FEDERAL INSTITUTE FOR RISK ASSESSMENT

BfR

Risiken erkennen – Gesundheit schützen

Mercury: Human toxicology and mercury speciation

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Toxicity of Mercury and Mercury compounds - Background (I)

Mercury and mercury compounds are commonly regarded as toxic

Mercury and Mercury compounds are widely used and distributed and have been used for a long time, so that (I) many possibilities of human exposure to mercury and mercury compounds exist and (II) a broad spectrum of different symptoms of mercury intoxication is known.

The types of symptoms of mercury intoxications and the target tissues of mercury intoxication are dependent on MERCURY SPECIATION

AIMS

Overview about the toxicological profile of different types of mercury compounds

Overview how mercury speciation influences mercury toxicity

Toxicity of Mercury and Mercury compounds - Background (II)

Toxic effects are dependent on the fate of a substance in the organism

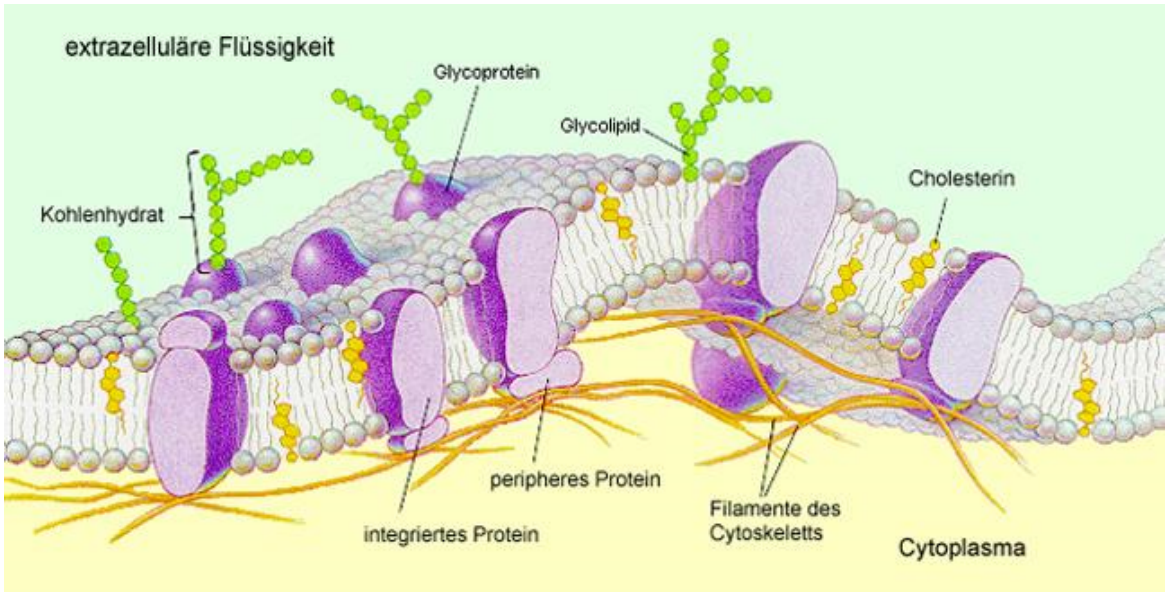
The fate of a substance within the body includes absorption (uptake), distribution, metabolism and excretion (TOXICOKINETICS)

Toxicokinetics is influenced by physico-chemical and structural properties of a substance

Factors which influence absorption are water solubility, log Pow, Molecular weight, vapour pressure

Different toxic effects of different mercury species are due to differences in physico-chemical properties and thus differences in toxicokinetics

Toxicity of Mercury and Mercury compounds - Background (III)



Transport through biological membranes

- Small lipophilic molecules diffuse through the lipid bilayer
- Small hydrophilic molecules diffuse through pores of the membrane
- Some molecules are actively transported by carrier molecules
- ionized molecules and large molecules:
  diffusion through membranes limited/not possible

Toxicity of elemental Mercury - Exposure

Mining of mercury

Production and use of thermometers, barometers, manometers

Batteries and accumulators

Laboratories

Amalgams (dental fillings, mining of gold and silver (Amazonas), sodium amalgam for chloro alkali electrolysis, historically: tin amalgam for the production of mirrors)

