A Small Dose of Lead

An Introduction To The Health Effects of Lead
Department of Labor and Industries
Lead Stakeholder Meeting
October 25, 2016

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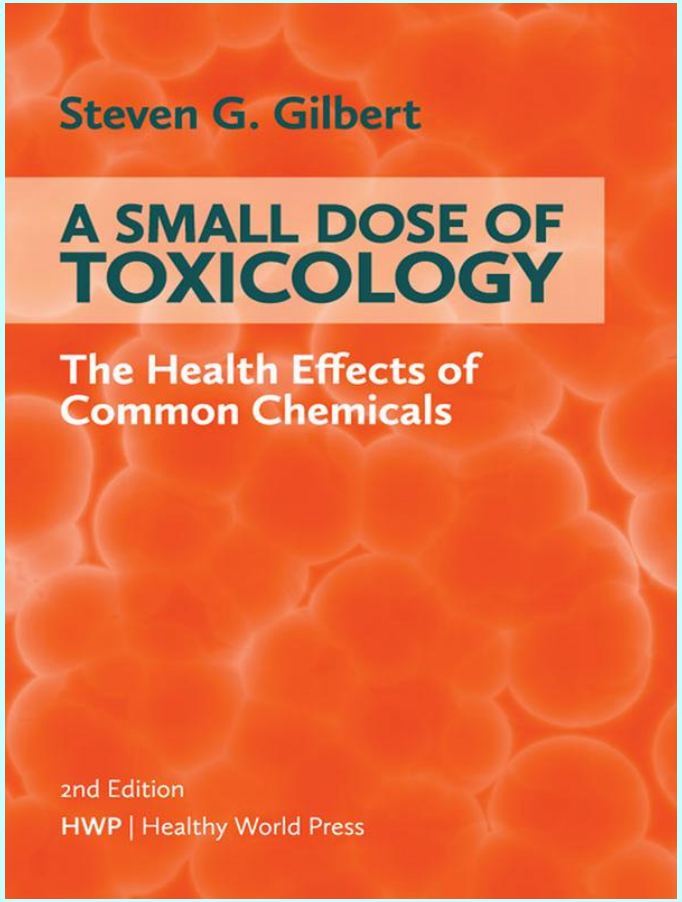
www.asmalldoseof.org
www.toxipedia.org

Lead Poisoning Prevention Week

October 23 – 29, 2016

A Small Dose of Toxicology 2nd Edition



Free e-book
Healthy World Press

PowerPoint slides for each chapter
Translated into German, Arabic, & Chinese

See: www.asmalldoseof.org

Protecting future generations

My grandchildren

Milestones of Toxicology

Milestones of Toxicology

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Contact information: Steven G. Gilbert at sgilbert@innd.org – more information at www.asmalldoseof.org – © 2005 Steven G. Gilbert

Antiquity 3000 BCE – 90 CE

Shen Nung 2696 BCE – The Father of Chinese medicine, noted for tasting 365 herbs and said to have died of a toxic overdose.

Ebers Papyrus 1500 BCE – Egyptian records contains 110 pages on anatomy and physiology, toxicology, spells, and treatment, recorded on papyrus.

Gula 1400 BCE – Sumerian texts refer to a female deity, Gula. This mythological figure was associated with charms, spells and poisons.

Homer 850 BCE – Wrote of the use of arrows poisoned with venom in the epic tale of *The Odyssey* and *The Iliad*. From Greek *toxikos* arrow poison.

Socrates (470-399 BCE) – Charged with religious heresy and corrupting the morals of local youth. Death by Hemlock - active chemical alkaloid coniine.

Hippocrates (460-377 BCE) – Greek physician, observational approach to human disease and treatment, founder of modern medicine, named cancer after creeping crab.

Mithridates VI (131-63 BCE) – Tested and dared to poison on himself and used prisoners as guinea pigs. Created mixtures of substances leading to term *mithridatic*.

L. Cornelius Sulla 82 BCE – *Lex Cornelia de sicariis et veneficis* – law against poisoning people or prisoners, could not buy, sell or possess poisons.

Cleopatra (69-30 BCE) – Experimented with strychnine and other poisons on prisoners and poor. Committed suicide with Egyptian Asp.

Pedanius Dioscorides (40-90 CE) – Greek pharmacologist and Physician, wrote *De Materia Medica* basis for the modern pharmacopeia.

Mount Vesuvius Erupted August 24th 79 CE – City of Pompeii & Herculaneum destroyed and buried by ash. Pliny the Elder suffocated by volcanic gases.

Middle Ages 476 CE – 1453

Greek Fire 673 CE – Ancient "napalm," described by the Crusaders as consisting of naptha, quicklime, sulphur, & saltpeter.

Ergot Outbreak 994 CE – 40,000 died from eating contaminated wheat/rye caused gangrene - known as *St. Anthony's Fire*.

Moses Maimonides (1135-1204) – Jewish philosopher & physician wrote *Treatise on Poisons and Their Antidotes*.

Albertus Magnus (1193-1280) – Dominican friar wrote extensively on compatibility religion and science and isolated arsenic in 1250.

Raymundus Lullius 1275 – Ether discovered by Spanish chemist and later called "sweet vitriol".

Knights Templars (1118-1307) – Christian military order alleged to be experts with poisons. They searched for the "Elixir of Life".

Petrus de Abano (1250-1315) – Italian scholar translated Hippocrates and Galen to Latin. Wrote book on poisons: *De Venenis*.

The Black Death (1347-1351) – Bubonic & pneumonic plague ravaged Europe leaving the highest number of casualties in history.

Venetian Council of Ten - 1419 – Group of people who carried out murders with poison for a fee.

Zhou Man 1423 – Chinese explorer lost 1000s of crew members from uranium exposure while mining lead in Jabiru Australia.

Rodrigo & Cesare Borgia (1400-1500) – Poisoned many people in Italy for political and monetary gain. Used arsenic in a concoction called "La Cantrella".

Renaissance 14th–16th Centuries

Leonardo de Vinci (1452-1519) – Experimented with bioaccumulation of poisons in animals and called the procedure "passages".

Pope Clement VII (1478-1534) – Died (possibly murdered) after eating *amanita Phalloides*, (death cap) mushroom.

Paracelsus (1493-1541) – "All substances are poisons, there is none which is not a poison. The right dose differentiates a poison from a remedy."

Georgius Agricola (1494-1555) – Wrote *De Re Metallica* published 1556. The most comprehensive book on mining and metallurgy.

Catherine Medici (1519-1589) – Queen of France, expert assassin, tested poisons on the poor and the sick.

William Piso 1640 – In Brazil, studied effects of *Cephaelis Ipecacuanha*, an emetic, treat dysentery.

Shakespeare (1564-1616) – From Romeo & Juliet - act 5 "Here's to my love! O true apothecary! Thy drugs are quick. Thus with a kiss I die."

Hieronyma Spara –1659 – Roman women & fortune teller organized wealthy wives and sold them a arsenic elixir to murder their husbands.

