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Scleroderma and Solvent Exposure among Women

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Exposure to solvents has been reported to increase the risk of scleroderma. The authors investigated the relation between exposures to solvents in occupational and hobby settings and the development of scleroderma among women in a case-control study with population-based controls in Michigan (1980–1991) and Ohio (1980–1992). A total of 660 cases and 2,227 frequency-matched controls were interviewed by telephone. Diagnoses of scleroderma were verified by medical records review. Paint thinners and removers were significantly associated with scleroderma both by self-report (odds ratio (OR) = 1.9, 95% confidence interval (CI): 1.4, 2.6) and after expert review (OR = 2.0, 95% CI: 1.5, 2.6). Other petroleum distillates (gasoline and mineral spirits) were not significantly associated with scleroderma after controlling for other correlated exposures in multivariable analyses. Trichloroethylene was associated with scleroderma both by self-report (OR = 2.0, 95% CI: 0.8, 4.8) and after expert review (OR = 1.9, 95% CI: 0.6, 6.6), but not significantly. Analyses by duration of exposure found that risk increased with the duration of use of any of the solvents (OR = 1.01/year of exposure, 95% CI: 1.01, 1.02), but there was no evidence of increasing risk with increasing duration of exposure for any specific solvent studied. In summary, exposures to paint thinners and removers were associated with scleroderma in women but showed no evidence of increasing risk with increasing duration. Exposures to other specific chlorinated and nonchlorinated hydrocarbon solvents were not clearly associated with scleroderma.

occupational exposure; scleroderma, systemic; solvents; tetrachloroethylene; trichloroethanes; trichloroethylene

Abbreviations: CI, confidence interval; OR, odds ratio.

Solvents, chemicals, and occupational exposures have been associated with scleroderma (systemic sclerosis) and scleroderma-like illnesses in a number of studies, but many of these have been case series, investigations lacking appropriate referent groups, or studies having limited information on the timing of exposure and the onset of disease (1, 2). Case-control studies have reported that systemic sclerosis is associated with occupational exposure to chlorinated and nonchlorinated solvents, dry cleaning, and aircraft industry work involving solvent exposure (3–6). Case reports have noted systemic sclerosis and systemic sclerosis-like illness in employees who work closely with benzene, toluene, xylene, aliphatic hydrocarbons, and epoxy resins (7–10), as well as chlorinated aliphatic solvents such as perchloroethylene, trichloroethylene (TCE), and 1,1,1-trichloroethane (TCA) (8, 10, 11). Vinyl chloride, the monomer from which polyvinyl chloride plastic is made, is an established cause of scleroderma-like illness among men in the vinyl chloride polymerization industry (12–14). Much of the concern about the risks of scleroderma related to chlorinated solvent exposures is based on structural similarities between vinyl chloride and chlorinated aliphatic solvents, such as trichloroethylene and perchloroethylene.

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A case-control study of scleroderma and undifferentiated connective tissue disease was conducted to investigate multiple potential risk factors for these rheumatic diseases (15–17). The study offered the opportunity to assemble a large group of women with systemic sclerosis from a defined geographic area in which cases were confirmed by medical records, and controls were representative of the population from which the cases arose. The analysis presented here considers the hypothesis that specific solvents are implicated in the causation of scleroderma in women.

MATERIALS AND METHODS

Study sample

Women diagnosed with systemic sclerosis between January 1, 1980, and December 31, 1991, in Michigan or December 31, 1992, in Ohio who were at least 18 years of age at the time of diagnosis were considered eligible. Cases were identified from several potentially overlapping sources: 1) a national hospital discharge code database (Health Care Investment Analysts, Inc., Ann Arbor, Michigan), 2) databases from University of Michigan hospitals (Ann Arbor, Michigan) and Wayne State University-affiliated hospitals (Detroit, Michigan), 3) a mailing list of all rheumatologists in Michigan and Ohio and of other relevant specialists in Ohio (dermatology, gastroenterology, internal medicine, family practice, general practice, and obstetrics and gynecology), and 4) the mailing list of the Southeast Michigan Chapter of the United Scleroderma Foundation. The methods of case recruitment have been described elsewhere (15, 16). Briefly, the Health Care Investment Analysts, Inc., database identified all women in the study area who had been diagnostically coded or discharged with scleroderma (*International Classification of Diseases*, Ninth Revision, Clinical Modification, code 710.1); the hospitals, rheumatologists, and other physicians identified all of their female patients treated for scleroderma or scleroderma-like conditions during the study period; and all members of the United Scleroderma Foundation, a support group for patients and their families, were asked to participate. After adjusting for patients identified from multiple sources, the response rate among eligible patients to mailings was estimated to be between 75 percent and 80 percent (an exact value was unknown because eligibility usually could not be determined prior to obtaining informed consent). Ninety percent of the potentially eligible women who returned consent forms agreed to participate.

