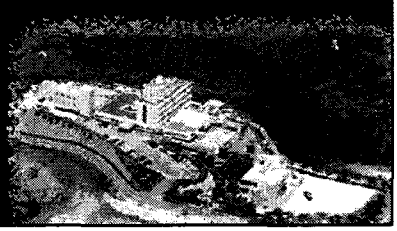
# Effects of methylmercury on the infants

*Mineshi Sakamoto*

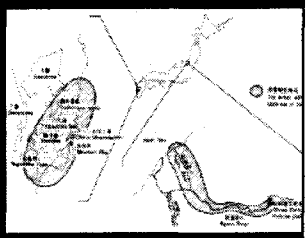
Dep of Epidemiology
National Institute for Minamata Disease,
Ministry Environment
Japan



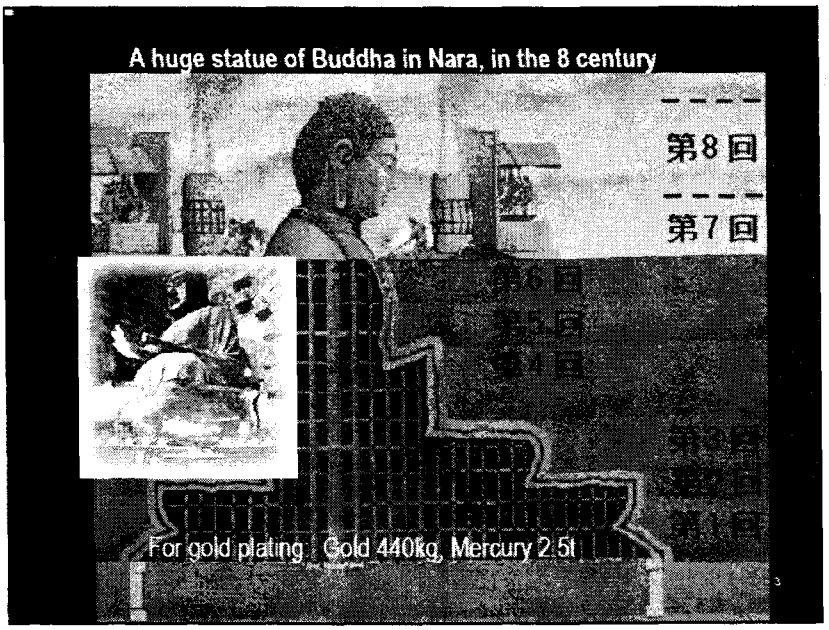
## Background of Hg intoxication

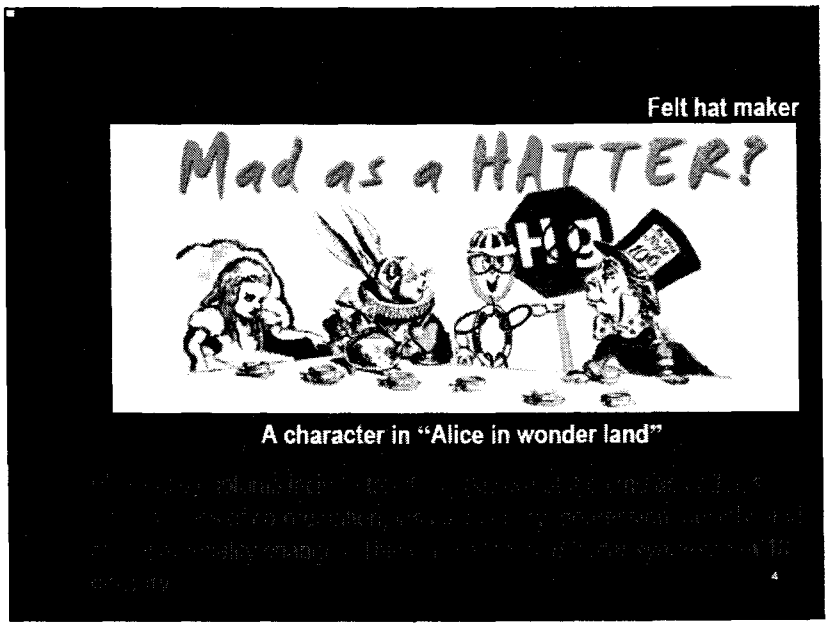
- Documented mercury poisoning cases were as follows:
  - **Work-related elemental and methyl mercury poisoning in the 15-18 c**
  - In the mid 1950's methylmercury poisoning
    - Minamata Disease
    - Kumamoto Prefecture (1956)
    - Kagoshima Prefecture
    - Niigata Prefecture (Agano River, 1965)

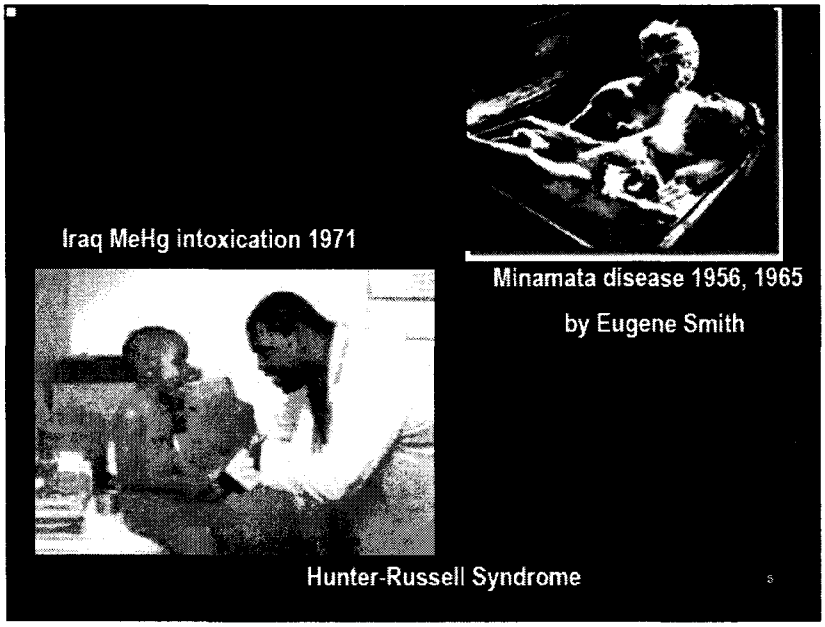
    About 3,000 were recognized as patient



