TOXİCOLOGY

METALS

Prof. Dr. Yalçın Duydu, PhD, ERT

Ankara University, Faculty of Pharmacy
Department of Toxicology, Tandoğan, Ankara

Mercury

Quick Silver,
(Hg), 80

	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	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	7 A	80 Hg	1 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	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

Mercury

Quick Silver,
(Hg), 80

What is mercury? (Mercury is also known as quicksilver or liquid silver)

- Naturally occurring metal
- Shiny, silver-White
- Odorless liquid at room temperature
- Vapor is odorless and colorless
- İnsoluble in water

Chemistry of Mercury

- Elemental mercury
- Inorganic mercury
- Organic mercury (methyl mercury)

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Chemistry of Mercury

- A gas, Hg^0 (elemental mercury)
- A liquide, Hg^0 (elemental mercury)
- An ionic solid, which is usually somewhat soluble in water, Hg^{2+}
- An organometallic ion dissolved in water, $MeHg^{1+}$ [CH_3Hg^{+1}]
- A volatile, liquid organometallic compound, Me_2Hg [$(CH_3)2Hg$]

Mercury

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Occurance

Occationally found free
Cinnabar ore (HgS) in Spain and Italy

Important salts include;

- Mercury chloride, $HgCl_2$ (corrosive sublimate)
- Mercurous chloride, Hg_2Cl_2 (calomel, was used in medicine)
- Mercury fulminate, $Hg(ONC)_2$, (detonator for explosives)
- Mercuric sulfide, HgS, (vermilion, high-grade paint pigment)

Vermilion

Cinnabar

Mercury

Quick Silver,
(Hg), 80

Historical use

In 1731 and 1732 it was «fashinable in London and Edinburgh to take one once of quick silver every morning for several weeks».

The internal use of calomel was accompanied by gastrointestinal symptoms so drastic that in the 19th century, not only chloride of mercury but also the other forms fell into general disfavor.

Industrial use

Thermometers, barometers, electrical switches, pesticides, was used in gold recovery from mining.

Mercury

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(Hg), 80

Toxicity

Inhalation:
Causes severe respiratory tract damage. Symptomes include sore throat, coughin, pain, tightness in chest, breathing difficulties, shortness of breath, headache, muscle weakness, anorexia, gastrointestinal disturbance, ringing in the ear, liver damage, fever, bronchitis and pneumonitis. Can be absorbed through inhalation with symptoms similar to ingestion.

Ingestion:
May cause burning of the mouth and pharynx, abdominal pain, vomiting, corrosive ulceration, bloody diarrhea. May be fallowed by a rapid and weak pulse, shallow breathing, paleness, exhaustion, tremors and collaps. Delayed death may occure from renal failure. Gastrointestinal uptake of mercury is less than 5% but its ability to penetrate tissues presents some hazards. Initial symptomes may be thirst, possible abdominal discomfort.

Skin Contact:
Causes irritation and burns to skin. Symptoms include redness and pain. May cause scin allergy and sensitization. Can be absorbed through the skin with symptoms to parallel ingestion.

Mercury

Quick Silver,
(Hg), 80

What is mercury?

Mercury has no positive role in the human body; in fact a safe level of mercury exposure is very difficult to determine. It can be present in the environment in several different forms, and while all forms of mercury are toxic to humans, the pattern of toxicity varies with its chemical form, the route of exposure, the amount, the duration and timing of exposure, and the vulnerability of the person exposed.

For example, pure elemental mercury (also known as quicksilver or Hg) is liquid at room temperature. If ingested, quicksilver has very low toxicity because it is not absorbed by the gastrointestinal tract and is eliminated completely in the stool.

If quicksilver is agitated or heated, however, the liquid mercury becomes a vapour which is readily absorbed by inhalation and is highly toxic to the lungs and central nervous system. The nervous system is the primary target of mercury toxicity, but, depending upon the specific exposure, the kidneys, liver and lungs are also important targets.

Mercury

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(Hg), 80

Human health effects

High doses of mercury can be fatal to humans, but even relatively low doses of mercury containing compounds can have serious adverse impacts on the developing nervous system, and have recently been linked with possible harmful effects on the cardiovascular, immune and reproductive systems. Mercury and its compounds affect the central nervous system, kidneys, and liver and can disturb immune processes; cause tremors, impaired vision and hearing, paralysis, insomnia and emotional instability. During pregnancy, mercury compounds cross the placental barrier and can interfere with the development of the foetus, and cause attention deficit and developmental delays during childhood.