Cases were asked to identify all locales at which they were treated, including both primary care and specialty care settings. The medical records of each consenting case were reviewed by a study rheumatologist to confirm the diagnosis of systemic sclerosis and to determine eligibility. The date of diagnosis was taken to be the date on which systemic sclerosis was first mentioned as a possible diagnosis by the attending physician. Subjects were considered eligible if they met the 1980 American College of Rheumatology classification criteria for systemic sclerosis (18) or exhibited signs and symptoms characteristic of systemic sclerosis (sclerodactyly or thick, tight skin over the fingers and at least one other manifestation among calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) and did not meet the criteria for other defined connective tissue diseases. Patients with linear or localized scleroderma (morphea) were excluded.

We estimated that we identified more than 80 percent of the incident cases in Michigan between 1985 and 1991 on the basis of the number of additional cases identified by a subsequent comprehensive study of prevalent and incident cases in the Detroit tricounty area between 1989 and 1991. A capture-recapture analysis that estimated completeness of ascertainment based on the overlap of the cases identified from different sources yielded an estimated capture proportion of 81 percent.

Control selection, questionnaire administration, and exposure classification

A total of 2,255 female controls were identified by the University of Michigan Institute for Social Research using random digit dialing telephone sampling (19). Controls were frequency matched to the systemic sclerosis cases by race, age (in 5-year intervals), and geographic region. The interview response rate (the proportion of completed interviews in homes in which an eligible woman was identified) was 80 percent in Michigan and 74 percent in Ohio. A 30-minute questionnaire was administered by telephone to all eligible, consenting cases and controls between August 1992 and February 1996. Although all controls were self-respondents, proxy respondents were required for 67 cases that were deceased. Sixteen controls were excluded from the data analysis because they did not report their date of birth, and 12 were excluded because they reported a diagnosis of systemic sclerosis, leaving 2,227 controls in the study.

Women were asked whether they had ever worked at least once a week for 3 months or more in any of 16 jobs or hobbies that commonly involve solvents that have been reported previously to be associated with systemic sclerosis. Each woman who reported ever participating in these activities was then asked the years in which she first and last participated, her job title, the specific tasks involved, the name of the place where she worked, and the type of industry or business. Each woman who had participated in these activities was also asked whether she worked with any of nine specific solvents or categories of solvents, the years in which she first and last used those solvents, whether she had worked directly with or near the solvent, and whether she had worn protective equipment (gloves, masks, clothing, and so on) while working with the solvent. All women were also asked whether they had used any of the nine specific solvents or categories of solvents in any activities other than the 16 jobs or hobbies, and the same detailed additional information was obtained for each reported use. In addition, all women were asked whether they had used any other solvents once a week for 3 months or more. For the purposes of this study, solvents were defined as liquids that are not mixed with water and that are used for their solvating properties. This definition excluded all aqueous solvent mixtures, such as ammonia-based cleaning agents, window cleaners, citrus oil-based cleaners, and so on. Exposures to specific solvents and

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categories of solvents were assessed both by self-report and by expert review to address misclassification of self-reported exposures (20, 21).

For each reported exposure to a solvent, an expert (D. H. G.) in retrospective exposure assessment reviewed the detailed descriptions to verify exposure, blinded to case or control status. Reference materials describing typical processes and materials used in these activities were reviewed to determine the types of solvents that are used in these tasks, the exposure levels associated with specific tasks, and the historical period in which specific solvents were used for specific tasks. A self-reported exposure was confirmed when 1) the solvent was commercially or industrially available during the period of reported use, 2) documentation existed that the solvent was used (or was a suitable substitute for solvents typically used) for the activity or purpose, and 3) exposure was of nontrivial frequency, intensity, and duration. A self-reported exposure was not confirmed when exposure was considered implausible or when exposure was of trivial frequency, intensity, or duration.