  - Methylmercury poisoning by eating MeHg sterilized wheat in Iraq (1971)
    - 6,530 poisoning victims
    - 459 deaths
  - Hg pollution due to gold mining (1980s)


A huge statue of Buddha in Nara, in the 8 century
第8回
第7回
For gold plating Gold 440kg, Mercury 2.5t
3


Felt hat maker
Mad as a HATTER?
A character in "Alice in wonder land"
4




## Characteristics of Minamata disease

**①First instance on record of severe methylmercury poisoning caused by manmade environmental pollution**

**②Neurological disorders by methylmercury which penetrates into the brain through BBB**

**③Fetal- type Minamata disease caused by maternal methylmercury exposure**

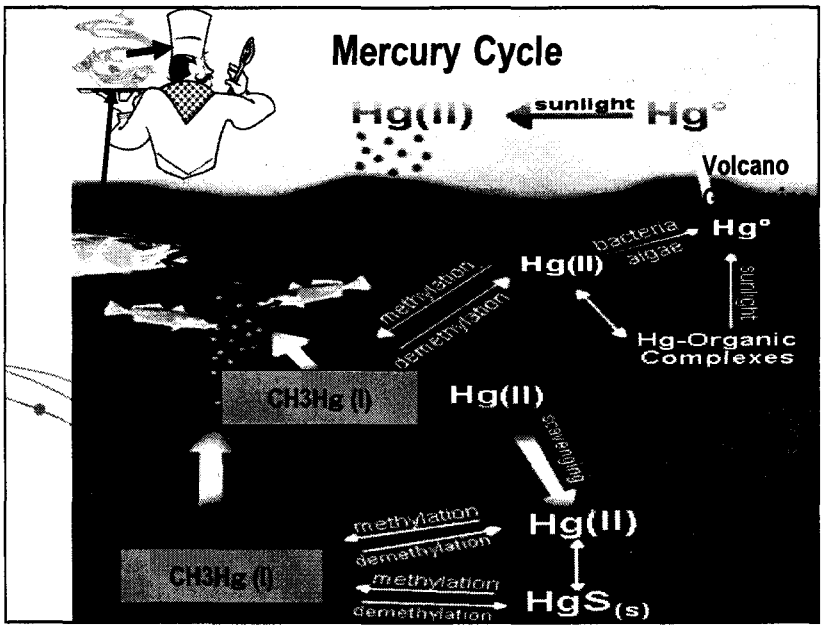
## Chemical forms of Hg

- Metallic : $Hg^0$
- Inorganic: $Hg^{++}$, $HgX_2$, $HgX_3^-$, $HgX_4^{2-}$
  ($X=OH^-$, $Cl^-$, $Br^-$)
- Organic: $CH_3Hg^+$, $CH_3HgCl$, $CH_3HgOH$

