Mercury: Human toxicology and mercury speciation

Dr. Ulrike Bernauer
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.
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)

Hg (elemental)
80% absorbed from lungs

CNS / Brain

Lung
Gastrointestinal tract

Hg (II)

Kidneys

Reduction
Oxidation
Toxicity of elemental Mercury - Effects

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

Acute effects:
- gastrointestinal effects (elevated salivation/gingivitis)
- 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)
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(NH₂)Cl: treatment of eye diseases

Today/near past
HgCl₂: Disinfection
Hg(CN)₂: Cleaning of surgical instruments
HgNO₂: 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)

Hg (elemental) 80% absorbed from lungs → CNS / Brain → 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
Transport of the GSH-complex into the kidney, enzymatic cleavage in the kidney, formation of a bicysteinyl-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

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

Phenylmercury compounds, Alkoxyalkylmercury compounds

• 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)

- **Methyl-/Ethyl Hg** 90% absorbed from GI
- **Phenyl Hg** 80% absorbed from GI
- **Hg (elemental)** 80% absorbed from lungs
- **Hg (II)** 20% absorbed from GI

**CNS/Brain**
- **Lung**
- **Gastrointestinal tract**
- **Kidneys**
- **Gastrointestinal tract**

**Methylation/Demethylation**

**Reduction**

**Oxidation**
Mechanisms of toxicity, tissue specificity 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)

\[
\text{CH}_3\text{-Hg-S-CH}_2\text{-CH-COO}^- \quad \text{CH}_3\text{-S-CH}_2\text{-CH}_2\text{-CH-COO}^- \\
\quad \text{NH}^3+ \quad \quad \text{NH}^3+
\]

Methylmercury complex
Methionine

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 cerebellar 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).
Exposure of the general population occurs through consumption 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


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“
Urgent need for additional studies:

- Methylmercury levels that do not cause effects on 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
Thank you for your attention

Dr. Ulrike Bernauer

Federal Institute for Risk Assessment
Thielallee 88-92 • D-14195 Berlin
Tel. +49 30-8412-3705 • Fax +49 30-8412-3851
u.bernauer@bfr.bund.de • www.bfr.bund.de