University of Idaho

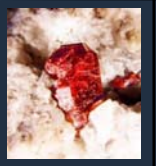
The Socrates Award Lecture 2004

Environmental Toxicology of Mercury

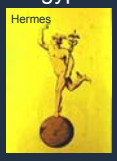
Professor Greg Möller
University of Idaho
Moscow, Idaho USA

Mercury in History

- HgS: Cinnabar, Vermillion
- Native mercury
- Ancient mining in Spain, Italy, China
- Found in 1500 BC Egyptian tombs

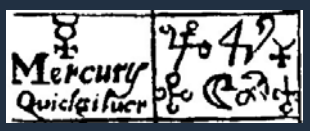


Bible, France, 13th c.

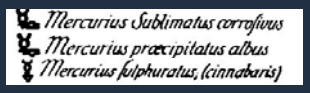


An Element of Mystery

- Native mercury: argentum vivum
- Mercury from condensing heated vapor of cinnabar: hydrargyrum (water silver, Gk)



From Basil Valentine, *Last Will and Testament*, London, 1671

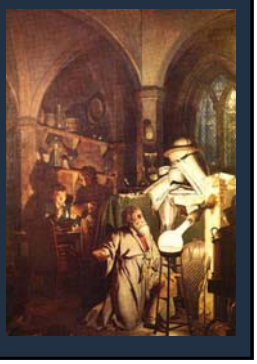


Chemiske forelasningar, Upsalla. 1775

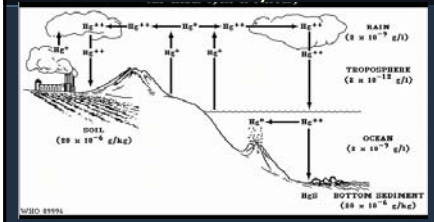
Medicinisch-Chymisch- und Alchemistisches Oraculum, Ulm, 1755

Turba Philosophorum

- One of the earliest Latin alchemical texts, the *Turba Philosophorum* or assembly of the alchemical philosophers, dates from the 12th century.
- *"In the estimation of all Sages, Mercury is the first principle of all metals."*
- *"As flesh is generated from coagulated blood, so gold is generated out of coagulated Mercury."*



Global Cycle of Mercury

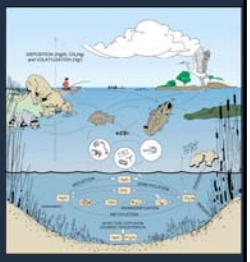


1. Degassing of mercury from rock, soils, and surface waters, or emissions from volcanoes and from human activities.
2. Movement in gaseous form through the atmosphere.
3. Deposition of mercury on land and surface waters.
4. Conversion of the element into insoluble mercury sulfide
5. Precipitation or bioconversion into more volatile or soluble forms such as methylmercury
6. Reentry to atmosphere or bioaccumulation in food-chain

Aquatic Mercury Cycle

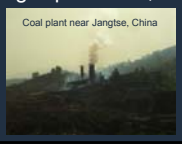
- In soil, mercury is relatively harmless in its elemental, divalent or particulate forms. It is only when Hg^{2+} is converted to methylmercury (CH_3Hg+) that it becomes a hazard.
- Methylmercury is produced as a by-product of the metabolic processes of sulfate reducing bacteria in anaerobic environments.
- It is not exactly known how inorganic mercury is converted to organic mercury during this process, but one hypothesis is that Hg2+ combines with S to form the salt HgS which is absorbed by the bacteria.

$$HgS \rightarrow CH_3Hg(II)X + H$$



Mercury in the Modern Environment

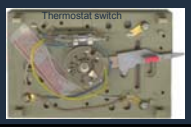
- 70% of mercury in the environment comes from anthropogenic sources: metal mining and smelting, municipal & medical waste incineration, sewage, coal-fired power plants and cement manufacturing.
- Mining and volcanic eruption are also sources.
- In the past 100 yrs, there has been a 3x increase in environmentally available Hg due to industrialization
- Hg is persistent, bioaccumulative and toxic.



Mercury Uses

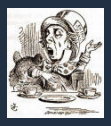
We use its unique properties to conduct electricity, measure temperature and pressure, act as a biocide, preservative and disinfectant and catalyze reactions.