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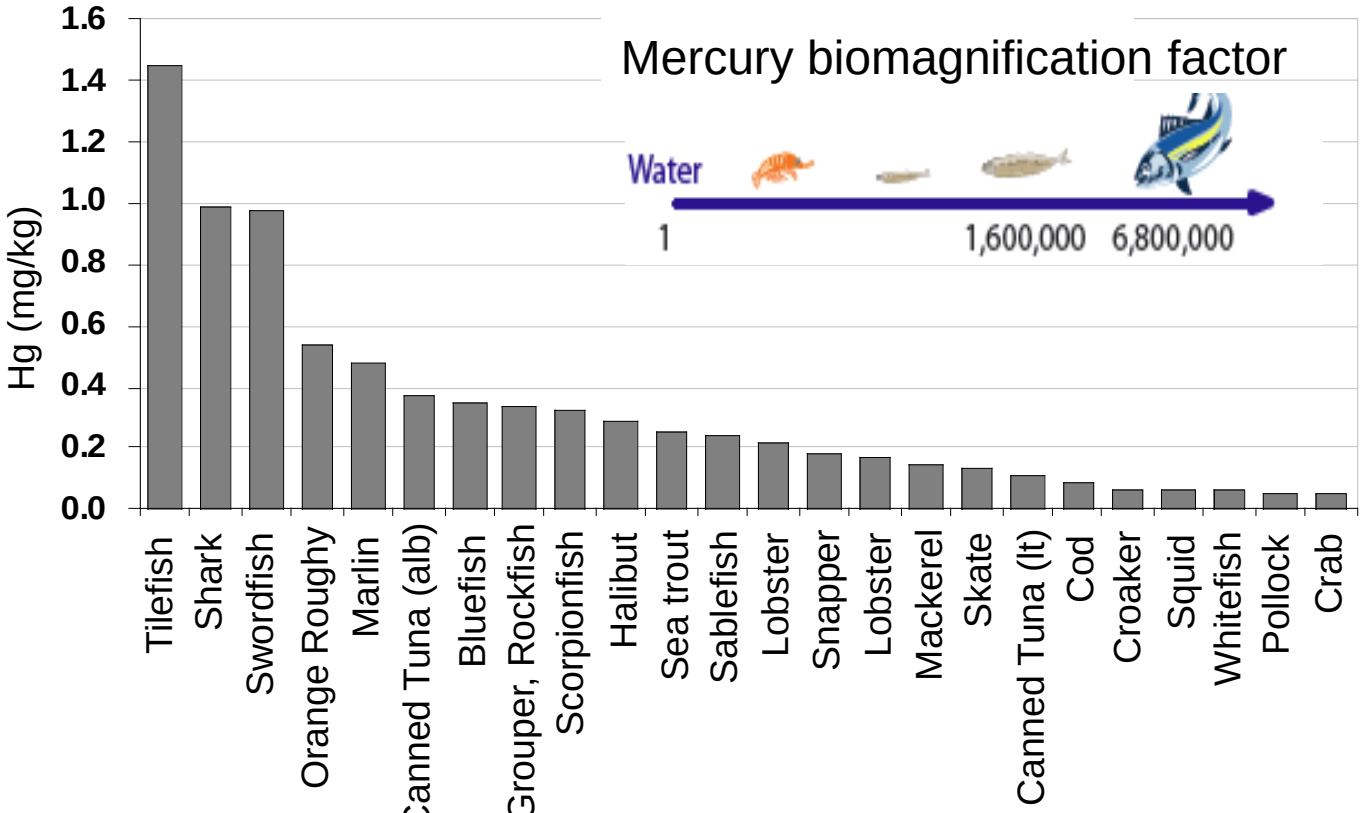
Mercury from fish consumption: a global environmental issue

EPA reference dose (RfD): 0.1 µg kg^{-1} d^{-1} (about 2 fish meals per week)

Children IQ deficits (fetal exposure)
Well-established

Adult cardiovascular effects
Suspected



Mercury

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EXPOSURE

Hg vapor is released naturally into the environment through volcanic activity and off-gassing from soils. Hg also enters the atmosphere through human activities such as combustion of fossil fuels. Once in the air, metallic mercury is photo-oxidized to inorganic mercury, which can then be deposited in aquatic environments in rain. Microorganisms can then conjugate inorganic mercury to form methyl mercury. Methyl mercury concentrates in lipids and will biomagnify up the food chain so that concentrations in aquatic organisms at the top of the food chain, such as swordfish or sharks, are quite high.

Mercury

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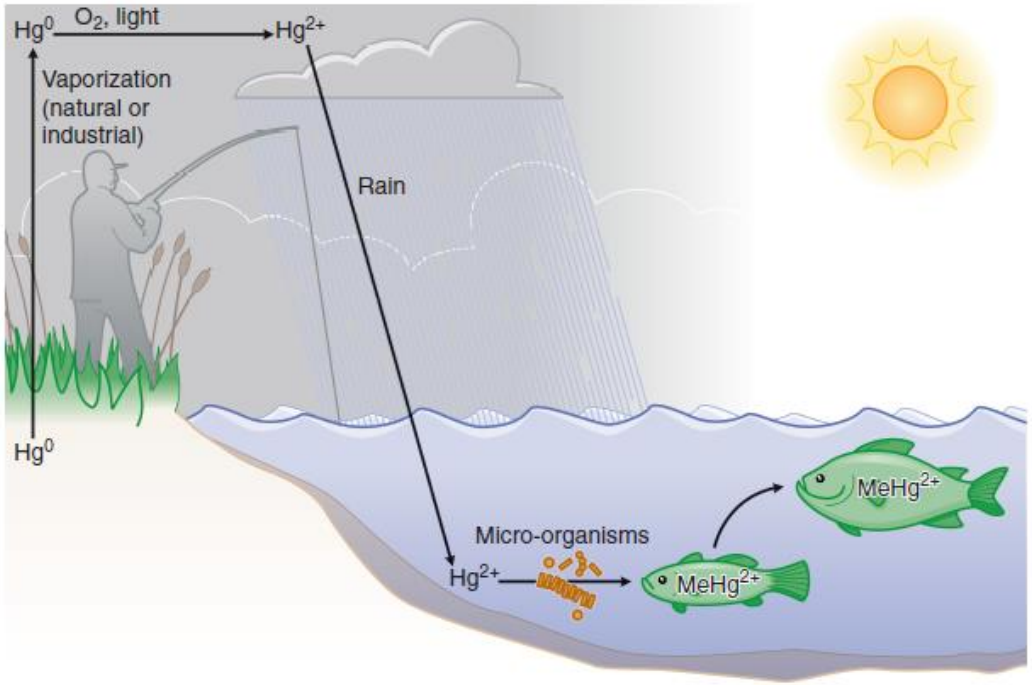
EXPOSURE



Mobilization of mercury in the environment. Metallic mercury (Hg^0) is vaporized from the Earth's surface both naturally and through human activities such as burning coal. In the atmosphere, Hg^0 is oxidized to form divalent inorganic mercury (Hg^{2+}), which falls to the surface in rain. Aquatic bacteria can methylate Hg^{2+} to form methyl mercury ($MeHg^+$). $MeHg^+$ in plankton is consumed by fish. Because of its lipophilicity, $MeHg^+$ biomagnificates up the food chain.