Statistical analysis

The average age of the cases at diagnosis was 2 years younger than the age of the controls at interview. This difference was of concern because of the possibility that controls' exposures during this 2-year period would be considered in the analyses, whereas cases' exposures after the date of diagnosis would not be considered. In order to preclude any bias resulting from this difference, a stratum was created for each case, and controls were matched post hoc on the year of birth. Within each stratum, each subject's exposure was considered up to the date of diagnosis of the case on whom the stratum was based; exposures of cases and controls after that point were excluded from the analyses (22). For each potential risk factor, conditional logistic regression calculations were performed, adjusted for the matching factors (23). Because many cases had the same year of birth, controls were eligible for inclusion in multiple strata. To adjust for this repeated use of controls, we calculated variance estimates using the method of Barlow (24). For each control included in more than one stratum, exposure was evaluated in each stratum using the date of diagnosis of the case in that stratum as the cutoff date for exposure.

For solvents to which either no cases or no controls were exposed, conditional logistic regression calculations could not be performed. In these instances, odds ratios were calculated using standard categorical methods for case-control studies (23), and exact confidence intervals were calculated using StatXact 3 for Windows (Cytel Software Corporation, Cambridge, Massachusetts). All other analyses were completed using the SAS statistical package (25). After expert review, the date of exposure was not known for 13 cases (15 solvent exposures) and 45 controls (52 solvent exposures). In these instances, these subjects were assigned the median age at exposure of all cases and controls, respectively, within each exposure category, and the regressions were repeated with and without these subjects. Insofar as the results did not appreciably differ, these observations were excluded from the analyses.

RESULTS

Overall, 660 eligible scleroderma cases diagnosed between 1980 and 1992, inclusive, and 2,227 controls were included in the analyses (table 1). Race/ethnicity, education, and marital status were similar among cases and controls, as were the frequencies of ever smoking cigarettes and consuming alcohol. Current cigarette smoking was significantly more common among the controls (23.5 percent) than among the cases (14.9 percent), which may have reflected cessation of smoking among cases after the onset of symptoms. Annual household income was significantly higher among controls, likely because of the negative impact of chronic disease on the economic status of the cases.

Paint thinners and removers were the most common exposures reported by both cases and controls (table 2). They were associated with systemic sclerosis both by self-report (odds ratio (OR) = 1.9, 95 percent confidence interval (CI): 1.4, 2.6) and after expert review (OR = 2.0, 95 percent CI: 0.5, 2.6). Self-reported exposure to mineral spirits, white spirits, or naphtha was associated with systemic sclerosis (OR = 1.5, 95 percent CI: 1.1, 2.0), but this association was not confirmed by expert review (OR = 1.2, 95 percent CI: 0.9, 1.8). Self-reported exposure to gasoline was associated with systemic sclerosis (OR = 1.8, 95 percent CI: 1.1, 3.1), but this association was not confirmed by expert review (OR = 1.3, 95 percent CI: 0.7, 2.6) because a number of the self-reported gasoline exposures were felt to be of trivial intensity and frequency (such as fueling automobiles for personal use).

None of the other specific solvents (xylene, benzene, trichloroethylene, perchloroethylene, or trichloroethane) was clearly associated with systemic sclerosis either by self-reported exposure or after expert review. The findings for trichloroethylene are of most interest because of previous reports that have associated this solvent with systemic sclerosis (4, 11, 26, 27). Although trichloroethylene use was associated with systemic sclerosis by self-report (OR = 2.0, 95 percent CI: 0.8, 4.8) and after expert review (OR = 1.9, 95 percent CI: 0.6, 6.6), neither of these associations was statistically significant. Insofar as the number of subjects exposed to this solvent was small and the study had low power to find a significant association, these findings suggest that trichloroethylene exposure may be associated with systemic sclerosis.