Catherine Monvoisin (LaVoisin) (1640-1680) – Accused sorcerer and convicted poisoner in France. She was burned at the stake.

Guilia Tophania (1635-1719) – Italian woman who supplied poison (arsenic) to wives looking to murder their husbands. Later executed by strangulation.

King Louis XIV 1682 – Passed royal decree forbidding apothecaries to sell arsenic or poisonous substances except to persons known to them.

1700s

Devonshire Colic 1700's – Devonshire, England. High incidence of lead colic drinking contaminated cider.

John Jones 1701 – English doctor wrote *The Mysteries of Opium Revealed* described many treatments of opium, but also withdrawal and addiction.

Richard Meade (1673-1754) – In 1702, wrote *A Mechanical Account of Poisons* dedicated to poisons makers, animal and plants.

Carl Wilhelm Scheele (1742-176) – Swedish apothecary and chemist, discovered oxygen, barium, chlorine, manganese, and hydrogen cyanide.

Percivall Pott (1714-1788) – British physician who recognized coal-tar caused cancer of the scrotum in chimney sweeps. Chimney Sweepers Act of 1788.

Felice Fontana 1767 – Italian chemist and physiologist who was the first to study venomous snakes. Discovered that viper venom affects blood.

Fredrich Serturner (1783-1841) – Isolated an alkaloid From opium poppy in 1803. Hermanned it *Morphine* after Morpheus, the Greek god of dreams.

Francoise Magendie (1783-1855) – Discovered emetine and studied effects of strychnine & cyanide. Called the father of experimental pharmacology.

Fowler's Solution 1786-1936 – Potassium arsenite solution prescribed as a general tonic. Arsenic was used from about 1786 to 1936. Used by Charles Darwin.

Pierre Ordinaire 1797-1915 – Created elixir using absinthe popularized and sold by Henry Pernod. Absinthe was used by Vincent Van Gogh, banned in 1915, subject of Degas.

Mateu J.B. Orfila (1787-1853) – Considered the father of modern toxicology in 1813 he published *Traite des Poisons*, which described the symptoms of poisons.

1800s

Thomas de Quincey (1785-1859) – English writer became addicted to opium in early 1804's and published *Confessions of an Opium Eater* in 1821.

James Marsh (1794-1846) – Chemist developed and perfected the Marsh test for arsenic. The improved Marsh test was used forensically for the first time in 1840 during the trial of Marie Lafarge.

Robert Christison (1797-1882) – Toxicologist at University of Edinburgh wrote *Treatise on Poisons* in 1829, invented poison harpoons for whaling that contained prussic acid.

Claude Bernard (1813-1878) – French physiologist studied the effects of carbon monoxide and curare, influenced by Francoise Magendie.

Ascanio Sobrero (1812- 1888) – Italian chemist, in 1847 discovered nitroglycerin, a powerful explosive and vasodilator. Alfred Nobel was his student.

Theodore G. Wormley (1826-1897) – Wrote the first American book dedicated to poisons in 1869 entitled *Microchemistry of Poisons*.

Joseph Caventon & Pierre Pelletier 1820 – French pharmacists isolated quinine from bark of Cinchona tree in back of their pharmacy.

Arsenic Act 1851 – Required arsenic to be colored with soot or indigo to prevent "accidental" poisoning.

Friedrich Gaedcke 1855 – Isolated cocaine from *Erythroxylon coca*.

Louis Lewin (1854-1929) – German pharmacologist studied and classified hallucinogenic plants, alcohols and other psychoactive compounds.

Emil Fischer 1852- 1919 – Isolated the stimulant caffeine from plant extracts in 1895.

Constantine Fahlberg Saccharin - 1879 – Constantine Fahlberg discovered saccharin while working in the laboratory of Ira Remsen (right) in 1879.

1900-1930s

Upton Sinclair (1878-1968) – Published *The Jungle* in 1905. Chronicled the unsanitary conditions in meat packing industry in Chicago.

Pure Food and Drugs Act - 1906 – Harvey Washington Wiley, MD (1844-1930). Law prevents production or trafficking of mislabeled, adulterated or poisonous foods, drugs, medicines, and liquors.

Chemical Warfare A Reality 1915 – German chemist Fritz Haber (1868-1934) developed blistering agents used in WWI, chlorine and cyanide gases.

U.S. Prohibition 1919-1933 – Law that made the production and sale of alcoholic beverages illegal but very profitable.

Geneva Protocol 1925 – Banned use of chemical weapons. Updated in 1993 as the "Chemical Weapons Convention" to include banning production.

Ginger Jake 1929 – Alcoholic tonic produced illegally during prohibition adulterated with TOCP produced OPIDN (Jake Leg), affecting 50,000 adults.

Hawk's Nest Incident 1927-1935 – Hundreds of black workers die from acute silicosis while digging tunnel for a hydroelectric project for Union Carbide.

Gerhard Schrader (1903-1990) – German Chemist accidentally made nerve agents, sarin, tabun, soman, and cyclosarin while developing pesticides 1938; agents used in WWII.

Elixir Sulfanilamide 1937 Food Drug & Cosmetic Act 1938 – 100 die, diethylene glycol as a vehicle.

Albert Hofmann 1938 – Lysergic acid (LSD) synthesized in the Sandoz Laboratory (now Novartis). In 1943 Hoffman tested LSD on himself.

Marijuana Tax Act 1937 – Federal criminal offense to possess, produce, or dispense hemp. Non-medical use prohibited in California (1915) and Texas (1919).

1940-1960s

DDT – 1939 – Recognized as insecticide by the Swiss scientist Paul Hermann Müller, who was awarded the 1948 Nobel Prize in Physiology and Medicine. Banned in 1972.

2,4-D – 1946 – Developed during WW II at British Rothamsted Experimental Station, by J.H. Quastela and sold commercially in 1946. Used to control broadleaf plants.

Minimata Japan (1950's) – Minimata Bay contaminated with mercury by chemical industry. Thousands adults and children were poisoned from eating fish contaminated with methyl mercury.

Poison Control Centers 1953 – First, Chicago **1953**, second at Duke University, NC in **1954**, and third opened in Boston **1955**.

***Journal of Tox. & App. Pharmacology* 1959** – Adopted by SOT until 1981 when SOT founded *Fundamentals of Applied Toxicology*.

Thalidomide (1959-1960's) – Drug prescribed to pregnant women for morning sickness induced birth defects. Frances Kelsey of FDA blocked approval in U.S.

Society of Toxicology 1961 – Founded March 4, 1961, first formal meeting held April 15, 1962 (9 founders, 183 charter members).

Alice Hamilton (1869-1970) – Pathologist and first female faculty member at Harvard Medical School. Associated workplace chemical hazards with disease. Studied effects of lead & rubber on workers.

Rachel Carson (1907-1964) – Scientist led crusade against the use of dichlorodiphenyltrichloroethane (DDT) a pesticide and persistent organic pollutant. Carson several books including *Silent Spring* published 1962.

Occupational Safety & Health Act 1970 – Act passed on December 29, 1970 to ensure every worker a safe and healthful workplace.