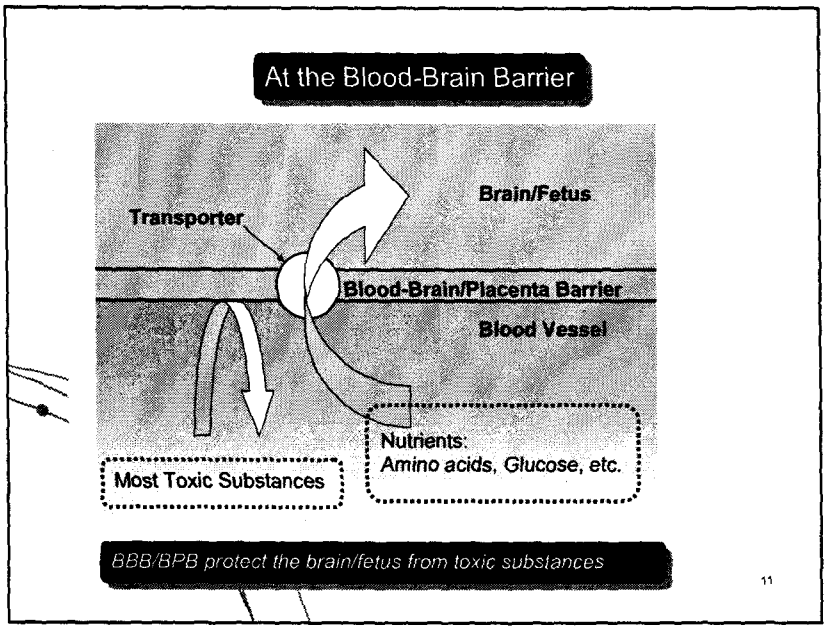
7

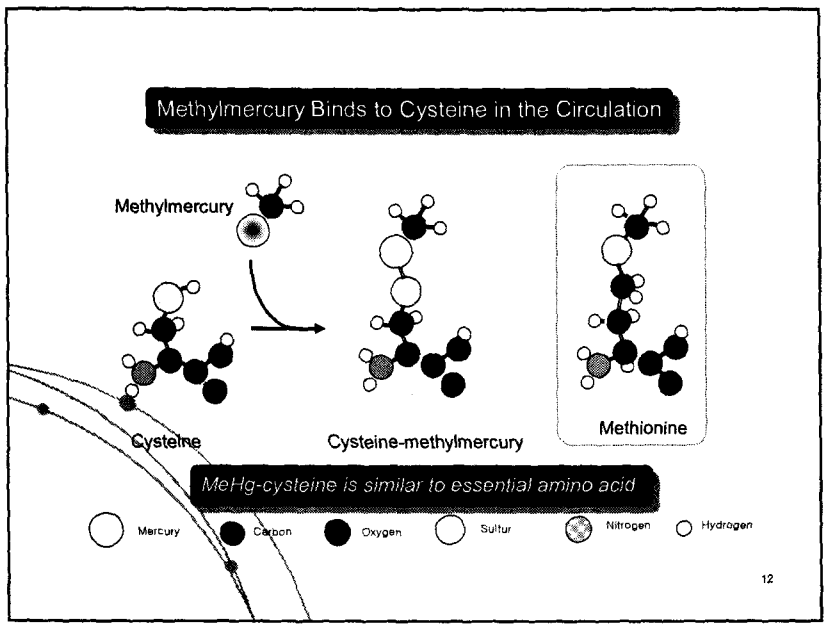
## Features of $CH_3Hg^+$

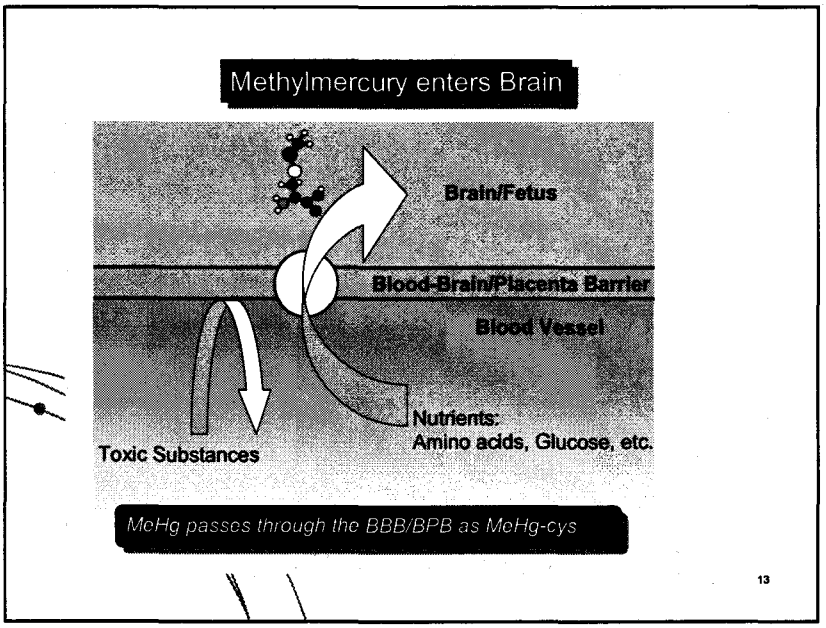
- $Hg^0 \rightarrow Hg^{++} \rightarrow CH_3Hg^+$
- MeHg is bioaccumulated through food chains in aquatic system.
- MeHg concentration in fish is the highest in aquatic system.
- Fish mercury must at first be measured for aquatic environment assessment.
- Human MeHg exposure is through fish and shellfish.




- MeHg conjugates with cysteine and is then easily absorbed as amino acids in the digestive tract, and easily penetrate the brain / fetus according to their amino acids demand, causing disorders in the brain and fetus.
- Fetuses and neonates are high-risk groups
- Hg in hair or blood (RBCs) is a good indicator for human exposure assessment.


At the Blood-Brain Barrier
Brain/Fetus
Transporter
Blood-Brain/Placenta Barrier
Blood Vessel
Nutrients:
Amino acids, Glucose, etc.
Most Toxic Substances
BBB/BPB protect the brain/fetus from toxic substances
11

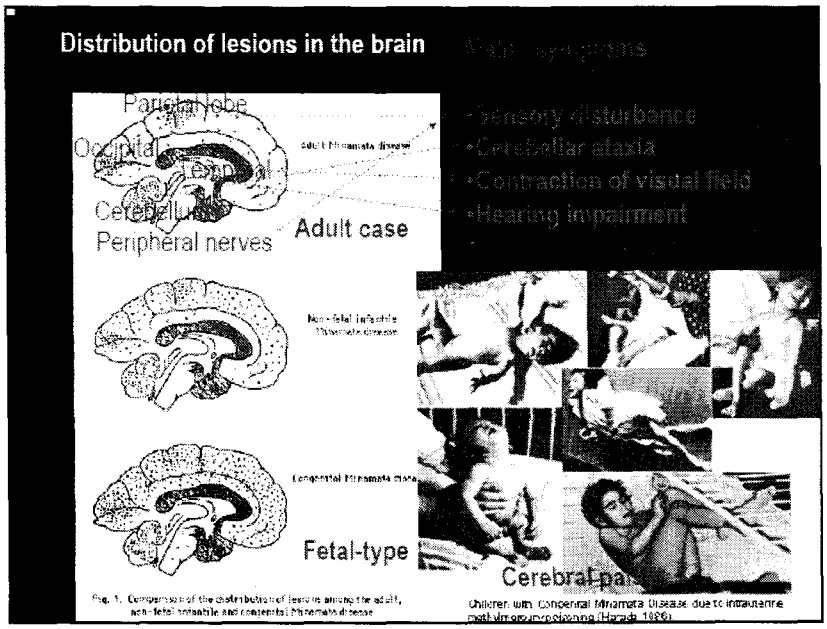

Methylmercury Binds to Cysteine in the Circulation
Methylmercury
Cysteine
Cysteine-methylmercury
Methionine
MeHg-cysteine is similar to essential amino acid
Mercury
Carbon
Oxygen
Sulfur
Nitrogen
Hydrogen
12




## Topics of MeHg effects on infants

1. **The reason why the distributions of the brain damage are differ between adult and fetal-type Minamata disease patients**
2. **MeHg and fatty acids transfers through placenta**
3. **Reproductive toxicity of MeHg (Effect of heavy MeHg exposure on birth sex ratio in Minamata area)**

