TOXİCOLOGY

METALS

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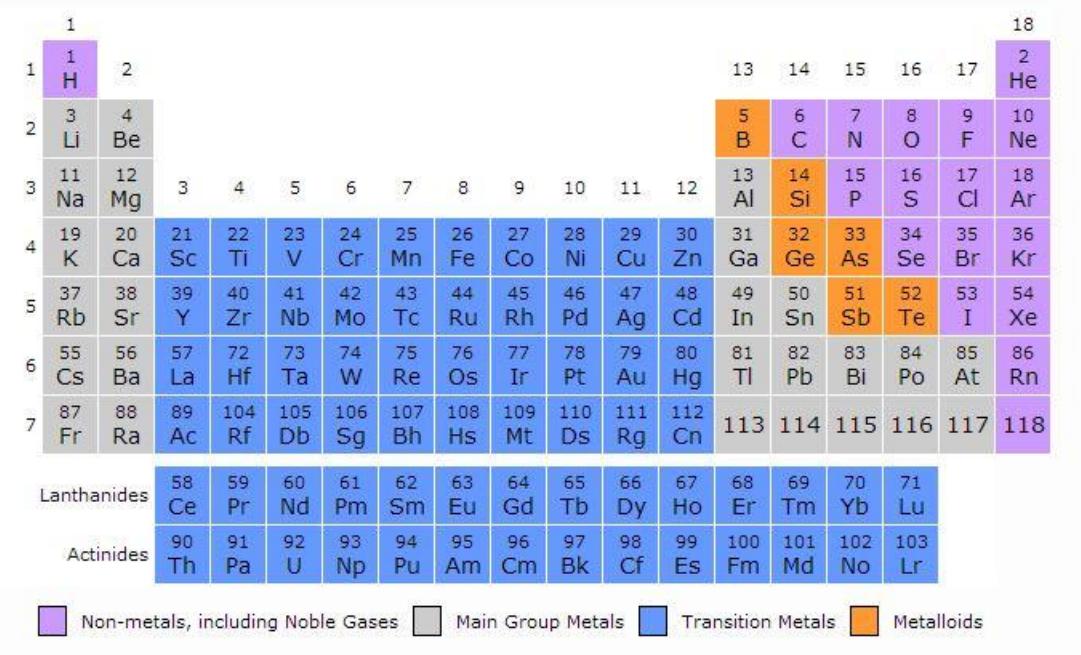
METALS…

The most important heavy metals that can be and have been used as poisons are;

Lead (Pb)
Mercury (Hg)
Arsenic (As)
Cadmium (Cd)



- Sources of exposure …?
- Toxic effets…?
- Kanserojenik etkileri…?
- Treatment of poisoning…?

International Agency for Research on Cancer

World Health Organization

Group 1: The agent is *carcinogenic to humans (120 agent)*.

Group 2.

Group 2A: The agent is *probably carcinogenic to humans (82 agent)*.

Group 2B: The agent is *possibly carcinogenic to humans (311 agent)*.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans (500 agent)*.

CAS No.	Agent	Group	Volume	Year	Additional information
105-60-2	Caprolactam	3	39, Sup 7, 71	1999	Moved to Group 3 following 2019 update to the IARC Monographs Preamble

https://monographs.iarc.fr/agents-classified-by-the-iarc/
(Accessed in 30.04.2019)

Arsenic

(As)
33

	1												13	14	15	16	17	18
1	1 H	2																2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg	3	4	5	6	7	8	9	10	11	12	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 Ac	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113	114	115	116	117	118

Lanthanides	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
Actinides	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

Non-metals, including Noble Gases | Main Group Metals | Transition Metals | Metalloids

Arsenic

(As)
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INTRODUCTION

Arsenic has been known and used since ancient times as the **POISON of KINGS** and/or the **KING of POISONS**.

Arsenicals have been used since ancient times as drugs and even today are very effective against **acute promyelocytic leukemia**.

Inorganic arsenic exists in the trivalent and pentavalent forms;

Inorganic trivalent arsenic:
Arsenic trioxide and Sodium Arsenite

Inorganic pentavalent arsenic:
Sodium Arsenate, Arsenic Pentoxide and Arsenic Acid.

Arsine (AsH_3):
Is an important gaseous arsenical.
Toxicity: < As5+ < As3+ < Arsine gas (AsH3).

Organic Arsenic:
Less toxic than inorganic arsenic. Produced by biomethylation

Arsenic

(As)
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INTRODUCTION

Sources of Arsenic:

- Groundwater
- Arsenic containing mineral ores
- Industrial processes
- Semiconductor manufactoring (gallium arsenide is used in the manufacture of light-emitting diode «LED»)
  - Fossil fuels
  - Wood trated with arsenic preservatives
  - Smelting and refining of metals and ores
  - Glas manufacturing
- Commercial Products
  - Wood preservatives
  - Pesticides
  - Herbicides
  - Fungicides
- Food
  - Seafood and fish
- Soil Pica Behaviour (when children ingest large amounts of soil at a time (up to 1 teaspoon or 5000 mg).

Arsenic

(As)
33

TOXICOKINETICS

ABSORTION

- Inorganic arsenic is well absorbed (80-90%) from the gastrointestinal tract.
- Often metabolized by methylation and then excreted primarily in urine.
- Arsenic compound of low solubility are absorbed less efficiently after oral exposure (e.g., arsenic trioxide, arsenic selenide, lead arsenide and gallium arsenide).
- Skin is a potential route of exposure to arsenic, and systemic toxicity has been reported in persons having dermal contact with solutions of inorganic arsenic.
- Airborn arsenic is largely trivalent arsenic oxide.
- Excretion of absorbed arsenic is mainly via the urine.

Arsenic

(As)
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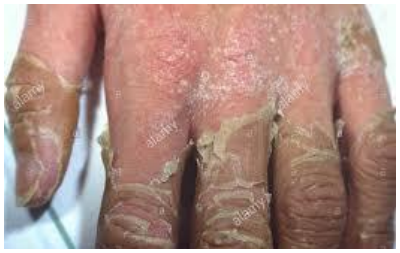
TOXICOKINETICS

EXCRETION

- Excretion of absorbed arsenic is mainly via the urine.
- Arsenic has a predilection for skin and is excreted by desquamation of skin and in sweat, particularly during periods of profuse sweating.
- $T_{1/2}$ of inorganic arsenic in the blood is 10 hours
- $T_{1/2}$ of organic arsenic in the blood is around 30 hours.
- 2-4 weeks after the exposure ceases, most of the remaining arsenic in the body is found in kreatinin-rich tissues (nails, hair and skin).



Arsenic

(As)
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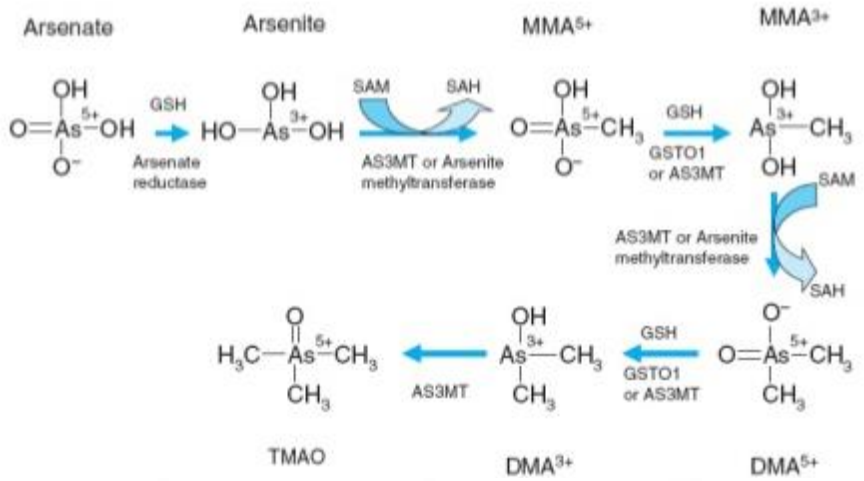
TOXICOKINETICS

METABOLISM

In humans, as in most mammalian species, inorganic arsenic is methylated to methylarsonic acid (MMA) and dimethylarsinic acid (DMA) by alternating reduction of pentavalent arsenic to trivalent and addition of a methyl group from S-adenosylmethionine. The major route of excretion of arsenic is via the kidneys. On average human urine contains 10-30% inorganic arsenic, 10-20% MMA and 60-80% DMA.



The intermediate metabolites, methylarsonous acid (MMA3+) and dimethylarsinous acid(DMA3+), are generated during this process, and these trivalent methylated arsenicals are now thought to be **more toxic** than even the inorganic arsenic species

Arsenic

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TOXICOKINETICS

METABOLISM

As^{5+} (Arsenate)

↓

As^{3+} (Arsenite)

↓

Methylarsenite (in liver)

↓

Dimethylarsenite

(readily eliminated – urine)

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ACUTE POISONING

- Ingestion of large doses (70-180 mg) of inorganic arsenic can be fatal.
- The oral LD50 values for inorganic arsenic compounds, depending on the arsenic species and the experimental animal, are in the range from 7 to 100 mg/kg body weight.
- Symptoms of acute intoxication include:
  - Fever
  - Anorexia
  - Hepatomegaly (enlarged liver)
  - Melanosis
  - Cardiac Arrhythmia
  - In fatal cases cardiac failure

Arsenic

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ACUTE POISONING

- Acute arsenic ingestion can damage;
  - Mucous membranes of the gastrointestinal tract (irritation, vesicle formation)
  - Sensory loss in the peripheral nervouıs system is the most common neurological effect, appearing at 1-2 weeks after large doses (a condition that is reversible if exposed is stopped).
  - Anemia and leucopenia (granulocytopenia)
  - Acute exposure to a single high dose can produce encephalopathy, with signs and symptoms of headache, lethargy, mental confusion, hallucination, seizures and coma.