U.S. EPA 1970 – Established to consolidate federal research, on monitoring, standard-setting and enforcement activities to ensure human & environmental protection.

1970-2006

Mr. Yuk 1971 – Symbol adopted by the Pittsburgh Poison Center at The Children's Hospital in 1971. Used to educate children and parents about poisons and to prevent accidental poisonings.

Iraq – Mercury 1971 – Pink-colored seed grain coated with a mercury fungicide was tragically consumed by Iraqis tragically affecting *over* 40,000 people.

Bangladeshi 1970s Arsenic poisoning – Tubewells, drilled to provide clean drinking water, are contaminated by arsenic resulting in millions of people harmed.

First Modern Toxicology Textbook 1975 – Louis J. Casarett & John Doull edited, *Toxicology The Basic Science of Poisons*, in 1975.

Love Canal Disaster 1978 – **August 7, 1978** US President Jimmy Carter declared Love Canal a federal emergency. 42 million pounds of over 200 chemicals contaminated Love Canal, disrupting many lives.

IUTOX 1980 – International Union of Toxicology **American Board of Toxicology (ABT) 1979** – First exam Aug. 1980 **Academy of Toxicological Sciences (ATS) 1981**.

Times Beach 1983 – Dangerous levels of dioxin discovered in Times Beach, MO. EPA orders the town evacuation and makes it a Superfund site. All residents gone by 1985.

Bhopal Disaster Dec. 3, 1984 – Accidental release 40 metric tons of methyl isocyanate from a Union Carbide Indian pesticide plant in heart of city resulted in the killing thousands, and injured 100s of thousands.

Chernobyl Accident April 26, 1986 – The Chernobyl nuclear power plant accident produced a plume of radioactive debris over the Ukraine, Eastern Europe, Scandinavia, UK and eastern USA.

Tokyo Subway Sarin Gas Attack 1995 – Members of religious group Aum Shinrikyo released sarin gas in 5 places in Tokyo subway, killing 12 and injuring 6,000.

Vioxx (1999-2004) – A nonsteroidal anti-inflammatory, COX-2 selective inhibitor for treatment of osteoarthritis, produced by Merck & Co. and voluntarily withdrawn because of risk of heart attack & stroke.

www.toxipedia.org

A free toxicology encyclopedia and resource center that anyone can edit. Toxipedia provides comprehensive, accurate, and scientifically based information on the hazards and risks of chemical and physical agents, with the goal of advancing human and environmental health. Toxipedia

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Washington State Constitution

ARTICLE II SECTION 35 PROTECTION OF EMPLOYEES.
The legislature shall pass necessary laws for the protection of persons working in mines, factories and other employments dangerous to life or deleterious to health; and fix pains and penalties for the enforcement of the same.

Current CDC/NIOSH Standards

Healthy People 2020, to reduce the rate of adults (age 16 or older) who have blood lead levels (BLL) equal or greater ≥10 µg/dL

In 2015, NIOSH designated 5 µg/dL (five micrograms per deciliter) of whole blood, in a venous blood sample, as the reference blood lead level for adults. An elevated BLL is defined as a BLL ≥5 µg/dL.

http://www.cdc.gov/niosh/topics/ables/description.html

Current Standards

The U.S. Department of Health and Human Services recommends that BLLs among all adults be reduced to <10 µg/dL.

Therefore, the most current guidelines for management of lead-exposed adults should be implemented by the medical community at the current CDC/NIOSH reference BLL of 5 µg/dL.

http://www.cdc.gov/niosh/topics/ables/description.html

Slide updated 12/18/2015

Reference Blood Lead Levels (BLL) for Adults in the U.S.

Blood lead concentration (μg/dL)

60
50
40
30
25
20
10
5
1.2

OSHA's Medical Removal BLL*

OSHA's Return to Work

ACGIH Biological Exposure Index

OSHA's NEP – lead (2008)

- Level for BLL testing every 6 months (AOEC, 2007)
- California DPH Medical Guidelines (2009)
- Healthy people 2020, OSH Objective 7 (2010)

- **Case Definition for an elevated BLL**: CSTE (2015), ABLES/ NIOSH/CDC (2015), CDC Nationally Notifiable Condition (2016)
- **Level not to exceed during pregnancy**: AOEC (2007), California DPH Medical Guidelines (2009), CDC (ACCLPP, 2010)

2009-2010 average BLL among adults (National Report on Human Exposure to Environmental Chemicals)

*The OSHA Lead Standards state that the examining physician has broad flexibility to tailor protections to the worker's needs.

Key Words of Toxicology

Dose / Response

Hazard + Exposure = Risk

Individual Susceptibility

Lead In Homes

Ancient Awareness

- 6500 BC. - Lead discovered in Turkey, first mine.
- 500 BC-300 AD.- Roman lead smelting produces dangerous emissions.
- 100 BC. - Greek physicians give clinical description of lead poisoning
- First recorded occupational disease (lead colic in a 4th century BC metal worker).

Ancient Awareness

"Lead makes the mind give way."

Greek
Dioscerides - 2nd BC

Lead Based Paint Products

Lead Based Paint

1887 - US medical authorities diagnose childhood lead poisoning

1904 - Child lead poisoning linked to lead-based paints

1909 - France, Belgium and Austria ban white-lead interior paint

1914 - Pediatric lead-paint poisoning death from eating crib paint is described

1921 - National Lead Company admits lead is a poison

1922 - League of Nations bans white-lead interior paint; US declines to adopt

1943 - Report concludes eating lead paint chips causes physical and neurological disorders, behavior, learning and intelligence problems in children

1971 - Lead-Based Paint Poisoning Prevention Act passed

1978 - Lead-Based Paint mostly Banned

Lead Industry Advertisements

History of Lead Industry Advertisements (LINK)

http://www.cincinnatichildrens.org/research/project/enviro/hazard/lead/lead-advertising/default.htm

Lead In Gasoline

1854 - Tetraethyl lead discovered by German chemist

1921 - Midgley discovers that tetraethyl lead curbs engine knock

1922 - Public Health Service warns of dangers of lead production, leaded fuel

1923 - Leaded gasoline goes on sale in selected markets

1936 - 90 percent of gasoline sold in US contains Ethyl

1972 - EPA gives notice of proposed phase out of lead in gasoline.