- Scientific apparatus
- Lighted athletic shoes
- Batteries
- Old latex and oil-based paints
- Vacuum gauges
- Tilt switches
- Solvents
- Pesticides
- Dyes and pigments
- Barometers and Manometers
- Pottery and arts
- Pharmaceuticals and cosmetics
- Human and animal vaccines
- Fungicides for seed and turf
- Old toys and chemistry sets
- Chloralkali process (Cl_2)



The Mad Hatter

- The Mad Hatter, made famous in Lewis Carroll's Alice in Wonderland, was "mad" as a result of mercury poisoning.
  - Mercury nitrate was used to preserve the beaver felt hats that were popular in 19th century fashion.
  - The workers in the beaver felt factories of the time would develop symptoms including high irritability a result of breathing mercury fumes, some effects of which are irreversible.



Medicinal Mercury

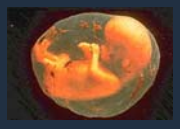
- The use of mercury salts in the 19th Century for the treatment of syphilis gave rise to severe side effects and many deaths.
- Mercury compounds have in the past been used as diuretics, anti-infectives, laxatives, eye and skin treatments ("Mercurochrome").
- Speculation as whether mercury toxicity from medicines contributed to the depression and apparent suicide of the explorer Meriwether Lewis following the Lewis & Clark Expedition.

Nephrotoxic

- Mercury exerts its principle nephrotoxic effect on the membrane of the proximal tubule cell.
- In low concentrations, Hg binds to sulfhydryl groups of membrane proteins and acts as a diuretic by inhibiting Na^+ reabosrption.
  - Organomercurials used clinically as diuretics 1920s-1960s
  - **"Mersalyl"** $C_{13}H_{17}HgNO_6$

Neurotoxicity of MeHg

- All forms of mercury are neurotoxic.
- Methylmercury (MeHg) is highly neurotoxic.
- Levels of MeHg too low to show a postnatal effect can be neurotoxic to a developing fetus.



 Philip W. Davidson

Methylmercury and Fish

- Principal source of human exposure is fish consumption.
- Sea mammals and shellfish also contain MeHg.
- Major source of MeHg in the aquatic environment is atmospheric mercury deposited on the surfaces of bodies of water that is then biomethylated by microorganisms and subsequently biomagnified as it ascends the food chain.
  - Most fish living in US waters have less than 0.5 ppm but some older, larger carnivorous fish at the top of the food chain can contain more than 1 ppm.
  - Tuna, shark, and swordfish all typically exceed 1 ppm.

MeHg Exposure: Infants and Children

- Dominant health concerns arise from *in utero* exposure, however infants and children can be exposed to MeHg from breast milk and from consumption of fish and fish products.

Methyl-Mercury Poisoning Incidents

- In the 1950s, MeHg poisoning from industrial discharges occurred in Minamata and Niigata, Japan. Over 21,000 individuals filed claims as victims of what became known as Minamata disease; almost 3,000 were certified by the government as actually having the disease. In Minamata nearly 600 people died. Fish contaminated by these discharges were subsequently caught and consumed by local residents. Poisoned individuals suffered severe neurological impairments.
- In 1971-72, a poisoning outbreak in Iraq resulted from the consumption of bread made from seed grain coated with a MeHg fungicide. This outbreak affected 6,530 individuals, 439 of whom died.

Japan's top court orders government to pay Minamata mercury poisoning victims 22 years after case filed

By: KOZO MIZOGUCHI - Associated Press October 15, 2004

TOKYO -- Japan's top court ordered the government Friday to pay $703,000 in damages to victims of the Minamata mercury poisoning 22 years after their famous case was filed over an industrial pollution disaster that killed more than 1,700 people and caused diseased mothers to give birth to deformed babies.

After the decision, several plaintiffs rushed from the courthouse and unfurled a banner declaring their victory to cheering supporters. The government apologized to victims for failing to prevent the pollution. "We assure you that this horrific incident won't ever be repeated," Environment Minister Yuriko Koike said, making a deep bow to plaintiffs in a meeting after the verdict. "The government will tell about the lessons learned here for generations to come."

The Minamata poisoning was Japan's worst case of industrial pollution. Since the 1950s, hundreds of people have contracted Minamata disease -- a neurological disorder caused by mercury poisoning -- from eating tainted fish. The disease, first discovered in the 1950s, was named for Minamata Bay in southern Japan where a company dumped tons of mercury compounds.

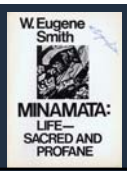
Babies of poisoned mothers were born with gnarled limbs. The victims were seared into memory by a famous series of photographs by W. Eugene Smith from the 1970s, including one of a woman holding her deformed child in a bathtub.

