Identifying environmental risk factors for disease: from slam dunks to needles in haystacks

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Departments of Environmental Health and Epidemiology

Feb 27, 2003
Illustrative examples

• Silica, silicosis, and lung cancer in diatomite workers (“slam dunk”)

• Semen quality in lead smelter workers (somewhere in the middle)

• Environmental and genetic risk factors for Parkinson’s disease (“needles in a haystack”)
Background: silica, silicosis, and lung cancer

- Two forms of silica—amorphous, crystalline (e.g., quartz, cristobalite); quartz ~2% earth crust
- Crystalline silica occupational exposures—mining, sandblasting, foundries, diatomaceous earth, pottery, brick, many others
- Silicosis (chronic lung scarring) recognized for millenia
- Excess lung cancer seen in silicotics since 1930s
- Epidemiologic studies in non-silicotics inconclusive
- IARC classified crystalline silica as “probable” human carcinogen (2B) in 1987
Silica, silicosis, and lung cancer in the diatomaceous earth industry*

Co-investigators:

Norm Breslow
Paul Demers
Nick Heyer
Janet Hughes (Tulane)
Noah Seixas
Hans Weill (Tulane)

*Supported by grants from Int’l Diatomite Prod Assoc, NIOSH (OH03126)
DIATOMACEOUS EARTH MINING AND PROCESSING

- Open Pit Quarry
- Crushing, Drying & Screening
  - Natural Powders
    - Calcined and flux-calcined powders
    - Rotary Kiln
    - Bag Packing Stations and Pallett Presses
- Warehouse
- Silicate Plant
- Brick Plant
- Transport via Truck or Train
Diatomaceous earth industry cohort study

• Cohort – 2342 male workers employed >12 months at a DE plant in Lompoc, CA
• Follow-up – 1942-94
• Outcomes
  – Radiographic silicosis
  – Mortality from numerous causes of death (lung cancer, non-malignant respiratory disease [NMRD] of most prior interest)
### Historical cohort analysis of silicosis in California diatomaceous earth workers*

<table>
<thead>
<tr>
<th>Cumulative exposure (mg/m³ –yrs)</th>
<th>Cases</th>
<th>Person-years</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>6</td>
<td>9,523</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;1.0 – 3.0</td>
<td>17</td>
<td>6,573</td>
<td>4.4</td>
</tr>
<tr>
<td>3.1 – 6.0</td>
<td>30</td>
<td>2,829</td>
<td>20.1</td>
</tr>
<tr>
<td>&gt; 6.0</td>
<td>28</td>
<td>1,356</td>
<td>40.4</td>
</tr>
</tbody>
</table>

Exposure-response trends for silicosis in California diatomite workers, by average exposure intensity*

Excess lifetime risk of silicosis for 45 years work at various exposure levels: based on California diatomite workers study

<table>
<thead>
<tr>
<th>Silica concentration ($\mu$g/m$^3$)</th>
<th>Excess risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td>20</td>
<td>3.9</td>
</tr>
<tr>
<td>50$^a$</td>
<td>6.8</td>
</tr>
<tr>
<td>100$^b$</td>
<td>10.0</td>
</tr>
</tbody>
</table>


$^a$Current OHSA permissible exposure limit for cristobalite

$^b$Current OHSA permissible exposure limit for quartz
Mortality among US diatomite workers: selected causes, 1942-94*

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Observed</th>
<th>Expected</th>
<th>Obs/Exp</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>749</td>
<td>737</td>
<td>1.0</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>77</td>
<td>59.9</td>
<td>1.3</td>
</tr>
<tr>
<td>NMRD</td>
<td>67</td>
<td>33.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Exposure-response trend for respirable crystalline silica and NMRD mortality: DE study*

Exposure-response trend for respirable crystalline silica and lung cancer mortality: DE study*

Is pulmonary fibrosis necessary for dust-induced lung cancer?