Toxicity of elemental Mercury - Toxicokinetics

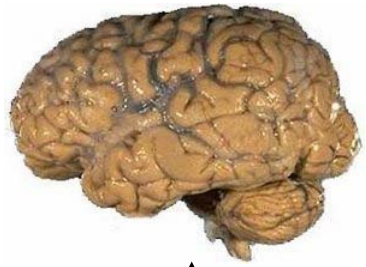
Rapid absorption from lungs (80 %) (vapour pressure), poor absorption from the gastrointestinal tract (formation of mercury sulfide which covers mercury in the stomach)

Distribution throughout the body, it crosses the blood-brain and the placental barrier , preference for brain

Distribution is paralleled by the oxidation of elemental mercury to the mercuric ion (Hg^{2+}), which has a limited ability to cross membranes

In the brain, elemental mercury is oxidized to the mercuric ion, which cannot return to the general circulation

Toxicokinetics and target tissues of Mercury toxicity (I)



CNS /Brain

Hg (elemental)
80 % absorbed from lungs

Lung

Gastrointestinal tract

Reduction

Oxidation

Hg (II)

Kidneys

Toxicity of elemental Mercury - Effects

Target tissues: lung, gastrointestinal tract, central nervous system, kidneys,

Acute effects:

- gastrointestinal effects (elevated salivation/gingivits)
- pulmonary dysfunction (coughing, edema, pneumonitis, respiratory failure)

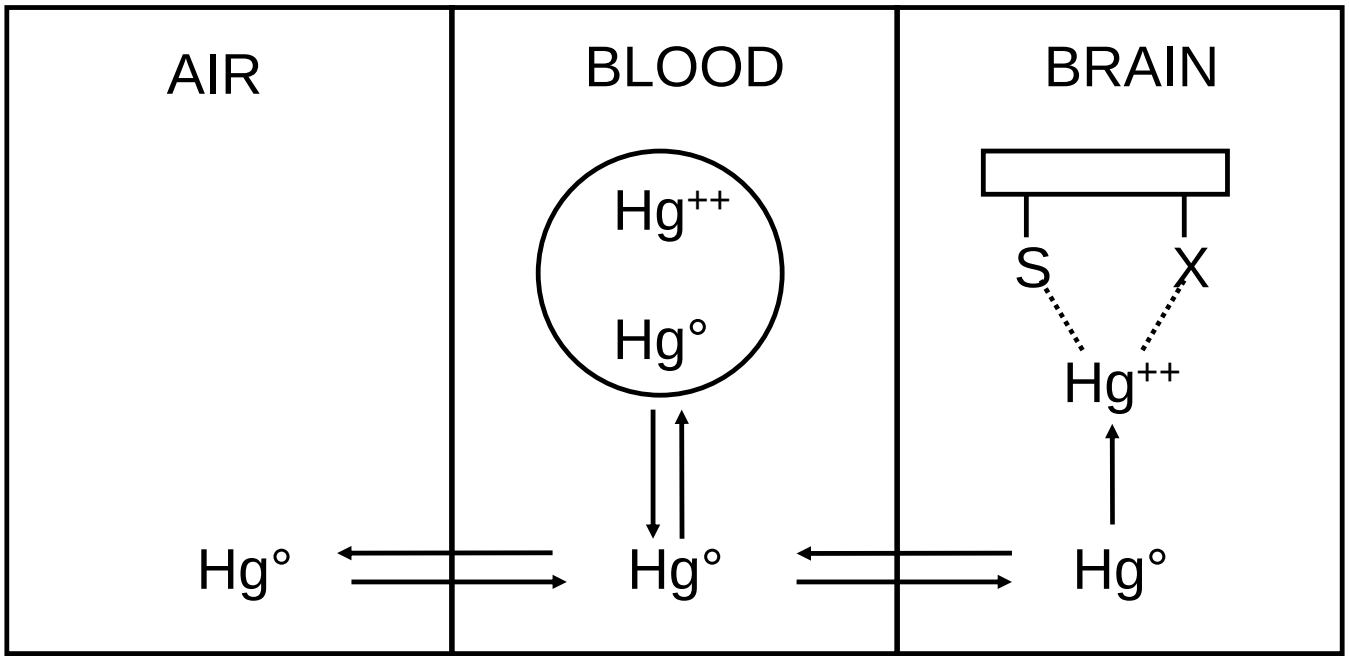
Chronic effects:

