Methylmercury and the developing brain

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MERCURY EXPOSURE AND ASSOCIATED DISORDERS

MINAMATA DISEASE
30,000+ affected; March 29, 2010
Japanese government settlement

AUTISM
1 in 88 children diagnosed with ASD

LEARNING & MEMORY, NEURO-Psychiatric DISORDERS, SENSORY DEFICITS

NEURODEGENERATIVE DISEASES – ????
ALZHEIMER’S DISEASE (AD)
7th leading cause of death; 5.3 million people with AD in U.S.
Follow-up studies of methylmercury exposures in Iraq revealed a significant dose-response relationship for prenatal methylmercury exposure:

**Increased mercury exposure leads to increased or more severe adverse neurological problems.**

**Conclusion:**

Prenatal exposures as low as 10 ppm measured in maternal hair samples might affect brain development of children exposed prenatally.
Inorganic mercury (Hg) is discharged into water and sediments, which can be bioaccumulated by edible fish. This process can lead to biomethylation, resulting in methylmercury (Hg-CH₃), which can then be ingested by humans, leading to methylmercury in humans. "A Small Dose of Toxicology" Web: www.asmalldoseof.org
270-year record

Major atmospheric releases
- Natural
  - Background (42%)
  - Volcanic (6%)
- Anthropogenic (52%)
  - Gold rush
  - WWII
  - Industrialization

The last 100 years
- Anthropogenic (70%)
<table>
<thead>
<tr>
<th>Species</th>
<th>Mercury content (mg/kg or PPM ± SD)</th>
<th>Atlantic ocean</th>
<th>Pacific ocean</th>
<th>Number of fish measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herring</td>
<td>0.14 ± 0.06</td>
<td>15</td>
<td>0.04 ± 0.02</td>
<td>131</td>
</tr>
<tr>
<td>Flounder</td>
<td>0.08 ± 0.04</td>
<td>60</td>
<td>0.07 ± 0.07</td>
<td>58</td>
</tr>
<tr>
<td>Halibut</td>
<td>0.25 ± 0.23</td>
<td>46</td>
<td>0.28 ± 0.09</td>
<td>11</td>
</tr>
<tr>
<td>Mackerel</td>
<td>0.22 ± 0.16</td>
<td>877</td>
<td>0.09 ± 0.06</td>
<td>30</td>
</tr>
<tr>
<td>Salmon (fresh)</td>
<td>0.13 ± 0.17</td>
<td>11</td>
<td>0.04 ± 0.01</td>
<td>289</td>
</tr>
<tr>
<td>Salmon (canned)</td>
<td>ND</td>
<td></td>
<td>0.04 ± 0.01</td>
<td>289</td>
</tr>
<tr>
<td>Snapper</td>
<td>0.28 ± 0.43</td>
<td>363</td>
<td>0.25 ± 0.09</td>
<td>17</td>
</tr>
<tr>
<td>Shark</td>
<td>0.75 ± 0.70</td>
<td>585</td>
<td>0.80 ± 0.37</td>
<td>35</td>
</tr>
<tr>
<td>Swordfish</td>
<td>0.98 ± 0.51</td>
<td>618</td>
<td>0.98 ± 0.51</td>
<td>618</td>
</tr>
<tr>
<td>Tuna (fresh)</td>
<td>0.28 ± 0.12</td>
<td>496</td>
<td>0.24 ± 0.10</td>
<td>555</td>
</tr>
<tr>
<td>Tuna (canned, light)</td>
<td>0.11 ± 0.10</td>
<td>199</td>
<td>0.11 ± 0.10</td>
<td>199</td>
</tr>
<tr>
<td>Tuna (canned, albacore)</td>
<td>0.37 ± 0.12</td>
<td>318</td>
<td>0.37 ± 0.12</td>
<td>328</td>
</tr>
</tbody>
</table>

What You Need to Know About Mercury in Fish and Shellfish
EPA-823-R-04-005
2004
EPA and FDA Advice For:
  Women Who Might Become Pregnant
  Women Who are Pregnant
  Nursing Mothers
  Young Children

Do not eat Shark, Swordfish, King Mackerel, or Tilefish.

Eat up to 12 ounces (2 average meals) a week of a variety of fish and shellfish that are lower in mercury, such as shrimp, canned light tuna, salmon, pollock, and catfish.

Albacore ("white") tuna has more mercury than canned light tuna. It is recommended that one can consume up to 6 ounces (one average meal) of albacore tuna per week.
Toxicological Effects of Methylmercury
Committee on the Toxicological Effects of Methylmercury
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council
NATIONAL ACADEMY PRESS (2000)
Washington, DC

BDML = benchmark dose level = lowest dose expected to be associated with a small increase in the incidence of an adverse outcome (typically 1% to 10%).
BMDL for methylmercury is 58 parts per billion (PPB) of mercury in cord blood; based on adverse outcomes on standardized learning and memory tests.