• Implications for carcinogenesis mechanisms

• Might suggest threshold of carcinogenic effect (i.e., at exposure level where silicosis occurs)

• Medico-legal implications (lung cancer case not compensable if no evidence of silicosis)
Lung cancer mortality by radiographic silicosis status in California diatomaceous earth workers*

<table>
<thead>
<tr>
<th>Cumulative exposure (mg/m³ – yr)</th>
<th>Silicosis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>Rel. Risk</td>
<td>Deaths</td>
<td>Rel. Risk</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>13</td>
<td>1.05</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5-1.9</td>
<td>13</td>
<td>0.86</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.0-4.0</td>
<td>10</td>
<td>1.25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>≥5.0</td>
<td>12</td>
<td>2.40</td>
<td>4</td>
<td>2.94</td>
</tr>
</tbody>
</table>

DE study conclusions

- Strong evidence for dose-response of silica and silicosis (as expected)

- Evidence supporting dose-response for silica and lung cancer

- Silicosis does not appear to be required for silica/lung cancer association
“Crystalline silica *inhaled* in the form of quartz or cristobalite from *occupational sources* is carcinogenic to humans (group 1)” [italics added]

- IARC (1997)
Studies influential in IARC classification of silica

- US gold miners
- S. Africa gold miners
- **US diatomite workers**
- UK pottery workers
- Chinese pottery workers
- Danish stone workers
- US granite workers
- US crushed stone workers
- Italian refractory brick workers
**Background: lead and adverse reproductive effects**

- Lead used to induce abortions during Roman Empire
- 20\textsuperscript{th} Century evidence for malformations, spontaneous abortion inconsistent
- Since 1970s sperm abnormalities seen occupational studies of men heavily exposed (>70 µg/dl blood lead level)*

*Current OHSA allowed blood level 50 µg/dl
Semen quality in lead smelter workers*

Co-investigators:

Bruce Alexander
Elaine Faustman
Charles Muller
Chris van Netten (Univ Brit. Columbia)

*Supported by grants from NIEHS (ES04696), NIOSH (OH02966)
Semen quality in Trail, B.C. lead smelter workers*

• Design – cross-sectional
• Subjects – 152 workers who provided blood and semen samples
• Exposure data – current and historical blood lead levels
• Semen quality measures: count, concentration, morphology, motility, computer-assisted analysis (e.g., sperm swimming velocity)
• Other outcomes: repro. hormones, history

*Bruce Alexander, PhD Dissertation, 1995
Sperm concentration by current blood lead levels: Trail, B.C. smelter study*

Sperm motility by current blood lead levels: Trail, B.C. smelter study*

Strict normal morphology by current blood lead levels: Trail, B.C. smelter study*

Sperm concentration by average past 10-yr blood lead levels, among men with current levels <40 µg/dl*

Summary of other findings: Trail, B.C. lead smelter study

- No trend of semen lead level and sperm concentration
- No associations with reproductive hormones
- Some suggestion of increase risk for stillbirth, malformations in partners of male workers
Trail, B.C. lead smelter study conclusions

- Moderate level occupational exposure related to reduced sperm production
  - Effect of current exposure
  - Also related to chronic exposure
- Other semen quality factors not consistently related to lead exposure
- Blood lead is a valuable biomonitoring method (cf. semen lead)
Subsequent studies of occupational lead exposure and semen quality

• South African battery workers (Robins et al., Am J Ind Med 1998;32:369-76)
  – No associations with sperm concentration
  – Increase abnormal sperm morphology
• UK, Belgium, Italy study of multiple Pb-exposed workplaces (Bonde et al., Occup Environ Med 2002;59:234-42)
  – Threshold ~45µg/dl for sperm concentration decline
Parkinson’s disease

• Chronic, neurodegenerative disorder due to dopamine deficiency
• Cardinal features: resting tremor; bradykinesia, gait disturbance, muscle rigidity
• First described by James Parkinson, 1817 (thought due to “fright”)
• Pathological lesion: destruction of dopamine-producing neurons in substantia nigra (Lewy body formation)
• Prevalence in US ~150/100,000 (~2% at ages >65)
• Incidence in US ~15/100,000/year
Figure 8–5. Typical flexed posture of a patient with parkinsonism.
Models of Causation of Parkinson’s Disease*

CHEMICAL STRUCTURE OF MPTP, MPP+, AND PARAQUAT

FIGURE 1.
What causes Parkinson’s disease?

