Health effects of mercury

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Toxicokinetics of Hg

- Depends on chemical form – Hg, Hg++, organic Hg
- Route of exposure
- Metallic Hg—inhalation; poorly absorbed from GI tract; lipophilic and crosses placenta and BBB
- Inorganic Hg—kidney toxicity; does not readily cross blood-brain barrier; T _ 20-60 days; somewhat better GI absorption

Toxicokinetics of Hg

- Organic mercury—CNS/neurotoxicity; readily absorbed from GI tract; T _ 70-80 days; primarily fecal excretion
- Dynamics of speciation not well understood
- Organic Hg
  - 90% of blood MeHg is bound to hemoglobin
  - 50% of dose in liver; 10% in head
  - Slowly demethylated in tissues

Toxicokinetics of Hg

- Organic Hg (methyl-, ethyl-) crosses blood-brain barrier, amino acid transport system
- Converted to inorganic Hg in brain with long half-life (?months, years)

Mechanisms of Hg neurotoxicity

- Affinity for proteins with sulfhydryl groups
- Adverse impacts on enzymes, membrane function, neurotransmitter levels
- Oxidative stress, lipid peroxidation, mitochondrial dysfunction
- Disrupts synaptic transmission, microtubule formation, amino acid transport
- Impairs cellular division and migration in developing brain – importance of timing of exposure
- No single mechanism is explanatory

Process	**Chemicals associated with disruption: (animal or human data)**
proliferation	radiation, ethanol, mercury, cholinesterase inhibitors
migration	radiation, mercury, ethanol
differentiation	ethanol, nicotine, mercury, lead
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs
gliogenesis & myelinization	dec. thyroid, ethanol, lead
apoptosis	ethanol, lead, mercury
signaling	ethanol, cholinesterase inhibitors, mercury, lead, PCBs

Est. daily intake and retention; general population (ug/day)

Exposure	Elemental Hg	Inorganic Hg	MeHg
Air	0.03	0.002	0.008
Food			
--fish	0	0.6	1-6
--non-fish	0	3.6	0
Water	0	0.05	0
Amalgams	3.8-21	0	0
Total	3.9-21	4.3	1-6

Neurobehavioral effects of developmental MeHg in monkeys

Birth to 7 yr old	LOAEL 50 ug/kg/day	Dec. visual contrast sensitivity at 3-4 yr old (Rice, 1982)
In utero	50-70 ug/kg/day	Impaired visual recognition memory (Gunderson, 1988)
Birth to 7 yr old	50 ug/kg/day	Inc. clumsiness at 13 yr old (Rice, 1989)

Neurobehavioral effects of developmental MeHg in monkeys

In utero	LOAEL 50 ug/kg/day	Reduced social play, inc. non-social behavior (Burbacher 1990)
In utero until 4 yr old	10-50 ug/kg/day	Dec. visual contrast sensitivity (Rice, 1990)
Birth to 7 yr old	50 ug/kg/day	Inc. pure tone threshold at 14 yr old (Rice, 1992)

Minamata, Iraq

- Some adults with severe neurological symptoms
- Fetal exposures – lower doses: psychomotor delays, mental retardation, weakness, seizures, hyperactivity, dysarthria, difficulty sucking, coordination disorders, blindness

Exposures: Minamata, Iraq

- Minamata – chronic exposures; estimates of maternal hair Hg levels 3.8-133 ppm; mean 41 ppm
- Iraq – acute exposures; maternal hair levels 1-674 ppm; estimate threshold for effects in offspring at 10 ppm Hg maternal hair

Seychelles Islands study

- Mean maternal hair Hg 5.9 ppm (0.6-30)
- DDST-R, Fagan, visual attn (6.5 mos)

  Bayley scales infant intelligence (29 mos)

  McCarthy, Preschool language, Bender-Gestalt, Woodcock Johnson, Child behavior check list (66 mos)
- No association with maternal hair Hg level

Seychelles Islands study

- 9 yr old follow up study (Lancet; May, 2003)
  - Mean maternal hair level 6.9 ppm Hg
  - Domain specific testing (including Boston Naming Test and continuous performance)
  - No association between prenatal exposures to Hg and neurological performance

