AN ASSESSMENT OF LOW LEVEL LEAD EXPOSURE ON ENCEPHALIZATION AND CORTICAL QUOTIENTS AND ITS RELATIONSHIPS WITH CORTICAL THINNING AND NEURODEGENERATION

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INTRODUCTION: HUMAN LEAD (PB) TOXICITY IN REVIEW

Adverse Health Effects of Lead Exposure

- Death
- Encephalopathy
- Nephropathy
- Frank Anemia
- Colic

- Decreased hemoglobin synthesis
- Increased vitamin D metabolism
- Increased risk of hypertension in adulthood
- Increased nerve conduction velocity
- Increased level of erythrocyte protoporphyrin
- Decreased vitamin D metabolism
- Decreased calcium homeostasis

- Developmental toxicity
  - Delayed puberty
  - Decreased growth & hearing
- Developmental toxicity
  - Decreased IQ levels & academic abilities
  - Attention-related behaviors
  - Anti-social behaviors

100 mL's = 1 dL

http://www.ehatlas.ca/lead/human-impact/health-concerns
http://brickleyenv.com/services/lead-paint-removal-contractor/
## Chronological Review of the United States CDC’s Threshold for Pb Poisoning Interventions

<table>
<thead>
<tr>
<th>Year of CDC Revision</th>
<th>Number of Years Between CDC Revision</th>
<th>CDC BLL Listed as Threshold</th>
<th>CDC BLL Considered to be Safe /Actionable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>10</td>
<td>60µg/dL</td>
<td>≤59µg/dL</td>
</tr>
<tr>
<td>1970</td>
<td>10</td>
<td>40µg/dL</td>
<td>≤39µg/dL</td>
</tr>
<tr>
<td>1975</td>
<td>5</td>
<td>30µg/dL</td>
<td>≤29µg/dL</td>
</tr>
<tr>
<td>1985</td>
<td>10</td>
<td>25µg/dL</td>
<td>≤24µg/dL</td>
</tr>
<tr>
<td>1991</td>
<td>6</td>
<td>10µg/dL</td>
<td>≤9µg/dL</td>
</tr>
<tr>
<td>2017</td>
<td>26</td>
<td>5µg/dL</td>
<td>≤0µg/dL</td>
</tr>
</tbody>
</table>

Today BLL’s of 39 µg/dL or greater require immediate chelation therapy.

*BLL = Blood Lead Levels

*CDC = Center for Disease Control

Pb produced consistent aberrant behaviors related to attention, visual-motor reasoning skills, social skills, mathematics and reading abilities at exposures of ~ 10µg/dL (Canfield et al., 2003; Lanphear et al., 2000; 2005; Wasserman et al., 1997)

Predicts for lifetime educational and emotional problems, delinquent and anti-social behaviors (Nevin, 2007).
Pb Induced Brain Volume Loss in Males

N = 85 Males ~ 5 years old BLL’s ~ 13.5 μg/dL Brain Imaged 19-24 years old

Pb Induced Brain Volume Loss in Females

$N = 74$ Females ~ 5 years old BLL's ~ 13.1 $\mu$g/dL Brain Imaged 19-24 years old

Figure 3. Childhood Lead Poisoning Structure-Function Relationships


http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050112
ENCEPHALIZATION QUOTIENTS

- Cross-specie cortical mass comparison calculation.
HYPOTHESES:

- Neurodevelopmental lead exposure would induce brain damage causing a reduced EQ and CQ?

- Gender would have differential EQ and CQ vulnerabilities to lead exposure?

- Neurodevelopmental lead exposure would cause different EQ and CQ outcomes based on the developmental time period of exposure?
DEVELOPMENTAL PB EXPOSURE PARADIGM

Pairing
Reg Diet
Reg Diet
Pb Diet 150 ppm

Developmental Period
Control (PND 0 – PND 22)
EPN (PND 0-55)
Peri (Gestation – PND 22)

Maturation
Reg Diet
Reg Diet
Reg Diet

PND 55-60
Encephalization & Cortical Quotient Measures

25 ppm Pb Acetate Food Produces The Following:
Early Post Natal (EPN) Rat BLLS ~ 1-3μg/dL
Perinatal (Peri) Rat BLLS ~ 2-6 μg/dL
Encephalization and Cortical Quotients (EQ & CQ) Calculations:

Following obtaining rat body and brain weights the EQ and CQ were calculated for each rat using the equations below, averaged, and statistically compared as a function of sex and treatment groups using an ANOVA.