1986 - Primary phase out of leaded gas in US completed

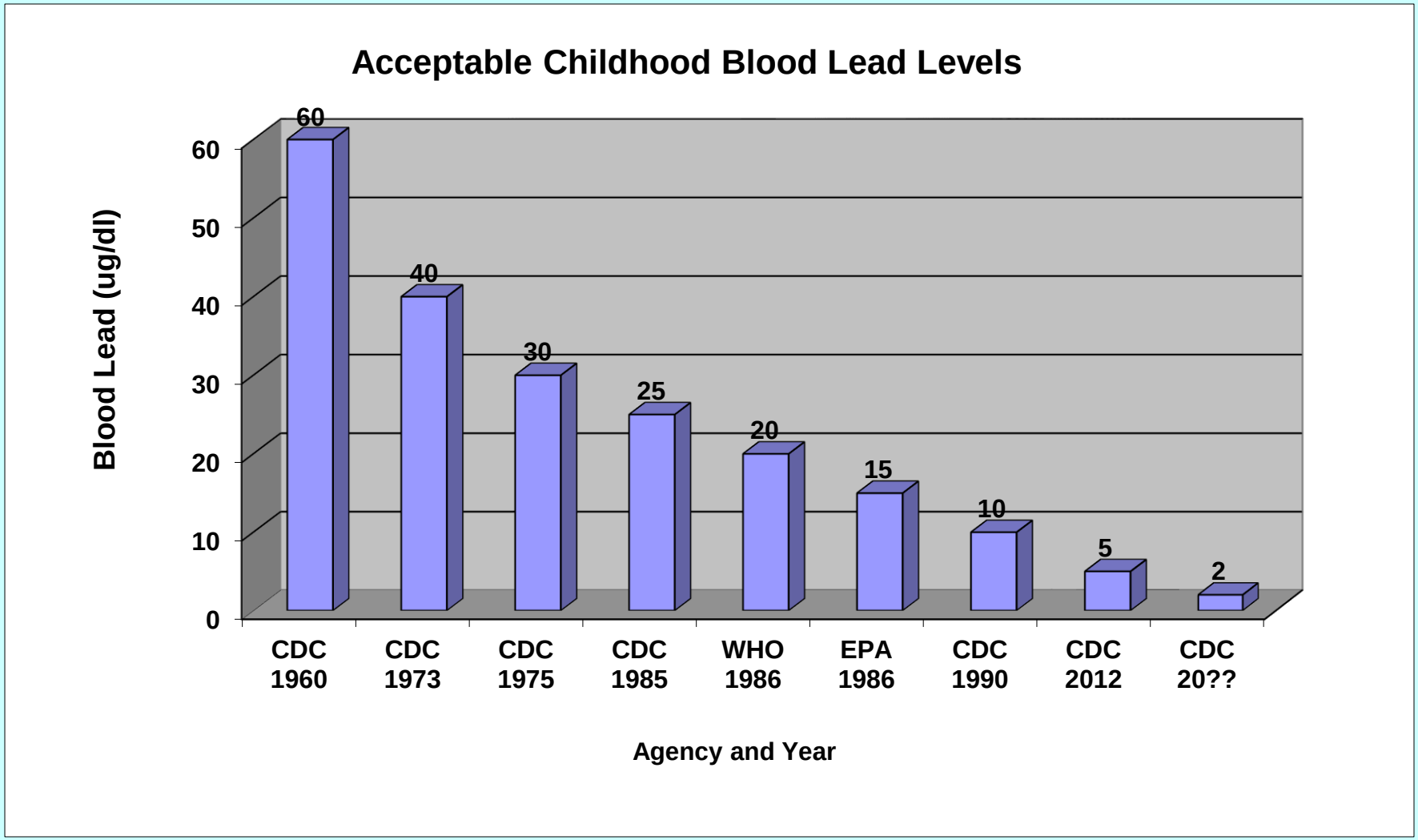
1994 - Study shows that US blood-lead levels declined by 78 percent from 1978 to 1991

2000 - European Union bans leaded gasoline

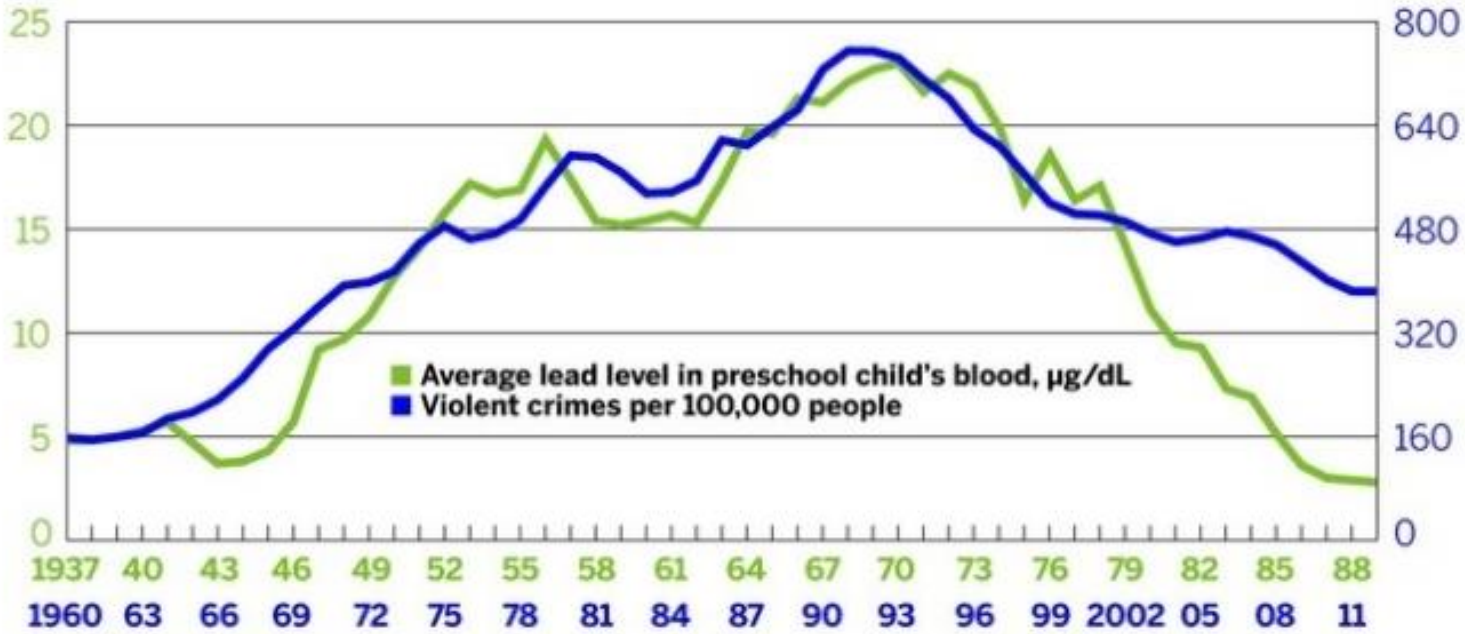
History Of Lead Toxicology

Investigator	Date	Blood	Findings
Dioscerides	2nd BC	100	"Lead makes the mind give way."
B. Franklin	1763	100	"Dry gripes"
A.J. Tuner	1894	80	Childhood plumbism
R. Byers	1943	80	Long-term sequelae
CDC	1973	40	Undue lead exposure
CDC	1975	30	Undue lead exposure
CDC	1985	25	Undue lead exposure
WHO	1986	20	Undue lead exposure
EPA	1986	15	Undue lead exposure
Fulton et al.	1987	15	IQ Deficits
Hansen et al.	1987	15	IQ Deficits
CDC	1990	10	Undue lead exposure
CDC	2012	5	Finally

