Review

Epidemiology of organic solvents and connective tissue disease

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Abstract

Case reports suggest that solvents are associated with various connective tissue diseases (systemic sclerosis, scleroderma, undifferentiated connective tissue disease, systemic lupus erythematosis, and rheumatoid arthritis), particularly systemic sclerosis. A small number of epidemiological studies have shown statistically significant but weak associations between solvent exposure, systemic sclerosis, and undifferentiated connective tissue disease. However, the interpretation of these positive findings is tempered by a lack of replication, an inability to specify which solvents convey risk, and an absence of increasing risk with increasing exposure. Existing studies, on aggregate, do not show conclusively that solvents (either as a group of chemicals or individual chemicals) are causally associated with any connective tissue disease. Further investigations should be carried out to replicate the positive existing findings and to specify the solvents and circumstances of exposure that carry risk.

Keywords: occupation, petroleum distillates, scleroderma, solvents, systemic sclerosis

Introduction

Since the first case reports of systemic sclerosis (SSc) associated with solvent use in 1957 [1,2] dozens of cases have been reported, and recently scientific studies of the associations between solvent exposure and connective tissue diseases have been published. This paper reviews the epidemiological evidence regarding the associations of solvents with SSc, scleroderma, undifferentiated connective tissue disease (UCTD), systemic lupus erythematosus (SLE), and rheumatoid arthritis.

The precise diagnosis of a number of the connective tissue diseases may be difficult to specify for a number of reasons, all of which pose difficulties for the conduct of epidemiological studies. Clinical features including Raynaud's phenomenon, polyarthritis, interstitial lung disease, pleuritis, pericarditis, and vasculitis can be seen in rheumatoid arthritis, SLE, SSc, polymyositis, dermatomyositis, and Sjögren's syndrome. There is also overlap in the serology associated with these disorders, including antinuclear antibodies, rheumatoid factors, and immunoglobulin G autoantibodies. Signs and symptoms may evolve over a period of years, making it difficult to specify a date of disease onset. It is also possible to have more than one systemic rheumatic disease concurrently. Partial overlap of features of two or more diseases has been

CI = confidence interval; HLA = human leukocyte antigen; OR = odds ratio; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; UCTD = undifferentiated connective tissue disease.

estimated to occur in 15–25% of tertiary referrals. Because of these issues, the identification of cases and the determination of the date of onset of disease for each case often require a detailed review of clinical records and the application of strict criteria in order to ensure the accuracy of data used in epidemiological studies.

Principles of epidemiological study design

The strengths and inherent limitations of each of the two basic epidemiological study types must be considered in order to assess the validity of the epidemiological literature. Cohort studies typically focus on two or more groups of people who are free of disease (in this case, the connective tissue disease under study) and who differ with regard to exposure (solvents). The groups are followed over time and the disease incidence rates for the exposure groups are calculated and compared. Strengths of the cohort design are that exposures are defined and exposure records are commonly maintained before the initiation of the study, and there is relative confidence that the exposure information is reliable. These are critical issues in establishing an association between exposure and disease outcome. Cohort studies typically do not rely on the recollections of individuals' past exposures, which can introduce substantial errors (including both random errors and bias). Even when written records of exposure are available, difficulties can arise in identifying the chemical composition of the exposure and in quantifying the exposure in terms of intensity, frequency, and duration. Reliance on biomarkers in future studies might partly overcome these limitations.