EPA's current Reference Dose (RfD) for methylmercury = 0.1 µg/kg per day (0.1 PPB)
0.0001 mg/kg per day
(Established in 1995)

Canned light tuna = 0.11 mg/kg methylmercury
(110 PPB)
Two prospective Faroe Islands cohort studies
based on 182 newborns at 2 weeks of age, or 917 children at 7 years of age, respectively.

Both methylmercury in maternal hair during pregnancy and in cord serum served as the exposure markers.

The 7-year-old children were tested for their performance on tasks associated with neuropathologic abnormalities seen in methylmercury poisoning in Japan and Iraq.

**Observed:** decreased attention, memory, and language skills
The Seychelles study is a prospective cohort approach based on 779 mother–infant pairs.

Neurodevelopmental and neurobehavioral examinations were performed at several ages up to 66 months (5.5 years).

Prenatal methylmercury exposure was estimated from maternal hair samples collected at birth.

At no age was significant exposure-related neurodevelopmental or neurobehavioral deficit observed in the Seychelles Islands study.
Faroes Islanders - displayed neurologic deficits
Seychelles Islanders – did not display neurologic deficits
Perhaps the combination of PCBs + mercury is important
Summary

Levels of methylmercury in food that affect cognitive function are controversial

PCBs are often found with methylmercury and the combination and/or PCBS may be more toxic

Other factors may be involved (smoking; alcohol, etc.)
Karienn S. Montgomery, Jessica Mackey, Kerry Thuett, Stephanie Ginestra, Jennifer L. Bizon and Louise C. Abbott

Chronic, low-dose prenatal exposure to methylmercury impairs motor and mnemonic function in adult C57/B6 mice

Mercury content in brains of adult and fetal mice exposed orally to a total dose of 0.1mg MeHg.

<table>
<thead>
<tr>
<th>ADULT FEMALE MICE EXPOSED AS ADULTS</th>
<th>TOTAL BRAIN LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROLS (no MeHg) (n=6)</td>
<td>0.003 ppm ± .001 (SE)</td>
</tr>
<tr>
<td>TREATED pregnant mice killed on gestational day 18 (n=4)</td>
<td>0.063 ppm ±  0.011 (SE)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E18 FETUSES EXPOSED PRENATALLY</th>
<th>TOTAL BRAIN LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROLS (no MeHg) (n=4 fetuses)</td>
<td>0.0015 ppm ± 3.083E-4 (SE)</td>
</tr>
<tr>
<td>TREATED MeHg given to pregnant dam (n=8 fetuses)</td>
<td>0.048 ppm ± 0.005 (SE)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>THREE-MONTH-OLD MICE EXPOSED PRENATALLY</th>
<th>BRAIN REGION LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROLS (no MeHg) - cerebellum (n=3)</td>
<td>0.0011 ppm ± 1.946E-4 (SE)</td>
</tr>
<tr>
<td>CONTROLS (no MeHg) - neocortex (n=3)</td>
<td>0.0011 ppm ± 2.379E-4 (SE)</td>
</tr>
<tr>
<td>TREATED PRENATALLY - cerebellum (n=5)</td>
<td>0.0010 ppm ± 1.526E-4 (SE)</td>
</tr>
<tr>
<td>TREATED PRENATALLY – NEOCORTEX (N=5)</td>
<td>0.0028 ppm ±  0.002 (SE)</td>
</tr>
</tbody>
</table>
methylmercury-exposed mice demonstrated a significantly narrower foot angle (*) compared to control mice.

Black bars = methylmercury-exposed mice
White bars = control mice
Error bars = standard error of the mean (S.E.M.).
All mice spent increased time on accelerating rotarod over sequential days of testing. Methylmercury (MeHg)-treated mice (black bars) spent significantly less time on rotarod compared to control mice (white bars). Error bars indicate standard error of the mean (S.E.M.).
Open field activity during first 10 min. Methylmercury (MeHg)-treated mice Made fewer vertical (A) and fewer horizontal (B) movements than control mice.

Methylmercury-treated mice spent less time in center of open field than control mice (C).

Error bars = standard error of mean (S.E.M).
- both groups improved over the course of training
- methylmercury (MeHg)-treated mice demonstrated significantly longer path lengths to hidden platform compared to control mice
strong trend
methylmercury-treated mice spent less time than control mice in target quadrant

methylmercury-treated mice spent less time in the target quadrant than control mice during last 10 seconds of probe trials