord blood lead levels and subsequent cognition
- Brigham and Women’s Hospital (Bellinger et al., NEJM 1987)

### Other Effects

- Renal Effects
  - Irreversible lead nephropathy (i.e., interstitial nephritis)
- Hematologic Effects
  - Inhibits several enzymes critical to the synthesis of heme
- Endocrine Effects
  - Interferes with a hormonal form of vitamin D
- Cardiovascular Effects
  - Hypertension
- Reproductive Effects
  - Sterility? Teratogen?
- Cancer Effects
  - Probable human carcinogen

### The Lead Effect?

### PbB Action Levels

- CDC reviewing proposals/data to reduce PbB Action Level to 5  $\mu\text{g}/\text{dl}$  or below.
- Questions of how to do clinical intervention to achieve lower results.

## Children's BLL

- Approximately 310,000 U.S. children aged 1-5 years have blood lead levels greater than the CDC recommended level of 10 µg/dl.
  - The major source of lead exposure among U.S. children is lead-based paint and lead-contaminated **dust** found in deteriorating buildings

## Regulatory Standards

- EPA, public drinking water systems: 15 µg/L
- FDA, 0.5 µg/mL for lead in products intended for use by infants and children and has banned the use of lead-soldered food cans
- FDA guidance level
  - 1.5 mg/kg Crustacea; 1.7 mg/kg Molluscan Shellfish
- Not allowed in paint or automobile gasoline
  - Paint intended for residential use is limited to 0.06% lead
- CDC action level for children 10 µg/dl, air - 0.5 mg/m<sup>3</sup>
- No EPA RfD or RfC
- No ATSDR MRL, California drinking water 2 µg/L.

## Mitigation Actions and Results

- Banned from house paint in 1978.
- U.S. food canners quit using lead solder in 1991.
- 25-year phaseout of lead in gasoline reached its goal in 1995.
- FDA's 1994-1996 Total Diet Studies showed that, since 1982-1984, daily intakes of lead from food dropped 96% in 2- to 5-year-olds (from 30 µg/da to 1.3) and nearly 93% in adults (from 38 µg/da to 2.5)

## Lead in Ceramicware and Utensils

- FDA has established maximum levels for leachable lead in ceramicware and utensils, and pieces that exceed these levels are subject to recall or other agency enforcement action.

### Lead in Ceramicware

- The levels are based on how frequently a piece of ceramicware is used, the type and temperature of the food it holds, and how long the food stays in contact with the piece.
  - e.g. cups, mugs and pitchers have the most stringent action level, 0.5 parts per million, because they can be expected



to hold food longer, allowing more time for lead to leach.

- Pitcher may be used to hold fruit juice.
- Coffee mug is generally used every day to hold a hot acidic beverage, often several times a day.

## Arsenic

### Natural Occurrence of As

### Anthropogenic Sources

### Human Dietary Exposure

- Food from high arsenic agricultural areas
- Foods naturally high in As
  - Arsenobetaine is the predominant arsenic compound found in most seafood (fish arsenic)
    - Not toxic because it is not metabolized by the body to release the active arsenic
    - Direct urinary excretion
- Drinking water

### Regulating Arsenic in Food (US)

- FDA currently has no tolerance levels for arsenic in food, except for the by-products of animals treated with veterinary drugs (Roxarsone).
- FDA has established tolerance levels for arsenic in by-products of animals treated with veterinary drugs.
  - Permissible levels range from 0.5 mg/kg in eggs and uncooked edible tissues of chickens and turkeys to 2 mg/kg in certain uncooked edible by-products of swine
- FDA Guidance
  - 76 mg/kg Crustacea
  - 86 mg/kg Molluscan Shellfish

### Speciation

- Inorganic species in drinking water are more prevalent and more toxic
- In solution, inorganic As forms oxyanions
- U.S. water: 1/3 As(III), 2/3 As(V)

### Aqueous As Speciation

### Arsenic Toxicology: Absorption

- Soluble ingested arsenic is well absorbed (60% to 90% absorption) by GIT

- Most tissues, except for skin, hair, and nails (keratin-rich tissues), rapidly clear arsenic
- After absorption arsenic initially accumulates in the liver, spleen, kidney, lungs, and gastrointestinal tract.
  - Some to bones and teeth

### Biotransformation and Excretion

- Arsenic undergoes methylation to less toxic metabolites in the liver
  - Methylarsonic acid and dimethylarsinic acid
- Primary route of excretion is kidney → urine (normal < 50 ug/L)

### Mechanistic Toxicity

- As impairs tissue respiration
- Arsenic binds with sulfhydryl groups and disrupts sulfhydryl-containing enzymes
  - Inhibition of the pyruvate and succinate oxidation pathways
  - Inhibition of tricarboxylic acid (TCA) cycle
  - Impaired gluconeogenesis
  - Reduced oxidative phosphorylation
  - Also: substitution of As(V) for phosphorus in many biochemical reactions
    - Leads to rapid hydrolysis of high-energy bonds in compounds such as ATP. That leads to loss of high-energy phosphate bonds and effectively "uncouples" oxidative phosphorylation.