Arsenic

(As)
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ACUTE POISONING

- Arsin gas (AsH_3);
  - Generated by electrolytic of metallic reduction of arsenic in nonferrous metal production.
  - It is a potent hemolytic agent, producing acute symptoms of nausea, vomiting, shortness of breath and headache accompanying the hemolytic reaction.
  - Exposure to arsine is fatal in up to 25% of the reported human cases.

Arsenic

(As)
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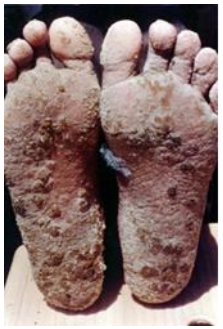
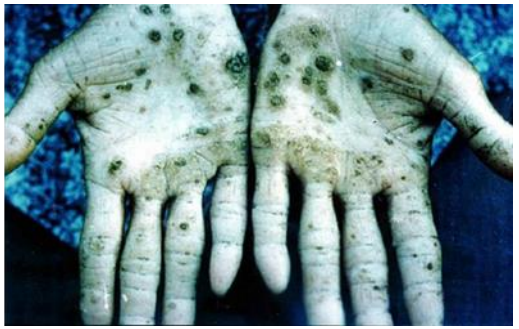
CHRONIC TOXICITY

SKIN;

- Major target organ in chronic arsenic exposure.
- Diffuse or spotted hiperpigmentation and , alternatively, hypopigmentation can first appear between 6 months to 3 years with chronic exposure to inorganic arsenic.
- Skin cancer is common with protracted high level arsenic exposure.

Palmar–plantar hyperkeratosis usually follows the initial appearance of arsenic-induced pigmentation changes within a period of years.





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CHRONIC TOXICITY

LIVER;

- Characteristics of long-term or chronic arsenic exposure, manifests;
  - Joundice
  - Abdominal pain
  - Hepatomegaly
  - Progress to chirrhosis
  - Hepatocellular carcinoma

Arsenic

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CHRONIC TOXICITY

PERIPHERAL NEUROPHATY;

- Repeated exposure to low level of inorganic arsenic can produce peripheral neurophaty;

- This neurophaty usually begins with:
  - Sensory changes (numbness in the hand and feet, painful pins and needle sensation)
  - Motor nerves be affected
  - Muscle tenderness
  - Weaknes

The effects are dose-related.

Arsenic

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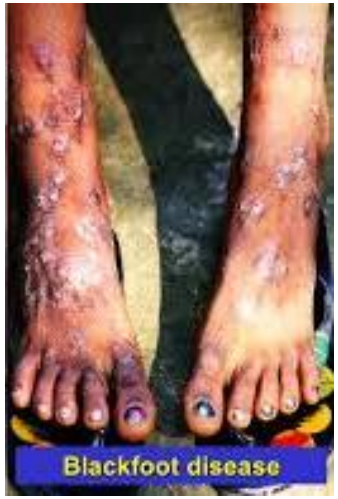
CHRONIC TOXICITY

CARDIOVASCULAR DISEASE;

- Peripheral vascular disease has been observed in persons with chronic exposure to inorganic arsenic.

- It is manifested;
  - Acrocyanosis
  - Raynoud's phenomenon
  - Progress to endarteritis and gangrene of the lower extremities (Black food disease).



Arsenic

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CARCINOGENICITY

- The carcinogenic potential of arsenic was recognized over 100 years ago.
- IARC has classified arsenic as a known human carcinogen, associated with tumors of the skin, lung, and urinary bladder and possibly kidney, liver and prostate.

International Agency for Research on Cancer

World Health Organization

Agents Classified by the *IARC Monographs*, Volumes 1–111

CAS No	Agent	Group	Volume	Year
007440-38-2	Arsenic and inorganic arsenic compounds	1	23, Sup 7, 100C	2012

Arsenic

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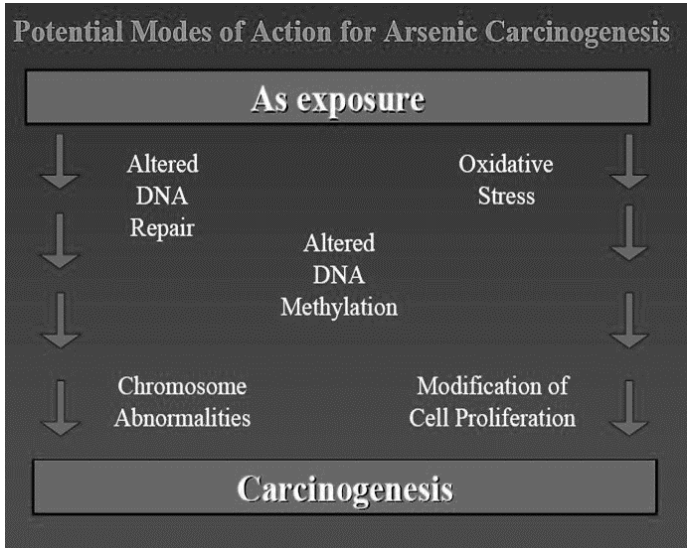

Arsenic

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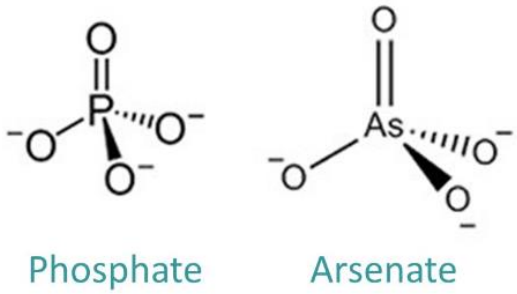
PATHOPHYSIOLOGY

Trivalent forms;
Bind to sulfhydryl groups leading to inhibition of enzymatic systems.
Inhibit the Krebs Cycle and oxidative phosporilation. These lead to inhibition of ATP production.

Pentavalent forms;
Can replace the stable phosphate ester bond in ATP and produce an arsenic ester stable bond which is not a high energy bond. In this way it bloks mitochondrial oxidative phosphorilation and finally inhibits ATP production.

Arsine gas;
Formed by the reaction of hydrogen with arsenic and is a potent hemolytic agent.

Chemical Structure of Phosphate and Arsenate



Phosphate Arsenate

Arsenic

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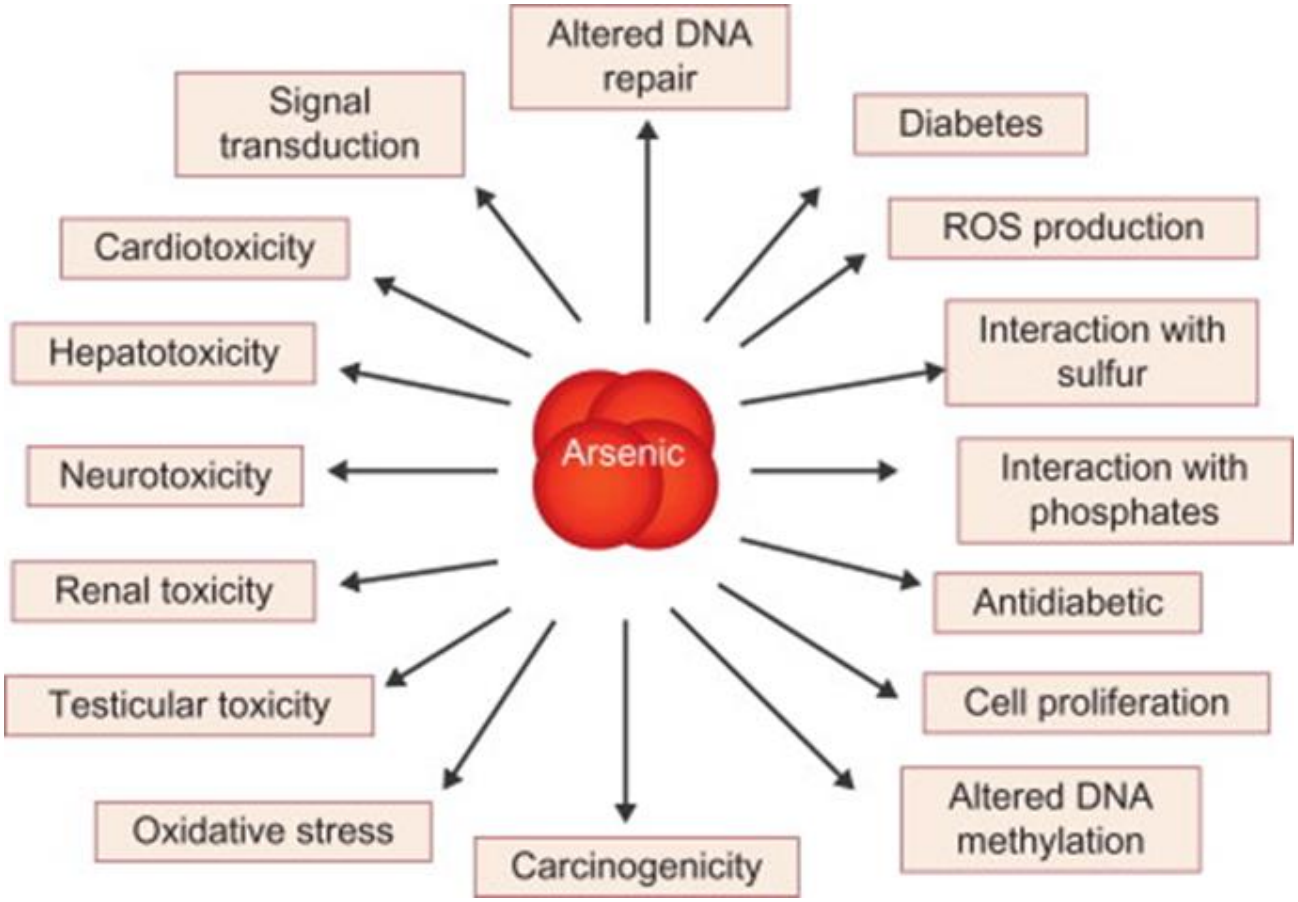
Summary of Arsenic mediated toxic effects



