# Biomarkers of Mercury Exposure and Determinants of Susceptibility

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# BIOMARKERS OF MERCURY EXPOSURE

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## Hg exposure

- Mercury (Hg), especially methylmercury (MeHg), is one of the many environmental contaminants that is of public health concern (FNB 2007, NRC 2000)
- Hg exposure in humans has therefore been extensively studied and illustrates several important concerns regarding heavy metal exposure
- MeHg bioaccumulates via aquatic food chains
- High *vs* low dose mercury exposure
  - Acute high dose Hg exposure (e.g., Minimata Bay) is uncommon
  - Low dose mercury exposure is common in HK and long-term adverse health outcomes are possible in high risk groups (NRC 2000, Fok et al 2007, Lam et al 2013)

## Hg exposure

- The different ways in which the population is exposed to different species of Hg necessitate different strategies for exposure risk reduction
- Children and adults are affected by toxins differently and to varying degrees
  - Different routes of exposure
  - Toxicokinetic differences
  - Different target organs and organ maturity

## Need for Hg exposure biomarkers

- In order to determine the risks of individuals and populations, biomarkers of Hg exposure have been investigated
- Hg concentrations can be measured in tissues such as
  - Blood, including cord blood
  - Hair
  - Nail
  - Urine
  - Umbilical cord tissue
- Different biomarkers can be employed to reflect different Hg exposure patterns
- Hg speciation is now increasingly available to measure MeHg

## Exposure biomarkers

- Hair Hg
  - Can reflect mercury exposure during different periods of time depending on portion of hair analysed
- Nail Hg
  - Used in recent studies in view of ease of collection
  - Toenails preferred
- Blood Hg
  - Majority of Hg in blood is in the form of MeHg and concentrated in red blood cells
  - Cord blood Hg is a biomarker for prenatal Hg exposure (thought to represent fetal exposure during the 3rd trimester of pregnancy)
- Urine Hg
  - More useful than the above as a marker of recent inorganic mercury exposure

## MeHg exposure – high dose effects

- Acute high-dose MeHg exposure predominantly causes neurotoxic effects
  - Paraesthesia
  - Ataxia
  - Visual
  - Hearing loss
- Latent period (weeks to months) possible before the development of symptoms
- Children more vulnerable to MeHg toxicity than adults and may exhibit more severe clinical features, e.g.,
  - asymptomatic mothers during the Minamata Bay outbreak gave birth to offspring with congenital Minamata disease
- Renal impairment rare without neurological symptoms

## Congenital Minamata disease

- Mean maternal hair mercury concentration 41 ppm
- Clinical features
  - Neurodevelopmental deficits
    - Mental retardation
    - Persistent primitive reflexes
    - Cerebellar ataxia
    - Dysarthria
    - Seizures
    - Strabismus
  - Impaired growth
  - Limb deformities
  - Hypersalivation

## Chronic mercury exposure

- Up till the early 20th century hat-makers cured felt with mercuric nitrate
- Chronic exposure to mercury caused erethism and thus "madness"

## Low dose MeHg exposure

- No definite level of MeHg exposure below which there are no adverse effects
- Evidence of neurotoxic effects of prenatal exposure to low dose MeHg from large cohort studies (Grandjean et al 1997, NRC 2000)

## Other effects of low dose exposure

- Cardiovascular effects of low-dose prenatal MeHg exposure (Sørensen et al 1999)
  - Increased blood pressure at 7 years of age associated with cord blood Hg concentrations even as low as 5 to 50 nmol/L
  - Decreased heart-rate variability (marker of cardiac autonomic control) in boys at the same range of cord blood Hg concentrations
- Adult data from Finland (Salonen et al 1995) show that men consuming at least 30 g fish per day or with hair Hg concentration ≥ 2 ppm had twice the risk of myocardial infarction
- Increase in male subfertility (Dickman et al 1998)

## Benchmark dose analysis

- Recent studies have used benchmark dose (BMD) analysis to guide risk assessment
- The US EPA (2001) defined the BMD as the dose of MeHg that would increase the tested parameter's abnormal population from an assumed 5% to 10%

## The benchmark dose level

- The lower limit of the 95% confidence interval for the BMD was defined as the BMDL
- Using Faroese data with the Boston naming test as the outcome yielded a BMDL of 290 nmol/L (58 µg/L) for cord blood Hg and 12 ppm for maternal hair Hg
- Applying an uncertainty factor of 10 to the BMDL gives cord blood mercury of 29 nmol/L or maternal hair mercury of 1.2 ppm as an upper limit that will protect most of the population from the toxic effects of MeHg (NRC 2000)

