Scleroderma and Solvent Exposure Among Women

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On Behalf of Co-investigators at the
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Background

• **Systemic Sclerosis (SSc)**
  – Autoimmune connective tissue disease
    • Thickening & tightening skin
    • Analogous internal organ changes

• **Major pathogenic events**
  – Aberrant vascular reactivity
  – Distorted endothelial cytoarchitecture
  – Immune dysfunction
  – Increased collagen synthesis
Etiology

• Unknown cause
• Extremely complex pathogenesis
  – No single, unifying hypothesis
• Key cell types involved
  – Fibroblasts
  – Endothelial cells
  – Immune cells
Epidemiology

• Annual U.S. incidence rate
  – 20 per 1,000,000

• U.S. prevalence
  – 240 per 1,000,000

• Representative studies difficult
  – Case definition and rarity
  – Case reports and hospital-based series
  – Few rigorous epidemiologic studies
University of Michigan Study

• Case-control study in Michigan and Ohio

• Objective:
  – Systematically investigate potential associations between SSc and environmental, medical, and other factors in population-based epidemiologic study

• Cases
  – Women 18 years or older at diagnosis
    • Jan. 1, 1980 – Dec. 31, 1992 in Ohio
Case Identification

- Four potentially overlapping sources
  - University of Michigan hospitals and Wayne State University-affiliated hospitals
  - National hospital discharge code database
    - HCIA, Ann Arbor, MI
  - Mailings to MI and OH rheumatologists
    - Other relevant specialists, e.g., dermatology
  - Mailings to Southeast Michigan Chapter of Scleroderma Foundation
- Estimated 75%-80% eligible women
Case Definition

• Medical record review
  – 1980 ACR classification criteria
    • Major criterion: Proximal scleroderma
    • Minor criteria (2 or more)
      – Sclerodactyly, digital pitting scars, bibasilar pulm. fibros.
  – Signs and symptoms characteristic of SSc
    • Sclerodactyly or CREST
      – Calcinosis, Raynaud’s Phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasias

• Estimated 80% of all incident cases in MI
Control Selection

• RDD telephone sampling
  – Frequency-matched on age, race, and region
  – 80% response in MI
  – 74% response in OH
  – 3:1 control:case ratio
Telephone Interviews

• UM Institute for Social Research
  – August, 1992 through February, 1996
• 30-minute telephone interview
  – Demographics, family history, occupations and hobbies, reproductive history, cigarette and alcohol use, personal medical history, medical devices
Exposure Ascertainment

• Occupations and hobbies that have high probability of exposure to solvents
  – At least once a week for 3 months or more
  – Ever work with solvents in those occupations and hobbies

• Ever work with individual solvents
  – At least once a week for 3 months or more
Occupations and Hobbies

Ever work at least once per week for 3 months or more in any of 16 jobs or hobbies

- Dry cleaning
- Chemical or dye mfg.
- Petroleum refining
- Vinyl chloride mfg.
- Plastics industry
- Rubber product mfg.
- Painting or paint mfg.
- Furniture refinishing
- Hair dressing
- Medical or diagnostic or pathology laboratory
- Prof. cleaning or maint.
- Film devel. or publish.
- Perf., cosm., drug mfg.
- Fiberglass industry
- Leather tanning or shoe mfg.
- Arts and crafts
Occupations and Hobbies (2)

- If yes, open-ended questions
  - Years in which participant first & last worked
  - Job title
  - Specific tasks involved
  - Name of place at which participant worked
  - Type of industry or business

- Ever work with 9 solvents or categories
  - Years in which participant first & last used
  - Directly or near; wore protective clothing
Occupations and Hobbies (3)

- Trichloroethylene (TCE)
- Perchloroethylene (Perc)
- Trichloroethane (TCA)
- Paint thinners / removers
- Mineral spirits, naphtha, or white spirits
- Gasoline
- Toluene
- Xylene
- Benzene

- Detailed use during occupations and hobbies
  - “Other solvents”

- For all women, ever use individual solvents
  - Details
  - “Other solvents”
Expert Review

- Solvent exposures reviewed by expert in exposure assessment (DHG)
  - Reviewed blinded to case or control status
  - Reference materials
    - Typical processes and materials used in these activities
    - Types of solvents used in these tasks
    - Exposure levels associated with specific tasks
    - Historical periods in which specific solvents were used for specific tasks
Expert Review (2)

• Confirmed exposures:
  – Solvent was commercially or industrially available during the period of reported use
  – Documentation existed that the solvent was used (or was a suitable substitute for solvents typically used)
  – Exposure was of nontrivial frequency, intensity, and duration

• Not confirmed exposures:
  – Implausible or trivial frequency, intensity, or duration
Statistical Analysis

- Adjusted for year of birth and attained age
  - Compared each case to all controls who were born in the same year
    - Solvent exposures only considered if they occurred before the case’s age at diagnosis
    - Many cases born in the same year, so controls used in multiple strata
  - Conditional logistic regression for ORs & CIs
    - Estimates relative risk (RR) of SSc as a function of exposure to TCE or other solvents
# Study Population