Arsenic

(As)
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Treatment of acute poisoning

- Gastric lavage
- Activated charcoal does not bind well inorganic arsenic
- Whole bowel irrigation with polyethylene glycol
- Skin decontamination in dermal exposure
- Supportive care

Arsenic

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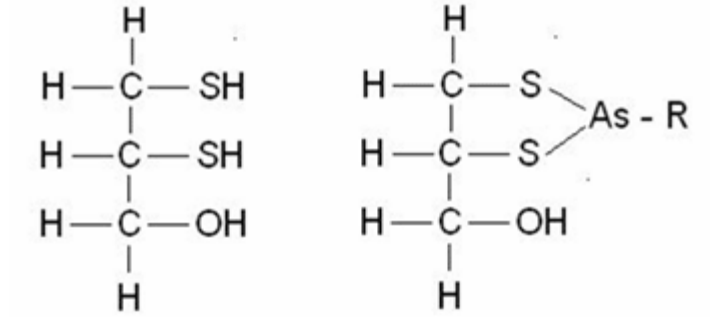
Treatment of acute poisoning

- Chelation therapy should be instituted promptly (minutes to hours)
  - Dimercaprol also called BAL (British anti lewisite) – IP
  - Succimer (DMSA) – PO
  - 2,3-dimercaptopropane-1-sulfonic acid, Na salt (DMPS) – PO, IV
  - D-Penicillamine – less effective

For chronic poisoning, chelation therapy has not proven effective in releiving symptoms.



Dimercaprol
also called
British Anti-Lewisite (BAL)

As - Dimercaprol

Arsenic

(As)
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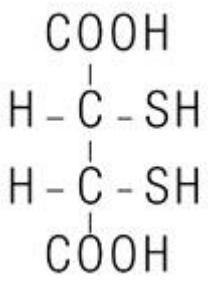
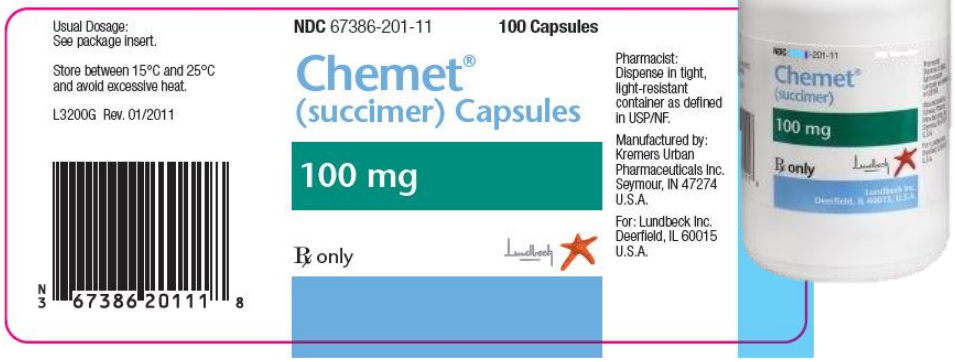
For chronic poisoning, chelation therapy has not proven effective in releiving symptoms.

Dimercaptosuccinic acid (DMSA), also called succimer, is a medication used to treat lead, mercury, and arsenic poisoning. [DMSA; Water soluble form of dimercaprol]





Arsenic

(As)
33

World Health Organization

Guidelines for Drinking-water Quality

FOURTH EDITION

Provisional guideline value	0.01 mg/l (10 µg/l)
	The guideline value is designated as provisional on the basis of treatment performance and analytical achievability.
Occurrence	Levels in natural waters generally range between 1 and 2 µg/l, although concentrations may be elevated (up to 12 mg/l) in areas containing natural sources
Basis of guideline value derivation	There remains considerable uncertainty over the actual risks at low concentrations, and available data on mode of action do not provide a biological basis for using either linear or non-linear extrapolation. In view of the practical difficulties in removing arsenic from drinking-water, as well as the practical quantification limit in the region of 1–10 µg/l, the guideline value of 10 µg/l is retained and designated as provisional.
Limit of detection	0.1 µg/l by ICP-MS; 2 µg/l by hydride generation AAS or flame AAS
Treatment performance	It is technically feasible to achieve arsenic concentrations of 5 µg/l or lower using any of several possible treatment methods. However, this requires careful process optimization and control, and a more reasonable expectation is that 10 µg/l should be achievable by conventional treatment (e.g. coagulation).

Arsenic

(As)
33

Arsenic contaminated drinking water

The discovery of arsenic contamination of groundwater in many nations, including Argentina, Chile, China, India, Mexico, Taiwan, Thailand, the United States and, now, Bangladesh shows that this is a global problem.

The contamination of groundwater by arsenic in Bangladesh is the largest poisoning of a population in history, with millions of people exposed. It is estimated that of the 125 million inhabitants of Bangladesh between 35 million and 77 million are at risk of drinking contaminated water. The scale of this environmental disaster is greater than any seen before; it is beyond the accidents at Bhopal, India, in 1984, and Chernobyl, Ukraine, in 1986.

Arsenic

(As)
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Arsenic in tube well water in Bangladesh: health and economic impacts and implications for arsenic mitigation

Sara V Flanagan, Richard B Johnston & Yan Zheng
Volume 90, Number 11, November 2012, 839-846

Arsenic concentration in drinking water and proportions exposed as determined by testing during national surveys, Bangladesh

Arsenic concentration (µg/L)	BGS/DPHE 2000 (*n* = 3 534)		MICS 2009 (*n* = 14 442)	
	Proportion (%)	Cumulative (%)	Proportion (%)	Cumulative (%)
0–10	57.9	57.9	68.0	68.0
10.1–50	17.1	75.1	18.7	86.6
50.1–100	8.9	84.0	7.2	93.8
100.1–150	4.2	88.2	1.4	95.2
150.1–200	2.9	91.1	1.4	96.6
200.1–250	2.1	93.2	1.1	97.8
250.1–300	1.8	94.9	0.4	98.2
300+	5.1	100	1.8	100

BGS, British Geological Survey; DPHE, Department of Public Health Engineering; MICS, Multiple Indicator Cluster Survey.

Lead

(Pb)
82

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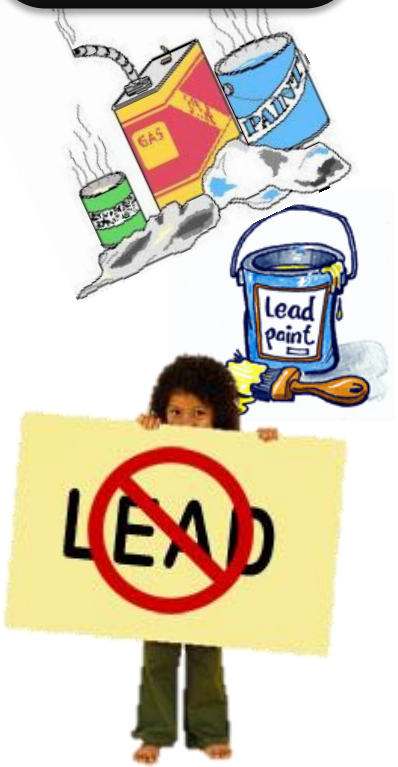
Non-metals, including Noble Gases | Main Group Metals | Transition Metals | Metalloids

Lead

(Pb)
82



Sources of Lead

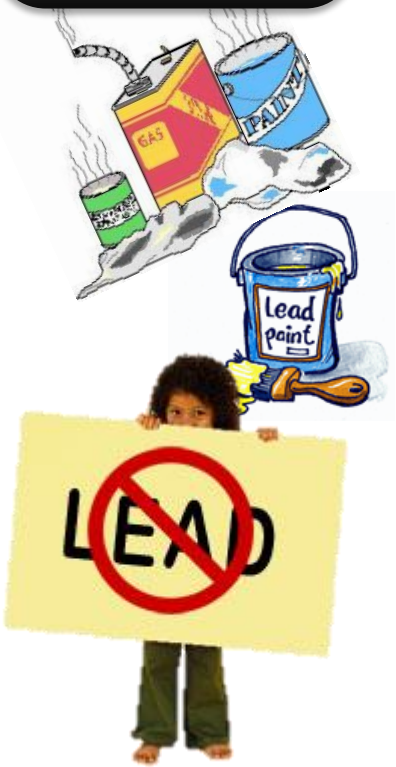
Soil:
Exposure to soil that contains particulate lead has been shown to be significantly hazardous for children, who are more commonly exposed by ingestion of house dust, soil and paint chips.