Mercury

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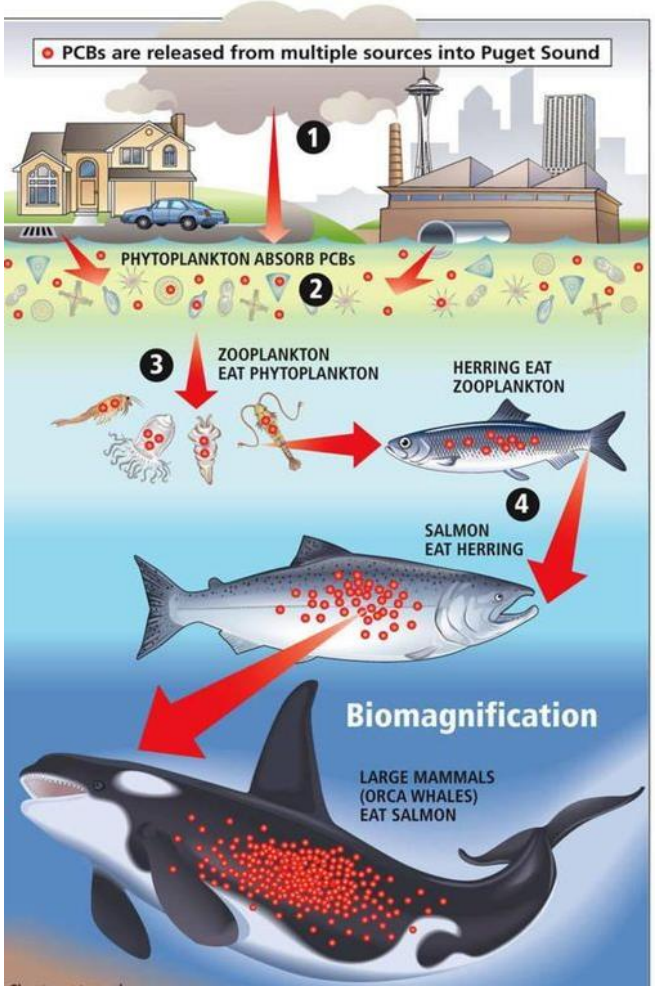
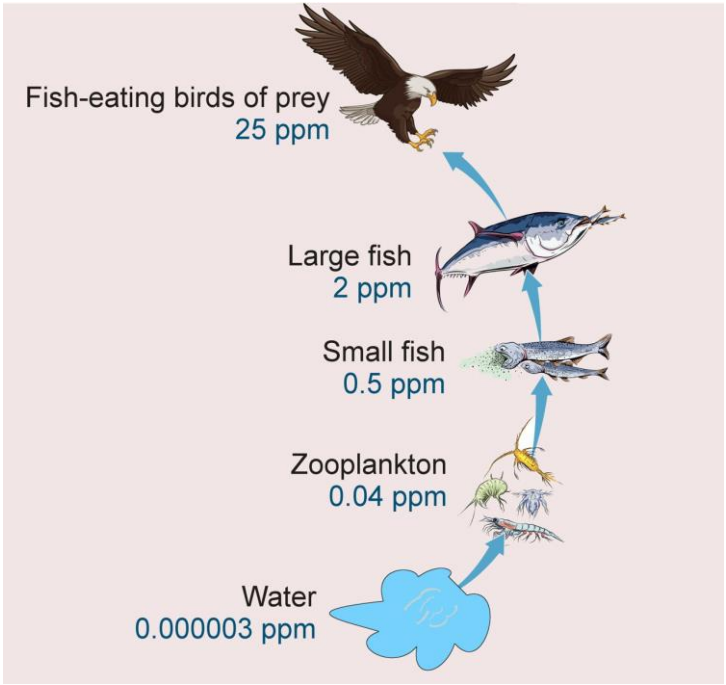
Biomagnification

Biomagnification is the increasing concentration of a substance (Methyl Mercury) in the tissues of tolerant organisms at successively higher levels in a food chain.





Mercury

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Chemistry and Mode of Action

There are 3 general forms of Hg of concern to human health. Metallic, or elemental, mercury (Hg^0) is the liquid metal found in thermometers and dental amalgam; it is quite volatile, and exposure is often to the vapor. Inorganic mercury can be either monovalent (mercurous, Hg^{1+}) or divalent (mercuric, Hg^{2+}) and forms a variety of salts. Organic mercury compounds consist of divalent mercury complexed with 1 or occasionally 2 alkyl groups. The organic mercury compound of most concern is methyl mercury ($MeHg^+$), which is formed environmentally from inorganic Hg by aquatic microorganisms. Both Hg^{2+} and $MeHg^+$ readily form covalent bonds with sulfur, an interaction that accounts for most of the biological effects of mercury. At very low concentrations, Hg reacts with sulfhydryl residues on proteins and disrupts their functions.

Mercury

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(Hg), 80

ADME

Hg^0 vapor is readily absorbed through the lungs (~70-80%), but GI absorption of elemental (liquid) Hg is negligible. Absorbed Hg^0 distributes throughout the body and crosses membranes such as the blood-brain barrier and the placenta via diffusion. Hg^0 is oxidized by catalase in the erythrocytes and other cells to form Hg^{2+} . Some Hg^0 is eliminated in exhaled air. After a few hours, distribution and elimination of Hg^0 resemble the properties of Hg^{2+}. Hg^0 vapor also is oxidized to Hg^{2+} and retained in the brain.