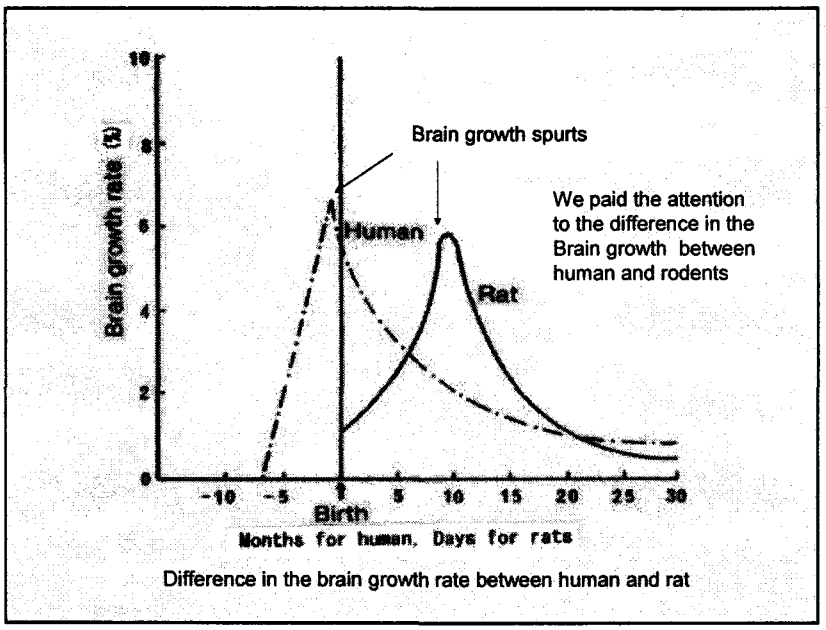
14



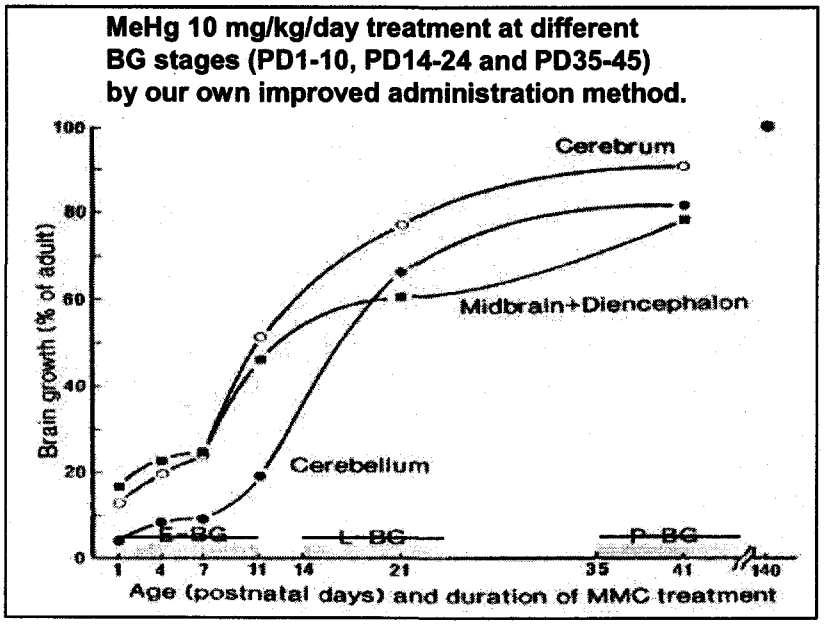

## The reason why the distributions of the brain damage are differ between adult and fetal-type Minamata disease patients

In the case of adult Minamata disease, neuronal degenerations were observed mainly in the cerebral cortex (Parietal, Occipital and temporal lobes), cerebellum and peripheral nerves. On the other hand, the fetal-type Minamata disease patients showed wide-spread neuronal degeneration in the brain and peripheral nerves. Our purpose is to explain the differences using neonatal rats.

16




Difference in the brain growth rate between human and rat



## Effects were completely different by the dosage periods !

| | | |
|---|---|---|
| P 1-10 | → | Weak symptoms<br>No body weight decline |
| PD 14-23 | → | Sevier symptoms |
| PD 35-34 | → | Body weight decline<br>Paralysis of hind legs |

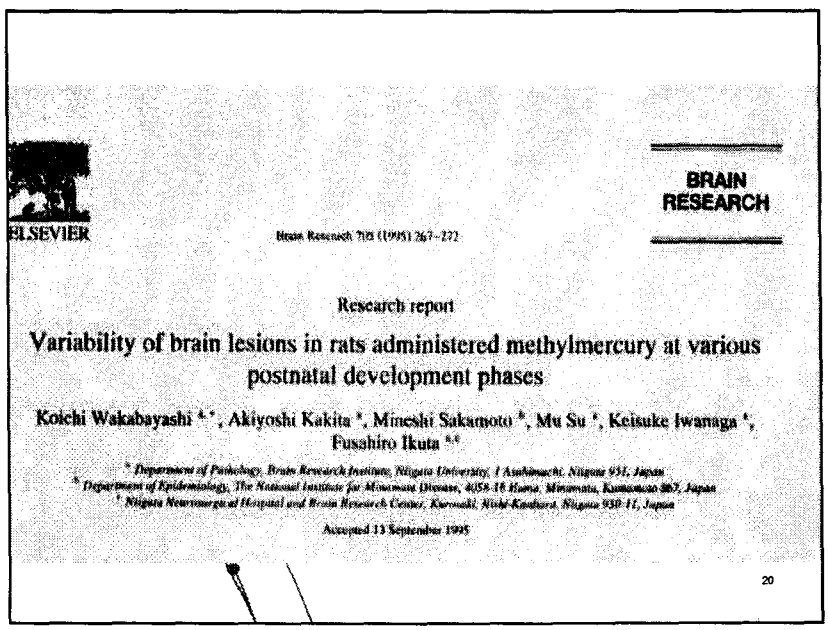
ENVIRONMENTAL RESEARCH 61, 43–50 (1993)

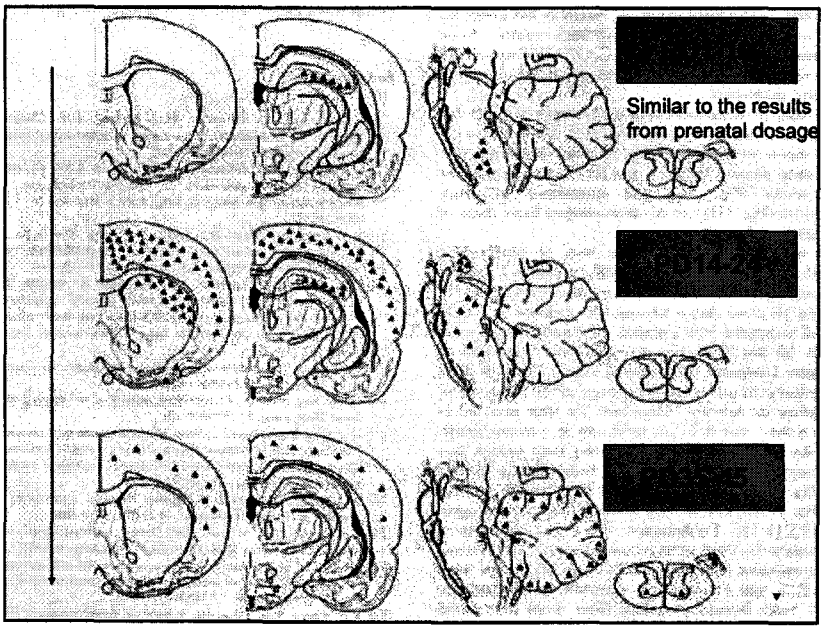
### Effects of Methyl Mercury in Postnatal Developing Rats[1]