Water:
Drinking water is also a majör source of lead exposure.

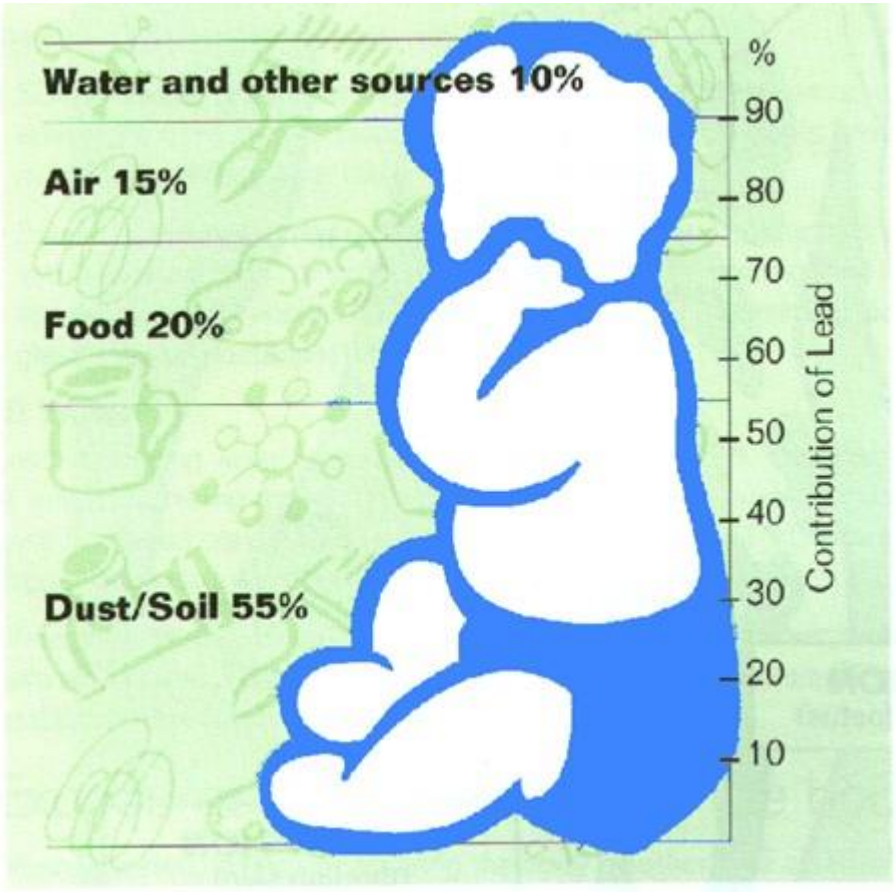
Occupational exposure:
Remodelling construction
Smelter
Batery factories
Ammunition factories
Ceramic glazes

Lead

(Pb)
82



Contribution of lead exposure sources



Lead

(Pb)
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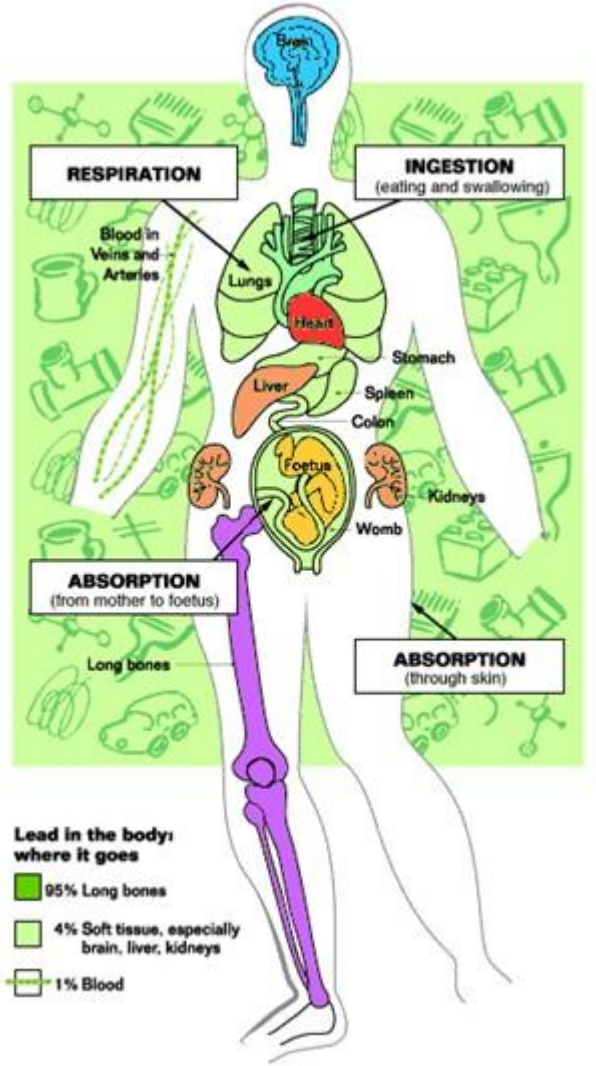
Distribution of lead (toxicokinetics)



Absorbtion of lead

Gastrointestinal tract:
Children absorb lead well orally (~50%) adults poorly (~10%).

Lead absrbtion is enhenced if diet is poor in iron or calcium.

High fat intake and inadequate calories have also been associated with enhenced lead absorption.

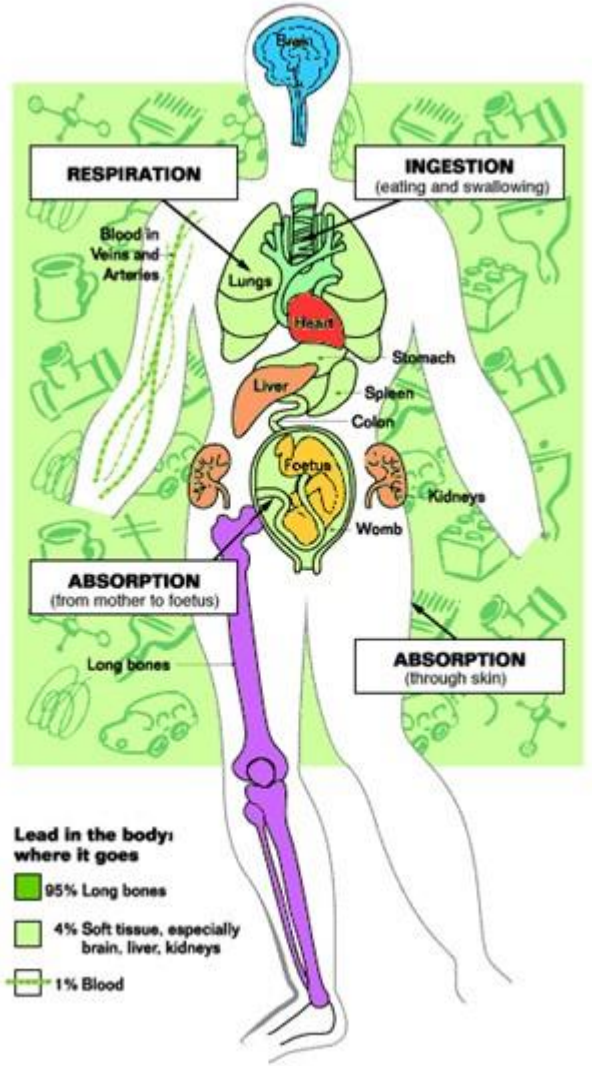
Respiratory:
Inorganic lead

Skin:
Organic lead

Lead

(Pb)
82

Distribution of lead (toxicokinetics)



Distribution:

95% in bone (70% in children).

4% in soft tissues (brain liver, kidneys, bone marrow).

1% in blood.

Lead readily crosses the placenta.