GI absorption of Hg salts averages ~10-15% but varies with the individual patient and the particular salt. Hg^{1+} will form Hg^0 or Hg^{2+} in the presence of sulfhydryl groups. Hg^{2+} primarily is excreted in the urine and feces; a small amount also can be reduced to Hg^0 and exhaled. With acute exposure, the fecal pathway predominates, but following chronic exposure, urinary excretion becomes more important. All forms of Hg also are excreted in sweat and breast milk and deposited in hair and nails. The $t_{1/2}$ for inorganic Hg is ~1-2 months. Orally ingested $MeHg^+$ is almost completely absorbed from the GI tract. $MeHg^+$ readily crosses the blood-brain barrier and the placenta and distributes fairly evenly to the tissues, although concentrations are highest in the kidneys. $MeHg^+$ can be demethylated to form inorganic Hg^{2+}. The liver and kidney exhibit the highest rates of demethylation, but this also occurs in the brain. $MeHg^+$ is excreted in the urine and feces, with the fecal pathway dominating. The $t_{1/2}$ for $MeHg^+$ is ~2 months. Complexes between $MeHg^+$ and cysteine resemble methionine and can be recognized by transporters for that amino acid and taken across membranes.

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Health Effects

Metallic Mercury;
Inhalation of high levels of Hg vapor over a short duration is acutely toxic to the lung. Respiratory symptoms start with cough and tightness in the chest and can progress to interstitial pneumonitis and severely compromised respiratory function. Other initial symptoms include weakness, chills, metallic taste, nausea, vomiting, diarrhea, and dyspnea. Acute exposure to high doses of Hg also is toxic to the CNS.

Toxicity to the nervous system is the primary concern with chronic exposure to Hg vapor. Symptoms include tremors (particularly of the hands), emotional lability (irritability, shyness, loss of confidence, and nervousness), insomnia, memory loss, muscular atrophy, weakness, paresthesia, and cognitive deficits. These symptoms intensify and become irreversible, with increases in duration and concentration of exposure. Other common symptoms of chronic Hg exposure include tachycardia, labile pulse, severe salivation, gingivitis, and kidney damage.

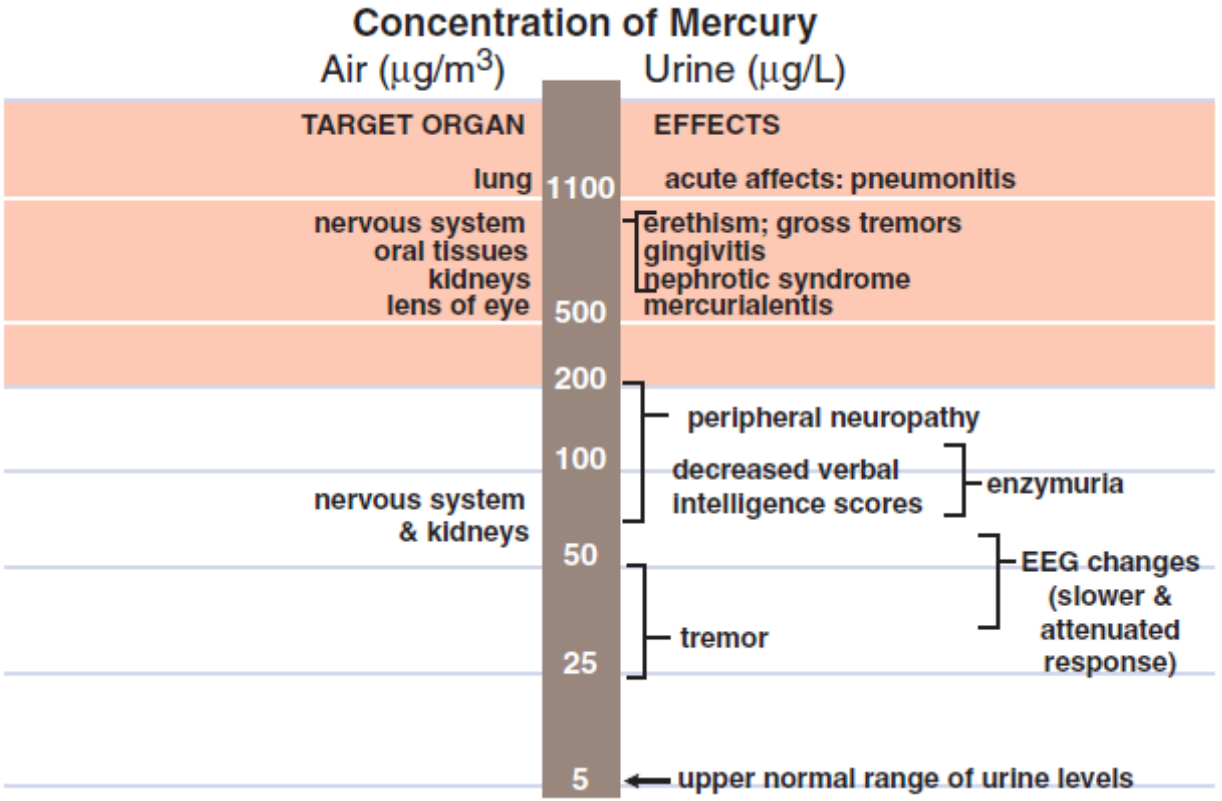
Mercury

Quick Silver, (Hg), 80

Health Effects

Inorganic Salts of Mercury;

Ingestion of Hg^{2+} salts is intensely irritating to the GI tract, leading to vomiting, diarrhea, and abdominal pain. Acute exposure to Hg^{2+} salts (typically in suicide attempts) leads to renal tubular necrosis, resulting in decreased urine output and often acute renal failure. Chronic exposures also target the kidney.



Mercury

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(Hg), 80

Health Effects

Organic Mercury;
The CNS is the primary target of methyl mercury toxicity. Symptoms of methyl mercury exposure include visual disturbances, ataxia, paresthesia, fatigue, hearing loss, slurring of speech, cognitive deficits, muscle tremor, movement disorders, and, following severe exposure, paralysis and death. Children exposed in utero can develop severe symptoms, including mental retardation and neuromuscular deficits, even in the absence of symptoms in the mother.