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Number</td>
<td>660</td>
<td>2,227</td>
</tr>
<tr>
<td>Age at interview</td>
<td>56.3</td>
<td>51.4</td>
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<tr>
<td>Age at diagnosis</td>
<td>49.5</td>
<td>n/a</td>
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<tr>
<td>White</td>
<td>86.8 %</td>
<td>89.5 %</td>
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<tr>
<td>Current smoker</td>
<td>14.9 %</td>
<td>23.5 %</td>
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<tr>
<td>High school graduate</td>
<td>84.2 %</td>
<td>85.2 %</td>
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# TCE Exposure

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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Total</td>
<td>No.</td>
<td>Total</td>
</tr>
<tr>
<td>Any TCE reported</td>
<td>8</td>
<td>606</td>
<td>15</td>
<td>2,138</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>2.0 (0.8 – 4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conf. by expert review</td>
<td>4</td>
<td>606</td>
<td>8</td>
<td>2,137</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.9 (0.6 – 6.6)</td>
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## TCA Exposure

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Total</td>
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<tr>
<td>Any TCA reported</td>
<td>9</td>
<td>612</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.5 (0.7 – 3.2)</td>
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<tr>
<td>Conf. by expert review</td>
<td>4</td>
<td>611</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.9 (0.3 – 2.8)</td>
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# Perc Exposure

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<tbody>
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<td>No.</td>
<td>Total</td>
</tr>
<tr>
<td>Any Perc reported</td>
<td>7</td>
<td>616</td>
</tr>
<tr>
<td></td>
<td><strong>OR (95% CI)</strong></td>
<td><strong>1.4 (0.6 – 3.4)</strong></td>
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<tr>
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<td>5</td>
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<tr>
<td></td>
<td><strong>OR (95% CI)</strong></td>
<td><strong>1.1 (0.4 – 2.9)</strong></td>
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## Jobs & Hobbies with Potential TCE Exposure

<table>
<thead>
<tr>
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<th>Cases</th>
<th>Ctrls</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Professional cleaning or maintenance</td>
<td>42</td>
<td>116</td>
<td>1.8</td>
<td>1.3 – 2.7</td>
</tr>
<tr>
<td>Plastics industry</td>
<td>17</td>
<td>52</td>
<td>1.3</td>
<td>0.7 – 2.3</td>
</tr>
<tr>
<td>Rubber product manufacturing</td>
<td>3</td>
<td>14</td>
<td>0.9</td>
<td>0.3 – 3.3</td>
</tr>
</tbody>
</table>
Results Summary

• TCE exposure was positively but not statistically significantly associated with SSc
  – Low frequency of exposure in both cases and controls
  – One-half of reported exposures not confirmed
    • But increased risk remained
    • Over-reporting did not appear to be the only reason for the potential increased risk
TCE & Anti-Scl-70 Antibodies

- Anti-Scl-70 Ab (Anti-topoisomerase I)
  - Highly specific for SSc
    - Prevalence: 26% SSc and 34% Diffuse SSc
  - Nietert et al. case-control study: positive association between TCE & SSc in men only who tested positive for anti-Scl-70 Ab
    - Solvents bind topoisomerase & trigger autoimmune response?

- Anti-Scl-70 Ab known for 255 of 660 SSc
  - 0 of 8 SSc cases exposed to TCE had (+) Abs
Undifferentiated Connective Tissue Disease (UCTD)

- CTD signs & symptoms overlap
  - Specific diagnosis not immediately apparent
  - 15%-25% patients present with non-specific or overlapping rheumatic symptoms

- UCTD case group
  - Did not meet ACR criteria for any CTD but had at least 2 documented signs, symptoms, or laboratory abnormalities
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<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Total</td>
<td>No.</td>
<td>Total</td>
</tr>
<tr>
<td>Any TCE reported</td>
<td>1</td>
<td>189</td>
<td>15</td>
<td>2,015</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.8</td>
<td>(0.1 – 7.0)</td>
<td></td>
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</tr>
<tr>
<td>Conf. by expert review</td>
<td>1</td>
<td>189</td>
<td>8</td>
<td>2,014</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.7</td>
<td>(0.2 – 14.9)</td>
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</table>
Study Strengths

• Large study population from representative area
• High levels of participation
• Extensive data collection
• Expert review of specific solvents
Study Limitations

- Low frequency of reported exposures
- Expert review only for reported exposures
  - No information on other unreported exposures
- Potential selection and information biases
  - Over 80% of eligible SSc patients & controls
  - Standardized interview
- Study included only women
Conclusions

- Suggestive evidence of an association between TCE exposure and risk of SSc
  - No conclusive evidence to date
- Exposure assessment is critical
  - Identifying & verifying specific exposures in populations are major challenges
  - Future studies should also consider bystander exposures
Research Team

- David Schottenfeld, MD
- David H. Garabrant, MD
- Maureen D. Mayes, MD
- Timothy J. Laing, MD
- James V. Lacey, Jr, PhD
- Brenda W. Gillespie, PhD
- Brenda C. Cooper, MS
- Carol J. Burns, PhD
- Kirsten H. Alcser, PhD
- Steven G. Heeringa, MS
- NIH 5 P60 AR-20557
- NIH ST32 AR-07080
- NIH 1F33 AR-08287
- Dow Corning Corporation
- Halogenated Solvents Industry Alliance
- Garabrant DH & Dumas C. Arthritis Res 2000;2:5