- Renal effects (e.g. proximal tubule damage)

CNS effects

- tremors (initially affecting the hands, then spreading to other parts of the body)
- erethism (emotional lability, irritability, nervousness, excessive shyness)
- insomnia
- neuromuscular changes (weakness, muscle atrophy, muscle twitching)
- polyneuropathy (paresthesia, sensory loss)
- memory loss and loss of cognitive function

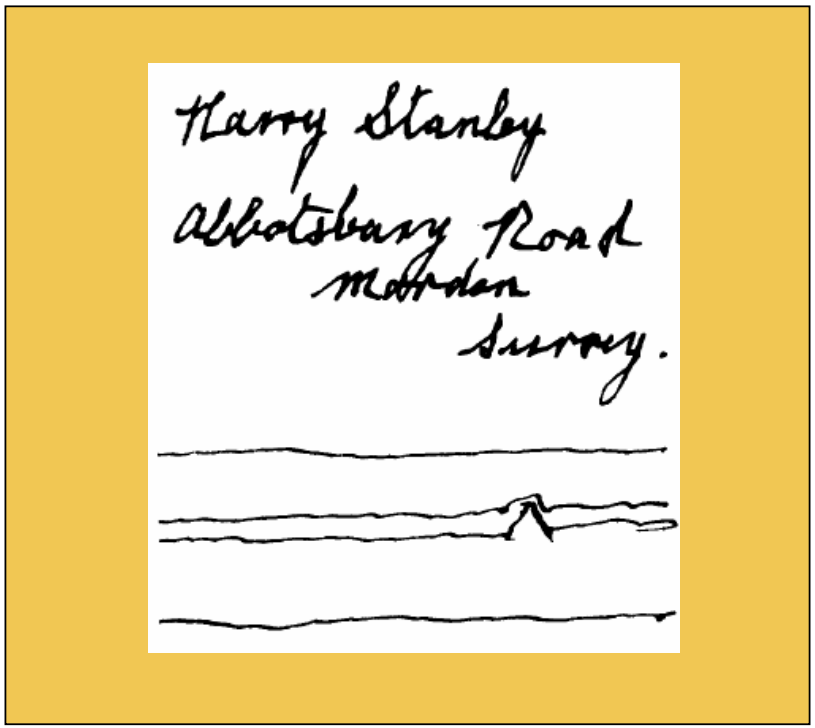
Toxicity of elemental Mercury - Examples and mechanisms



- Oxidation to divalent mercury Hg^{2+} (Catalases)
- Hg^{2+} has high affinity to -SH groups (amino acids, proteins, enzymes)
- destruction of target cells at the site of contact (brain, kidney, GI-tract)

Toxicity of elemental Mercury - Examples and mechanisms

Example: Mercury Tremor



Toxicity of Inorganic Mercury - Exposure and History (I)

Paracelsus 1493 - 1543 (Theophrastus Bombastus PHILIPPUS AUREOLUS PARACELSUS von Hohenheim)

Grey ointment (against syphilis)

Yellow ointment (against eye diseases)

„What is not a poison ? Everything is a poison. The dose alone makes something a poison“

Toxicity of Inorganic Mercury - Exposure and History (II)

Occurrence and use

Historically

HgO: constituent of Paracelsus‘ yellow ointment (against eye diseases)

$Hg(NH_2)Cl$: treatment of eye diseases

Today/near past

$HgCl_2$: Disinfection

$Hg(CN)_2$: Cleaning of surgical instruments

$HgNO_2$: processing of furs

Mercury fulminate (for the production of explosives)

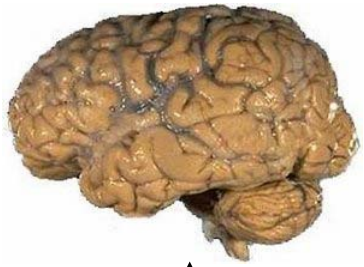
further inorganic compounds are used as catalysts, as mordants

Toxicity of Inorganic Mercury - Toxicokinetics

Target tissues: kidneys, gastrointestinal tract

- Absorption of inorganic mercury from the gastrointestinal tract is dependent on the particular mercury salt involved (solubility)
- approximately 20 % absorbed
- Absorption occurs by electrostatic interaction with the brush-border membrane and limited passive diffusion
- uptake may be enhanced by certain factors (corrosive action, milk diet)
- limited capacity for penetrating blood-brain or blood-placenta barriers
- In limited amounts: reduction to elemental mercury and exhalation is possible
- excretion mainly via feces