Mercury

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(Hg), 80

Minamata Disease;

Methylmercury poisoning was first recognized in Minamata, Japan. Hundreds of fishermen and their families were severely poisoned during the 1950s by methyl mercury that bio accumulated in fish as a result of the release of mercury to the bay from a local chemical plant. Many severe effects were observed including parasthesia (abnormal physical sensations such as numbness), gait disturbances, sensory disturbances, tremors, hearing impairment and many mortalities. By 1960 the serious and mysterious affliction, affecting both adults and infants, was recognized as methyl mercury poisoning, a hitherto unrecognized disease. High level exposure produced serious neurological disease in adults, but the most dramatic manifestation was congenital Minamata disease in infants born to mothers with high mercury levels. These babies were born with severe cerebral palsy, blindness and profound mental retardation. Some severely affected children were born to mothers who themselves showed no evidence of mercury-related impacts.

Mercury

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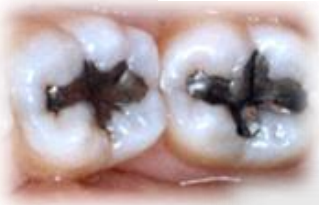
(Hg), 80

Other sources of mercury exposure

Human exposure to organic Hg primarily is through the consumption of fish.



The primary source of exposure to metallic Hg in the general population is vaporization of Hg in dental amalgam.

There also is limited exposure through broken thermometers and other Hg-containing devices.

Hg is a component of many devices, including alkaline batteries, fluorescent bulbs, thermometers and scientific equipment, and exposure occurs during the production of these devices.

Mercuric salts are used as pigments in paints.

Hg can be used to extract gold during mining.

Mercury

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Treatment

With exposure to metallic Hg, termination of exposure is critical and respiratory support may be required. Emesis may be used within 30-60 min of exposure to inorganic Hg, provided the patient is awake and alert and there is no corrosive injury. Maintenance of electrolyte balance and fluids is important for patients exposed to inorganic Hg. Chelation therapy is beneficial in patients with acute inorganic or metallic Hg exposure.

- Succimer (DMSA, 2,3-dimercaptosuccinic acid) is taken by mouth to treat poisoning by lead, mercury and arsenic. Serious side effects are uncommon.
- Dimercaprol (British Anti-Lewisite, BAL) is given by injection to treat severe lead poisoning (with edetate calcium disodium), mercury poisoning, and arsenic poisoning. A variety of side effects have been reported, usually dose-related; high doses can cause coma and seizures.
- Penicillamine is sometimes used to treat bismuth, copper, lead, mercury, and nickel toxicity. When used for acute poisoning, the primary adverse effect is an allergic reaction in people who are also allergic to penicillin.

There are limited treatment options for methyl mercury. Chelation therapy does not provide clinical benefits, and several chelators potentiate the toxic effects of methyl mercury. Non-absorbed thiol resins may be beneficial by preventing reabsorption of methyl mercury from the GI tract.

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International Agency for Research on Cancer

World Health Organization

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

CAS No	Agent	Group	Volume	Year
007439-97-6	Mercury and inorganic mercury compounds	3	58	1993

Mercury

Quick Silver,
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World Health Organization

Guidelines for Drinking-water Quality

FOURTH EDITION

Guideline value	0.006 mg/l (6 µg/l) for inorganic mercury
Occurrence	Mercury is present in the inorganic form in surface water and groundwater at concentrations usually below 0.5 µg/l, although local mineral deposits may produce higher levels in groundwater
TDI	2 µg/kg body weight for inorganic mercury based on a NOAEL of 0.23 mg/kg body weight per day for kidney effects in a 26-week study in rats and applying an uncertainty factor of 100 (for interspecies and intraspecies variation) after adjusting for daily dosing
Limit of detection	0.05 µg/l by cold vapour AAS; 0.6 µg/l by ICP; 5 µg/l by flame AAS
Treatment performance	It should be possible to achieve a concentration below 1 µg/l by treatment of raw waters that are not grossly contaminated with mercury using methods that include coagulation/sedimentation/filtration, PAC and ion exchange.

Kadmiyum

Cadmium (Cd)

48

	1												13	14	15	16	17	18
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Non-metals, including Noble Gases | Main Group Metals | Transition Metals | Metalloids

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Cadmium (Cd)

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INTRODUCTION

Encountered in earth's crust combined with chlorine ($CdCl_2$), oxyen (CdO) and sulphur (CdS).

Exist as small particles in air, results of smelting, soldering or other high temp. İndustrial processes.

By-product of smelting of zinc, lead, copper ores.

Used mainly in metal plating, producing pigments, batteries, plastics and as a neutron absorbent in nuclear reactors.

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Cadmium (Cd)

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Exposure Sources

Tobacco smoke (a one pack a day smoker absorbs roughly 5 to 10 times the amount absorbed from the average diet).

Tobacco smoke is an important source of Cd exposure.

Low levels are found in grains, cereals, leafy vegetables and other basic foods.

Exposure to the general population occurs through cigarette smoke, food consumption, drinking water, and incidental ingestion of soil. For nonsmokers food is the largest nonoccupational source of exposure.

Man made sources of cadmium in the environment include the release of Cd used in;

- Electroplating
- Pigments
- Solders
- Nickel-cadmium batteries

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Cadmium (Cd)

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Kinetics

Absorbtion:
Cadmium is more efficiently absorbed from the lungs (25-60% absorbed) than the gastrointestinal tract (5-10 % absorbed). It is estimated that on average, adults absorb 1.4-8 µg of cadmium per day by oral exposure.

Distribution:
Cadmium is widely distributed in the body bound mainly to red blood cells or high molecular weight proteins in the plasma. Cadmium is accumulated (50-70% of body burden) in the kidneys and liver, where it induces the production of metallothionein that binds approximately 80-90 % of cadmium in the body. For individuals who are chronically exposed to environmental levels of cadmium either by diet or smoking, the highest concentrations of cadmium are measured in the renal cortex. Cadmium concentrations in the kidney are low at birth but, if exposure to cadmium remains constant, body burden increases in a linear manner with age up until approximately 50 or 60 years of age after which they plateau or decline. Various studies have reported a mean cadmium concentration of 10-50 µg/g in the renal cortex at age 40 – 50. Liver concentrations also are low at birth and increase to approximately 1-2 µg/g by the age of 20-25 years, after which time they only slightly increase.