• Risk increases with age
• Slight male excess
• Inheritance (Mendelian) causes ~10% cases
• Environmental factors ??
• Variants of common genes??
• Interactions between genes and environment??
Suspected environmental risk and protective factors for PD

• **Increase risk**
  – Pesticides
  – Metals
  – Industrial solvents

• **Decrease risk**
  – Cigarette smoke
  – Caffeine
  – Anti-oxidant micronutrients
  – Estrogen
  – Anti-inflammatory medications
Cigarette smoking as a “protective” factor in PD

• Inverse dose-response seen consistently
  – Found in cohort and case-control studies
  – Not explained by selective survival of non-smokers

• Monoamine oxidase B (MAO-B) enzyme activity decreased in smokers’ brain
  – MAO-B activates MPTP
  – MAO-B catabolizes dopamine
Environmental and genetic risk factors for Parkinson’s disease*

Co-investigators:

Theo Bammler  Gary Franklin
Lucio Costa    Will Longstreth
Paola Costa-Mallen  Curt Omiecinski
Dave Eaton     Phillip Swanson
Fred Farin     Jim Woods

*Supported by grants from NIEHS (ES04696, ES10750, ES07033)
Environmental and genetic risk factors for Parkinson’s disease

- **Design**: case-control
- **Cases**: Newly diagnosed PD cases from Group Health Cooperative and UW neurology clinics [target N=400]
- **Controls**: Age/gender- matched from GHC enrollees, free of PD and other neurodegenerative diseases [target=600]
- **Data collected**: occupations, environmental exposures, smoking, diet, medical history, DNA for genetic polymorphism analyses
### Smoking and PD: Seattle Study case-control*

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>112</td>
<td>132</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>98</td>
<td>215</td>
<td>0.5</td>
</tr>
<tr>
<td>Current smoker</td>
<td>7</td>
<td>36</td>
<td>0.3</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>91</td>
<td>179</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Odds ratio, adjusted for age, ethnicity, gender

PD relative risk by cumulative cigarette smoking history*

Coffee and PD: Seattle Case-Control Study*

<table>
<thead>
<tr>
<th>Coffee (cups/day)</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>63</td>
<td>96</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;0-1</td>
<td>32</td>
<td>66</td>
<td>0.8</td>
</tr>
<tr>
<td>2-3</td>
<td>69</td>
<td>105</td>
<td>1.1</td>
</tr>
<tr>
<td>4-6</td>
<td>30</td>
<td>48</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;6</td>
<td>16</td>
<td>32</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for age, ethnicity, gender, education, smoking

Other sources of caffeine and PD: Seattle case-control study*

<table>
<thead>
<tr>
<th>Source</th>
<th>Cups/day</th>
<th>Cases</th>
<th>Controls</th>
<th>Rel. Risk +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tea</td>
<td>0</td>
<td>138</td>
<td>202</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;0-1</td>
<td>61</td>
<td>110</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>11</td>
<td>35</td>
<td>0.4</td>
</tr>
<tr>
<td>De-caff. coffee</td>
<td>0</td>
<td>132</td>
<td>216</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;0-1</td>
<td>42</td>
<td>75</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>36</td>
<td>56</td>
<td>1.1</td>
</tr>
<tr>
<td>Cola</td>
<td>0</td>
<td>128</td>
<td>196</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;0-1</td>
<td>71</td>
<td>125</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>11</td>
<td>26</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for age, ethnicity, gender, education, smoking, coffee

Joint effects of dietary iron (Fe) and manganese (Mn) on PD risk: Seattle case-control study*