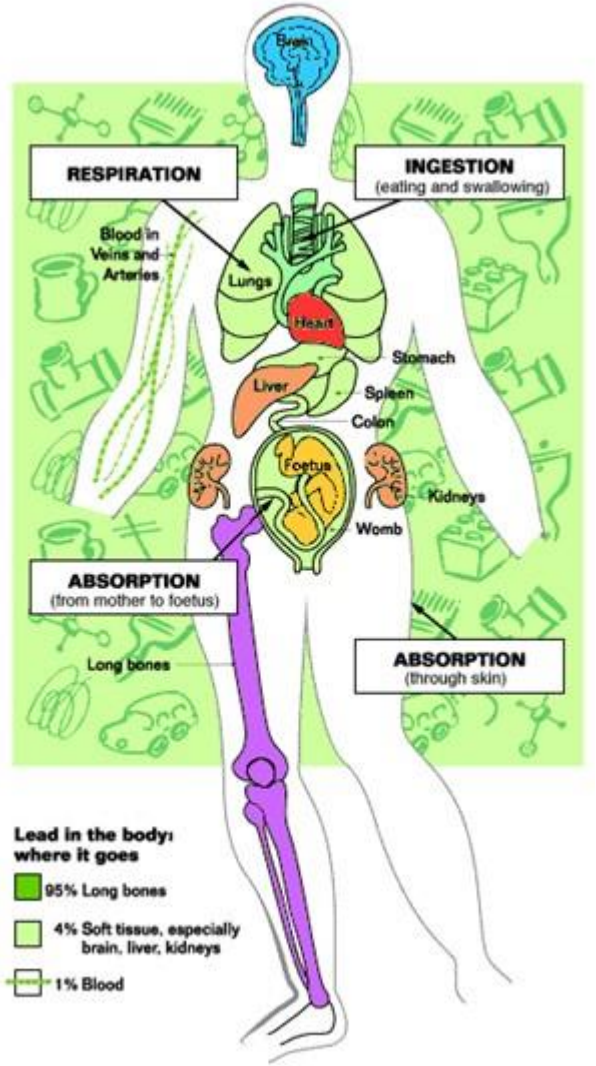
Half life of lead:

- 25 days – blood
- 40 days – soft tissue
- 20 years – bone

Lead

(Pb)
82

Distribution of lead (toxicokinetics)



Hepatic metabolism and excretion:

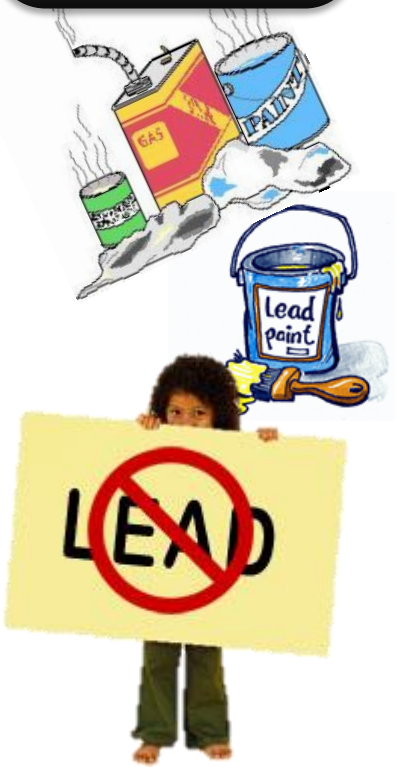
Inorganic lead is not metabolized but is excreted unchanged.

Organic or alkyl lead (leaded gasoline, tetraethyl and tetramethyl-lead) undergoes oxidative dealkylation to the highly neurotoxin metabolites, triethyl-lead and trimethyl-lead.

The major rout of excretion of absorbed lead is the kidney.

Urine: %65, Bile: %35

Lead
(Pb)
82



Toxic effects of lead

Nervous system

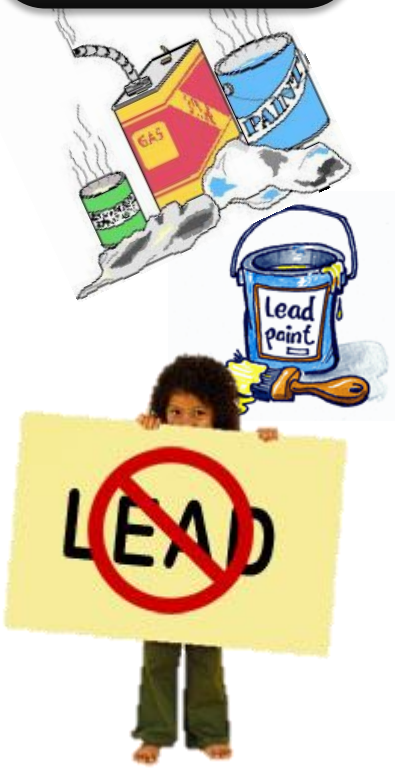
Neurological, Neurobehavioural and Developmental effects in children

Clinically overt lead encephalopathy may ocur in children with high exposure to lead, probably at BLL of 70 µg/dL or higher.

Symptoms of lead encephalopathy:
Lethergy,
Vomiting,
Irritability,
Loss of appetite
Dizziness

Progressing to obvious ataxia, and a reduced level of consciousness, which may progress to coma and death.

Lead
(Pb)
82



Toxic effects of lead

Nervous system

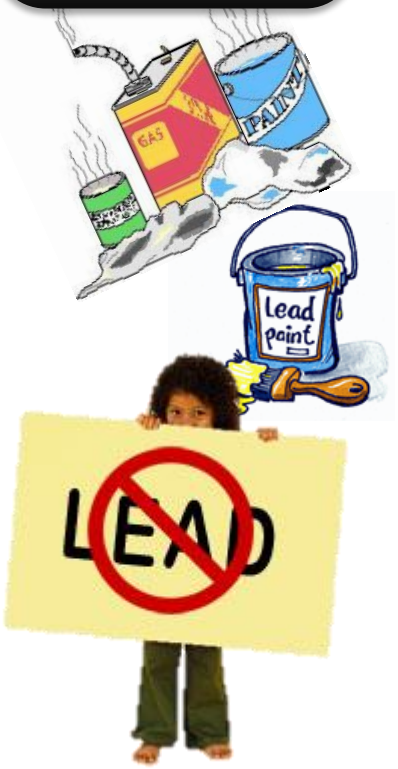
Neurological, Neurobehavioural and developmental effects in children

The pathological findings at autopsy are severe edema of the brain due to extravasations of fluid from capillaries in the brain. This is accompanied by the loss of neuronal cells and an increase in glial cells.

Recovery is often accompanied by sequelae including epilepsy, mental retardation and in same cases optic neuropathy and blindness.

Most studies report a 2- to 4-point IQ deficit for each µg/dL increase in BLL within the range of 5-35 µg/dL.

Lead
(Pb)
82



Toxic effects of lead

Nervous system

Neurological, Neurobehavioural and developmental effects in children

Lead can affect the brain by multiple mechanisms;

Lead can act as a surrogate for calcium and/or disrupt calcium homeostasis.

Lead effects every neurotransmitter system in the brain, including glutamatergic, dopaminergic and cholinergic systems.

All these systems play a critical role in synaptic plasticity and cellular mechanisms for cognitive function, learning and memory.

Lead
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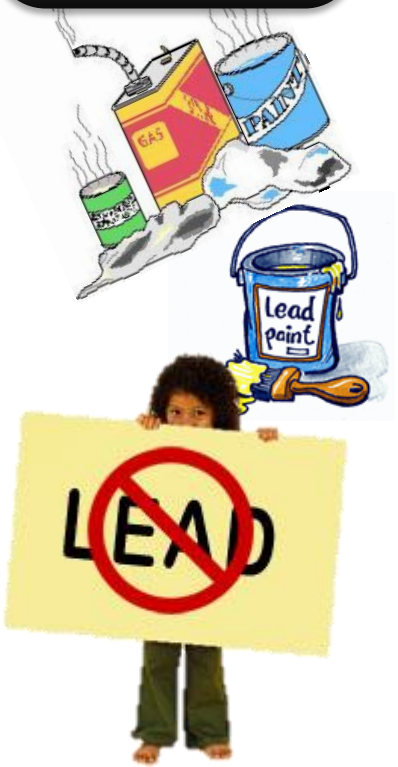


Toxic effects of lead

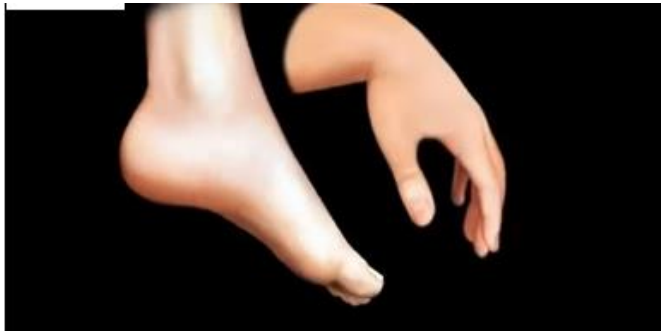
Nervous system

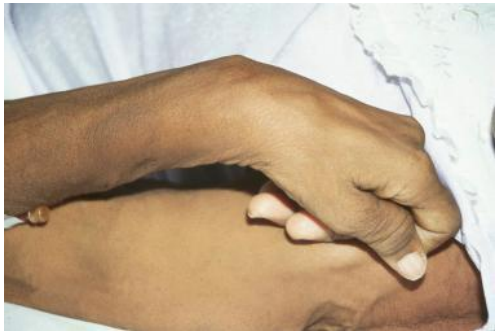
Neyrotoxic effects in adults

Central Nervous System (CNS):
Fatigue, irritability, lethargy, insomnia, headache, difficulty in concentrating, memory loss and tremor.

Severe lead intoxication can result in an encephalophaty characterized by depressed counsciousness, seizure, and coma in association with serebral edema.

Peripheral Nervous System (PNS):
Many years ago, foot drop and wrist drop characterised the house painter and other workers with excessive occupational exposure to lead.