Toxicokinetics and target tissues of Mercury toxicity (II)



CNS /Brain

Hg (elemental)
80 % absorbed from lungs

Lung

Gastrointestinal tract

Reduction

Oxidation

Hg (II)
20 % absorbed from GI

Kidneys

Gastrointestinal tract

Toxicity of Inorganic Mercury - Effects

Symptoms:

acute:

- corrosive effects in mouth, throat, oesophagus
- diarrhoea, vomiting
- kidney failure, necrosis of the proximal tubule cells
- anuria and uremia

chronic:

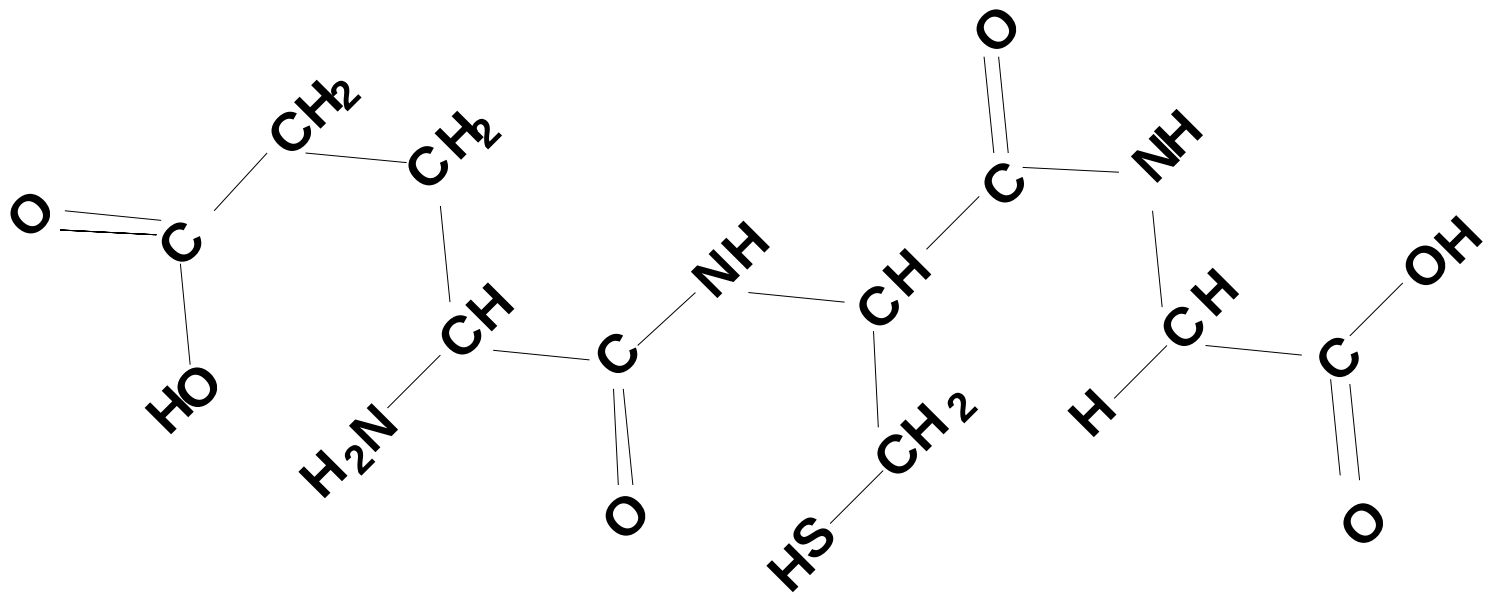
- nephrotic syndrome, kidney damage
- enhanced salivation

Toxicity of Inorganic Mercury - GI toxicity and Kidney toxicity

GI toxicity: High affinity of Hg^{2+} for sulfhydryl groups

What is the reason for the kidney-specific toxicity of inorganic mercury ?

