Resolved:

Methyl Mercury is a contributing cause to CVD;

Cost/Benefit Analysis

Gary Ginsberg, Toxicology
Connecticut Dept of Public Health
Prior Risk-Benefit Assessment of Mercury Controls

Rice et al. ES&T 2010
Methyl Mercury is a contributing cause to CVD.

Cost/Benefit Analysis

We recommend the development of a dose-response function relating meHg with MI for use in regulatory benefits analysis” Roman et al., EHP, 2011
Virtanen et al. 2005
1871 Finnish Men, Prospective Design

<table>
<thead>
<tr>
<th>Baseline</th>
<th>13.9 Years</th>
<th>1.7 RR Acute MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair Hg</td>
<td></td>
<td></td>
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<tr>
<td>No CHD</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence of acute coronary event</th>
<th>Lowest Third RR</th>
<th>Middle Third RR (95% CI)</th>
<th>Highest Third RR (95% CI)</th>
<th>P for Trend</th>
<th>Highest vs lower Two Thirds Combined RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1*</td>
<td>1</td>
<td>1.02 (0.74–1.41)</td>
<td>1.61 (1.20–2.17)</td>
<td>0.001</td>
<td>1.59 (1.25–2.03)</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1</td>
<td>1.04 (0.75–1.44)</td>
<td>1.55 (1.14–2.11)</td>
<td>0.003</td>
<td>1.52 (1.19–1.94)</td>
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<tr>
<td>Model 3‡</td>
<td>1</td>
<td>1.08 (0.77–1.50)</td>
<td>1.67 (1.22–2.30)</td>
<td>0.001</td>
<td>1.60 (1.24–2.06)</td>
</tr>
<tr>
<td>Model 4§</td>
<td>1</td>
<td>1.07 (0.77–1.49)</td>
<td>1.66 (1.20–2.29)</td>
<td>0.001</td>
<td>1.60 (1.24–2.06)</td>
</tr>
</tbody>
</table>

- Virtanen et al.: Temporality and Dose Response
- Guallar et al. 2002: Dose Response
Guallar et al. 2002; 684 cases, Europe and Israel
Mercury a stronger risk factor than cigarette smoking
Temporality and Dose Response
Reproducibility:
- Faroese men (Choi et al. 2009)
- Polish chemical workers (Skoczyńska et al. 2009)
- IM thickness not assoc/with Hg in Italian fish eaters (Buscemi et al. 2014)
What About Negative Epi Studies?

N=3427 Cases/Controls
2 Large US Cohorts
Plausability: Does an AOP Exist?

MIE \[ \rightarrow \text{Prot-SH} \rightarrow \text{Redox/ROS} \]

meHg

Key Event:
\( \downarrow \)ed PON1
\( \uparrow \)ed PLases/COX
\( \downarrow \)ed Nitric Oxide

Host Risk Factors
Aging/Dx Process

AO

Oxidized Lipids
Endothelial Damage
Vasoconstriction

\( \uparrow \)ed Int Media thickness

\( \uparrow \)ed MI risk
**FIGURE 4.** Relationship between blood mercury and PON1 in a Canadian Inuit population relative to estimated intake dose (adapted from Ayotte et al. 2011). Intake dose estimated from blood levels based upon a one compartment pharmacokinetic model as described in text. Different letters above the bars indicate mean values that are significantly different from one another, $p < .05$.

**Plausibility:** meHg assoc/with lower PON1 at RfD
Ginsberg et al. 2014
Plausibility: Mercury Effects on Endothelial Cells in Animal Testing

Wiggers et al. 2016

- 4.6 ug/kg in rats
- ↑ed Superoxide generation in isolated arteries
- ↓ed NO generation
- ↑ed vasoconstriction to pressor agents
- ↓ed relaxation to bradykinin
- Other papers by this group – low dose vascular dysfn in rats
Summary

• Epi Associations with Coronary Events
  – Suggestive at common levels of exposure
    • Finnish prospective study – temporality
    • Lack of associations – competing benefits from fish ingestion

• Epi Associations with Upstream Events
  – Intima Media thickness in 3 populations
    • Finnish prospective study – temporality
  – PON1 decrease
    • Dose response in fish eating population

• Experimental evidence in animals and cells
  – Oxidative stress/Protein denaturation
    • NFkB activation
    • PLase activation
    • Nitric Oxide impairment

Oxidized Lipids
Endothelial dysreg/damage
Vasoconstriction
Summary Continued

• Strength of Association
  – Moderate to strong
    • Several studies, several endpoints

• Temporality
  – Strong in Finnish prospective studies
  – Strong in animal/in vitro experiments

• Plausibility
  – Strong mechanistic support

• Dose response
  – Yes in both epi and animal experiments
  – Effects in human populations at near background

• Research Needs
  – Intersection between meHg CV effects and disease process