Scleroderma and Solvent Exposure Among Women

James V. Lacey, Jr., Ph.D.
National Cancer Institute

On Behalf of Co-investigators at the
University of Michigan School of Public Health

Garabrant DH, et al. *Am J Epidemiol* 2003;157:493-500

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
  - Diagnosed Jan. 1, 1980 – Dec. 31, 1991
    - 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
      - *C*alcinosis, *R*aynaud's Phenomenon, *E*sophageal dysmotility, *S*clerodactyly, *T*elangiectasias
- 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

	Cases	Controls
Number	660	2,227
Age at interview	56.3	51.4
Age at diagnosis	49.5	n/a
White	86.8 %	89.5 %
Current smoker	14.9 %	23.5 %
High school graduate	84.2 %	85.2 %

TCE Exposure

	Cases		Controls	
	No.	Total	No.	Total
Any TCE reported	8	606	15	2,138
OR (95% CI)		2.0 (0.8 – 4.8)		
Conf. by expert review	4	606	8	2,137
OR (95% CI)		1.9 (0.6 – 6.6)		

TCA Exposure

	Cases		Controls	
	No.	Total	No.	Total
Any TCA reported	9	612	25	2,131
OR (95% CI)		1.5 (0.7 – 3.2)		
Conf. by expert review	4	611	17	2,131
OR (95% CI)		0.9 (0.3 – 2.8)		

Perc Exposure

	Cases		Controls	
	No.	Total	No.	Total
Any Perc reported	7	616	21	2,146
OR (95% CI)		1.4 (0.6 – 3.4)		
Conf. by expert review	5	616	17	2,146
OR (95% CI)		1.1 (0.4 – 2.9)		

Jobs & Hobbies with Potential TCE Exposure

	Cases	Ctrls	OR	95% CI
Professional cleaning or maintenance	42	116	1.8	1.3 – 2.7
Plastics industry	17	52	1.3	0.7 – 2.3
Rubber product manufacturing	3	14	0.9	0.3 – 3.3

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

TCE & UCTD

	Cases		Controls	
	No.	Total	No.	Total
Any TCE reported	1	189	15	2,015
OR (95% CI)	0.8 (0.1 – 7.0)			
Conf. by expert review	1	189	8	2,014
OR (95% CI)	1.7 (0.2 – 14.9)			

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, et al. *Am J Epidemiol* 2003;157:493
- Lacey JV Jr, et al. *Am J Epidemiol* 1999;149:671
- Garabrant DH & Dumas C. *Arthritis Res* 2000;2:5