Reaction with glutathione (GSH), formation of the complex GSH-Hg-GSH



Toxicity of Inorganic Mercury - GI toxicity and Kidney toxicity

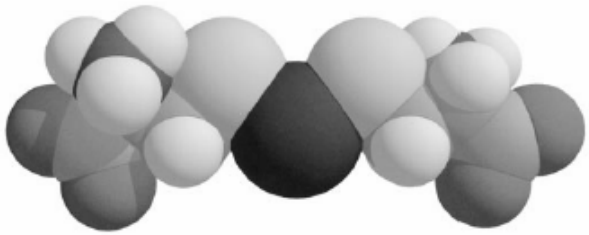
Transport of the GSH-complex into the kidney, enzymatic cleavage in the kidney , formation af a biscysteinyl-Hg-complex Cys-Hg-Cys

Cys-Hg-Cys mimics the endogenous compound Cys-Cys

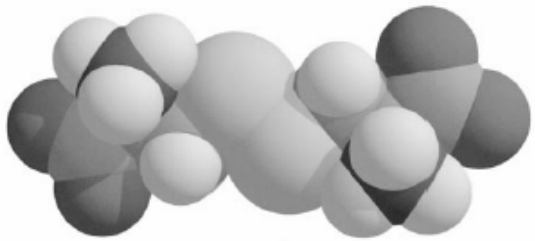
A selective Cys-Cys transport system which cannot distinguish from the mercury complex brings the complex into the proximal tubule cells

Once in the cells, toxic effects towards cellular constituents can be enabled

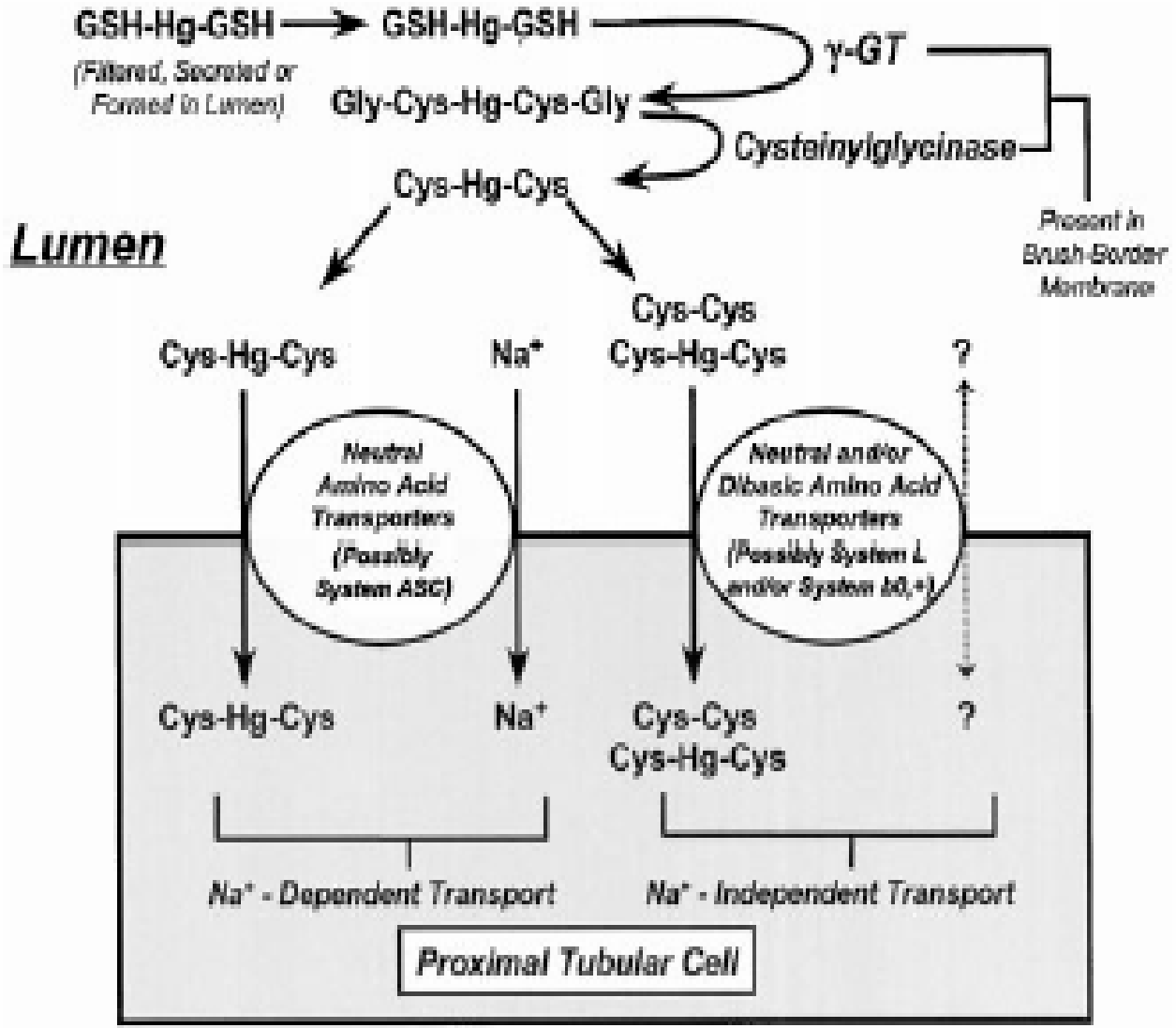
Toxicity of Inorganic Mercury - Kidney toxicity