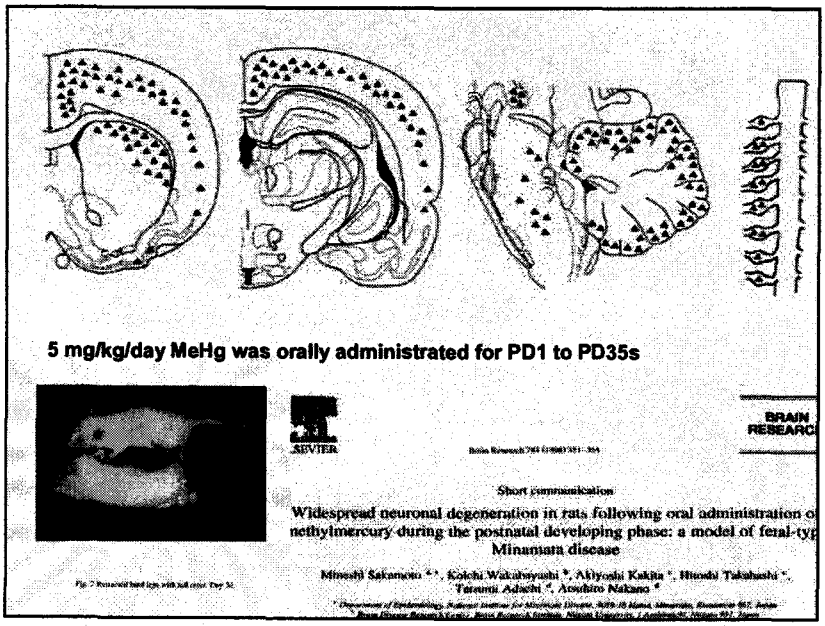
MINESHI SAKAMOTO, ATSUHIRO NAKANO, YUJI KAJIWARA,* ICHIRO NARUSE,* AND TADASHI FUJISAKI*

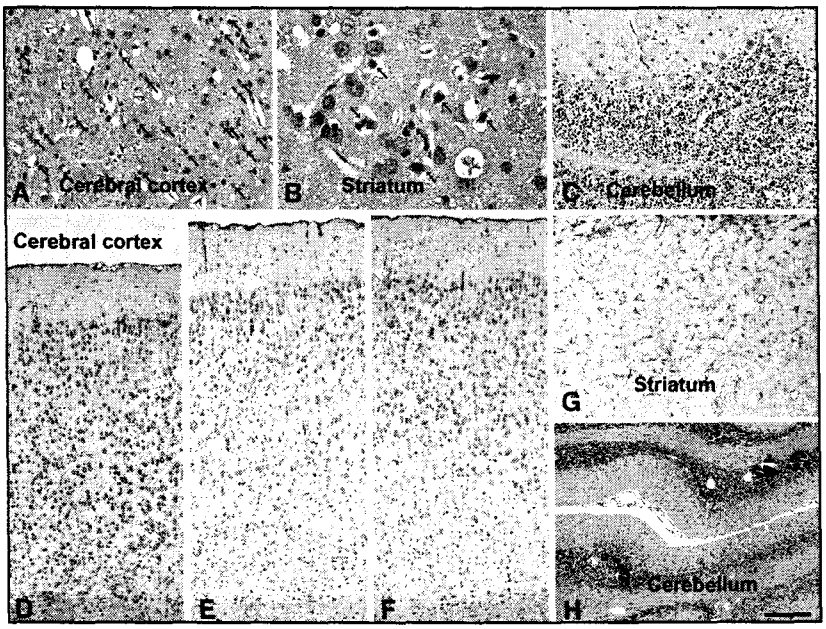
*Department of Epidemiology and *Basic Medical Sciences, The National Institute for Minamata Disease, 4058-18 Hama, Minamata, Kumamoto 867, Japan*

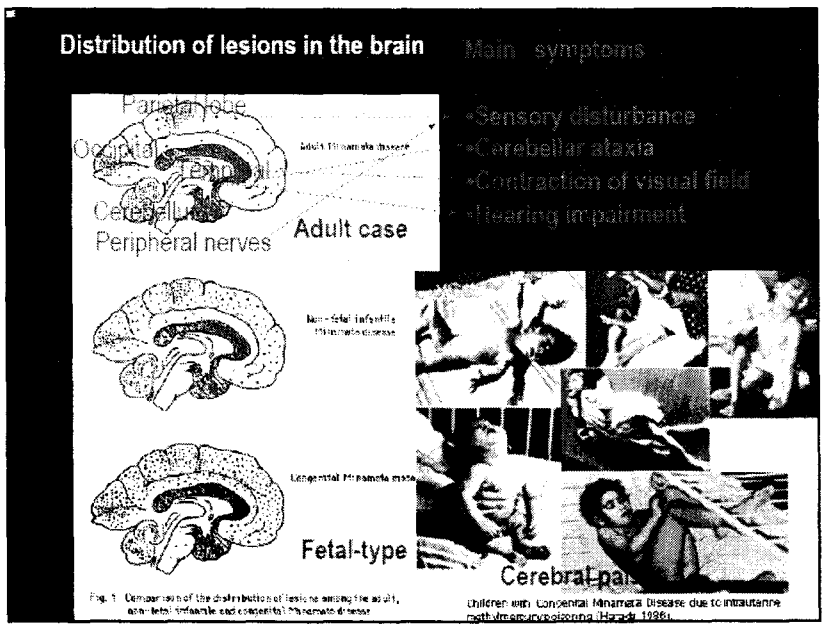
Received May 31, 1991




Similar to the results
from prenatal dosage


5 mg/kg/day MeHg was orally administrated for PD1 to PD35s
ELSEVIER
BRAIN
RESEARC
Short communication
Widespread neuronal degeneration in rats following oral administration o
nethylmercury during the postnatal developing phase: a model of feral-typ
Minamata disease
Mitsuhi Sakamoto, Koichi Wakabayashi, Akiyoshi Kakita, Hitoshi Takahashi,
Tatsumi Adachi, Atsuhiro Nakano


A Cerebral cortex
B Striatum
C Cerebellum
Cerebral cortex
G Striatum
H Cerebellum
D
E
F


Distribution of lesions in the brain
Main symptoms
•Sensory disturbance
•Cerebellar ataxia
•Contraction of visual field
•Hearing impairment
Peripheral nerves
Adult case
Fetal-type
Cerebral pal

## Conclusion

**Distribution pattern of the brain lesion differed with MeHg dosages at various stages of rat brain development.**

**The widespread neuronal degeneration in the brain was made by the prolonged MeHg treatment during the brain growth**

**MeHg administration during PD14-24 will provide the rat-model with the neuronal degeneration mainly in cerebrum, without the damage in cerebellum and peripheral nerve, for the cognitive study.**