Lead
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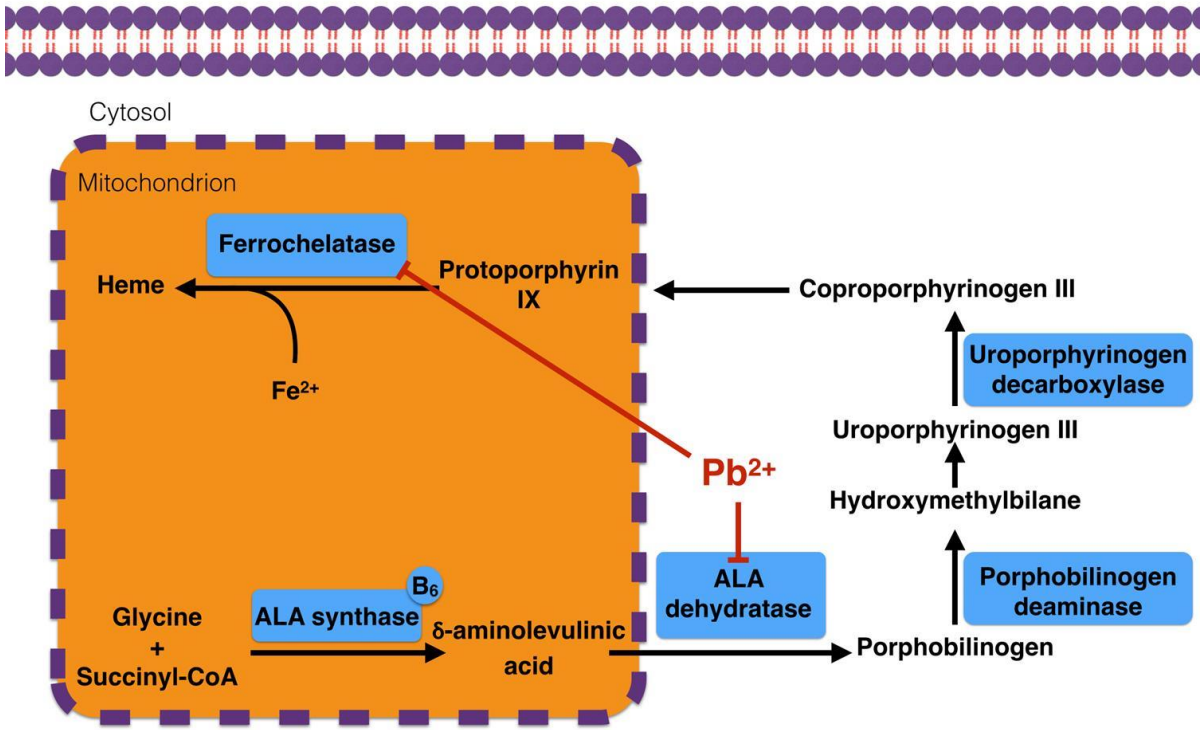
Toxic effects of lead

Hematologic Effects

Lead has multiple hematological effects ranging from inreased urinary porphyrins, coproporphyrins and δ-aminolevulinic acid (ALA) and zinc protoporphyrin to anemia.



Lead
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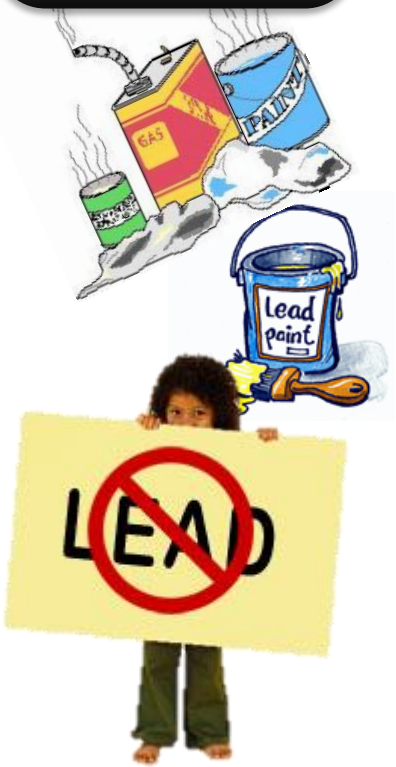

Toxic effects of lead

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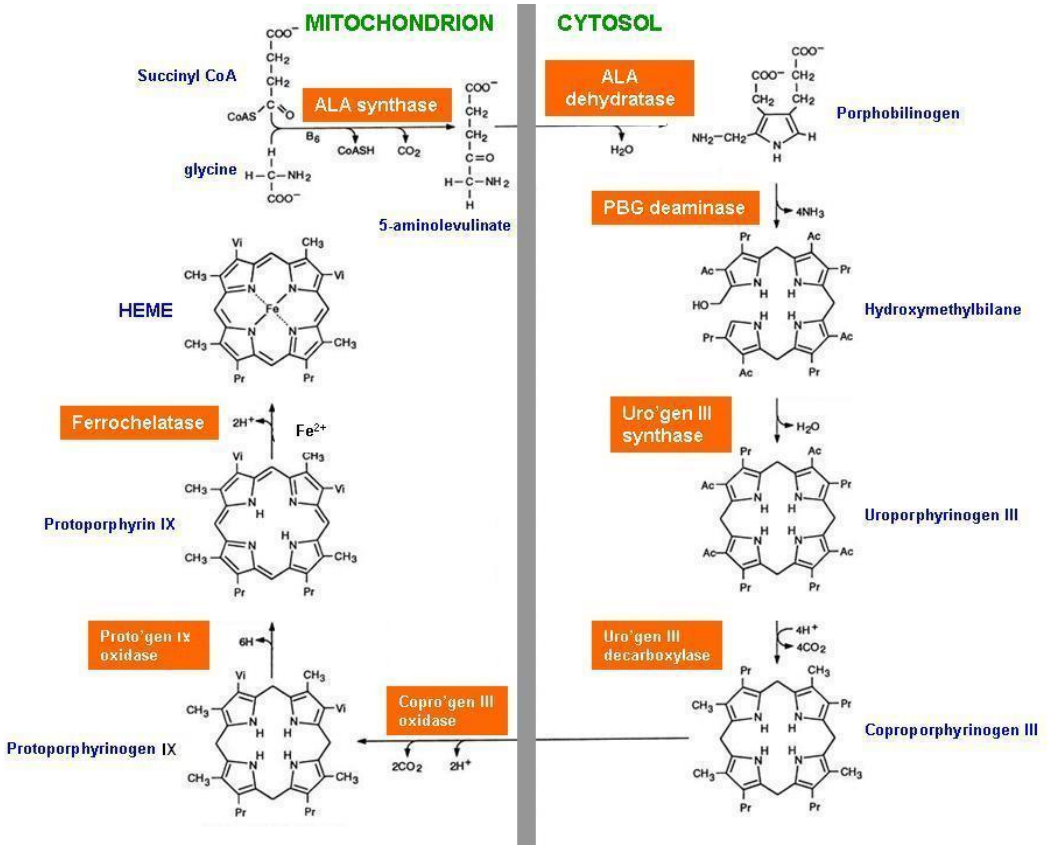

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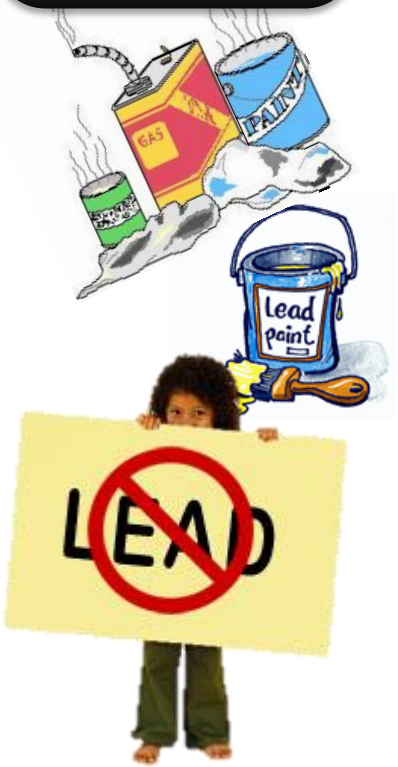

Toxic effects of lead

Effects on Cardiovascular System

The most important manifestation of lead toxicity on the cardiovascular system is hypertension.

Effects on Reproductive System:

Impairment of both male and female reproductive function is associated with plumbism.

Effects on Gastrointestinal System:

Lead colic is a major gastrointestinal symptom of severe lead poisoning and is characterized by abdominal pain, neusea, vomiting, constipation and cramps.

