LONG TERM HEALTH EFFECTS OF HUMANS EXPOSED TO PCBS AND PCDFS

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29/10/2011, Carpi
Yucheng (oil-disease) episode

- Outbreak in 1979
- Acne-form skin eruption, pigmentation of the skin and nail, hypersecretions of the Meibomian glands of the eyes
- Approximately 2000 victims involved

(Guo et al., JTEH 1994)
Piped in heat-medium to deodor the rice oil at a final stage of production. Leakage of the heat medium caused contamination in oil, and intoxication in people Yusho, Japan, 1968
Life-time exposure

Serum level = dioxin toxic equivalency (TEQ)

Serum level vs age graph:
- Yucheng
- Population
- WHO safe level
Dr. Patterson, US CDC

Professor Lambert, UMDNJ
(Dioxin99, Venice)

Dr. Needham, US CDC
(ISEE 2004, New York)
Dioxin: Multiplicity of Toxicity

- Carcinogenicity
- Immunotoxicity
- Dermatological Toxicity
- Hepatotoxicity
- Neurotoxicity
- Reproductive and Developmental Toxicity
- Effects on endocrine system

How about health consequences in humans?
Mortality by 24 year follow-up

(Standardized mortality ratio, compared to national death certificates)

• 1980-87: Increased chronic liver diseases and cirrhosis, SMR= 3.7 (95%CI 1.6 – 7.2, 8 deaths)
• 1988-1995: Increased systemic lupus erythematosus, SMR=19.8 (95%CI 2.2-71.3, 2 deaths)
• 1996-2003: Increased systemic lupus erythematosus, SMR=18.9 (95%CI 3.8-55.2, 3 deaths), increased TB, SMR=3.6 (95%CI 1.0-9.1, 4 deaths)

(Yu et al., AJIM 1997; Tsai et al., STE 2007)
<table>
<thead>
<tr>
<th>Yr of death</th>
<th>Age at death</th>
<th>PCB level (ppb) /yr measured</th>
<th>Work</th>
<th>Causes of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>27</td>
<td>61/1985</td>
<td>None</td>
<td>SLE Pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1994</td>
<td>33</td>
<td>15/1981</td>
<td>Housewife</td>
<td>SLE pneumonia Septicemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>39</td>
<td>162/1980</td>
<td>None</td>
<td>SLE septicemia brain edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>40</td>
<td>92/1980</td>
<td>Farmer</td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>44</td>
<td>75/1982</td>
<td>Manufacture umbrella</td>
<td>SLE</td>
</tr>
</tbody>
</table>

All SLE subjects were females. Age at exposure: 17, 18, 22, 22, 24
Background PCB level: 1.7 ppb.
(Tsai et al., STE 2007)
Yucheng morbidity vs. controls

Women
- Anemia 2.3x
- Stillbirth of baby 2x

Men
- Spine problems 3x
- Arthritis 4x

DM, HTN, CAD: not different

(Guo et al., EHP 1999)
**Reported diseases ever diagnosed as of 2003 (24 yr later, age 62), in women**

<table>
<thead>
<tr>
<th></th>
<th>Yucheng (n=332)</th>
<th>Reference (n=332)</th>
<th>AOR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 2 DM</strong></td>
<td>11.3</td>
<td>5.6</td>
<td>2.1 (1.1-4.5)</td>
</tr>
<tr>
<td><strong>On therapy</strong></td>
<td>7.7</td>
<td>3.2</td>
<td>2.5 (1.0-6.5)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>18.5</td>
<td>14.4</td>
<td>1.3 (0.8-2.2)</td>
</tr>
<tr>
<td><strong>Cardiovascular Diseases</strong></td>
<td>10.6</td>
<td>8.6</td>
<td>1.4 (0.8-2.5)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, smoking, and alcohol use

(Wang et al., *Diabetes Care* 2008)
Reported diseases ever diagnosed as of 2003, by chloracne, in Yucheng women

<table>
<thead>
<tr>
<th>Chloracne</th>
<th>-- (n=186)</th>
<th>+ (n=58)</th>
<th>AOR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>5.9%</td>
<td>24.1%</td>
<td>5.5 (2.3-13.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14.4%</td>
<td>37.9%</td>
<td>3.5 (1.7-7.2)</td>
</tr>
<tr>
<td>Cardiovascular Diseases</td>
<td>11.8%</td>
<td>25.9%</td>
<td>3.0 (1.5-8.6)</td>
</tr>
<tr>
<td>Serum PCB (ppb)</td>
<td>73</td>
<td>121</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, smoking, and alcohol use

(Wang et al., Diabetes Care 2008)
Neurocognitive functioning

- Yucheng and control people aged 60 or above
- Neuropsychological test battery
  - Mini-mental state examination (MMSE)
  - Wechsler’s Adult Intelligence Scale (digit span and digital symbol)
  - Wechsler’s Memory Scale-Revised (WMS-R)
  - Geriatric Depression Scale, Short-form (GDS-S)
  - Bathel’s index of Activities of Daily Living (ADL)
  - Motor skill and tactile performance
Visual Memory Span (VMS)
Neurocognitive testing in women

VMR: \(-0.48/\text{yr of age}\), adjusted for education
VMS: \(-0.22/\text{yr of age}\), adjusted for education