<table>
<thead>
<tr>
<th>Nutrient category</th>
<th>Cases</th>
<th>Controls</th>
<th>Rel. Risk +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Mn, Low Fe [reference]</td>
<td>55</td>
<td>116</td>
<td>1.0</td>
</tr>
<tr>
<td>High Mn, Low Fe</td>
<td>43</td>
<td>78</td>
<td>1.1</td>
</tr>
<tr>
<td>Low Mn, High Fe</td>
<td>47</td>
<td>78</td>
<td>1.2</td>
</tr>
<tr>
<td>High Mn, High Fe</td>
<td>105</td>
<td>116</td>
<td>1.9</td>
</tr>
</tbody>
</table>

+Odds ratio adjusted for age, gender, education, smoking, total caloric intake

### Pesticide-related occupations worked at least 6 months and PD: Seattle study (men)*

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Cases (N=135)</th>
<th>Controls (N=226)</th>
<th>Rel. Risk$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy farmer</td>
<td>14</td>
<td>28</td>
<td>0.81</td>
</tr>
<tr>
<td>Orchardist</td>
<td>6</td>
<td>9</td>
<td>1.49</td>
</tr>
<tr>
<td>Pesticide applicator</td>
<td>4</td>
<td>4</td>
<td>3.88</td>
</tr>
<tr>
<td>Farmer – any</td>
<td>45</td>
<td>69</td>
<td>1.25</td>
</tr>
</tbody>
</table>

$^+$Odds ratio, adjusted for age, smoking

*Firestone J, UW Dept. Env Health thesis, 2002
**Self-reported pesticide occupational pesticide exposures and PD: Seattle study (men)**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Duration (yrs)</th>
<th>Cases (N=135)</th>
<th>Controls (N=226)</th>
<th>Rel. Risk$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any pesticide</td>
<td>0.5-5</td>
<td>6</td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>10</td>
<td>12</td>
<td>1.3</td>
</tr>
<tr>
<td>Insecticides</td>
<td>0.5-5</td>
<td>5</td>
<td>11</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>9</td>
<td>11</td>
<td>1.2</td>
</tr>
<tr>
<td>Herbicides</td>
<td>$\geq$0.5</td>
<td>2</td>
<td>6</td>
<td>0.6</td>
</tr>
<tr>
<td>Paraquat</td>
<td>0.5-5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>2</td>
<td>1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

$^+$Odds ratio, adjusted for age, smoking

*Firestone J, UW Dept. Env Health MPH thesis, 2002*
Home-use of pesticides and PD, men and women combined: Seattle study*

<table>
<thead>
<tr>
<th>Duration of use</th>
<th>Cases (N=210)</th>
<th>Controls (N=352)</th>
<th>Relative risk$^+$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever (&gt;6 months)</td>
<td>165</td>
<td>275</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt;0 - ≤5 yrs</td>
<td>36</td>
<td>58</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt; 5 yrs</td>
<td>129</td>
<td>221</td>
<td>0.7</td>
</tr>
</tbody>
</table>

$^+$Odds ratio, adjusted for age, gender, smoking

*Firestone J, UW Dept. Env Health MPH thesis, 2002
Gene/environment and gene/gene interactions in PD

• *Gene/environment interactions*: persons with gene variants (polymorphisms) are
  – particularly susceptible to neurotoxic exposures
  – Or, most protected by factors that reduce risk

• *Gene/gene interactions*: combinations of genetic polymorphisms increase (or decrease) risk
Genetic polymorphisms studied to date: all (but one*) negative results

- **Dopamine metabolism**: MAO-B*, MAO-A, DRD2 dopamine receptor, COMT

- **Environmental chemical activation or de-toxification**: CYP2D6, CYP2E1, CYP1A1, GSTM1, GSTT1, GSTP1, sEH, mEH, NQ01, NQ02, SOD1, SOD2, PON1

- **Other**: Mitochondrial Complex I (ND1 subunit)
Monoamine oxidase B (MAO-B)

- **Enzyme functions**
  - Metabolizes dopamine
  - Activates MPTP (PD-inducing chemical)
  - Reduced activity in brain of smokers