Case–control studies, when correctly designed, are conducted within the source population from which cases are identified. The exposure status of the cases is usually determined by their recollections of past exposures (although written exposure records are used if they exist). Control individuals are selected from the same source population for the purpose of estimating the distribution of exposures in the population from which the cases arose. In order to achieve this, control individuals must be selected independently of their exposure status, and their exposure status must be established in the same manner as for the cases. One of the principal limitations of case–control studies pertains to the limited accuracy of individuals' recollections regarding distant past exposures. This is especially problematic when individuals are asked to recall past chemical exposures, because they might not know the names of the chemicals, they might be unable to differentiate between meaningful and trivial exposures, and they might be unaware of exposures that they do not smell or touch. In addition, cases may be biased toward reporting exposures that they think may have contributed to their illness, whereas control individuals have no comparable motivation. This bias may create an apparent association between exposure and disease. These issues are of concern in many of the published studies on solvents and connective tissue diseases, and they affect the reliability of the findings of those studies. Investigators often take steps to increase the reliability of exposure information. These steps include inferring exposures based on the individuals' descriptions of jobs, hobbies, and chemical use; and having the individuals' recollections reviewed by an expert to judge the reliability of the information based on the expert's knowledge of typical exposure levels in various tasks and industrial processes.

Biomarkers of exposure are available for a number of the common solvents that have been associated with connective tissue diseases. These include measures of urinary phenol excretion (benzene exposure), urinary hippuric acid excretion (toluene exposure), urinary methylhippuric acid (xylene exposure), urinary trichloroethanol and trichloroacetic acid excretion (trichloroethylene and 1,1,1-trichloroethane exposure), and urinary tetrachloroethylene and trichloroacetic acid excretion [tetrachloroethylene (perchloroethylene) exposure]. All of these biomarkers must be measured during exposure or within 24 h of the end of exposure in order to be meaningful. This requirement limits their utility in epidemiological studies of connective tissue disease in which the onset of the disease is rarely in a close temporal relationship with solvent exposure. Historic databases of solvent biomarkers would be of great value to epidemiological studies, but few exist and none have yet been used in the published epidemiological studies. Nonetheless, biomarkers potentially offer great advantages in the assessment of individual exposures if they are available during the period of exposure for individuals whose connective tissue disease risks are subsequently investigated.

Case reports form much of the literature on solvents and connective tissue disease, and these reports should not be confused with case–control studies. Case reports are descriptions of patients who have the disease of interest and who have had exposure to various factors (such as solvents) that the author believes are sufficiently unusual that they merit a report. These reports play the important role of suggesting new hypotheses and associations that may deserve further scientific inquiry. Case reports often provide no evidence that the reported associations are causal. This is because the authors have no systematic knowledge of whether the cases they have seen are more likely to have been exposed than are people without the disease, or whether the cases they have seen represent a biased sample of the source population. When case reports provide evidence of an appropriate temporal association of the exposure with the syndrome, lack of alternative causes, positive dechallenge and positive rechallenge, dose response, and specificity of exposure and response, they can support a causal interpretation. In the absence of such rigorous evidence, however, these reports should be

Table 1

Typical uses, upper range of reported exposure levels, and recommended exposure limits for solvents reported to be associated with connective tissue diseases

Solvent	Typical industrial uses	Exposure levels (mg/m^3)	ACGIH TLV: 8 h TWA (mg/m^3)
Benzene	Petroleum refining product; a component of gasoline [83]	0.1–27.2	1.6
Toluene	Tire vulcanization	5.66	188
	Leather finishing	735	
	Hospital laboratory	47.5	
	General manufacturing [84]	452	
Xylene	Hospital laboratory	1700	434
	General manufacturing [84]	61	
Trichloroethane	Nonflammable cold cleaning solvent; used alone or blended [4]	Not typically used in consumer products	1910
Trichloroethylene	Nonflammable liquid that dissolves fats, greases, tars, and waxes; used for cold cleaning [4].		269
	Degreasing [85]	4833	
	Also used in typographic correction fluids [86]		
Perchloroethylene	Nonflammable liquid used in cold cleaning where slow evaporation is desired [4]		170
	Degreasing	12 204	
	Dry cleaning [85]	3899	
VM & P naphtha	Paint thinner with a boiling point range of 100–160°C [3]		1370
Mineral spirits (Stoddard solvent)	Moderate flammability solvent with a boiling point range of 149–205°C; dissolves oil and grease [4] Commonly used in dry cleaning and as a paint thinner		525

ACGIH, American Conference of Governmental Industrial Hygienists; TLV, threshold limit value; TWA, time weighted average; VM & P, varnish maker's and painter's.

viewed as providing new ideas that deserve investigation, but not as providing any scientific evidence of causal associations.