The case came to symbolize the dark side of Japan's remarkable growth to the world's second-largest economy in the post World War II era.

…According to government figures, 2,955 people contracted Minamata disease, and 1,784 people have since died. Under a special law, victims can receive free medical care and compensation. ….Another 12,000 people who were sickened had received a one-time government payout but weren't eligible for free medical care…

"Tomoko in Her Bath"

W. Eugene Smith photographed in front of "Tomoko Uemura in Her Bath, 1971," at a 1974 Minamata exhibit in Tokyo, Japan. Photo by Takeshi Ishikawa, who worked with Gene and Aileen Smith in Minamata.



Minimata Disease

- A neurological disorder caused by ingestion of large quantities of fish or shellfish contaminated with methylmercury by two industrial effluents in Minamata and Niigata, Japan

Learning from The Minamata Experience

- Mercury pollution of the environment has created some serious hazards for man.
- Health and environment considerations must be integrated into the process of economic and industrial development from a very early stage.

Yukio Takizawa
Akira Sekikawa

Chronology Related to Minamata Disease

Year	Events
1956	First report unknown disease to Minamata Public Health Center (the official discovery of Minamata Disease). Restraint measures initiated to restrict intake of fish and marine creatures from Minamata Bay, etc.
1965	Showa Denko., Ltd. Stopped manufacturing of acetaldehyde. Discovery of Niigata Minamata Disease. Restraint measures initiated to restrict intake of fish and shellfish from the Agano River.
1968	Chisso Co., Ltd., stopped manufacturing of acetaldehyde. The collective view of the government on the cause of Minamata Disease announced.
1969	Law Concerning Special Measures for the Relief of the Pollution-related Disease enacted.
1970	Water Pollution Control Law established.

1971	Court decision on the first suit concerning Niigata Minamata Disease issued. (The responsibility of Showa Denko Co., Ltd. to pay compensation for damage recognized.)
1973	Court decision on the first suit on Kumamoto Minamata Disease issued. (The responsibility of Chisso Co., Ltd. to pay compensation for damage recognized.) The agreement on compensation between the patients and Showa Denko Co., Ltd., reached. The agreement on compensation between patients and Chisso Co., Ltd. reached.
1974	Dredging of the polluted bottom sediment of the Minamata Bay began.
1976	Dredging of the polluted bottom sediment of the Agano River began.
1990	Dredging the bottom sediment of Minamata Bay finished. Legal Reconciliation recommended

Research on the Cause

- What was suspected as being the most likely cause at the time this disease was prevalent was encephalitis, followed by chemical intoxication. However, it became clear that this disease differed from general food poisoning. Thus the disease was presumed to be chemical poisoning.
- Men and Women of all ages, excluding infants, became victims and cats in victim's families often showed similar symptoms. Thus fish- and shellfish- mediated food poisoning was first to become suspect.

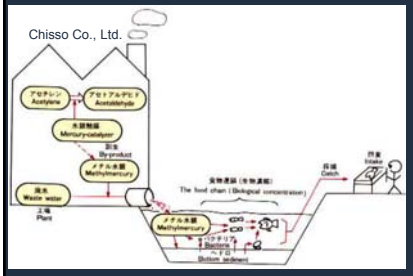
Yukio Takizawa
Akira Sekikawa

Disease Investigation

- Taking into consideration the geographical and chronological distribution of the victims, it was surmised that a chemical substance contained in the waste discharge from an acetaldehyde plant located on the shores of Minamata Bay was causative agent.
- Mercury was not suspected at the beginning, and it took years for the mercury theory to be formulated. This was due to the peculiar etiology of this disease.

Yukio Takizawa
Akira Sekikawa

MeHg from Acetaldehyde Manufacturing



CH_3CHO

Used as a starting material in the synthesis of acetic acid, n-butyl alcohol, ethyl acetate, and other chemical compounds

Japan Ministry of Environment

Former Clinical Knowledge Was Not MeHg

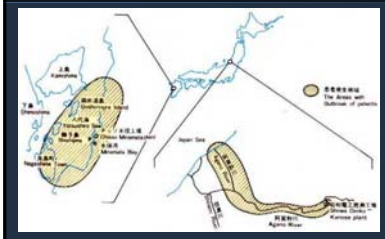
- This disease can be clearly distinguished from traditional industrial mercury poisoning. It took 12 long years to reach an official conclusion as to the cause of this disease from the first outbreak.
- This is because scientific knowledge about and experience with transmission of mercury compounds up the food chain in those days were very limited, as were the techniques for analyzing very small concentrations of methylmercury.