Dicysteinylmercury

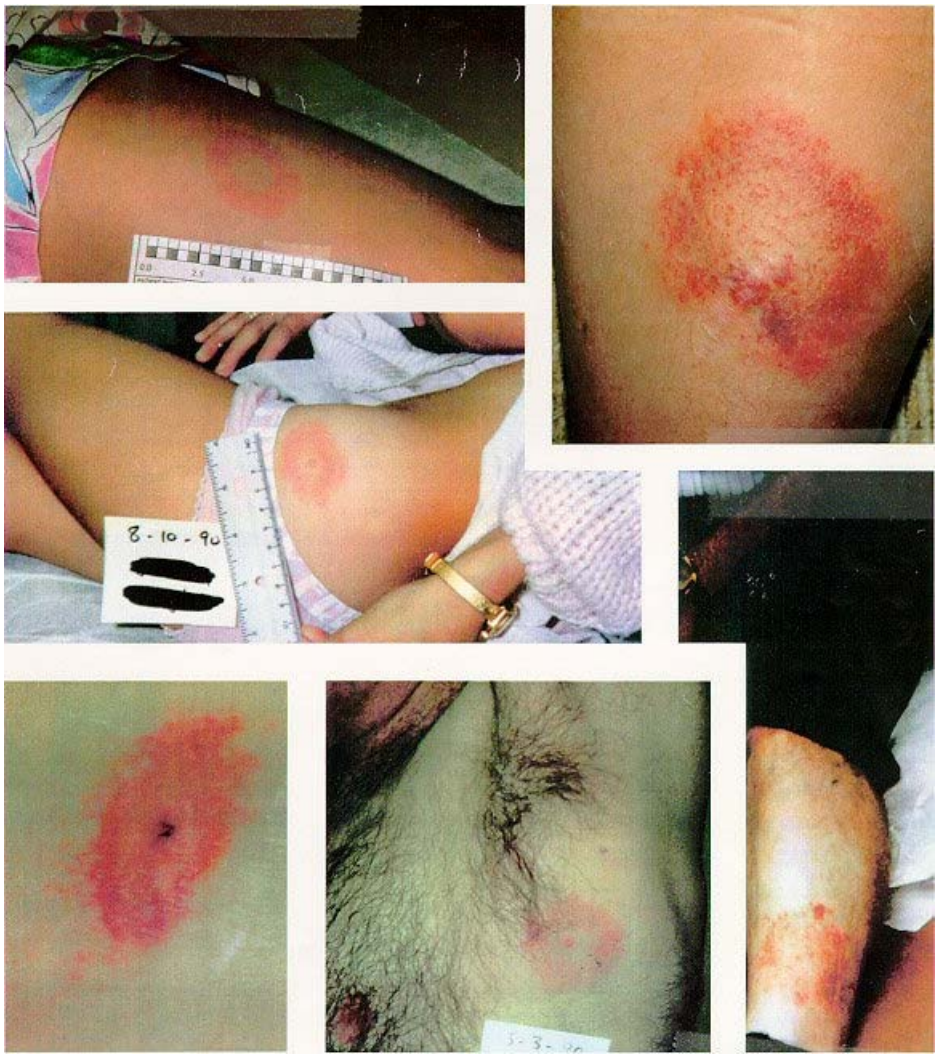


Cystine



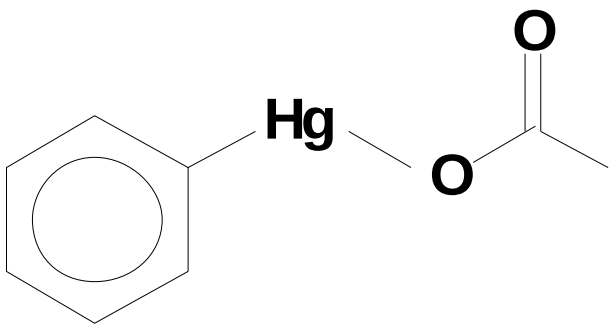
Zalups, R. (2000), Pharmacological reviews 52, 113-143

Toxicity of Inorganic Mercury - Mercurous mercury



Pink Disease / Acrodynia

- Due to the use of products containing monovalent mercury (e.g. teething powder)
- hypersensitivity response



Toxicity of Organic Mercury - Exposure/History

Occurrence and use

Bactericides, Fungicides (intentionally synthesized)

treatment of seeds (e.g. hydroxyphenylmercury, N-ethylmercury-p-toluenesulfonide)

in hospitals (phenylmercuryacetate)

ophthalmic and cosmetic preparations (ethylmercurycompounds)

Short-chain-Alkylmercury compounds (today: unintentionally present)

Methylmercury compounds (formed as an industrial waste product or by microbial metabolism)

Enrichment in the aquatic food chain

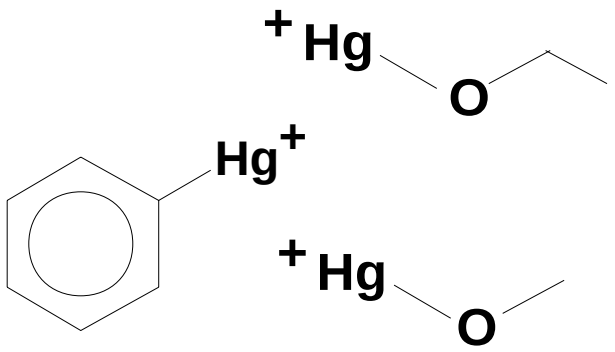
human exposure through consumption of fish

Toxicity of Organic Mercury- Stable and unstable compounds

„Unstable“ organic mercury compounds

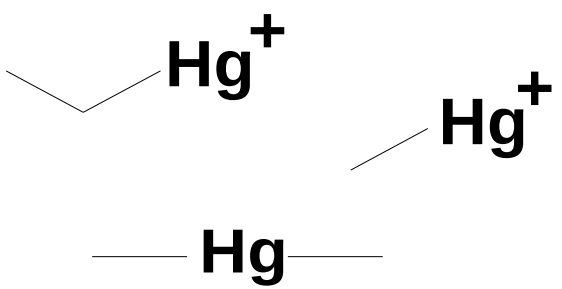
<u>Phenylmercury compounds, Alkoxyalkylmercury compounds</u>

- Absorption via gastrointestinal tract, skin, lungs
- Cleavage of the C-Hg bond, mainly in the liver
- rapid transformation into inorganic mercury



„Stable“ organic mercury compounds

Methylmercury- and Ethylmercury compounds



Toxicity of Organic Mercury - Severe fatalities

Effects from organic (methyl-)mercury compounds are known from several fatal incidents

Minimata and Niigata 1950s

Iraq, 1971-1972

Toxicity of Organic Mercury - Severe fatalities

Minimata, 1956

Release of methylmercury containing waste into the Minimata bay

Severe poisonings in fish consumers of that area

Iraq, 1970-1971

Most serious outbreak of a series of poisonings due to the use of fungicide-treaded grain for the preparation of bread

6530 cases of poisoning, 459 hospitalized deaths

Toxicity of Organic Mercury - Effects

Effects in adults

- long latency period (16 - 38 days)
- paresthesia
- ataxia
- blurred vision and constriction of visual fields
- heavily poisoned persons: blindness, coma, death
- focal brain damage

Effects in children

- brain damage and mental retardation in children which were exposed in utero or via breast feeding
- cerebral palsy
- mental retardation
- general brain damage