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Cadmium (Cd)

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Metabolism:
There is little or no metabolism of cadmium, although it binds to various macromolecules and proteins. Metallothionein is largely involved in the binding of cadmium, which is generally thought to reduce the toxicity of cadmium. In the liver, its production is sufficient to bind all cadmium accumulated. The metallothionein-bound cadmium is released from the liver into the blood where it is cleared by glomerular filtration in the kidney and taken up by the renal tubules, where the metallothionein is cleaved and cadmium is released. The synthesis of metallothionein in the kidney is lower and insufficient to bind all the free cadmium, resulting in tubular damage or cell membrane destruction via activation of oxygen species.

Excreation:
As a small fraction of the cadmium is absorbed from the GI tract following ingestion, most of the oral dose is excreted in the faeces. Following inhalation, excretion via the urine and faeces are approximately equal. In individuals continuously exposed to cadmium, the amount excreted in urine will progressively increase in proportion with body burden. However, the amount excreted is only a small fraction of the total body burden, unless kidney toxicity occurs in which case urinary cadmium increases substantially.

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Cadmium (Cd)

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Source and route of human exposure

The main route of exposure to cadmium is via inhalation or ingestion via food or cigarette smoke. Skin absorption is rare.

Cadmium is prevalent in the three main environmental compartments, namely air, water and soil. The majority of cadmium exposure arises from air and soil, by atmospheric deposition and by the ingestion of vegetables such as lettuce, spinach, celery and cabbage that accumulate cadmium. Foods such as potatoes and peas take up less amounts. As part of the 2006 Total Diet Survey carried out by the Food Standards Agency (USA), cadmium in the diet was analysed. Toddlers (1.5 – 4.5 years of age) has the highest dietary intake of approximately 0.4 µg kg/bw/day whereas the mean intake across all age groups was about 11 – 13 µg/day. Recent reports have acknowledged that house dust may also be a significant route of exposure to cadmium. Minimal exposure of cadmium arises from water.

The inhalation of cadmium also contributes to the total cadmium burden, albeit to a lesser extent than oral intake, with the exception of smokers or those undergoing occupational exposure. Cigarette smoke considerably adds to cadmium exposure. A daily intake of 2-4 µg cadmium was estimated from smoking one packet of cigarettes per day.

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Cadmium (Cd)

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Mechanism of toxicity

Cadmium affects cell proliferation, differentiation, and apoptosis. These activities interact with DNA repair mechanism, the generation of reaction oxygen species (ROS) and the induction of apoptosis. Cadmium binds to the mitochondria and can inhibit both cellular respiration and oxidative phosphorylation at low concentration.

It results in chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA- protein crosslinks in cell lines. Cadmium causes mutations and chromosomal deletions potentially. Its toxicity involves depletion of reduced glutathione (GSH), binds sulfhydryl groups with protein, and causes to enhance production of reactive oxygen species (ROS) such as superoxide ion, hydrogen peroxide, and hydroxyl radicals. Cadmium also inhibits the activity of antioxidant enzymes, such as catalase, manganese-superoxide dismutase, and copper/zinc-dismutase. Metallothionein is a zinc – concentrating protein that contains 33% cysteine. Metallothionein also can act as a free- radical scavenger. It scavenges hydroxyl and superoxide radicals. Generally, the cells that contain metallothioneins are resistant to cadmium toxicity. On the other hand, the cells that cannot synthesize metallothioneins are sensitive to cadmium intoxication.

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Cadmium (Cd)
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Health effects of acute exposure

Inhalation:
The acute toxic effects following inhalation of cadmium are summarised in the table below. An initial sign of cadmium inhalation is slight irritation of the upper respiratory tract, although symptoms may be delayed for 4-8 hours. Inhalation of cadmium may also cause a metallic taste, headache, dyspnoea, chest pain and muscle weakness.

Dose (mg/m^3)	Signs and symptoms
0.01-0.15	Cough, irritation of the throat, gastroenteritis symptoms - vomiting, abdominal cramps, diarrhoea
0.5	Threshold for respiratory effects after 8 hour exposure
1-5	Immediately dangerous to health - facial oedema, hypotension, dysrhythmias, confusion, oliguria, metabolic acidosis and acute centrilobular necrosis of the liver, pulmonary oedema, tracheobronchitis, pneumonitis
5	lethal after 8 hours
39	lethal after 20 minutes
250	Lethal after 10 minutes
2500	Lethal after 1 minute

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Cadmium (Cd)
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Ingestion:
The acute toxic effects following oral exposure to cadmium are summarised in the table below. Following cadmium exposure an asymptomatic period of up to 60 minutes may precede clinical symptoms. The ingestion of cadmium exceeding 15 mg/kg body weight (bw) may give rise to gastrointestinal symptoms such as vomiting, abdominal cramps and diarrhoea, whereas doses of 20-30 mg/kg/bw have caused human fatalities. The lowest emetic dose reported is 0.07 mg/kg/bw. Fatigue, sleep disturbances, sensory and motor function disturbances, anorexia, peripheral neuropathy and headaches may also arise. The ingestion of cadmium chloride has been reported to produce an elevation in serum haemoglobin and haematocrit. Acute oral exposure to 350 – 8900 mg, corresponding to doses of about 20 to 130 mg/kg/bw in a 70 kg adult has caused fatal intoxication. In such cases, within 7-14 days of the initial
symptoms, hypovolaemia leading to shock, renal failure, hypotension, liver damage and death may occur. No studies were retrieved that reported respiratory effects in humans following oral exposure to cadmium.