The category "other solvents" (which included all other solvents reported by the subjects that were not queried by name) was associated with systemic sclerosis by self-report (OR = 2.6, 95 percent CI: 1.9, 3.7) and after expert review (OR = 2.0, 95 percent CI: 1.3, 3.1). There was no single agent identified within this category that explained this association. It is noteworthy that expert review failed to confirm 46 percent of the self-reported exposures among cases and 38 percent among controls, because exposures were felt to be implausible or infrequent or to involve materials that did not meet the definition of solvents used in this study. Thus, an appreciable amount of overreporting of solvent exposure occurred among both cases and controls, and overreporting was slightly more common among the cases. When all reported solvent exposures (including those listed by name and the category "other solvents") were combined into a single exposure category, exposure to any of these solvents

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TABLE 1. Demographic characteristics, smoking history, and alcohol consumption among 660 systemic sclerosis cases and 2,227 controls, Michigan (1980–1991) and Ohio (1980–1992)

	Cases		Controls		Chi-square *p* value
	No.*	%	No.*	%	
White	573	86.8	1,992	89.5	
Black	76	11.5	212	9.5	
Hispanic	11	1.7	23	1.0	0.13
Annual income† at least $15,000	447	75.4	1,634	81.7	0.001
High school graduate	552	84.2	1,892	85.2	0.53
Ever married	603	98.4	2,089	99.2	0.07
Mean age‡ at interview	56.3		51.4		<0.00001§
Mean age‡ at diagnosis	49.5		N/A¶		
Ever smoked	336	51.1	1,134	51.1	0.98
Current smoker	98	14.9	522	23.5	0.001
Pack-a-day smoker	168	25.8	573	25.7	0.92
Mean age‡ started smoking	19.7		19.8		0.95§
Ever drank at least 12 drinks/year	407	61.9	1,364	61.3	0.79
Average consumption per week					
1 drink	158	55.6	597	55.5	
2–3 drinks	53	18.7	239	22.2	
4–6 drinks	30	10.6	120	11.2	
7 or more drinks	43	15.1	120	11.2	0.22

* Excludes responses of "don't know" and "refused."
† Household income in year prior to telephone interview.
‡ Age in years.
§ *t*-test *p* value.
¶ N/A, not applicable

was associated with systemic sclerosis by self-report (OR = 2.1, 95 percent CI: 1.7, 2.6) and after expert review (OR = 2.0, 95 percent CI: 1.5, 2.5). Overreporting was again evident, but it did not explain this association. However, it should be noted that cases may have spontaneously recalled more exposures than controls and that the expert review served only to confirm the plausibility of these exposures. Thus, recall bias may have contributed to this association in spite of the expert review.

The issue of correlated exposures has direct relevance to the interpretation of the exposures in this study, because the solvent exposures reported by the subjects are not mutually exclusive and in many instances reflect overlapping sets of chemical constituents. Consequently, the analyses of exposures in this study examined combinations of exposures in order to determine which combinations of solvent exposures had the greatest explanatory value for systemic sclerosis risk, and which solvents showed no association with systemic sclerosis after controlling for other solvent exposures. A series of hierarchic models was constructed that included each of the solvents alone, then each combination of two solvents, then combinations of three solvents, and then combinations of four solvents. This was done to determine the best-fitting model, using the likelihood ratio test to determine whether each more complex model was appreciably better than the previous simpler model. These models indicated that the best model included only paint thinners and removers and "other" solvents. The addition to the model of any additional solvent alone or in combination resulted in a model that had less predictive ability. In the best-fitting model, the odds ratio for paint thinners and removers was 1.9 (95 percent CI: 1.4, 2.6), and the odds ratio for "other" solvents was 1.8 (95 percent CI: 1.1, 2.9). These models also indicated that, once paint thinners and removers and "other" solvents were included in any model, no additional solvent was significantly associated with systemic sclerosis. Of interest, these models also indicated that exposures to mineral spirits and paint thinners or removers were correlated, and that mineral spirits were not independently associated with systemic sclerosis after controlling for paint thinners or removers. Similarly, self-reported exposure to gasoline was not associated with systemic sclerosis after controlling for paint thinners or removers.

Because the above analyses indicated that exposure to paint thinners and removers was associated with systemic sclerosis, we examined how risk changed with increasing duration of exposure and with latency since first exposure. There was no evidence of increasing risk of systemic sclerosis with increasing duration of exposure to paint thinners or removers (OR = 0.99 per year of exposure, 95 percent CI: 0.98, 0.99) or for any of the other specific solvents studied. The only finding of increasing risk with increasing years of

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TABLE 2. Self-reported and expert-reviewed exposure to solvents among 660 systemic sclerosis cases and 2,227 controls, Michigan (1980–1991) and Ohio (1980–1992)