### Chronic Exposure: Cardiovascular Effects

- Long-term ingestion of arsenic in drinking water has resulted in pronounced peripheral vascular changes
  - Vasospasm and peripheral vascular insufficiency
- “Blackfoot” disease: gangrene of the extremities
  - Association w/ skin cancers
- Raynaud's phenomenon (vasospasm) and acrocyanosis (decreased O<sub>2</sub>): cold and blue hands and feet
- Fibrous thickening of small and medium arteries and myocardial hypertrophy

### Neurologic Effects

- Peripheral neuropathy
- Sensory and motor nerves affected
  - Symmetrical, stocking-glove distribution
- Dysesthesia

### Dermal Effects

- Pigment changes and palmoplantar hyperkeratosis
- Benign arsenical keratoses may progress to malignancy
- As skin lesions: hyperpigmentation, hyperkeratosis, and skin cancer

### Hematopoietic Effects

- Bone marrow depression
  - Anemia (decreased RBC) and leukopenia (decreased WBC)

### Reproductive Effects

- Increased frequency of spontaneous abortions and congenital malformations has been linked to arsenic exposure
- Reproductive toxicant and a teratogen
- Crosses the placental barrier

### Carcinogenic Effects

- Chronic arsenic ingestion is strongly associated with an increased risk of skin cancer, and may cause cancers of the lung, liver, bladder, kidney, and colon
  - As effects on enzymes involved in DNA replication and repair?

### Health Effects - Acute

- 50 to 300 mg of inorganic As fatal to humans
- Gastrointestinal injuries, kidney damage
- Circulatory collapse, respiratory failure
- Industrial exposures
  - Mining, agriculture
- Opportunistic exposures
  - Diet, treated wood; Paris Green
- Intentional exposures
  - Arsenical drugs
    - Roxarsone-swine/chickens
    - Arsenic trioxide-Leukemia

### Health Effects, Chronic

- 1) As builds up in tissues - skin, hair
- 2) Melanosis, keratosis, unusual pigmentation
- 3) Lesions, vascular system damage
- 4) Skin, lung, bladder, lymph glands, kidney, prostate, and liver cancers

### As: Common Drinking Water Contaminant

- US, Taiwan, Chile, Mexico, Argentina, Bangladesh, India (others)
- WHO drinking water standard 10 ug/L

- Many countries, especially the less industrialized, maintain a 50 ug/L standard
- US standard: 50 ug/L changing to 10 ug/L (compliance by 2006).

### U.S. Arsenic Regulation (past)

- As is a Class A, known human carcinogen
  - 1-2 in 1000 risk (1 in 100?) at 50 ug/L
- As was listed before 1987, and had no BAT
- As MCL was 50 µg/L

### U.S. Arsenic Regulation (present)

- EPA's new MCL was 10 µg/L (Jan. 22, 2001)
  - Same level specified by WHO
  - Below this food becomes the predominant source
  - BAT's were named
- Bush administration suspends new rule (March, 2001)
- New rule promulgated October 2001

### As in the United States Regulatory Standards

- EPA - Drinking water 10 µg/L (0.01 ppm)
- EPA - RfD - 0.3 µg/kg/day
- OSHA - Workplace air 10 µg/m<sup>3</sup>
- ATSDR – MRL (Minimal risk level) - 0.3 µg/kg/day

### Scope of the Bangladesh Problem

“With more than an estimated 20 million of its 126 million people assumed to be drinking contaminated water and another 70 million potentially at risk, Bangladesh is facing what has been described as perhaps the largest mass poisoning in history.”  
(World Bank)

"Bangladesh makes the Chernobyl disaster look like

a Sunday-school picnic."  
(R. Wilson, Harvard U.)

## History of the Bangladesh Problem

“The story beggars belief. In the 1970s, international agencies headed by the United Nations Children’s Fund (UNICEF) began pumping millions of dollars of aid money into Bangladesh for tubewells to provide “clean” drinking water. According to the World Health Organization, the direct result has been the biggest outbreak of mass poisoning in history. Up to half the country’s tubewells, now estimated to number 10 million, are poisoned. Tens, perhaps hundreds of thousands will die.”  
(F. Pearce, UNESCO)

## Bangladesh – Public Health Concerns

- In the early 1970s, most of Bangladesh's rural population got its drinking water from surface ponds and nearly a quarter of a million children died each year from water-borne diseases.
  - The provision of tubewell water for 97 percent of the rural population has been credited with bringing down the high incidence of diarrheal diseases and contributing to a halving of the infant mortality rate.
- Paradoxically, the same wells that saved so many lives now pose a threat due to the unforeseen hazard of arsenic.

## Exposure

- Drinking water wells contaminated 50-400 ug/L
- Arsenic is getting into rice, Bangladesh's staple crop, through irrigation water pumped from contaminated soils

Arsenic Lesions: Hands and Feet of Woman

Arsenic Lesions on Hand, Cancer

Keratosis on the Palm of a Patient

Arsenic Lesions, Chest/Arms of Young Boy

Gangrene Caused by Arsenic Lesions

## Bangladesh – Cultural/Social Factors

- The social consequences of the arsenic crisis are far-reaching and tragic.
  - Because of illiteracy and lack of information, many confuse the skin lesions caused by arsenicosis with leprosy.
    - The most hard-hit villages where health problems have gripped a large population are treated much like isolated leper colonies. Within the community, arsenic-affected people are barred from social activities and often face rejection, even by immediate family members.
  - Women are unable to get married, and wives have been abandoned by their husbands.
  - Children with symptoms are not sent to school in an effort to hide the problem.

### Collection of Water from Tubewell

### Detection of Arsenic by Field Kit

### Water Quality Management

- Coloring a tubewell after testing water, green-safe, red-unsafe

### Household Water Treatment

- Housewife pouring contaminated water over a three pitcher homemade filter unit.

Portrait of Pinjira Begum and her Daughter. Both Died of Arsenic Related Causes.