Conclusions

- In 1968, the Japanese government sorted out all the knowledge related to Minamata disease that had been gathered up to that time, and announced its view point:

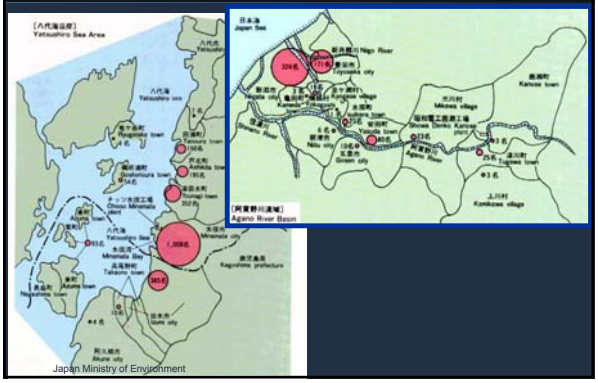
"Minamata disease is a poisoning disease of the central nervous system caused by methylmercury compound, which was produced as by-product in the process of manufacturing acetaldehyde at Chisso Co. Ltd. in Minamata City and Showa Senko Co. Ltd., located upstream of Agano River".

Outbreak of Minamata Disease



Some Minamata inhabitants who ate 300-1500 g/ day with an average mercury concentration of 3-4 ug/g suffered poisoning.

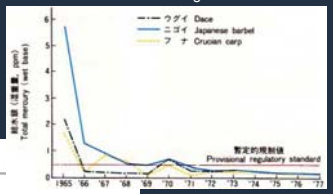
Distribution of Certified Patients 2001



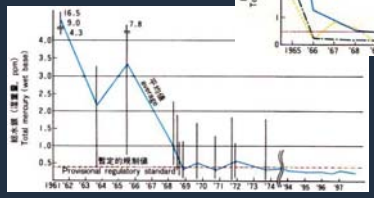
Japan Ministry of Environment

Contamination Level in Fish

Agano River Basin



Minamata Bay Area



Environmental Pollution Control

- Cessation of process using mercury
- Industrial effluent control
- Environmental restoration, including removal of contaminated sediments
- Restrictions on intake of fish and other seafood

Clinical Features I

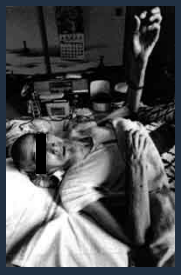
- Sensory disorder in the distal portion of four extremities.
- Cerebellar ataxia.
- Bilateral concentric constriction of the visual field.
- Central disorder of ocular movement.
- Central hearing impairments.
- Central disequilibrium.

Clinical Features II

- Infant Minamata Disease.
- Intellectual disorder.
- Various degrees of neurological disorders subsequent to ataxia.
- Signs and symptoms of acquired Minamata disease but absence of sensory disturbance.

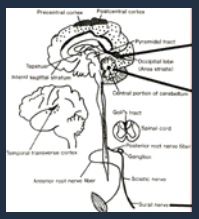
Infant Minamata disease consists of both fetal Minamata disease which originates in a fetus exposed to methylmercury through the placenta of the exposed mother and post-natal Minamata disease due to oral ingestion of methylmercury after birth.

Muscular Contracture in the Fingers



This sign was observed on typical Minamata disease patients.

Neuropathology of Chronic Occurrence



A calcarine area of a chronic onset case running the course of 11 years (KU No. 5583, 65-year-old male), not less than 50% of neurons are lost, which is classed as grade 3. Klüver-Barreera's staining, X 150.

- Typical neuropathological findings in methylmercury poisoning were first described by Hunter-Russell (1954). Minamata disease exhibits a variety of neuropathological features, from severe changes at the early stage to mild changes.
- The pronounced changes in the white matter in the brains were usually unobservable in the first three yrs following poisoning but emerged (4-6 years) and became widespread after 10 yrs.
- Preferential, localized neuropathologic disintegration in the brain occurred mainly in the calcarine cortex, precentral and postcentral cortices and central portion of the cerebellum in typical cases.
- The changes were characterized by tissues coarseness, sclerosis was observed in some cases, and the later stages were characterized by thinning of the myelin.