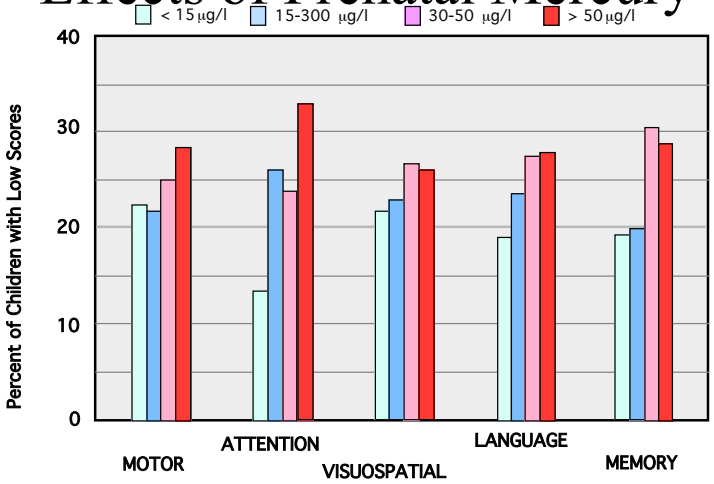
New Zealand study

- 2 grps: maternal hair levels < or > 6 ppm Hg; mean in "high" grp 8.3 ppm
- DDST (4 yrs), Test of language development, WISC-R, MSCA (6 yrs)
- Higher Hg levels associated with poorer performance on IQ, language development, visual-spatial skills, gross motor skills

Faroe Islands study

- Umbilical cord blood Hg levels (mean 22.9 ug Hg/L; mean maternal hair level 4.3 ppm)
- Neurobehavioral evaluation system, WISC-R, Bender Gestalt, Calif. Verbal Learning Test, Boston Naming Test
- At age 7 yrs, inc. cord blood Hg associated with adverse effects on motor skills, attention, visual spatial, language, memory, blood pressure, heart rate variability

Effects of Prenatal Mercury



Source: Grandjean, et. al., "Cognitive Deficit in 7-year-Old Children with Prenatal Exposure to Methylmercury", Neurotoxicology and Teratology, Vol. 19, No. 6, 1997

Figure shows prenatal mercury exposure levels of Faroese children with scores in the lowest quartile after adjustment for cofounders. For each of the five major cognitive functions, one neuropsychological test with a high psychometric validity was selected.

(SWAT.A.08)

Possible explanations of why studies are inconsistent

- Cultural differences; cultural relevance of tests
- Seychelles children entered at 6 mos of age; Faroes children at entered at birth and cord blood levels measured
- Different dosing patterns—continuous vs bolus
- Unlikely to be due to PCBs in Faroes (mercury regression coeff. greatest in low PCB grp; interaction: PCB effects seen in highest Hg exposure group)

Hg and cardiovascular disease

- Hair level > 2 ppm Hg assoc with 2 fold increased risk of CV death (Salonen, 1995) and increased progression arteriosclerosis (Salonen, 2001)
- Mercury diminishes cardioprotective effects of omega 3 FA (Guallar, 2002)
- Inc. blood pressure and dec. heart rate variability in infants (Grandjean)

Immunotoxicity of Hg

- Animal studies – altered white cell counts, dec. natural-killer cell activity, inc. thymus wgt., altered B-cell and T-cell subtypes
- Autoimmune response in animals (kidneys)
- Limited evidence of autoimmune response in humans exposed occupationally to metallic Hg (kidneys); no studies with MeHg

US population exposures to Hg

- Current reference dose is 0.1 ug/kg/day
- EPA concludes that up to 620,000 babies born every year in the US with methylmercury exposures above EPA's reference dose

Conclusions

- A large database from animal and human studies shows diverse impacts of Hg exposure
- Developmental effects seem to be the most sensitive
- Low level prenatal exposures associated with deficits in attention, language, memory, visual-spatial and motor skills; reduced heart rate variability
- Current levels of exposure in US population of concern