	Cases (no.)		Controls (no.)		OR*,†	95% CI*
	Exposed	Total‡	Exposed	Total‡		
Hydrocarbons						
Paint thinners and removers	84	639	199	2,182	1.9	1.4, 2.6
Confirmed by expert review	78	638	180	2,181	2.0	0.5, 2.6
Mineral spirits, naphtha, or white spirits	58	629	174	2,161	1.5	1.1, 2.0
Confirmed by expert review	44	628	152	2,160	1.2	0.9, 1.8
Gasoline	22	648	56	2,194	1.8	1.1, 3.1
Confirmed by expert review	12	648	43	2,193	1.3	0.7, 2.6
Toluene	9	622	25	2,153	1.7	0.8, 3.8
Confirmed by expert review	7	620	17	2,153	1.7	0.7, 4.1
Xylene	5	621	14	2,157	1.5	0.5, 4.2
Confirmed by expert review	4	621	8	2,156	1.9	0.6, 6.3
Benzene	13	625	35	2,160	1.5	0.8, 2.9
Confirmed by expert review	3	623	14	2,158	0.8	0.2, 2.6
Chlorinated solvents						
Trichloroethylene	8	606	15	2,138	2.0	0.8, 4.8
Confirmed by expert review	4	606	8	2,137	1.9	0.6, 6.6
Perchloroethylene	7	616	21	2,146	1.4	0.6, 3.4
Confirmed by expert review	5	616	17	2,146	1.1	0.4, 2.9
Trichloroethane	9	612	25	2,131	1.5	0.7, 3.2
Confirmed by expert review	4	611	17	2,131	0.9	0.3, 2.8
Other solvents	60	643	124	2,176	2.6	1.9, 3.7
Confirmed by expert review	33	642	80	2,176	2.0	1.3, 3.1
Any of the above solvents	157	623	384	2,129	2.1	1.7, 2.6
Confirmed by expert review	124	611	311	2,106	2.0	1.5, 2.5

* OR, odds ratio; CI, confidence interval.
† Adjusted for age and year of birth.
‡ Excludes responses of "don't know" and "refused."

exposure was for the duration of exposure to "any of the solvents" (OR = 1.01 per year of exposure, 95 percent CI: 1.01, 1.02). However, our analyses assumed continuous exposure between the dates of first and last exposure, and this assumption may be incorrect in some instances. As a result, conclusions regarding dose-response should be made cautiously. Analyses of risk in relation to latency (the elapsed time from first exposure to the date of diagnosis of each case) showed that risk increased by 2 percent for every 1-year increase in latency since first use of paint thinners and removers (OR = 1.02, 95 percent CI: 1.01, 1.04). There were no significant findings for latency since first exposure for any of the other solvents.

Our study recorded the anti-Scl-70 antibody status of 255 cases for whom it was available in the medical records. Anti-Scl-70 antibody status was not known for the remaining 405 cases or any of the 2,227 controls. Associations between solvent exposure and systemic sclerosis were examined according to anti-Scl-70 status. These analyses were based on the assumption that all controls were anti-Scl-70 negative. This assumption was justified because anti-Scl-70 antibody (also known as anti-topoisomerase I) is highly disease specific for systemic sclerosis (28) with estimated prevalences of 26 percent in scleroderma and 34 percent in diffuse systemic sclerosis. There was no significant difference in the odds ratio for any solvent exposure between cases who were anti-Scl-70 positive and those who were anti-Scl-70 negative. Specifically, for paint thinners and removers, the odds ratio was 2.3 (95 percent CI: 0.8, 6.3) among anti-Scl-70-positive cases and was 2.0 (95 percent CI: 1.3, 3.1) among anti-Scl-70-negative cases. For trichloroethylene (which has been reported previously to be strongly associated with systemic sclerosis among anti-Scl-70-positive cases (4)), our study found no cases who were anti-Scl-70 positive (odds ratio inestimable) and three cases who were anti-Scl-70 negative (OR = 3.4, 95 percent CI: 0.9, 13.7). These results suggest that the presence of anti-Scl-70 antibodies does not increase the effect of solvent exposure on systemic sclerosis risk.