- **Genetics**
  - Located on X chromosome
  - Intron polymorphisms (introns 2, 13) associated with PD (mixed evidence)
Interactions between *MAO-B* intron 13, gender, and smoking on PD risk*

<table>
<thead>
<tr>
<th>Smoking pack-yrs</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>MAO-B</em> G allele</td>
<td><em>MAO-B</em> A allele</td>
<td><em>MAO-B</em> G allele</td>
<td><em>MAO-B</em> A allele</td>
</tr>
<tr>
<td>0 [ref.]</td>
<td>1.0(^+)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1-19</td>
<td>0.2</td>
<td>1.4</td>
<td>1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>≥ 20</td>
<td>0.2</td>
<td>0.9</td>
<td>0.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\(^+\) Relative risk (odds ratio)

Gender-specific interactions of *MAO-B* intron 13 and smoking on PD risk: Nurses Health Study and Harvard Health Professionals Study*

<table>
<thead>
<tr>
<th>Smoking (pack-yrs)</th>
<th>Men A allele</th>
<th>Men G allele</th>
<th>Women A Allele</th>
<th>Women G Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 [ref.]</td>
<td>1.0*</td>
<td>1.0*</td>
<td>1.0*</td>
<td>1.0*</td>
</tr>
<tr>
<td>1-9</td>
<td>1.0</td>
<td>0.7</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>10-25</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;25</td>
<td>0.5</td>
<td>0.3</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Odds ratio adjusted for age

Future directions on PD study

- Further analysis of environmental, lifestyle, factors
- Analysis of medications
- Continue the gene search
- Collaborate with outside groups to assess gene/environment interactions (need huge sample sizes!)
The essentials for discovering environmental risk factors for disease

- Plausible research question(s)
- The right study population (large size, well characterized exposure and health outcome)
- And…
The question you have to ask yourself is....
...a little luck
Acknowledgments: Diatomaceous earth workers study

<table>
<thead>
<tr>
<th>Brian Boehlecke</th>
<th>John Montgomery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norm Breslow</td>
<td>Joe Picciano</td>
</tr>
<tr>
<td>Janice Camp</td>
<td>Anthony Proto</td>
</tr>
<tr>
<td>Paul Demers</td>
<td>Noah Seixas</td>
</tr>
<tr>
<td>Melanie Henry</td>
<td>Arlene Stebbins</td>
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<td>Nick Heyer</td>
<td>Hans Weill</td>
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<tr>
<td>Tony Horstman</td>
<td>Esther Welp</td>
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<tr>
<td>Janet Hughes</td>
<td>Jerome Wiot</td>
</tr>
<tr>
<td>Robert Jones</td>
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</tr>
</tbody>
</table>
Acknowledgments: Lead and semen quality study

- Bruce Alexander
- William Bremner
- Linda Coxall
- Tim Ewers
- Elaine Faustman
- Peter Fulcher
- Joel Kaufman
- Graham Kenyon
- Beth Mueller
- Chip Muller
- Iris Nielsen
- Genna Ratiu
- Chris van Netten
- Tom Vaughan
- Tom Wynn
- Karin Yeatts
- Changpu Yu
Acknowledgments: Parkinson’s disease study

Zhara Afsharinejad
Cheryl Anderson
Theo Bammler
Shirley Beresford
Lucio Costa
Paola Costa-Mallen
Julia Dilley
Dave Eaton

Janet Erro
Fred Farin
Jordan Firestone
Mark Fishel
Gary Franklin
Clem Furlong
Robert Gotshall
Chris Hassett
Acknowledgments: Parkinson’s disease study (cont.)

<table>
<thead>
<tr>
<th>Ann Hunt</th>
<th>Will Longstreth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pat Janssen</td>
<td>Richard Mesher</td>
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Acknowledgments: Administrative Support (all projects)

Heidi Curtiss
Gail Gilliland
Michaele Montemurro
Jennifer Rene
Megan Schuknecht