25

## MeHg and fatty acids transfers through placental

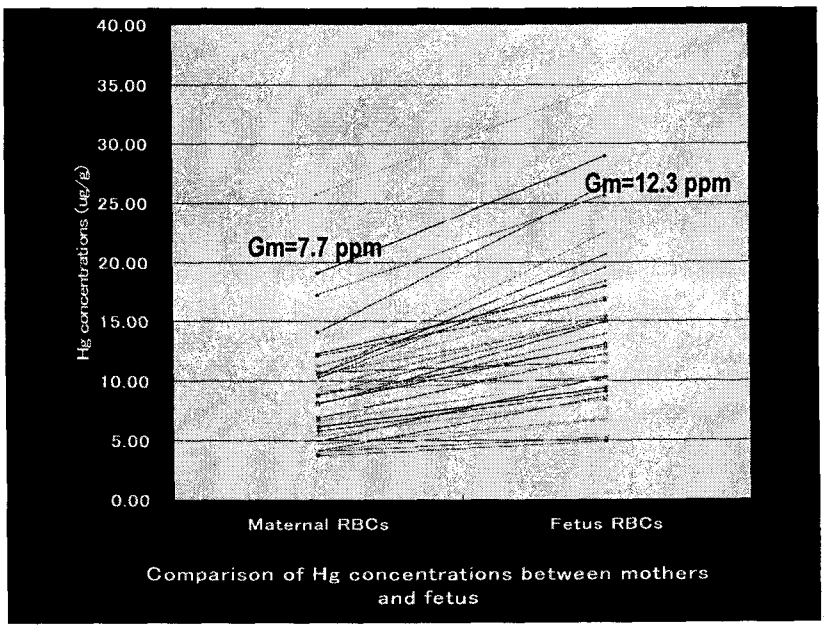
**Maternal fish consumption brings both risks and benefits to the fetus from the standpoint of MeHg and n-3 PUFA. MeHg is one of the most risky substances to come through fish consumption, and mercury concentrations in RBC-Hg are the best biomarker of MeHg exposure. DHA (C22:6n-3), which is one of the most important fatty acids for normal brain development and function, is also derived from fish consumption.**
**Objective of this study is to determine the relationship between the MeHg exposure and n-3 PUFA concentrations in fetus in order to consider the risks and benefits of maternal fish consumption during the late gestation period .**

26

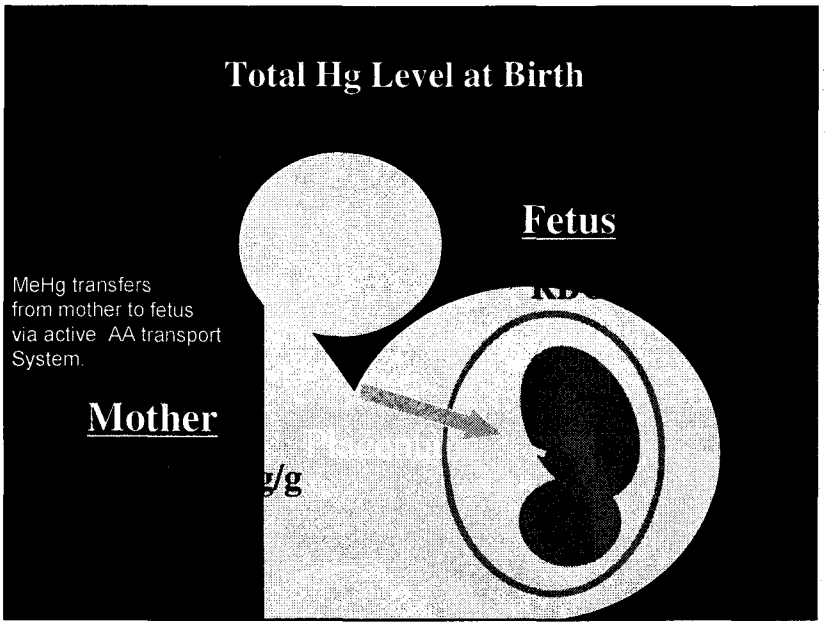
## *Samples* ; 50 pairs

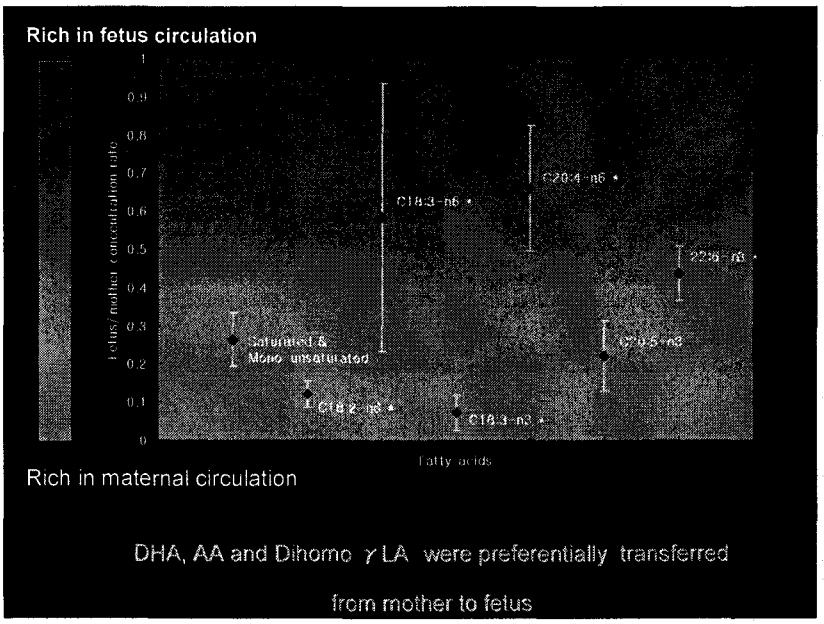
*Maternal blood*

*Cord (fetal) venous blood*




Comparison of Hg concentrations between mothers and fetus


Total Hg Level at Birth
Fetus
MeHg transfers
from mother to fetus
via active AA transport
System.
Mother


Rich in fetus circulation
Fetus/ mother concentration ratio
Saturated &
Mono unsaturated
C18:3-n6
C20:4-n6
C18:2-n6
C18:3-n3
C20:5-n3
Fatty acids
Rich in maternal circulation
DHA, AA and Dihomo γ LA were preferentially transferred
from mother to fetus