Common solvents and their uses

The determination of the solvents to which an individual has been exposed is critical to the reliability of epidemiological studies. It is often difficult to infer correctly the exact agent, not only because of the limits of the individual's knowledge, but also because the common uses for solvents often do not require a specific chemical, but rather only require chemical properties that can be satisfied by a number of chemicals or mixtures. Although numerous chemicals have solvating properties, only certain chemicals are thought of as solvents because of their widespread use for this purpose. Solvents that mix freely with water are polar (ketones and alcohols, for example). The solvents most often reported to be associated with connective tissue disease are nonpolar, such as petroleum distillates, trichloroethylene, and perchloroethylene. Some solvents are pure chemical compounds (ie toluene, perchloroethylene etc). On the other hand, many applications do not require high purity chemicals, and therefore less expensive mixtures are commonly used, such as paint thinner (a petroleum distillate with a range of boiling points). Varnish maker's and painter's naphtha is a mixture of paraffins, cycloparaffins, olefins, and aromatic hydrocarbons with a boiling point range of 100–160°C [3]. Stoddard solvent (mineral spirits) is a moderately flammable mixture with a higher boiling point range of 149–205°C [4]. The term 'paint thinner' almost invariably refers to petroleum distillates that do not contain chlorinated solvents. In addition, many solvent products are named by their intended use rather than by chemical content, and products having the same common name may contain different ingredients. Paint removers are typically mixtures of solvents with additional ingredients such as alkali (which dissolve polymerized paint resins and waxes). Some contain chlorinated aliphatic solvents such as methylene chloride, whereas many do not.

Solvent exposure levels in various tasks and industry

One of the major limitations of the existing epidemiological studies is the lack of quantitative exposure information on the study subjects. None of the published studies reviewed below is based on measurements of solvent exposures of the study participants, and most are based on crude quali-

tative estimates of whether exposure did or did not exist in the distant past. In putting these studies into context, it is useful to review the uses and typical industrial exposure levels of various solvents (Table 1). Measurements of industrial exposure to solvents vary widely depending upon the type of use or particular facility investigated. Exposures in household settings and hobby uses such as cleaning, furniture restoration, and crafts are even more variable because of the variations in ventilation, the absence of training, the lack of legal regulations, and the idiosyncratic nature of people's work habits in the home.

The exposure levels given in Table 1 represent the upper end of the typical exposures for these agents in various settings, rather than the entire range. Because exposure measurements can range from low as the limit of detection, the actual exposure levels in any setting may range from negligible to the levels contained in Table 1. Some of the reported high exposures are from historic reports, and such exposures would be unlikely to occur at the present time in regulated settings. Table 1 also contains the American Conference of Governmental Industrial Hygienists recommended maximum exposure level over a full 8-h work day for each solvent. These recommendations, which are referred to as threshold limit values for 8-h time weighted average exposures, are airborne concentrations that are believed to be without appreciable health consequences for almost all adults. That these limits are not exceeded is not enforced by any regulatory authority in any country, but they are widely regarded as reasonably safe in many nations.

Systemic sclerosis and scleroderma

SSc is a rare disease that is estimated to affect between 2 and 10 people/million each year in the Western world [5]. Females are more commonly affected than males, with a female : male ratio of between 3 : 1 and 8 : 1, which is more marked in early adulthood and which diminishes later in life [5]. Although reasons for the female predominance are unknown, the higher prevalence of solvent exposure among males than among females suggests that solvent exposure is unlikely to explain a large proportion of female cases. There is no urban–rural difference in incidence [6]. The incidence is slightly higher among blacks than among whites in the USA [7]. Traditionally, it was thought that genetic factors were not major causes of scleroderma. This belief was based on studies of twins that did not show findings that are inconsistent with chance. Also, early immunogenetic studies of human leukocyte antigen (HLA) [5] showed either weak or inconsistent associations that were unable to explain risk. Several recent investigations suggest that genetic factors play a complex role in scleroderma, however.