**Encephalization Quotient (EQ)**

\[
\text{Encephalization Quotient (EQ)} = \frac{\text{Brain weight}}{0.12 \times (\text{Body weight}) - (\text{Brain weight})}
\]

**Cortical Quotient (CQ)**

\[
\text{Cortical Quotient (CQ)} = \frac{\text{Cortex weight}}{0.12 \times (\text{Brain weight}) - (\text{Cortex weight})}
\]
ANALYSIS METHODS & RESULTS:

- The following image will compare both Long Evans (LE) male and female, overall body weights (Fig. 1), total brain weights (Fig. 2), and cortex weights (Fig. 3). The data are presented with the dependent variables weight measured in grams on the Y-Axis and the independent variables (Gender and Treatment Conditions) on the X-Axis.

- Fig. 4 shows a different rate of EQ total brain volume loss, while Fig. 5 shows a different rate of CQ cortex volume loss as a function of developmental time period of lead exposure.

- The data are presented with the dependent variables (EQ and CQ) on the Y-Axis and the independent variables (Gender and Treatment Conditions) on the X-Axis.

- All rats were tested at the same time of day under the same conditions to ensure consistent tissue processing and measurements across all subjects under study.
**RESULTS:**

![Bar chart showing weight differences between males and females across different treatment groups.](chart.png)

**Fig. 1.** Weight differences between males and females as a function of lead treatment and time period of exposure. The data revealed a significant effect of Treatment $F_{(3)}=55.88, p = 0.001$, Sex $F_{(1)}=126.96, p = 0.001$, and a Treatment X Sex interaction $F_{(3,1)}=17.39, p = 0.001$ (** indicates male differences Compared to control, whereas ### indicates female differences compared to control).
RESULTS:

Fig. 2 Brain weight and Fig. 3 cortex weight differences between males and females as a function of lead treatment and time period of exposure. Fig. 2. The data revealed a significant effect of Treatment $F_{(3)}=5.41, p = 0.003$ and Sex $F_{(1)}=13.30, p = 0.001$. Fig. 3. The data revealed only a significant Treatment X Sex interaction $F_{(3,1)}=3.45, p = 0.03$ (*** indicates male differences compared to control, whereas ### indicates female differences compared to control).
RESULTS:

**Fig. 4.** Encephalization Quotient (EQ) differences between males and females as a function of lead treatment and time period of exposure. The data revealed a significant effect of Treatment $F_{(3)}=27.15$, $p = 0.001$, Sex $F_{(1)}=71.23$, $p = 0.001$, and a Treatment X Sex interaction $F_{(3,1)}=4.10$, $p = 0.001$ (** indicates male differences compared to control, whereas ### indicates female differences compared to control).
**RESULTS:**

Fig. 5. Cortical Quotient (CQ) differences between males and females as a function of lead treatment and time period of exposure. The data revealed a significant effect of $Treatment F_{(3)}=14.74$, $p = 0.001$ and $Sex F_{(1)}=34.80, p = 0.001$ (** indicates male differences compared to control, whereas ### indicates female differences compared to control).
• Lead treatment had a significant effect on body, brain, and cortical weights.

• Rats are a sensitive model to evidence how lead exposure shrinks brain and cortical volume using the EQ and CQ calculations.

• Such early and time dependent exposures to lead resulted in sex based differences in EQ and CQ.

• Such early brain and cortical volume loss is suggestive of accelerated cortical thinning and neurodegeneration. Thus, lead poisoning may predispose people to neurodegenerative disorders.
CONCLUSION & LIMITATIONS:

- Lead differentially effects both males and females rats in a gender specific manner.

- Moreover, lead effects rats differentially based upon the developmental time period of exposure (i.e., EPN vs. Peri).

- Children may be best served clinically with fMRI brain volume studies following the detection of lead in their body.

- Combining such technology with relative old environmental diseases (i.e., lead poisoning) may perhaps help us to better serve these children across their lifespan.

- Our study was limited as we need to increase the number of control rats in all conditions to publish the results of our study.

- Future studies can look into higher levels of lead exposure to determine whether or not a larger amount of brain volume loss is detected or whether such a phenomenon is restricted to low lead level exposures.
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REFERENCES:


THANK YOU!

Lead Free KIDS for a Healthy Future

Runs better unleaded