Dose (mg/kg/bw)	Signs and symptoms
0.07	Emetic dose
> 15	Gastrointestinal symptoms – vomiting, abdominal cramps, diarrhoea
20 – 30	Extensive fluid loss, shock, pulmonary oedema, hypotension, oliguria, multiorgan failure, death

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Cadmium (Cd)
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Health effects of chronic exposure

Inhalation:
The chronic toxic effects following inhalation of cadmium are summarised in the table below. The kidney is the critical organ for long-term low--level exposure. Accumulation of cadmium in the kidney results in loss of tubular function, leading to tubular proteinuria, evidenced by an increase in urinary excretion of β2-microglobulin, retinol binding protein and α1-microglobulin. Such proteinuria may occur following inhalation of 25-134 µg/m^3 cadmium for at least ten years.

Cadmium-induced proteinuria has been reported to occur when the concentration of cadmium reaches a critical level. 200 µg/g (wet weight) cadmium in the renal cortex has been reported to be associated with a 10 % prevalence of tubular effects and proteinuria in the general population and corresponded to a concentration of cadmium in the urine of approximately 10 µg/g creatinine.

Dose (mg/m^3)	Time of exposure	Signs and symptoms
25 – 134	10 years	Proteinuria
66	20 years	Bronchitis, obstructive lung disease - dyspnoea, reduced vital capacity and increased residual volume
50 - 356		Emphysema and dyspnoea

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Cadmium (Cd)

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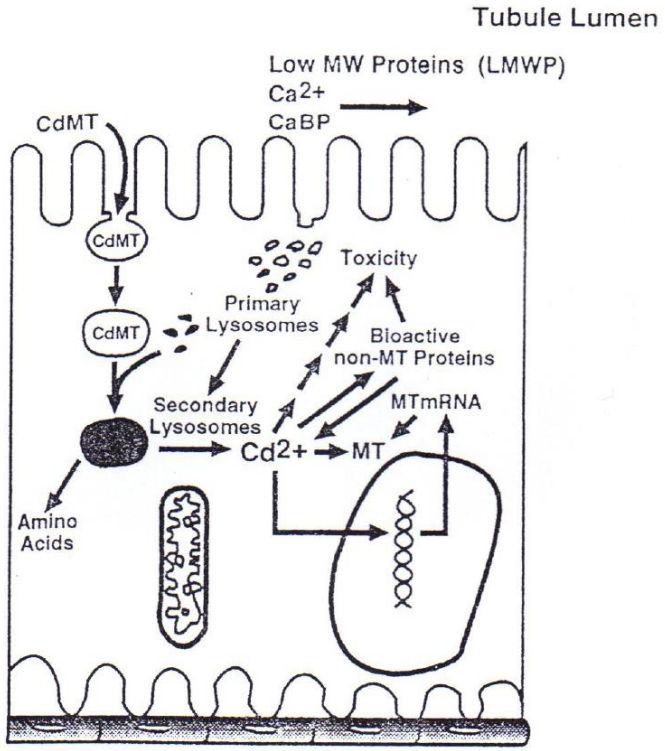
Accumulation of cadmium in the kidney may affect vitamin D metabolism and may increase the excretion of calcium and phosphorus into the urine. This may lead to a disruption of the calcium balance, resulting in osteomalacia, osteoporosis and spontaneous fractures. A number of reports have documented disorders of calcium metabolism and bone effects amongst men occupationally exposed to cadmium, and decreased bone density and increased risk of fractures were reported in women. Bone disease resulting from exposure to cadmium in the general environment has only been reported in people from a highly contaminated region in Japan (Itai-itai disease), characterised as osteomalacia, osteoporosis, increased fractures and renal tubular dysfunction.



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Cadmium (Cd)

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Ingestion:
Following long-term cadmium ingestion, kidney effects such as proteinuria and loss of tubular function may occur, as with inhalation exposure. Osteomalacia, osteoporosis and spontaneous fractures may also as a late manifestation of severe chronic cadmium poisoning.

Liver damage is only observed at high concentrations of cadmium due to the presence of a high concentration of metallothionine in the liver. Ingestion of 150 g cadmium chloride was reported to cause focal hepatic necrosis.

In a Japanese population, long-term ingestion of water and food contaminated with Cd was associated with a crippling condition ‘ itai-itai’ (ouch-ouch) disease.
The syndrome is characterized by pain in the back and joints, osteomalacia (adult rickets), bone fractures, and occasional renal failure.
Women are mostly affected.

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Carcinogenicity:

IARC has classified cadmium and cadmium compounds as category 1 carcinogens. i.e. İs carcinogenic to humans. There is sufficient evidence from occupational studies and animal data to indicate that inhalation of cadmium and cadmium compounds increases the risk of lung cancer. It was assumed that this was induced via a genotoxic mechanism and hence did not to exhibit a dose threshold. However, in a recent assessment EFSA concluded that cadmium exerts its genotoxicity via the production of reactive oxygen species and by inhibiting DNA repair. Both such mechanisms are expected to have a threshold.

A number of recent case-control studies have reported an association between exposure to cadmium and kidney cancer. Other recent research has suggested that exposure to cadmium in the general population may increase the risk of cancer of the endometrium, breast, testes, bladder, pancreas and gall bladder

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International Agency for Research on Cancer
World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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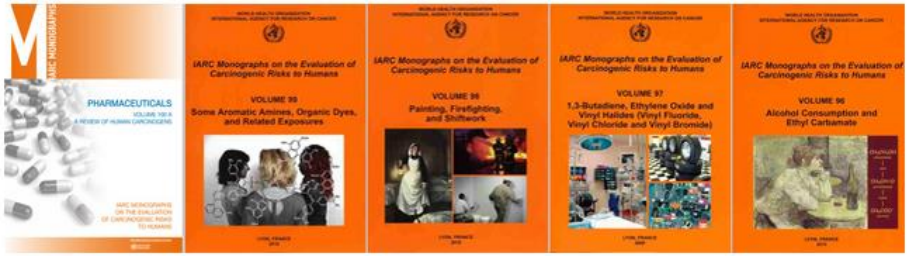