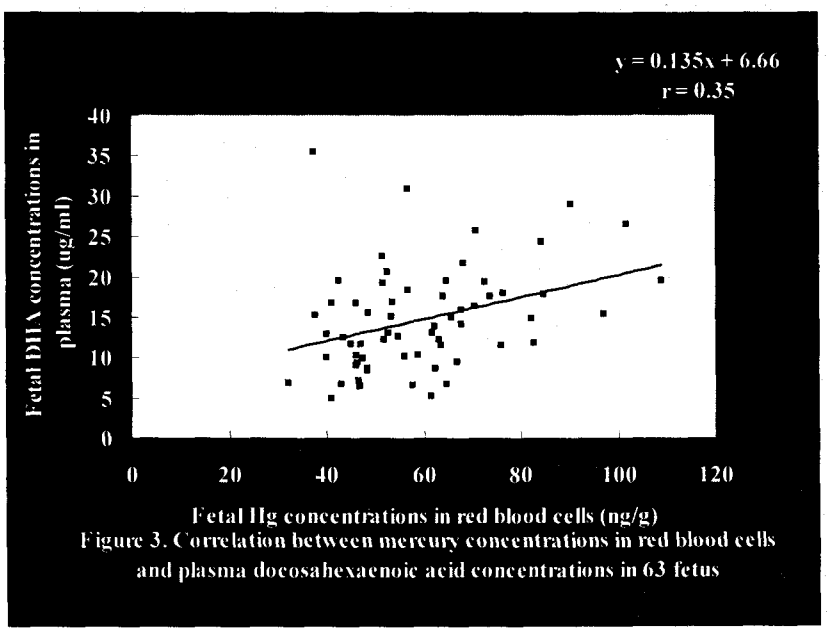
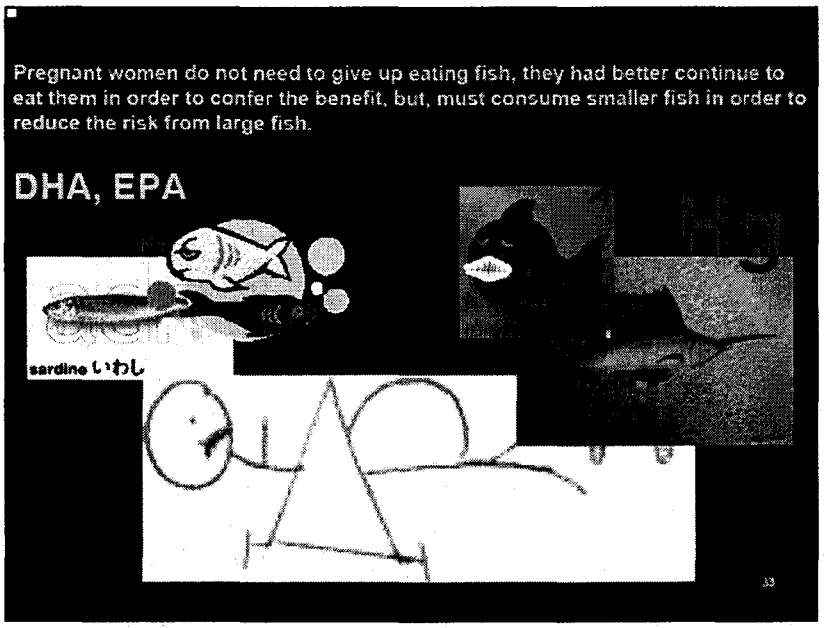
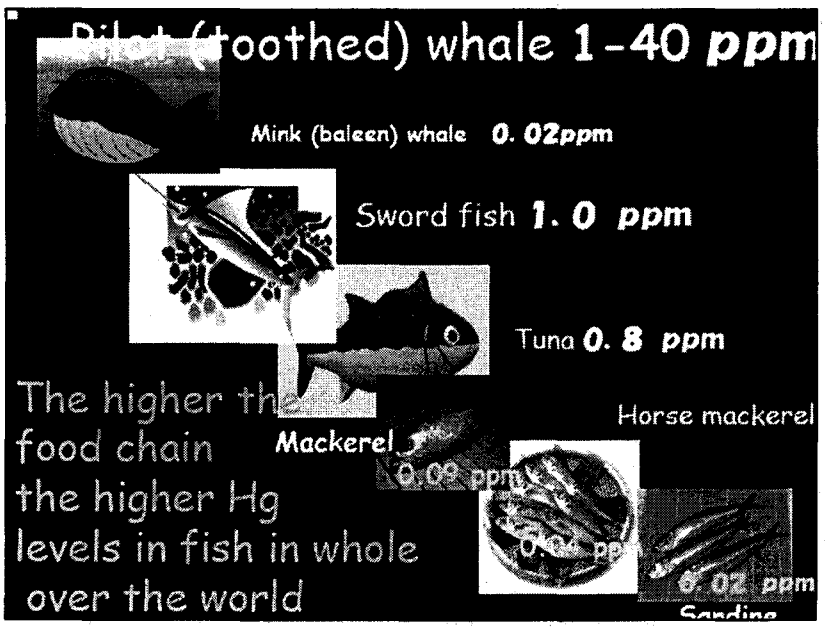


Figure 3. Correlation between mercury concentrations in red blood cells and plasma docosahexaenoic acid concentrations in 63 fetus

## Conclusion

- Fetal FA, AA and MeHg levels reflect the levels in maternal circulation indicating the importance of maternal nutrition state.
- MeHg will be actively transferred to the fetus across the placenta via the amino acid transport system.
- AA and DHA, which are important for the brain development and function, may be preferentially transferred to the fetus.
- MeHg and DHA, which derived from fish consumption, showed a positive correlation in the maternal and fetal circulations.