Lead
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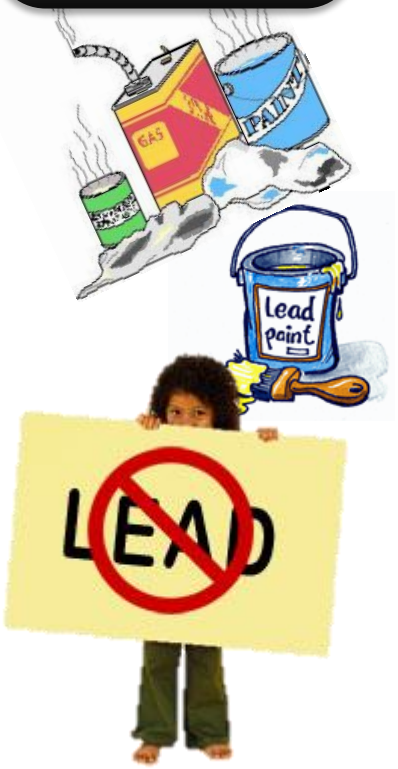
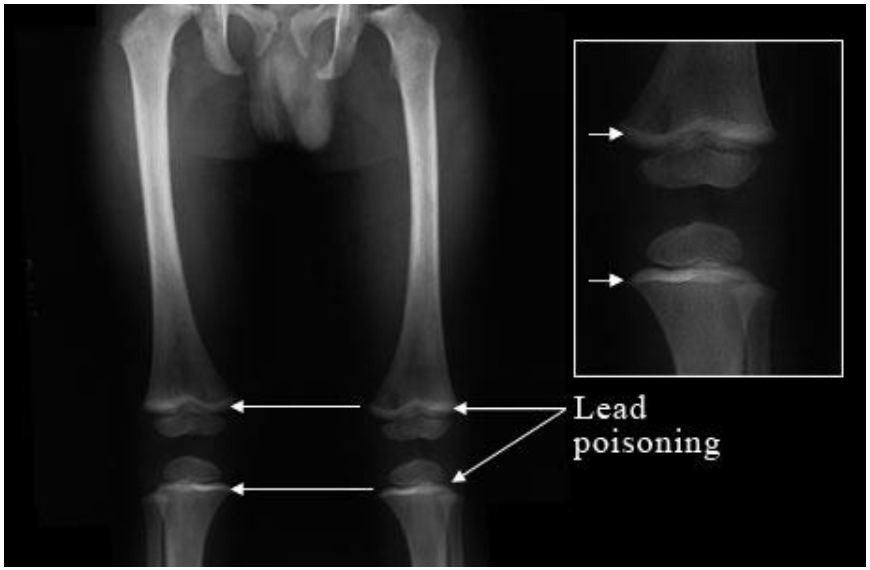


Toxic effects of lead

Bone Effects:

Lead has anextremely long half-life in bone, accounting for over 90% of the body lead in adults. Lead can affect bone by interfering with metabolic and homeostatic mechanisms including parathyroid hormeone, calcitonin, vitamin D and other hormones that influence calcium metabolism.

Lead substitutes for calcium in bone.
Lead exposure has been associated with osteoporosis and delays in fracture repair.



This X-ray shows white bands of lead collected in the growth plates of the knee joints of a child.

Lead

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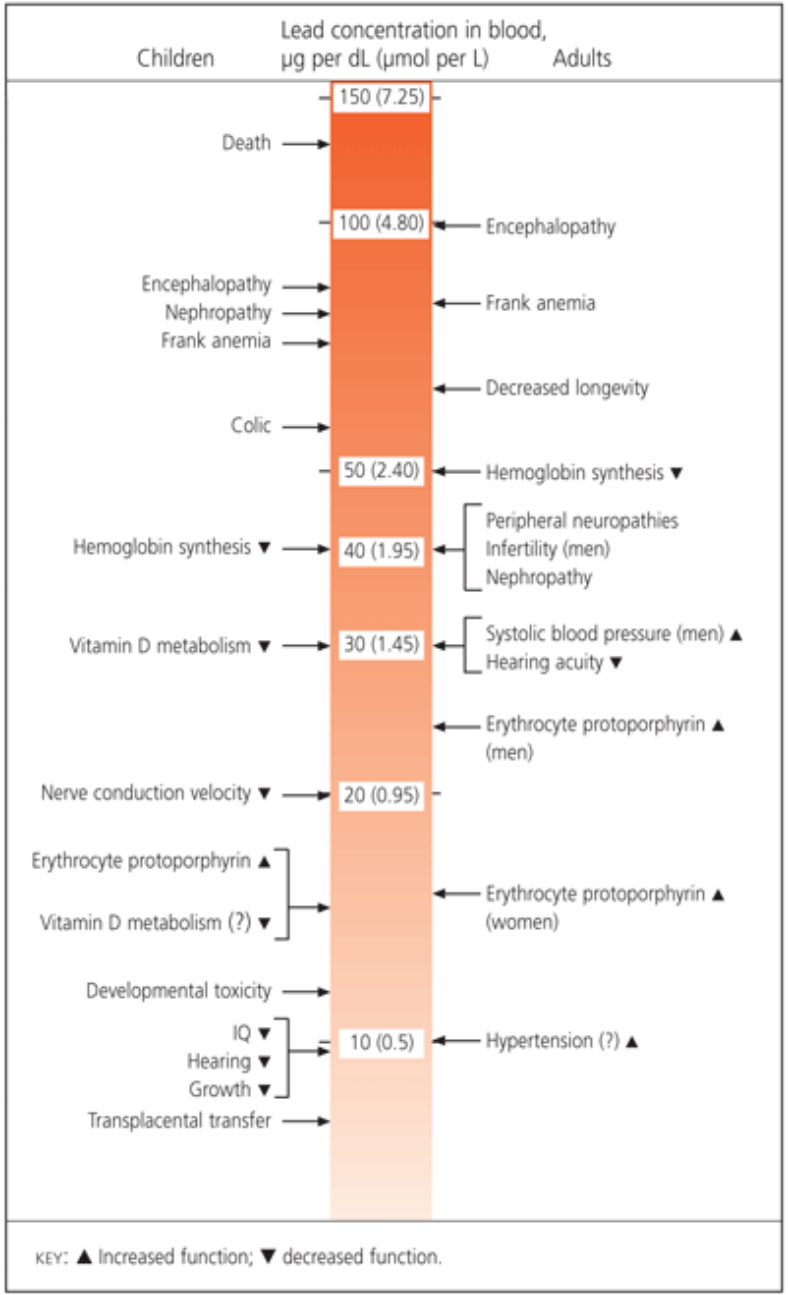
Toxic effects of lead



Lead

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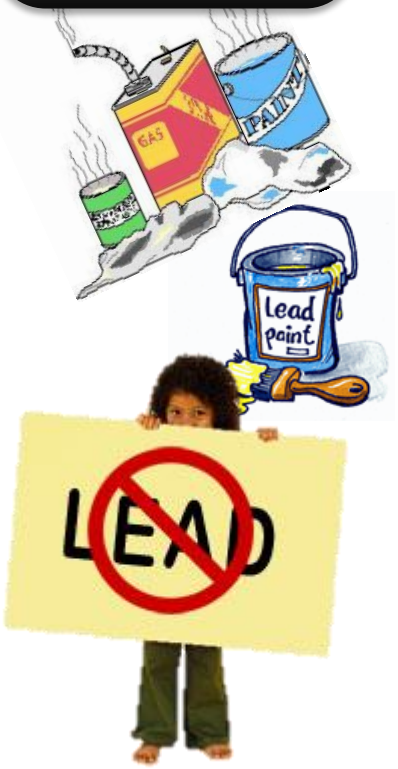
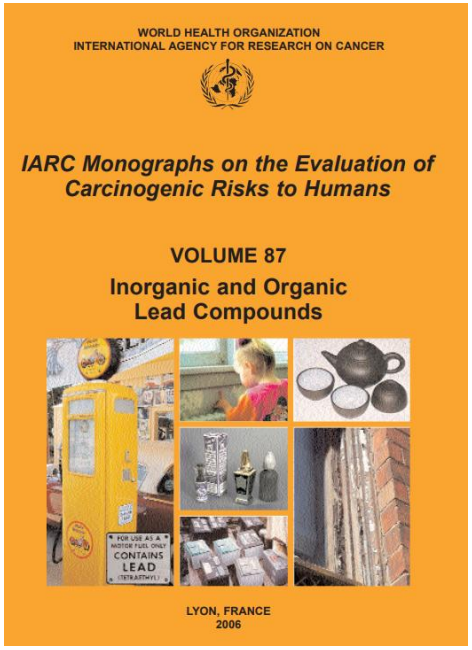


Toxic effects of lead

Carcinogenic effects:

- Inorganic lead compounds are probably carcinogenic to humans (Group 2A).
- Organic lead compounds are not classifiable as to their carcinogenicity to humans (Group 3)



International Agency for Research on Cancer

World Health Organization

Agents Classified by the *IARC Monographs*, Volumes 1–111

CAS No	Agent	Group	Volume	Year
	Lead compounds, inorganic	2A	Sup 7, 87	2006

Lead

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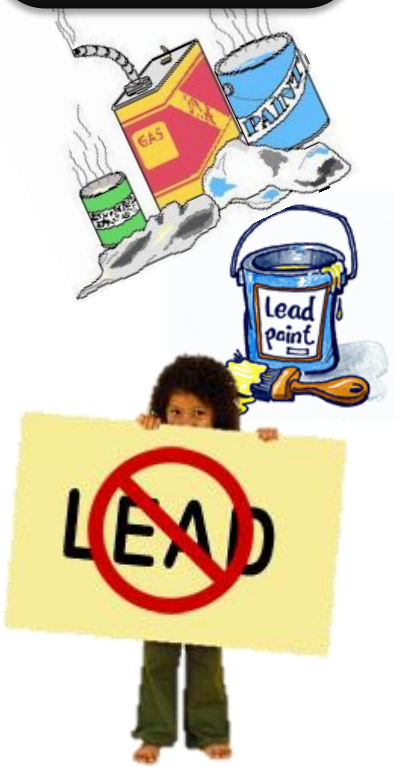

Critical Lead Levels:

