Assessing Methylmercury’s Health Impact on Piscivorous Wildlife by Use of Neurochemical Biomarkers

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A Simplified Mercury Cycle

*** all steps are extremely complex!!!
2004: % of waterways under advisory

Percentage of Lake Acres/River Miles under Advisory in 2004
2004 National Listing of Fish Advisories (www.epa.gov/waterscience/fish)

1993-2004: over-time trends increasing

Percentage of River Miles and Lake Acres Under Advisory (1993-2004)
2004 National Listing of Fish Advisories (www.epa.gov/waterscience/fish)
Number of Lake Acres Under Advisory for Various Pollutants in 2004
2004 National Listing of Fish Advisories (www.epa.gov/waterscience/fish)

What we know

>1ppm Hg
high levels

Increasing Biological Organization

Irreversible Damage

adverse effects

cell tissue organ individual population
What we do NOT know

< 1ppm Hg
relevant levels

> 1ppm Hg
high levels

???

Increasing Biological Organization →

MERCURY

BRAIN CHEMISTRY

NEUROTOXIC

Increasing Biological Organization →

Irreversible Damage

Irreversible Damage
Research Hypothesis

Neurochemical research can further our knowledge of the mechanisms and impacts of aquatic pollutants towards the health of humans, wildlife, and ecosystems.

Mercury $\rightarrow$ BRAIN CHEMISTRY $\rightarrow$ Neurotoxic

objective/quantitative method to assess early/subtle effects

model pathway – Cholinergic System

- well-studied neurochemical pathway
- sensitive to Hg (\textit{in vitro} and \textit{in vivo})

<table>
<thead>
<tr>
<th>Cholinergic disorders</th>
<th>Mercury poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>salivation</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>ataxia</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>loss of vision</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>Alzheimer's relevant diseases</td>
<td>Minamata</td>
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</tbody>
</table>

Wess et al., 2005; Kobayashi, 1981
model organism – **Mink**

- high-trophic, fish-eating mammal common across North America & Europe
- Hg-related effects (lesions, behavior) similar to other wildlife and humans
- declines in wild mink populations associated with Hg pollution
- studied in nature and the laboratory

*Basu et al., 2007; Aulerich et al., 1999*

**Integrative Approach**

Does mercury affect the cholinergic receptor in mink?

- **IN VITRO STUDIES**
- **ANIMAL BIOASSAYS**
- **FIELD STUDIES**

Increasing Biological Organization →

Irreversible Damage
**In vitro study – does Hg inhibit mAChR?**

![Graph showing mACH Receptor Binding (% of Maximal) against log [HgCl] Molar](image1)

**ECOLOGICALLY RELEVANT MERCURY**

**Field study – Hg α mAChR?**

![Graph showing mACH Receptor Bmax (fmol/mg) against Total Hg (ppm)](image2)

**Changes in neurochemistry**

**Adverse clinical outcomes**

$r = 0.546, p < 0.001$

LOAEL$^{1,2}$

1 Wren et al. 1987

2 Wobesor et al. 1976
Lab study – corroboration?

Laboratory Data
\[ y = 129.8 \ln(x) + 1507.5 \]
\[ R^2 = 0.175 \]

Field Data
\[ y = 118.8 \ln(x) + 629.4 \]
\[ R^2 = 0.259 \]

SIMILAR SLOPE-RESPONSE RELATIONSHIPS
Mid-Talk Summary

Mercury disrupts the cholinergic receptor in mink

- ecologically relevant levels disrupt brain neurochemistry
- changes are potentially of physiological and ecological significance
- continuum of effects is established

WHAT ABOUT OTHER SIGNALING PATHWAYS?
WHAT ABOUT OTHER FISH-EATING WILDLIFE?

Comparative Approach

*Multiple neurochemical pathways affected by mercury in rodents*

<table>
<thead>
<tr>
<th>Neurochemical Pathway</th>
<th>Function</th>
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<tbody>
<tr>
<td>Cholinergic</td>
<td>Cognitive/sensory</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Motor deficits</td>
</tr>
<tr>
<td>GABA</td>
<td>Inhibitory function</td>
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<tr>
<td>Glutamate</td>
<td>Excitatory function</td>
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</table>
“In ecoepidemiology, the occurrence of an association in more than one species and species population is very strong evidence for causation.”

A Global “Ecosystem” Approach

Hg & mAChR: MINK

Total Hg (ppm)

mACh Receptor Bmax (fmol/mg)

Environ Toxicol Chem 24: 1444-1450
Hg & mAChR: COMMON LOON

Brain Total Hg (ppm, d.w.)

mACh receptor (fmol/mg)

r = 0.41, p < 0.01

Ecotoxicology 17: 93-101

Hg & mAChR: BALD EAGLE

Brain Total Hg (ppm, d.w.)

mACh receptor (fmol/mg)

r = 0.50, p < 0.001

Ecotoxicology 17: 93-101
Mercury disrupts cholinergic receptor in mink

Mercury disrupts the brain chemistry in mink

Mercury disrupts the brain chemistry in several fish-eating wildlife, lab animals (and humans?)

“So WHAT”???
### Implications to Policy and Assessment #1

<table>
<thead>
<tr>
<th>Fish MeHg</th>
<th>Brain Hg</th>
<th>Fur Hg</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>5</td>
<td>20</td>
<td>150</td>
<td>Death</td>
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<tr>
<td>2</td>
<td>8</td>
<td>60</td>
<td>Tissue lesions, reproductive impairment, behavioural changes, death</td>
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<td>1</td>
<td>4</td>
<td>30</td>
<td>Biochemical (sub-clinical?)</td>
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<td>0.5</td>
<td>2</td>
<td>15</td>
<td>Biochemical (adaptive?)</td>
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- neurochemical disruption at relevant levels
- changes of physiological/ecological concern

### Implications to Policy and Assessment #2

- Hg
- Crude Oil
- Tot PCBs
- P&P effluent
- DE-71

**NEUROTOXIC**

- COGNITION, SENSES, MOTOR, H-P AXIS
A Neurochemical Fingerprint?

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<thead>
<tr>
<th>Pollutant</th>
<th>Memory</th>
<th>Motor</th>
<th>Visual</th>
<th>Conduct Signals</th>
<th>Coordination</th>
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<td>Mercury</td>
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Implications to **Policy and Assessment #3**

- brain regions have specific functions
- semi-quantitative, objective measure?
Thanks!
Questions?

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