Agents Classified by the *IARC Monographs*, Volumes 1–111

CAS No	Agent	Group	Volume	Year
007440-43-9	Cadmium and cadmium compounds	1	58, 100C	2012

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TREATMENT

Chelating agents

Ethylenediaminetetraacetic acid (EDTA): EDTA significantly increased urinary elimination of cadmium. One important point is that EDTA may increase Cd content in the kidneys and may increase the risk of renal dysfunction. Normal dose of EDTA is 500 mg of Ca2+ EDTA in combination with 50 mg/kg of glutathione (GSH) via IV infusion over the next 24 hours and repeated over 12 consecutive days. Renal dysfunction could be reversed if its initial urine cadmium concentration is <10 µg/gr of creatinine. Urine cadmium concentration more than 10 µg/gr of creatinine may induce irreversible renal damage.

Penicillamine (DPA): Penicillamine used to reduce toxic concentrations of mercury and lead exposure, is not efficient in cadmium overdose.

Dimercaprol: Dimercaprol [British anti- Lewisite (BAL)] is efficient antidote in heavy metal poisoning. BAL and their analogues meso-2, 3-dimercaptosuccinic acid DMSA and 2, 3-dimercapto-1-propanesulfonic acid DMPS are used as antidote course of therapy for heavy metal poisoning.
BAL must be administered in the first 4 hours of poisoning. Deep intramuscular injection of a dose 3-4 mg/kg in gluteal muscle is recommended. It is given every 4 hours for the first two days, and twice daily for the next 10 days. It has been reported, however, that cadmium-BAL complex has more nephrotoxic effects than cadmium alone and the combination is not helpful. Possibly, BAL therapy may increase the risk of nephrotoxicity. In addition, BAL increases kidney and liver cadmium burdens, may decrease survival and enhances nephrotoxicity. For these reasons, it is not given in cadmium intoxication.

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Dithiocarbamates: N- tetramethylene dithiocarbamate (ATC) is one of derivatives of dithiocarbamates with chelating action. It enhances the urinary and biliary excretion of cadmium, also reduces the side effects and general symptoms of poisoning. It may be useful for primary diagnostic evaluation of the efficacy of chelating agents. The efficacy of dithiocarbamates has been confirmed in reducing cadmium toxicity in animal studies. There is a necessity for the administration of these chelating agents in humans to be documented.

Meso 2, 3-dimercaptosuccinic acid (Succimer, DMSA): It is a water-soluble analogue of BAL. Tolerable dose of DMSA is10 mg/kg, three times a day but it is not an intracellular chelator. Cadmium binds tightly to metallothionein and stores in liver and kidneys. In consequence, it seems that DMSA cannot be a drug of choice in cadmium poisoning.

2, 3- dimercapto-1-propane sulfonic acid (Unithiol, DMPS): It is a water soluble analogue of BAL. It is available in different dosage forms as oral, intravenous, rectal, or topical. DMPS is transported into intracellular space. It has not shown major adverse effects. DMPS is oxidized to disulfide form. At least 80% of DMPS is oxidized within the first 30 min and 84% of total DMPS is excreted by the kidneys within 96 hours. Dose: 5 mg/kg intravenously 4 hourly for 24 hours, and may be increased to 100 mg twice a day, if needed.

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New DMSA analogues:

DMSA mono and diesters are more effective and safe antidotes for heavy metal poisoning compared to DMSA alone. Among these monoesters, monoisoamyl DMSA (MiADMSA) was shown to be effective for lead, cadmium, mercury and gallium arsenide overdose. MiADMSA is a water- soluble, lipophilic chelating agent. It can enter intracellularly and access to different endogenous ligands. Consequently MiADMSA is more preferred than its parent compound.

MiADMSA can enter into cell and bind to intracellular cadmium. Because of the effects of antioxidants, cadmium-induced oxidative stress is delayed due to the presence of MiADMSA.

Monomethyl DMSA (MmDMSA) and Monocyclohexyl DMSA (MchDMSA) are the other DMSA analogues. They are lipophilic compounds and can penetrate into cells. They are efficient after oral administration and may reduce the whole body cadmium levels following its overdose.

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Plasma exchange-hemodialysis-plasmapheresis:

Plasma exchange may have started 24-36 hours after the appearance of clinical signs and symptoms, when life-threatening toxicity happened and the health team could not choose any alternative treatment. Plasma exchange must only be used in emergency situations. Hence, it can potentially be helpful in heavy-metal toxicity

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Hemoperfusion and hemodialysis are not useful in the treatment of cadmium poisonings. Furthermore, cadmium is eliminated very differently, it has very low residual renal function and inefficient cadmium removal via dialysis. In severe renal damage, hemodialysis has benefits in replacing kidney function.

Some of the toxic substances can strongly bind to plasma proteins and cannot be removed through hemodialysis. Plasmapheresis is practical and sensible to remove protein- bound heavy metals in plasma. Nonetheless, there are no controlled studies on plasmapheresis in any specific intoxication.

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World Health Organization

Guidelines for Drinking-water Quality

FOURTH EDITION

Guideline value	0.003 mg/l (3 µg/l)
Occurrence	Levels in drinking-water usually less than 1 µg/l
Limit of detection	0.01 µg/l by ICP-MS; 2 µg/l by flame AAS
Treatment performance	0.002 mg/l should be achievable using coagulation or precipitation softening
Guideline value derivation	
• allocation to water	10% of provisional tolerable monthly intake (PTMI) because of high intake from food
• weight	60 kg adult
• consumption	2 litres/day

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ANKARA ÜNİVERSİTESİ ECZACILIK FAKÜLTESİ

F. Toksikoloji Anabilim Dalı, 06100 Tandoğan, Ankara

Prof. Dr. Yalçın Duydu, PhD, ERT

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