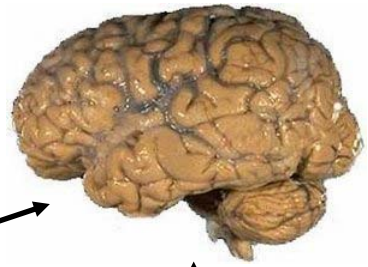
Toxicity of Organic Mercury - Toxicokinetics

Example: Methylmercury

Target tissues: central nervous system

- approximately 90 % absorption from the gastrointestinal tract
- rapid distribution to all tissues
- methylmercury transport is mediated by the formation of complexes (e.g. methylmercury-cysteine complex - preferential uptake into brain)
- Half-live: 70 days
- Accumulation in the fetal organism (fetal red blood cells: 30 % higher methylmercury levels compared to maternal levels)
- Metabolic transformation: oxidation to Hg^{2+}
- Effects on adult brain different from effects in infant brain

Toxicokinetics and target tissues of Mercury toxicity (II)



CNS /Brain

Methyl-/Ethyl Hg
90 % absorbed from GI

Hg (elemental)
80 % absorbed from lungs

Lung

Gastrointestinal tract

Methylation/
Demethylation

Reduction

Oxidation

Hg (II)
20 % absorbed from GI

Kidneys

Gastrointestinal tract

Phenyl Hg
80 % absorbed from GI

Toxicity of Organic Mercury - Mechanisms of Toxicity

Mechanisms of toxicity, tissue specifity and duration of latent period are only poorly understood

Adult brain:

Brain selectivity: molecular mimicry, methionine transporter

Focal selectivity (cell specific repair mechanisms, axonal transport)

Mechanisms:

Inhibition of protein synthesis

Interference with lipids, myelin, mitochondrial DNA synthesis and glutathione peroxidase

Effects on neurotransmitters and receptors

Toxicity of Organic Mercury - Mechanisms of toxicity

The developing CNS is more sensitive to damage from methylmercury than the adult nervous system (Minimata: slightly poisoned mothers gave birth to infants with severe cerebral palsy).

Iraq: severe damage to CNS in prenatally exposed children

Difference to adults : damage is generalized throughout the brain

Incomplete and abnormal migration of neuronal cells to the cerebrellar and cerebral cortices

Damage to astrocytes (which are believed to play a role in supporting neuronal migration)

Inhibition of cell division (Cell division is inhibited by causing metaphase arrest, presumably by disruption of the mitotic spindle).

Toxicity of Organic Mercury - Exposure of the general population

Exposure of the general population occurs through consumtion of fish

In populations consuming high amounts of fish, associations between methylmercury exposure and CNS effects have been investigated (by e.g. neurophysiological and neurological tests; mercury was determined in hair samples and cord blood)

Methylmercury exposure (based on hair analysis) was much lower compared to the big accidental poisonings

From two epidemiological studies (Seychelles, Faroe Islands) the authors of the Faroe study concluded that in utero exposure to methylmercury affects several domains of cerebral function.

Toxicity of Mercury and Mercury Compounds - Recommendations

Mercury exposure cannot be avoided - beneficial effects of fish consumption

Derivation of Reference values (different values dependent on philosophy and mathematical model) which are assumed to be protective

Provisional tolerable weekly intake (PTWI) for Methylmercury:

1.6 µg/kg bw/wk

Pregnant women eating up to 2 portions fish (not top predatory fish such as swordfish or shark) per week are unlikely to exceed the PTWI for methylmercury

Toxicity of Mercury and Mercury Compounds - Recommendations

Risher JF, J. Environ Health 67 (2004)

53 yr old woman, 1-2 fishmeals per day, swordfish 2 x/week

After several years of continued heavy fish consumption
„stomatitis, tremor, ringig in head and ears“

Analysis: 20 x PTWI

„The dose alone makes something a poison“

Toxicity of Mercury and Mercury Compounds - Research needs

Urgent need for additional studies:

- Methylmercury levels that do not cause effects on to the offspring
- lower end of the dose response curve (epidemiologic studies, confounding, exposure assessment - analytics/biomonitoring)
- develop objective measures for clinical manifestations
- Mechanisms of damage to the brain remain to be elucidated, there are too many open questions
- Vulnerability of the brain at different stages of pregnancy
- Selective damage of the nervous system and the long latency period are not understood

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Thank you for your attention

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