## MeHg exposure in HK

- Children in Hong Kong
  - Ip et al 2004: blood mercury – mean 17.6 nmol/L (SD 2.4 nmol/L)
  - Fok et al: cord blood mercury – median 44.0 nmol/L (IQR 31.6, 61.6 nmol/L)
- Pregnant women in Hong Kong
  - Fok et al: maternal blood mercury at delivery – median 24.6 nmol/L (IQR 18.2, 34.3 nmol/L)
- Women of child-bearing age in other populations:
  - North American cohort (Mahaffey et al 2004): blood mercury concentration median 4.7 nmol/L (IQR 2.1, 10.4 nmol/L)
  - Swedish cohort (Björnberg et al 2005): blood mercury concentration median 8.5 nmol/L

## Prenatal MeHg exposure


*Adapted from KM Kwok's MPhil thesis (CUHK 2011)*

## DETERMINANTS OF SUSCEPTIBILITY

## Susceptibility to adverse effects of Hg

- Several factors influence the susceptibility of individuals to Hg toxicity, e.g.,
  - Dietary factors
    - Selenium
  - Genetic susceptibility
  - Age
    - Younger age groups more vulnerable to neurotoxic effects
  - Sex
    - Evidence that boys are more susceptible to girls
  - Patterns of exposure
    - "Spiky" *vs* consistent exposure

## Dietary factors – selenium

- One important factor is body selenium (Se) status
- Individuals with decreased Se levels may be at higher risk of adverse outcomes associated with Hg exposure
- Animal studies:
  - Se concentration and the activity of glutathione peroxidase, a selenoenzyme, were depressed by MeHg in the mice neural tissue. (Watanabe et al., 1999)
  - Neurobehavioral dysfunction worst in mice given lowest amount of Se and highest amount of Hg (Watanabe et al., 1999)

## Selenium – an antagonist of Hg

- High binding affinity between Hg and Se
→ irreversible inhibitor of selenoenzymes

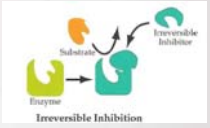
- Protective effect against Hg toxicity?
  - Sequestration of Hg → prevent Hg from exerting its toxic effects

(Ganther et al., 1972,Prohaska and Ganther, 1977, Watanabe et al., 1999a, Watanabe et al., 1999b, Ralston et al., 2007 and Yang et al., 2008)

***OR***

- Se supplement ensure adequate Se is available to compensate for loss of Se → maintain normal selenoprotein activities

(Prohaska and Ganther, 1977 and Watanabe et al., 1999b)




## Genetic associations

- Genetic factors have recently also been found to play important roles in Hg metabolism
- Several studies (Engstrom 2011, Wang 2012a, Wang 2012b) have shown that genetic polymorphisms:
  - Are involved with pathways which play a role in the metabolism of MeHg
  - Can lead to modification of the association between mercury intake and retention
  - Can modify the intake levels at which toxic levels may occur

## Genetic susceptibility – glutathione synthesis

- Several polymorphisms have been shown to be involved in glutathione-related genes (Engstrom 2011)
- These genes are responsible for production of
  - Glutamyl-cysteine ligase (GCL), a rate-limiting enzyme for glutathione synthesis
  - Glutathione transferase pi 1 (GSTP1), which conjugates glutathione to electrophilic compounds

## Metallothioneins

- Metallothioneins (MT) are thiol-rich proteins that bind heavy metals,e.g., Hg and can help protect the body from toxicity (Wang 2012a)
- MT isoforms:
  - MT1
  - MT2
  - Brain-specific MT3
  - MT4
- Gene polymorphisms in these genes can potentially lead to modification of mercury levels in the body at given low-dose exposures (Wang 2012a)
- In a study of a group of 515 dental professionals, results suggested that some MT genetic polymorphisms could influence Hg biomarker concentrations at levels of exposure relevant to the general population (Wang 2012a)

## Summary

- Hg exposure biomarkers can be employed to measure different aspects of Hg-related exposure
- Multiple factors determine the susceptibility of individuals to Hg toxicity
- Judicious use of such biomarkers and the associated genetics can play an important part in the development of evidence based guidelines to diagnose, treat and manage Hg exposure at individual and government levels

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