Congenital Minamata Disease

- In Minamata, pregnant women who consumed the contaminated fish manifested mild or no symptoms, but gave birth to babies with severe developmental disabilities, including cerebral palsy, mental retardation, and seizures.
- This outcome, called Congenital Minamata disease, first indicated that the fetal brain may be highly sensitive to MeHg exposure.
  - Following the outbreaks, 22 cases were documented.
  - Level of prenatal exposure was never ascertained; no dose response information.

Diagnosis

- Because various symptoms of Minamata disease can be caused by other diseases as well, diagnosis of the disease in people who have been exposed to methylmercury compound is carried out on the basis of diagnostic criteria, in order to raise the level of diagnostic probability.
- While diagnosis on this basis is fairly easy for typical patients who have all the major symptoms, in the case of incomplete type or moderate type of this disease, however, it may be difficult to distinguish it from other disease.

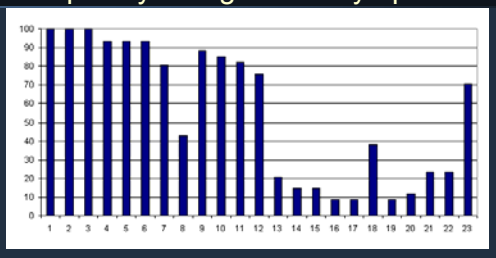
Criteria for Post-Natal Minamata Disease

Classification of symptoms	Sensory system disorders	Ataxia	Disequi-librium	Constriction of the visual field	Central nervous disorders (Ocular system)	CNS disorders	Other symptoms
a	O	O					
b (1)	O	X	O				
b (2)	O	X		O			
c (1)	O			O	O		
c (2)	O			O		O	
d	O	X					O

O : Observed, X : Possible

Differential Diagnosis:
Polyneuritis of various origins
Cerebrovascular disturbance
Cervical spondylosis
Psychogenic disorders

Frequency of Signs and Symptoms



1; Constriction of visual filed, 2; Superficial sensory disturbance, 3; Deep sensory disturbance, 4; Ataxia (adiadochokineses), 5; Ataxia in writing, 6; Ataxia in buttoning, 7; Ataxia in finger-finger, in finger-nose tests, 8; Ataxia (Romberg's sign), 9; Impairment of speech, 10; Impairment of hearing, 11; Impairment of gait, 12; Tremor, 13; Muscular rigidity, 14; Ballism, 15; Chorea, 16; Athetosis, 17; Contracture, 18; Exaggerated tendon reflex, 19; Weak tendon reflex, 20; Hemiplegia, 21; Salivation, 22; Sweating, 23; Slight mental disturbance

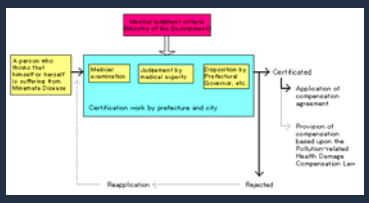
Treatment

- There is no specific effective therapy for the disease.
- Mercury eliminators:
  - Penicillamine, Thiola, Gulation, EDTA-Ca, with combined use of vitamins
- Function training therapy.

The drugs are usually mixed with Ringer solution or 5% glucose solution and administered via intravenous drip infusion in the early stage of the disease.

The eliminators used in Iraq methylmercury poisoning were D-penicillamine, N- acetyl-DL- penicillamine, thiol resin, etc.

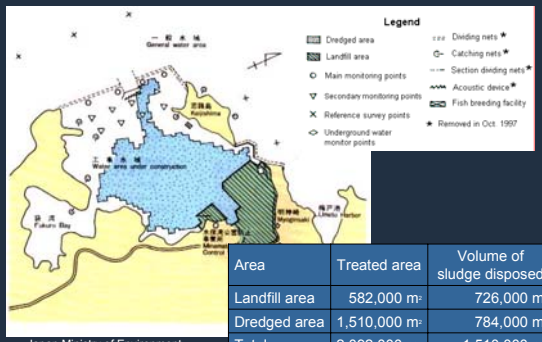
Relief of Minamata Disease Patients



Dredging of Minimata Bay

- It was ascertained that more than 70-150 tons of mercury were discharged into Minamata Bay by Chisso Co. Ltd. To dispose of this mercuric sludge quickly and safely, the nation, Kumamoto Prefecture, and Chisso, in 1974, shared the expenses of dredging Minamata Bay and reclaiming some of the land.