Of the 16 self-reported job categories specifically investigated (table 3), three showed significantly increased risks: medical diagnostic or pathology laboratory jobs (OR = 2.1,

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TABLE 3. Self-reported jobs and hobbies with potential exposure to solvents among 660 systemic sclerosis cases and 2,227 controls, Michigan (1980–1991) and Ohio (1980–1992)

	Cases (no.)		Controls (no.)		OR*,†	95% CI*
	Exposed	Total‡	Exposed	Total‡		
Medical diagnostic or pathology laboratory	17	657	40	2,224	2.1	1.2, 3.8
Professional cleaning or maintenance	42	653	116	2,221	1.8	1.3, 2.7
Film developing or publishing	38	657	106	2,220	1.6	1.1, 2.4
Perfume, cosmetic, or drug manufacturing	3	659	5	2,226	1.5	1.0, 2.4
Fiberglass industry	6	658	15	2,225	1.9	0.7, 4.9
Leather tanning or shoe manufacturing	4	659	7	2,225	1.7	0.5, 5.9
Dry cleaning	31	657	83	2,221	1.4	0.9, 2.2
Chemical or dye manufacturing	2	658	6	2,225	1.3	0.2, 7.4
Plastics industry	17	658	52	2,221	1.3	0.7, 2.3
Hair dressing	26	659	65	2,226	1.2	0.5, 2.7
Rubber product manufacturing	3	657	14	2,226	0.9	0.3, 3.3
Arts and crafts using glues, paints, or solvents	8	656	41	2,221	0.9	0.4, 2.0
Painting or paint manufacturing	4	659	23	2,222	0.8	0.3, 2.2
Furniture refinishing	0	657	4	2,226	0.0	0.0, 5.1§
Petroleum refining	0	659	2	2,226	0.0	0.0, 18.0§
Vinyl chloride manufacturing	0	659	1	2,224	0.0	0.0, 131.6§
Any of the above activities	168	644	471	2,212	1.7	1.4, 2.0

* OR, odds ratio; CI, confidence interval.
† Adjusted for age and year of birth.
‡ Excludes responses of "don't know" and "refused."
§ Crude odds ratio with exact confidence interval.

95 percent CI: 1.2, 3.8), professional cleaning and maintenance jobs (OR = 1.8, 95 percent CI: 1.3, 2.7), and film developing and publishing (OR = 1.6, 95 percent CI: 1.1, 2.4). Expert review of those jobs in which solvent exposure was reported revealed that many of the women did not use or have exposure to solvents. For example, many of the women who reported professional cleaning or maintenance jobs worked in residential house cleaning and reported using only water-soluble cleaning products. Women in medical diagnostic and pathology laboratories frequently reported tasks such as phlebotomy, centrifugation, and cell counting, which typically do not involve solvents other than isopropanol. Many of the women who reported jobs in film developing were medical x-ray technicians who did not handle solvents. Thus, although these job categories were associated with systemic sclerosis, the descriptions of the job tasks in many of these jobs did not confirm the use of, or exposure to, solvents. When all 16 job categories were combined, work in these jobs was more common among the cases than among controls (OR = 1.7, 95 percent CI: 1.4, 2.0).

Insofar as there were 67 proxy-interviewed cases and no proxy-interviewed controls, we were concerned whether the results were influenced by the proxy interviews. Reanalyses of the data after excluding the proxy-interviewed cases showed that in every instance adjusted odds ratios for the expert-confirmed exposures changed by less than 10 percent, and that there was no change in statistical significance.

DISCUSSION

These results indicate that exposure to paint thinners and removers is associated with systemic sclerosis and that risk increased with increasing latency since first exposure. However, there was no evidence of increasing risk with increasing duration of exposure. No other solvent that could be identified by the subjects was clearly associated with systemic sclerosis once paint thinners and removers were taken into account.

The mechanisms by which solvents might increase the risk of systemic sclerosis are not known. Solvent overexposure has also been implicated in Goodpasture's syndrome and is believed to play a role in the formation of autoantibodies to alveolar basement membrane (29) and glomerular basement membrane (30, 31). Nietert et al. (4) found that the association between systemic sclerosis and solvent exposure was significantly stronger in men and women who were anti-Scl-70 autoantibody positive, suggesting that certain human lymphocyte antigen genotypes may facilitate susceptibility to the effects of solvents. Our study did not confirm their finding.