Agency Blood Lead Levels



BLL & Violent Crimes



A timeline of lead reduction

1970 CDC sets acceptable blood-lead level of **40 µg/dL**

1973 EPA mandates a phaseout of leaded gasoline

1978 CPSC bans residential lead paint

1991 CDC sets acceptable blood-lead level of **10 µg/dL**

1996 EPA eliminates lead from all U.S. motor fuel

2012 CDC describes blood-lead level of **>5 µg/dL** as elevated

Health Effects

- Encephalopathy
- Colic
- Frank Anemia
- Hemoglobin Synthesis
- Peripheral Neuropathies
- Infertility (MEN)
- Systolic Blood Pressure (MEN)
- Nerve Conduction Velocity
- Erythrocyte Protoporphyrin
- DEVELOPMENTAL TOXICITY
- IQ, Memory, Learning
- Growth

Sources Of Lead

- Lead Paint
- Dust, Soil
- Water
- Industry
- Hobbies
- Traditional Ethnic Remedies

Lead Contaminated Town

Herculaneum, Missouri

Doe Run – Lead smelter

160,000 tons of lead per year

One of the largest lead smelters in US

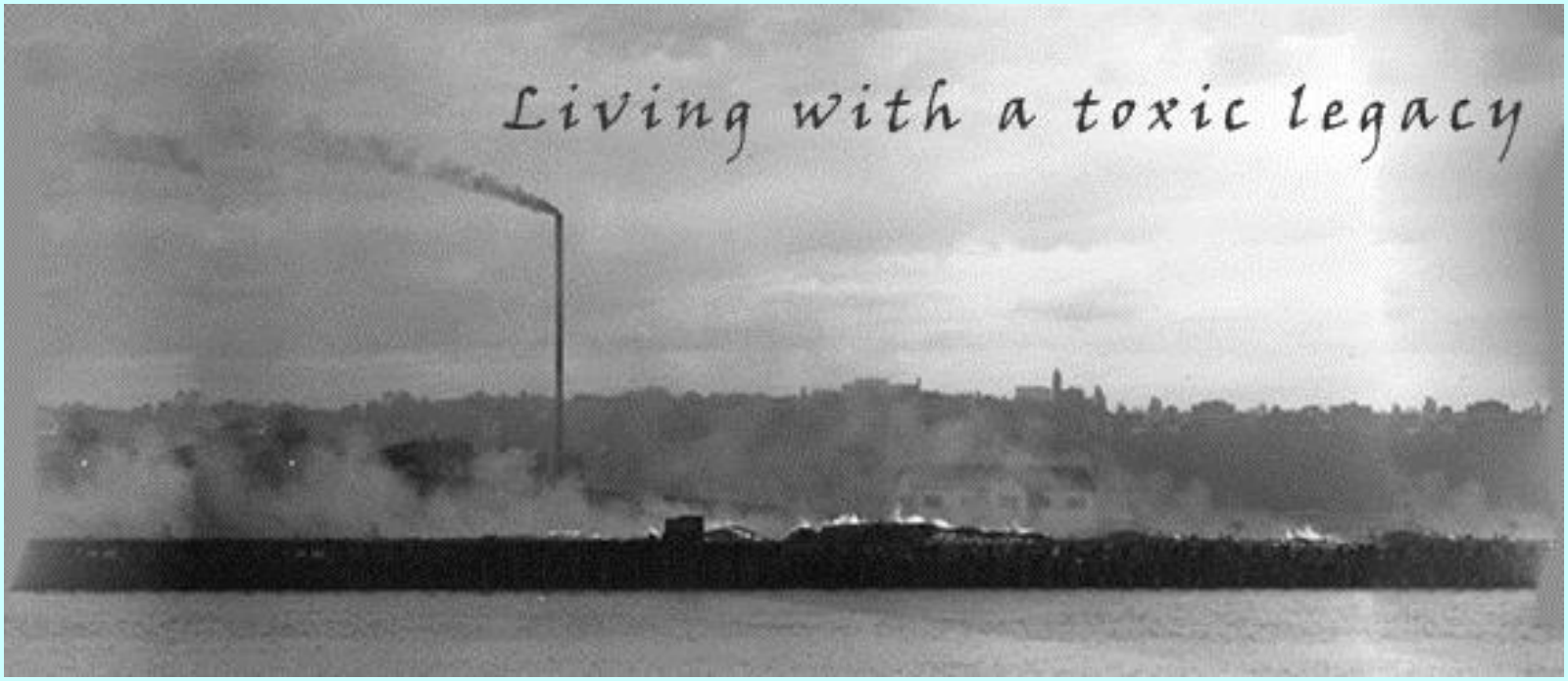
Past over 800 tons of lead released into the environment as part of the smelting process.

Reduced to 81 tons in 2001

Target is 34 tons in 2002.

NY Times, Jan 19, 2002

Tacoma Smelter



Air pollution from the smelter settled on the surface soil over more than 1,000 square miles of the Puget Sound basin.

http://toxipedia.org/display/toxipedia/Tacoma+Smelter

Take Home Lead Exposure

California, 1998

Lead poisoning in furniture workers and their families

Father 46 μg/dL

18-month-old child BLL 26 μg/dL

4-month-old daughter BLL 24 μg/dL

two refinishers BLLs of 29 and 54 μg/dL,

the four carpenters BLLs of 46, 46, 47, and 56 μg/dL.

MMWR - April 06, 2001 / 50(13);246-8

Lead - Absorption

Orally Consumed Lead Absorbed
In Place of Calcium

CHILDREN – 30-50% OF LEAD
ADULTS – 5-10% OF LEAD

Increased During Pregnancy

Lead - Nutrition

NUTRITIONAL DEFICIENCIES INCREASE ABSORPTION

(high fat diets, iron, calcium)