< 0.48 µmol/L (10 µg/dL) – Normal Level

> 0.48 µmol/L (10 µg/dL) – Elevated Level

> 0.72 µmol/L (15 µg/dL) – Substantially Elevated Level

> 1.20 µmol/L (25 µg/dL) – Dangerously Elevated Level

> 2.20 µmol/L (45 µg/dL) – Symptomatic

Lead

(Pb)
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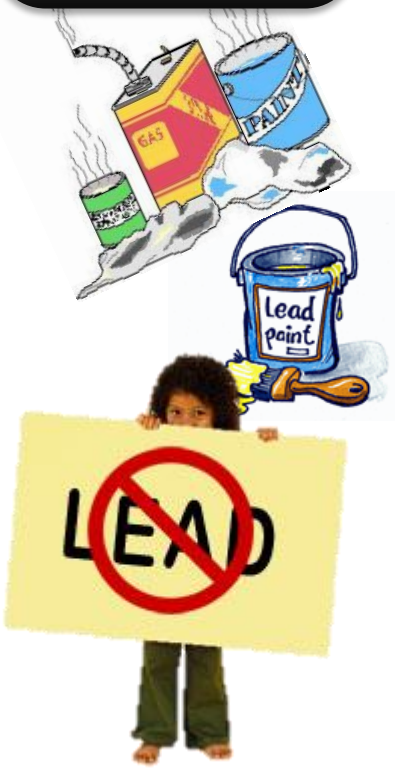

Recomended Lead Levels:

Lead:
WHO Drinking Water Guideline Provisional guideline value: 0.01 mg/L (10 µg/L)

EU's drinking water standards: 0.01 mg/L (10 µg/L)

World Health Organization

Guidelines for Drinking-water Quality

FOURTH EDITION

Provisional guideline value	0.01 mg/l (10 µg/l)
	The guideline value is provisional on the basis of treatment performance and analytical achievability.
Occurrence	Concentrations in drinking-water are generally below 5 µg/l, although much higher concentrations (above 100 µg/l) have been measured where lead fittings are present. The primary source of lead is from service connections and plumbing in buildings; therefore, lead should be measured at the tap. Lead concentrations can also vary according to the period in which the water has been in contact with the lead-containing materials.
Basis of guideline value derivation	The guideline value was previously based on a JECFA PTWI, which has since been withdrawn, and no new PTWI has been established, on the basis that there does not appear to be a threshold for the key effects of lead. However, substantial efforts have been made to reduce lead exposure from a range of sources, including drinking-water. Because it is extremely difficult to achieve a lower concentration by central conditioning, such as phosphate dosing, the guideline value is maintained at 10 µg/l but is designated as provisional on the basis of treatment performance and analytical achievability.

Lead
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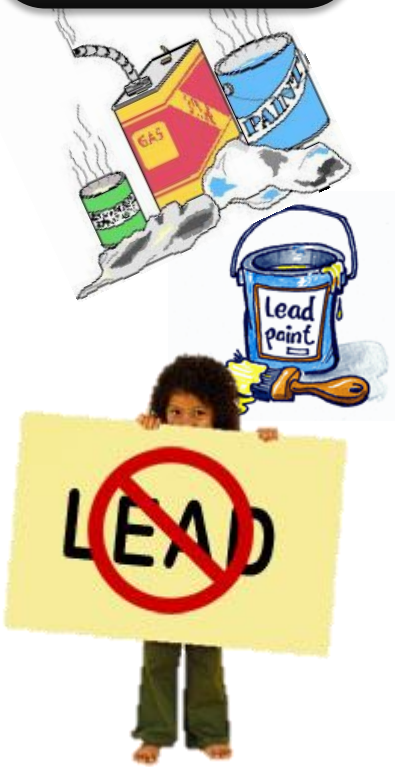

Management

Identify and Remove from the source of Exposure

Nutrition Therapy

Diets high in iron and calcium

Examples of foods high in iron are:
Cheese, fish, meat, eggs, beans, spinach and raisins

Examples of food high in calcium are:
Milk, cheese, ice cream, yoğurt, bread, fish, meat, broccoli, fruit and nuts.

Lead
(Pb)
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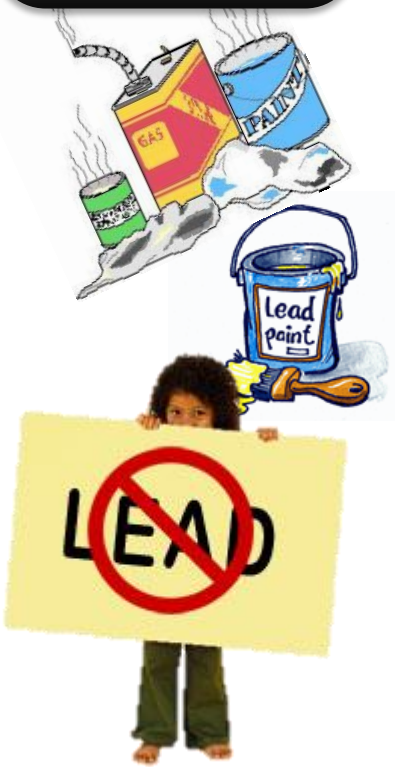

Chelating Therapy

Chelating therapy is widely recomended for asymptomatic children with BLL >45 µg/dL .

EDTA – Sodium Calcium Edetate
1000 – 1500 mg/m2/day, IV or IM
IV for severe toxicity, particularly for encephalophaty.
Well tolerated,
<1% nephrotoxicity

BAL – Dimercaprol
450 mg/m2/day
IM for severe toxicity only, particularly encephalopathy.

DMSA – 2,3 dimercaptosuccinic acid
Oral administration
Well tolerated
The main problem is foul taste and smell
Minimal side effects in decades of experience

D-Penicillamine
10-15 mg/kg per day for 4-12 week based on severity.

Lead
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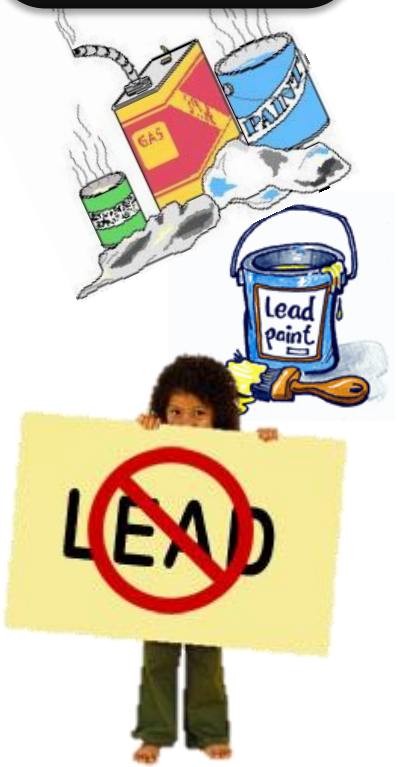
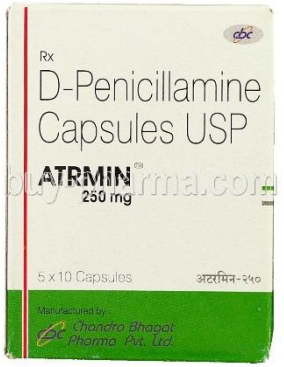


Chelating Therapy

Edetate Disodium Calcium ($CaNa_2EDTA$)
Dimercaprol (BAL)
} parenteral

Succimer
D-Penicillamine
} Oral



Calcium disodium edetate ($CaNa_2EDTA$)

- Calcium chelate of Na_2EDTA is used clinically instead of Na_2EDTA – ethylene diamine tetracetic acid
- High affinity for Pb, Zn, Cd, Mn, Cu and some radioactive metals
- **MOA:** Removes the metals by exchanging with Ca++
- Highly ionized – not absorbed orally and that's why acts extracellularly – rapidly excreted via kidney
- Given IV as not absorbed in gut – IM is painful
- No CSF penetration
- Uses:
  - Lead Poisoning – 1 gm is diluted in 200-300 ml of NS infused over 1 hr twice daily – 2nd course repeated after 1 week
  - Fe, Zn, Cu and Mn poisoning – but not in Hg poisoning
- **ADRs:** 1. **Kidney damage** – toxic metal dissociate in tubule – should enhance urine flow; 2. **febrile reactions** – chills, body ache, malaise, tiredness etc. 3. **Anaphylactoid reactions**

Penicillamine

- Degraded product of Penicillin (beta dimethylcysteine)
- Prepared by alkaline hydrolysis of benzyl penicillin – d-penicillamine
- Strong Cu chelating property - useful in Cu poisoning
- MOA is same as others – selective chelating of Cu, Hg, Pb and Zn
- Absorbed orally - available as 250 mg capsules, metabolized in liver and excreted in urine
- Uses:
  - Wilson`s disease: hepatolenticular degeneration due to genetic deficiency of ceruplasmin (Cu deposition in body) – life long therapy (0.5-1 gm daily)
  - Cu and Hg (alternative) Poisoning
  - Chronic Pb poisoning (adjuvant to edetate)
  - Cystinuria and cystine stones
  - Scleroderma: benefits by increasing soluble collagen
- ADRs: Cutaneous dermatological reactions
  - General: headache, sore throat, fever, rash, loss of taste, neuritis
  - Blood: leucopenia, thrombocytopeenia, aplastic anaemia etc.
  - Renal: nephrotic syndrome, haematuria
  - Autoimmune: Myaesthenia like syndrome, diabetes, SLE etc.

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Teşekkür ederim….