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>Controls (N=162)</th>
<th>(\leq 30\text{ppb} (N=42))</th>
<th>30-90ppb (N=63)</th>
<th>(\geq 90\text{ppb} (N=43))</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMR</td>
<td>(p&lt;0.05, test for trend)</td>
<td>29.1 ± 7.5</td>
<td>26.8 ± 7.3</td>
<td>26.5 ± 6.9</td>
<td>26.1 ± 8.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>4.8 yrs</strong></td>
<td><strong>5.4 yrs</strong></td>
<td><strong>6.3 yrs</strong></td>
</tr>
<tr>
<td>VMS</td>
<td>(p&lt;0.05, test for trend)</td>
<td>10.8 ± 2.9</td>
<td>10.0 ± 2.5</td>
<td>9.7 ± 2.7</td>
<td>9.6 ± 3.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>3.6 yrs</strong></td>
<td><strong>5.0 yrs</strong></td>
<td><strong>5.5 yrs</strong></td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and education

(Lin et al., *EHP* 2008)
Menstrual cycle length among Yucheng women and their neighborhood referents
Adjusted for age at interview, BMI, smoking, alcohol, and marital status by multiple regression analysis

(Yang et al., *Env Res* 2011)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Menstrual cycle length (day) mean ± SD</th>
<th>Differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yucheng</td>
<td>197</td>
<td>28.2 ± 2.2</td>
<td>−0.5 (−0.9 to −0.1)**</td>
</tr>
<tr>
<td>Referents</td>
<td>218</td>
<td>28.7 ± 2.2</td>
<td>Reference</td>
</tr>
<tr>
<td>Considering skin manifestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yucheng</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With skin manifestation</td>
<td>36</td>
<td>27.5 ± 2.3</td>
<td>−1.2 (−1.7 to −0.7)***</td>
</tr>
<tr>
<td>Without skin manifestation</td>
<td>161</td>
<td>28.4 ± 2.1</td>
<td>−0.3 (−0.7 to 0.0)</td>
</tr>
<tr>
<td>Referents</td>
<td>218</td>
<td>28.7 ± 2.2</td>
<td>Reference</td>
</tr>
</tbody>
</table>

p = 0.0028 by trend test
Yucheng women fertility
Average age of exposure: 15 yr

Fecundability ratio = 0.9
(95% CI 0.8-1.0)

(Yang et al., *EHP* 2008)
How about 2nd generation?

(Rogan et al., Science, 1988)
Cognitive Development

Matched for gender, age, mother age, residence, SES

(Yu et al., 1991, Chen, Guo, et al., JAMA 1992)
Tooth problems
Tooth defects (%) according to PCB level at pregnancy

(Wang et al., *Env Res* 2003)
Otitis media

Between 8-14 years of age, the Yucheng children had 10x otitis media compared to neighbors

(Chao et al., AECT 1997)
Figure 1: Changes in Child Behavior Checklist (CBCL) scores over age (Yucheng vs. Control). The data is adjusted for sex and year of birth. Source: Lai et al., Arch General Psychiat, 2002.
• Yucheng children had **more problems** especially on Somatic complaints, Attention problems, Delinquent behavior, Aggressive behavior, Introversion, and Extroversion

• Yucheng and control children scored **similarly** in Withdrawn, Anxiety/Depressed Mood, Social problems, and Thought problems
Semen Analysis

Yucheng 12 young men (16-20 yr old) compared with 23 controls

Volume and count: no difference

Morphology: 38% vs. 26% abnormal (~50% increase)

Motile sperm: 35% vs. 57% (40% drop)

Speed by CASA: reduced velocity by 20% in motile sperm

Chinese hamster oocyte penetration: 66% vs. 75% (12% drop)

(Guo et al., Lancet 2000)

Science News 2000;158:303

Semen lab in Lukang
Penis length (cm)* in Yucheng and Control Boys by Age

*Measured by “Blinded” physicians
<table>
<thead>
<tr>
<th></th>
<th>Yucheng (n=17)</th>
<th>Unexposed (n=15)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/ml)</td>
<td>3.0 ± 2.4</td>
<td>4.2 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>48.6 ± 53.9</td>
<td>21.3 ± 13.2</td>
<td>*</td>
</tr>
<tr>
<td>Testosterone/estradiol</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>*</td>
</tr>
</tbody>
</table>

(Hsu et al., JTEH 2005)
Lake Apopka Alligators, Florida, USA

- reduced fertility
- smaller-than-normal penises
- Female dominance in sex
- exposed to runoff of pesticides, mainly DDE

Professor Louis J. Guilette
Future studies

1st generation
• Health-related quality of life
• Mortality and morbidity due to cancer and chronic diseases
• Early changes potentially leading to SLE

2nd generation
• Mechanisms behind semen quality change
• Epigenetic changes

Both
• Mechanisms behind neurocognitive changes
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- Food Safety, Canada
  - John Jake Ryan
- Japan
  - Masuda, Ikeda, Yoshimura, Furue, Iida
Grazie!
Proportion of male births of Yucheng Fathers, 1980-1999

Year of Birth

Unexposed
Exposed

(see B-Gomez, Guo, et al.)
Duration of Breast Feeding (weeks) and Mothers’ Serum 2,3,4,7,8-PnCDF Levels

(Guo et al., AECT 1997)
Estimated 1,2,3,4,7,8-HxCDF at 1 year of age by duration of breast-feeding

\[ y = 40.82x + 289.05 \]

(Ryan et al., Chemosphere 1994)
1992年血中濃度，美國CDC協助檢測
1992年血中濃度，美國CDC協助檢測

PCDF毒性當量

PCB (ppb)
After the Yucheng intoxication

- No effective therapy, long half lives of internal exposure
- ↑ mortality due to chronic liver diseases early after exposure, and SLE later
- ↑ goiter, chloracne, headache, peripheral neuropathy
- Men: ↑ arthritis & spine problems, ↓ semen quality
- Women: ↑ DM, CVD (?), anemia, and stillbirth, ↓ fecundability