Dredging of Minamata Bay



Japan Ministry of Environment

Area	Treated area	Volume of sludge disposed
Landfill area	582,000 m²	726,000 m²
Dredged area	1,510,000 m²	784,000 m²
Total	2,092,000 m²	1,510,000 m²

New Hg Standards

Various Indices showing the Threshold Value for Onset of Symptoms in Human Body
(Level at which neurological symptoms would appear in the most sensitive adults)

Average daily intake	3-7 μg/kg
Body burden	15-35mg（50kg weight)
Total mercury concentration in blood	20-50μg/100ml
Total mercury concentration in hair	50-125μg/g

Effluent Standard for Mercury Based Upon the Japanese Water Pollution Control Law

Total mercury	0.005mg/l
Alkyl mercury compounds	Must not be detected (Limit of detection 0.0005mg/l)

Japan Ministry of Environment

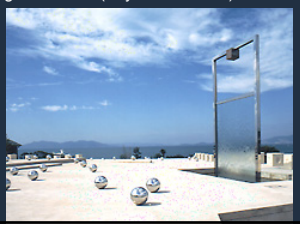
Minamata Memorial

Completed in 1996, the 40th anniversary of the official discovery of Minamata disease:

1) As a prayer and requiem for those sacrificed to Minamata disease;

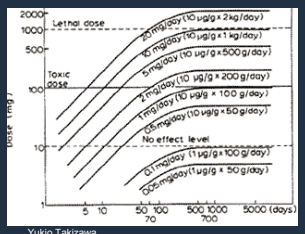
2) As a pledge, based on the experience of Minamata disease, to never allow the repetition of such disasters;

3) so as to pass on the lessons of Minamata disease to future generations. (City of Minamata)



Estimated MeHg Accumulation Curve

- Kitamura (1971) has presented an accumulation curve for methylmercury compound, assuming the biological half-time to be about 70 days. He calculated that slightly affected victims must have eaten more than 500 g/ day of poisonous fish containing 10 ug/g methylmercury. The toxic dose line above which symptoms develop (i. e., 100 mg of accumulated mercury) was taken as one- tenth the lethal dose, as deduced from analytical values for methylmercury in the viscera of deceased victims.



Yukio Takizawa
Akira Sekikawa

Provisional Tolerable Weekly Intake

- The Joint FAO/ WHO Expert Committee on Food Additives recommended that "any use of mercury compounds that in creases the level of mercury in food should be strongly discouraged".
- It recommends a provisional tolerable weekly intake of 0.3mg total mercury per person, of which no more than 0.2mg should be present as methylmercury.
- The Ministry of Health and Welfare of Japan set the tolerable intake for adults (body weight 50Kg) as total mercury of 0.25mg and methylmercury of 0.17mg.

Seychelles, Faeroe Islands

Child Development Study, 1998

- Two well-designed and well-executed cohort studies of populations consuming large quantities of seafood.
- Both studies determined prenatal MeHg exposure and ascertained neurodevelopmental outcomes following delivery. Exposure levels were similar (mean 4.0 ppm in Faeroes and 6.0 in Seychelles).
  - The Seychelles Child Development Study examined their main cohort (n = 779) five times following birth (6.5, 19, 29, 66, and 107 months).
  - Faeroese cohort was examined at 7 years and again at 14 years.

Child MeHg: Divergent Findings

- The findings from the two studies were different.
  - Seychelles, of 46 primary endpoints across five ages, only one endpoint showed a possible adverse association with prenatal MeHg exposure.
  - Faeroes, reported adverse associations between prenatal MeHg exposure and tests of memory, attention, language, and visual spatial perception measured at seven years.
  - In some cases, these divergent results occurred on identical test measures.

MeHg Reference Dose

- ATSDR, NRC, NIEHS reviewed MeHg studies.
- USEPA recommends reference dose (RfD) lowered from 0.5 ug/kg/day to 0.1 ug/kg/day.
- NRC concurs with EPA RfD (2000).
  - Seychelles data discounted because no significant adverse effects were reported.
- Fish tissue residue criterion 0.3 mg MeHg/kg (EPA 2001).
- ! Faeroes group reported (PCBs) in whale meat may confound Hg exposure.
- Raises questions about NRC's conclusions.

Public Policy Issues

- Challenge: MeHg is a potent neurotoxin with increased bioavailability hence governments need public health policies to minimize exposure.
- Focus: limit Hg in vaccines (thiomersal), dental amalgams and fish consumption during pregnancy.
- In US some differences arising between agencies (FDA, EPA, ATSDR) from low dose data quality.
  - Fish consumption advisories have problems.
  - e safety & public health concerns.
- L e research needed.