VITAMIN D (from sun) INCREASES

Half-life Of Lead

- 25 DAYS -- BLOOD
- 40 DAYS -- SOFT TISSUE
- 20 YEARS -- BONE

Children Vulnerability

CHILDREN are more vulnerable exposure than ADULTS

Size

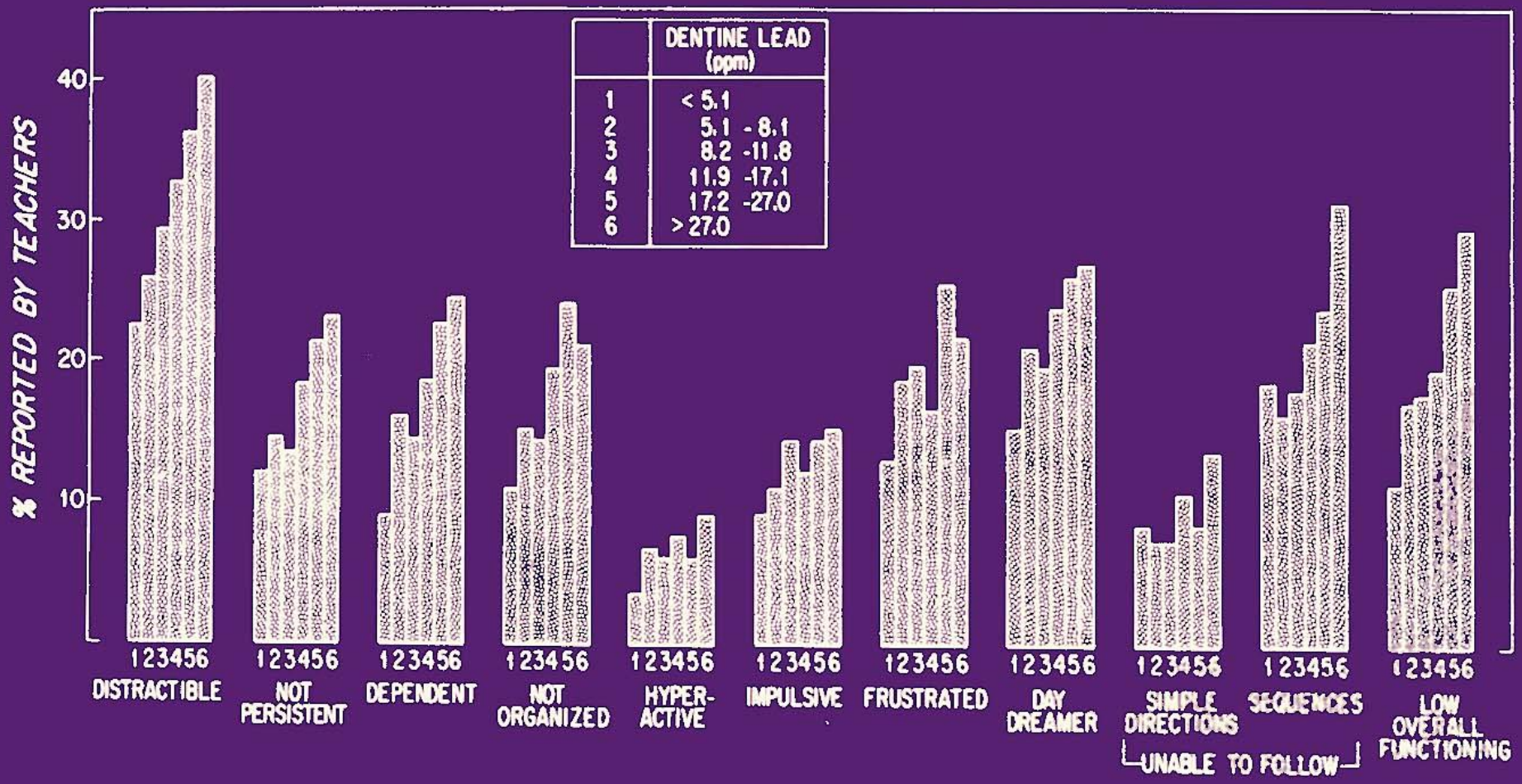
Consume More Food

Inhale More Air

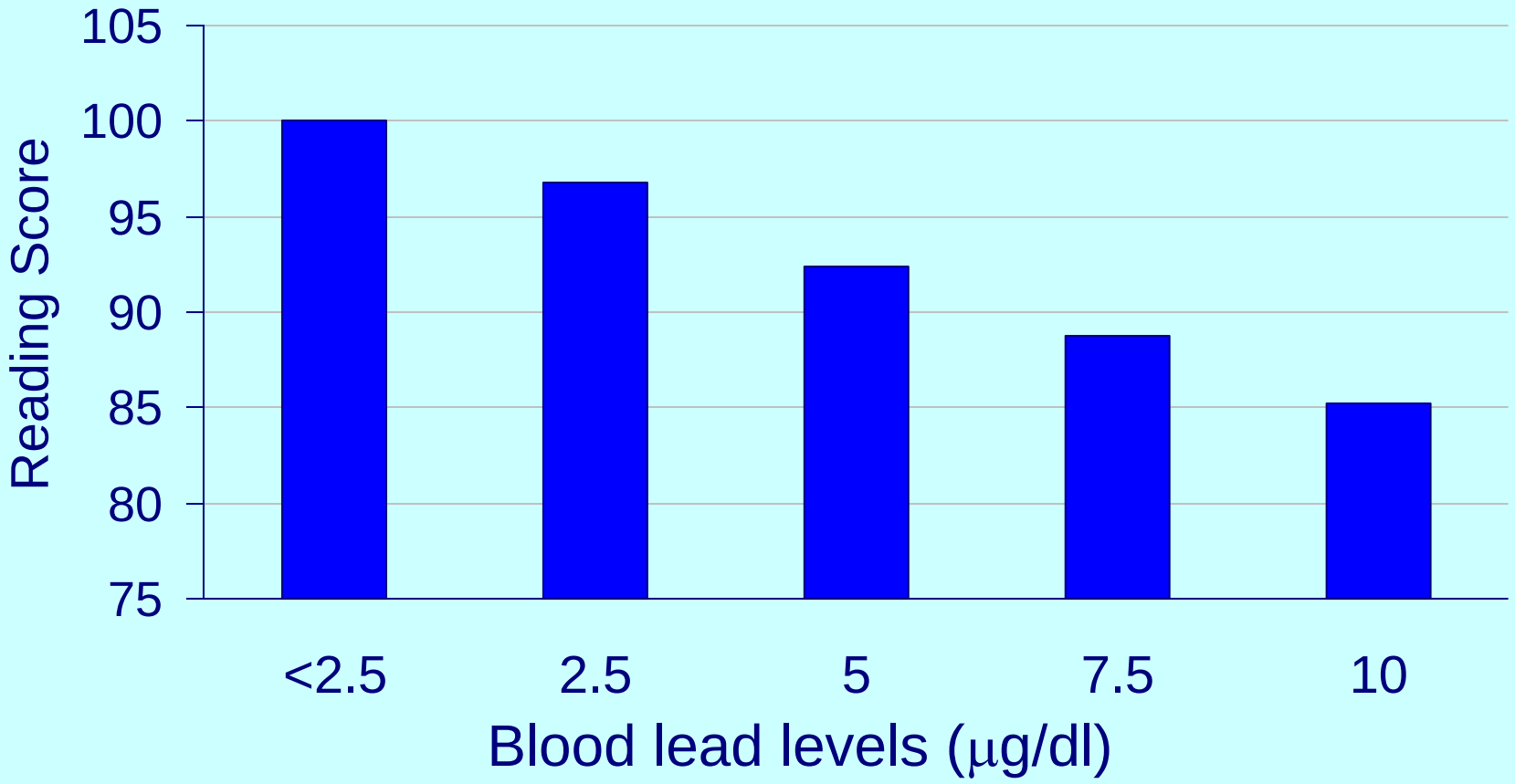