Pregnant women do not need to give up eating fish, they had better continue to eat them in order to confer the benefit, but, must consume smaller fish in order to reduce the risk from large fish.
DHA, EPA
sardine いわし


toothed) whale 1-40 ppm
Mink (baleen) whale 0. 02ppm
Sword fish 1. 0 ppm
Tuna 0. 8 ppm
Horse mackerel
Mackerel
The higher the
food chain
the higher Hg
levels in fish in whole
over the world
0. 02 ppm
0. 07 ppm

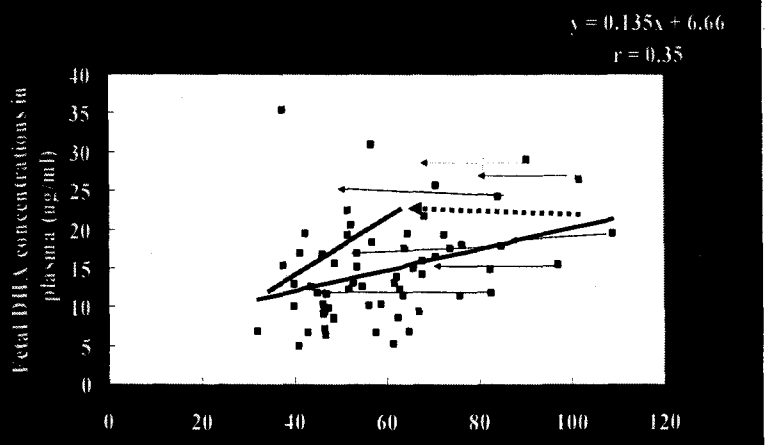
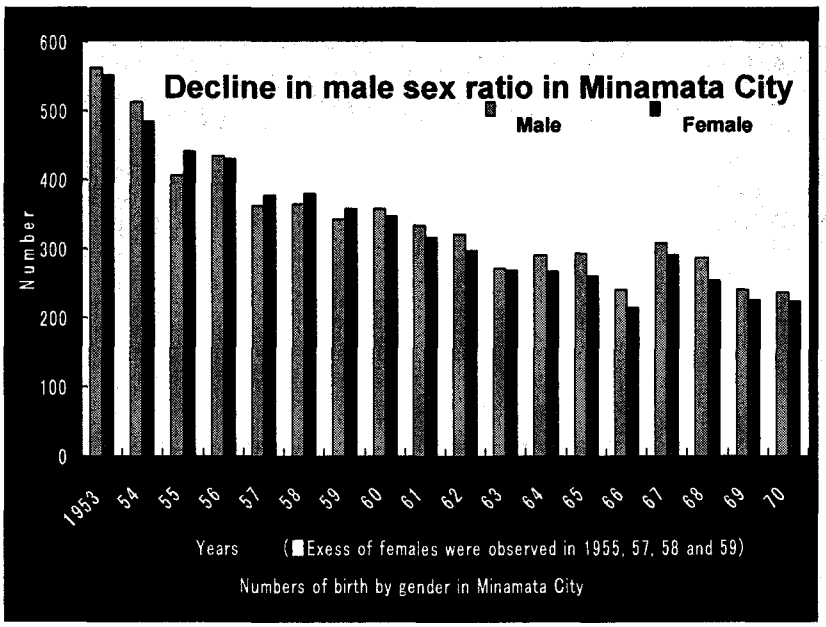
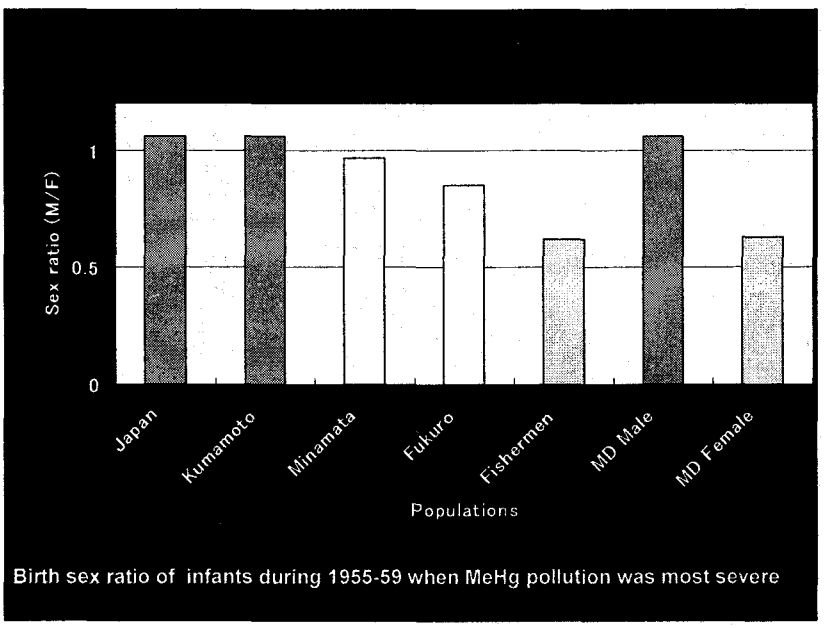



Figure 3. Correlation between mercury concentrations in red blood cells and plasma docosahexaenoic acid concentrations in 63 fetus

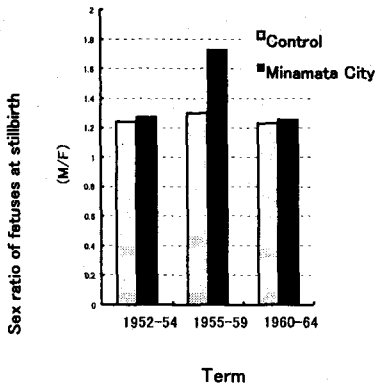
## Reproductive toxicity of MeHg

Recently, changes in the offspring sex ratio at birth due to hazardous chemicals have become a matter of international concern. Our purpose is to examine the MeHg pollution on the sex ratio of at birth in Minamata City.


Decline in male sex ratio in Minamata City
Male
Female
Number
600
500
400
300
200
100
0
1953
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
Years
(Exess of females were observed in 1955, 57, 58 and 59)
Numbers of birth by gender in Minamata City


Sex ratio (M/F)
1
0.5
0
Japan
Kumamoto
Minamata
Fukuro
Fishermen
MD Male
MD Female
Populations
Birth sex ratio of infants during 1955-59 when MeHg pollution was most severe

## Sex ratio at stillbirth




Decrease in male birth rate were observed in offspring in the overall city population, in fishermen, and in maternal Minamata disease patients in the city in 1955-1959. An increase in the ratio of male stillborn in the city was observed at the time.

## Summary

- In the natural course of events, most human exposure to MeHg is through fish/shellfish consumption. The methylmercury exposure levels depends on the amount and species of fish/shellfish consumed daily. The developing brain in the late gestation period is known to be most vulnerable. Further, more methylmercury accumulates in the fetuses than in mothers. Therefore, efforts must be made to protect the fetuses from the risk of methylmercury, especially in populations which consume a lot of fish/shellfish.