Assessing solvent exposures is complex because specific solvents are often mixed in commercial products, multiple names are used for similar products, and brand names and chemical names are often used interchangeably. For example, the term "paint thinner" typically refers to a petroleum distillate defined by boiling range (150–200°C) (32), while Stod-

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dard solvent, mineral spirits, naphtha, and white spirits are petroleum distillates that boil between 95°C and 210°C, and these materials are also commonly used as paint thinners. However, the term "paint thinner" almost invariably refers to petroleum distillates that do not contain chlorinated solvents. Paint removers are more varied in composition than paint thinners and may contain methanol, acetone, toluene, 1,1,1-trichloroethane, methylene chloride, petroleum distillates, phenols, cresols, detergents, and concentrated alkali (e.g., sodium hydroxide) (33–37). Thus, the finding that work with paint thinners and paint removers is associated with systemic sclerosis does not allow the specific chemical agents to be identified. It is of concern that a growing body of evidence implicates solvents in the etiology of systemic sclerosis (3–9, 11, 26, 27, 38–45) but that no specific chemical agent has emerged consistently. Overall, this suggests either that the mechanisms are related to a common physiologic effect shared by many solvents, or that the recollection of distant past exposures to solvents is too nonspecific to identify specific causative agents. The latter seems more likely insofar as the solvents that have been implicated in previous reports have little in common with respect to toxicity.

Most of the women who reported exposure to chlorinated hydrocarbon solvents reported these exposures in the dry cleaning industry. Dry cleaning is typically based on perchloroethylene, while trichloroethylene, 1,1,1-trichloroethane, and mineral spirits have been used less commonly, and various chlorinated and nonchlorinated solvents have been used to remove spots and stains at the service counter (46). In our study, neither dry cleaning nor any of the specific chlorinated solvents showed clear evidence of an association with systemic sclerosis either by self-report or after expert review. Although case reports of systemic sclerosis have suggested an association with trichloroethylene (3, 26, 27, 40), only one epidemiologic study (4) has confirmed these reports.

The observation that trichloroethylene was associated with a twofold risk of systemic sclerosis (by self-report and after expert review) could be due to chance, but we cannot exclude the possibility of a true association that is constrained by the small numbers of exposed subjects (less than 1 percent). If this latter interpretation is correct, it indicates that trichloroethylene would account for a small proportion of systemic sclerosis cases. Overall, our study, which is the largest investigation to date of systemic sclerosis and solvent exposures, does not provide clear evidence that trichloroethylene or any other chlorinated hydrocarbon solvent is a risk factor for systemic sclerosis. The findings regarding gasoline are also of interest because of its widespread use. The association between self-reported exposures to gasoline and systemic sclerosis was not confirmed after expert review and appeared to be due to correlation with other exposures. Thus, there was no convincing evidence that gasoline exposure is a risk factor for systemic sclerosis in women.

Workers employed in medical diagnostic or pathology laboratories, professional cleaning and maintenance, and film developing or publishing were significantly associated with systemic sclerosis. Although there is potential solvent exposure in professional cleaning and maintenance and in medical diagnostic or pathology laboratories, expert review of the job descriptions and tasks indicated that most of the subjects (both cases and controls) reported trivial exposure to solvents. The associations between specific occupations and systemic sclerosis should be interpreted cautiously insofar as these associations were not explained by solvent use.

This study relied on both self-reported exposure and expert reviews. Although the reliability of expert ratings in some studies is quite good (21), expert ratings are limited by the inability to recognize unorthodox chemical uses and "bystander exposures" that result from chemical use by nearby workers. Because our data were based on self-reports and we had no knowledge of exposures that were not reported by the subjects, underreporting of exposures may have occurred when subjects failed to recognize or recall exposures. The expert review also indicated that overreporting occurred, although it was nondifferential between cases and controls.

Selection bias and nonrepresentative sampling of the cases are a concern in studies of systemic sclerosis because of the possibility that milder cases would be less likely to seek medical care than more serious cases. However, we recruited cases from multiple sources throughout two states, including both hospitals and outpatient settings, and no differences in consent rates by age group or disease severity were observed. The degree of participation was investigated by examining the consent rates at the University of Michigan hospitals and Wayne State University hospitals, where the investigators were granted expanded access to medical records. Of the 202 eligible cases, 86 percent agreed to participate. Living cases had higher consent rates (89 percent) than family members of deceased subjects (71 percent), which was unlikely to have biased the results unless an exposure caused a particularly fulminant form of the disease. Finally, the study hypotheses were not mentioned to the participants, and there is little common knowledge that solvent exposures have been reported to be associated with systemic sclerosis.

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