Developing Nervous System

Increased need for Calcium

Needleman, NEJM, 1979

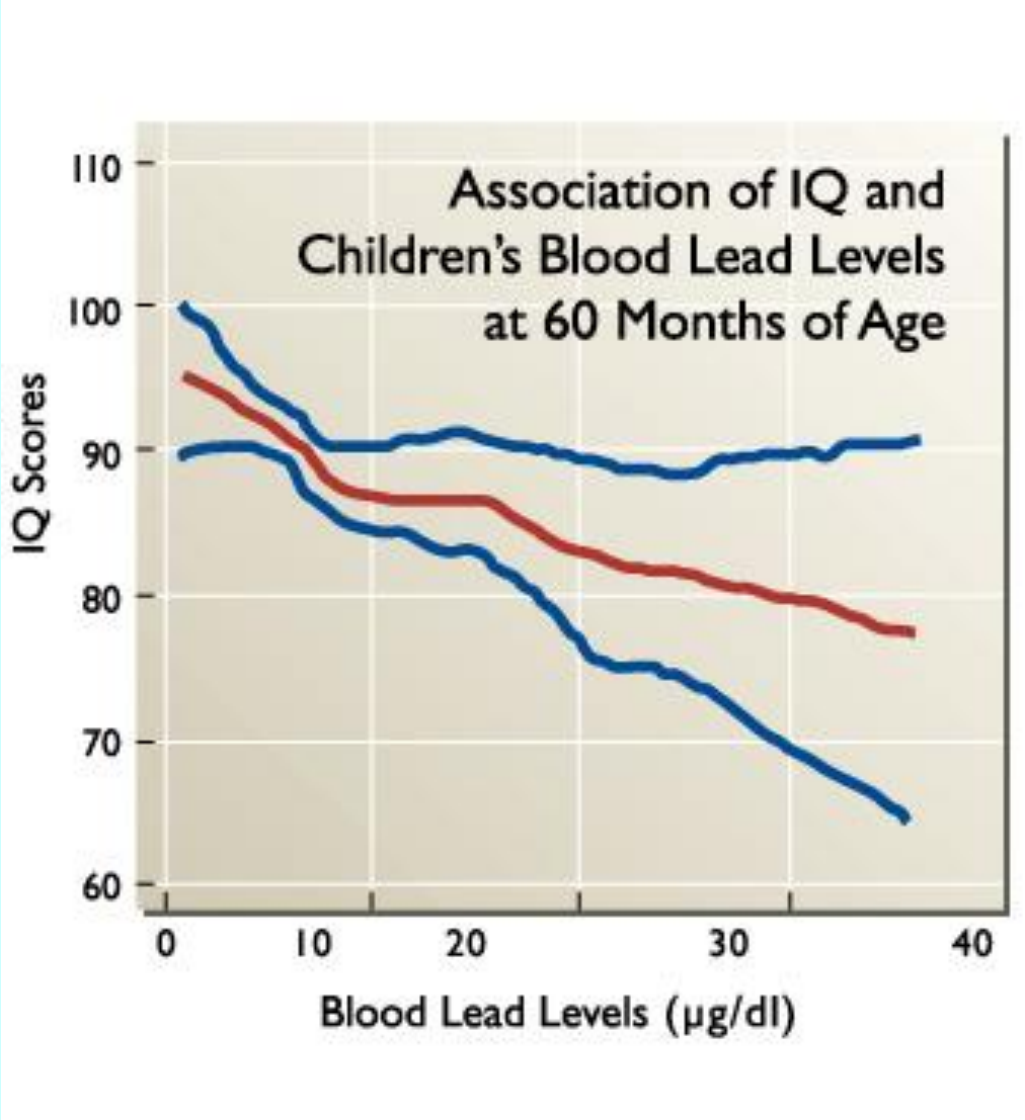


Lead-associated Reading Deficits in U.S. Children



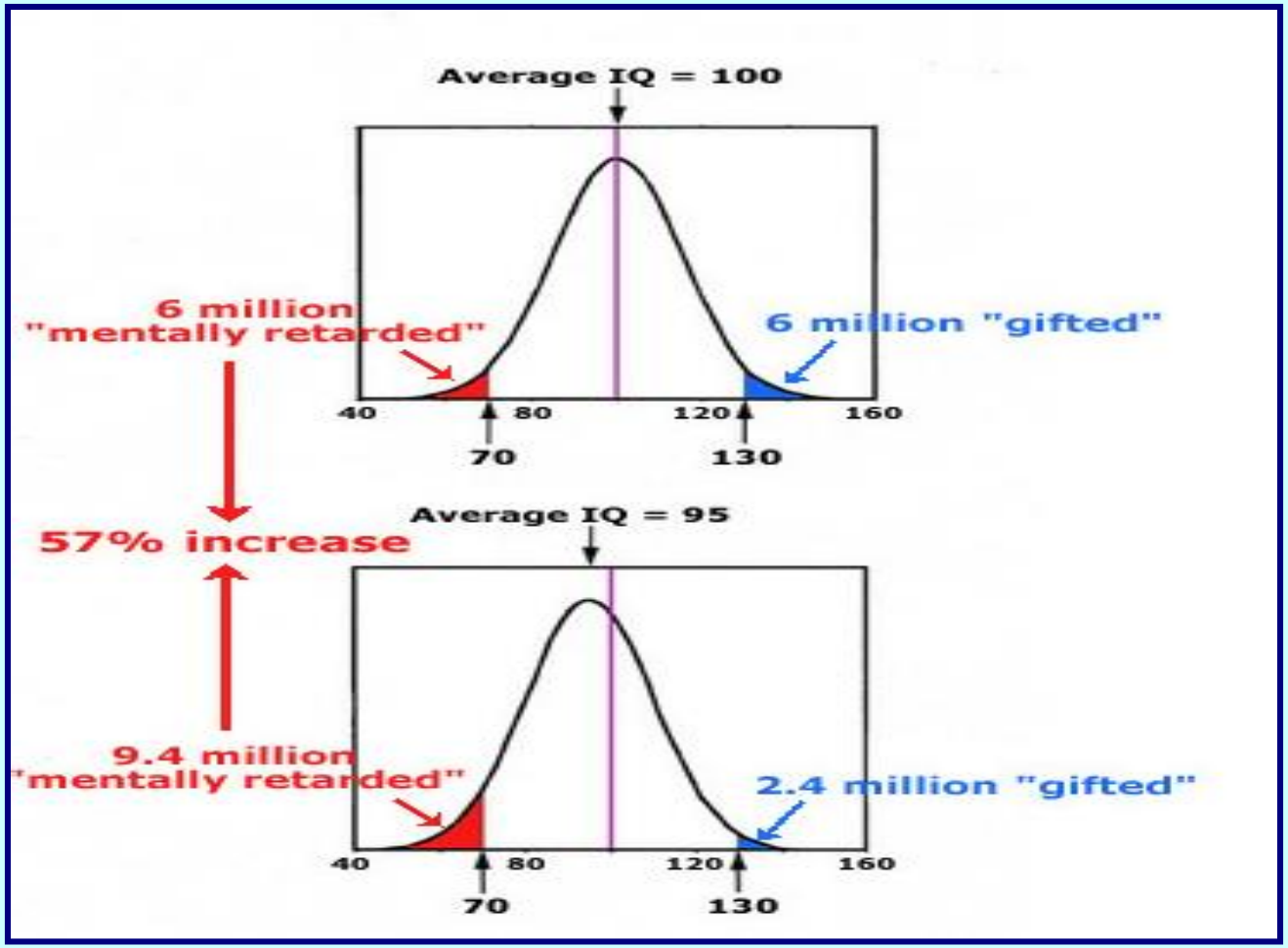
Lanphear BP, et al. Public Health Reports 2000;115:521-529. (BL's slide)

IQ and Blood Lead



Canfield R, et al. NEJM 2003;348:1517-1526. (slide from BL)

A 5-Point (5%) Shift in IQ Scores in a Population of 100 Million



CHILDREN

Blood Lead (ug Pb/dl)

ADULTS

150

Death

100

Encephalopathy

Encephalopathy
Nephropathy
Frank Anemia

Frank Anemia

Decreased Longevity

Colic

50

Hemoglobin Synthesis

Peripheral Neuropathies

Hemoglobin Synthesis

40

Infertility (MEN)
Nephropathy

Systolic Blood Pressure (MEN)

Vitamin D Metabolism

30

Hearing Acuity

Nerve Conduction Velocity

20

Erythrocyte Protoporphyrin
Vitamin D Metabolism(?)

Erythrocyte Protoporphyrin (Women)

DEVELOPMENTAL TOXICITY

10

Hypertension (?)

IQ
HEARING
GROWTH

Transplacental Transfer
- Low birth weight
- Miscarriages, Stillbirth
- Premature birth

Reproductive Effects Of Lead

WOMEN

- lead crosses the placenta
- low infant birth weight
- retarded mental development
- miscarriages
- premature birth
- stillbirth

MEN

- decreased sex drive
- impotence
- sterility
- altered sperm-birth defects

Why Screen For Lead Exposure

Find the source

Reduce risky behaviors

Education about the hazards

Education about nutrition

Why set an action level of 5 ug/dl ?

1. Protective / precautionary
2. Consistent with Science
3. Consistent with Medicine
4. Consistent with CDC / NIOSH
5. Sends a strong message
6. Protect young workers (16)
7. Protect women
8. Protect the home and family
9. Educational
10. Environmental justice

Recent Commentary

Environmental Health News – 9/12/16

- Commentary: Lead exposure beyond Flint—protecting our nation's workers

Seattle Times Editorial – 7/31/16

Outdated Lead Standards Put Washington State Workers & Families at Risk

By – Rachel Shaffer and StevenGilbert

Lead 10 to 2

Rationale for Lowering the Blood Lead Action Level From 10 to 2 µg/dL

Steven G. Gilbert and Bernard Weiss

Neurotoxicology Vol 27/5, September 2006, pp 693-701.
http://dx.doi.org/10.1016/j.neuro.2006.06.008

Lead - References

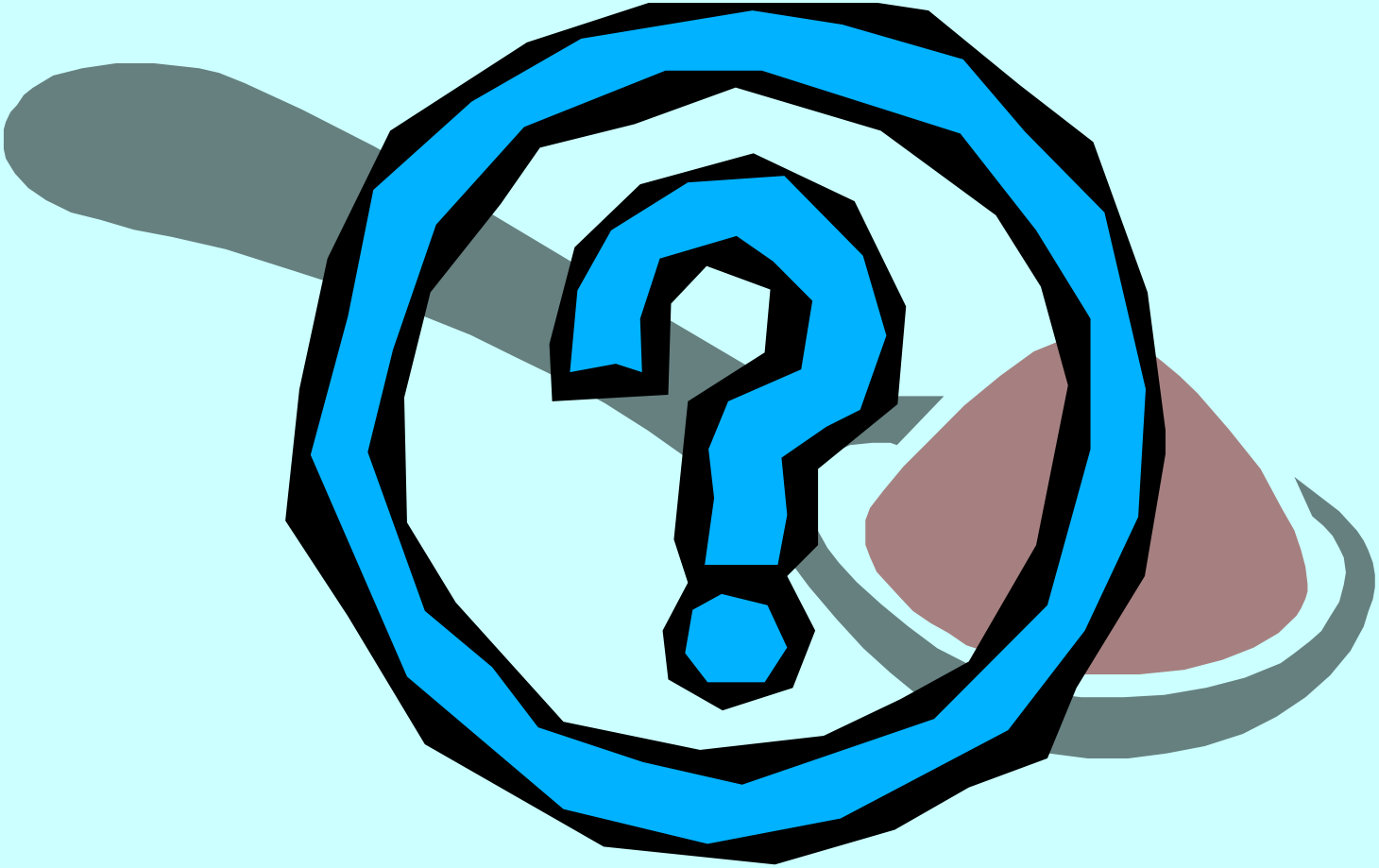
EPA – Lead site – the best

http://www.epa.gov/opptintr/lead/index.html

CDC Childhood Lead Poisoning Prevention Program
http://www.cdc.gov/nceh/lead/lead.htm

A Small Dose of Toxicology
www.asmalldoseof.org

A Small Dose of ™ Lead



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