Englert *et al* [8] investigated familial risk estimation in a retrospective cohort study involving 715 SSc patients and 371 randomly recruited age-matched and sex-matched controls in Australia. They found that the relative risk for SSc in a subsequent first-degree relative was in excess of 11-fold, compared with risk in an initial first-degree family member.

The Choctaw Native Americans in southeastern Oklahoma have the highest prevalence of scleroderma or systemic sclerosis yet found (469/100 000). Tan *et al* [9] studied 25 cases and 77 controls within this population. They found that a particular genetic marker [a 2 cM haplotype on chromosome 15q that contains fibrillin 1 gene (FBN1)] was significantly more frequent in SSc cases than in controls. In a subsequent study that involved 18 cases and 76 controls within this same population, Tan *et al* [10] found another haplotype (an extended HLA-DR2 that includes the class I and III regions) that was also significantly associated with scleroderma.

Fanning *et al* [11] performed genetic studies on 130 SSc cases and 602 cadaveric controls in the UK. They speculated on the possibility of three distinct disease types, based on their finding of three distinct and mutually exclusive antinuclear antibody types that were each correlated with different alleles and disease characteristics.

Further studies of HLA class II genes were carried out by Kuwana *et al* [12] on 105 unrelated Japanese SSc patients and 104 race-matched healthy control individuals. Those authors concluded that particular alleles do not significantly affect the likelihood of developing disease, but they do affect the type of autoantibody produced if disease does develop. The particular type of autoantibody then controls the clinical presentation of the disease. For example, HLA class II alleles DRB1*0101-DQB1*0501-DPB1*0402 result in expression of anticentromere antibody and this results, clinically, in a limited cutaneous variant of the disease.

The role of genetic factors in the development of SSc creates potential complications in terms of epidemiological study design assumptions, if certain genotypes have different disease susceptibilities. Frank *et al* [13] performed a retrospective study with 30 SSc cases exposed to quartz/metal dust, 50 idiopathic cases of SSc, and 314 healthy control individuals, in Germany. Genetic studies indicated that the HLA-DRB1*0301 (DR3) haplotype was very frequent in the quartz/metal dust antitopoisomerase-responding group (ie a susceptibility haplotype), whereas in the idiopathic group this haplotype was infrequent in the antitopoisomerase-responding group (ie a neutral or protective haplotype). Significant confounding effects might have been present in this particular study design, however, because the quartz/metal exposed group consisted of uranium miners (29 out of 30 were men) and the idiopathic group consisted mainly of women (46 out of 50). Future genetically oriented epidemiological studies will be helpful in answering the issues posed by these studies.

The role of environmental exposures has received increasing scrutiny in recent years, in part because crystalline silica (silicon dioxide) [14–20] is an established cause of SSc and vinyl chloride monomer [21,22] causes a syndrome that has many features in common with SSc [23].

There have been a number of reviews of the literature on chemicals and SSc, which contain detailed lists of the agents reported to be associated with SSc. In 1996 Silman and Hochberg [24] reviewed the evidence on environmental causes of scleroderma. They listed many chemical compounds that have been linked to scleroderma in case reports [benzene, bis(4-amino-3methyl-cyclohexyl) methane, dieseline, dimethylbutylphenyldiamine, heptane, metaphenylenediamine, toluene, toluidene, trichloroethane, trichloroethylene, vinyl chloride, xylene, and xylidene]. Haustein and Herrmann [25] reported that trichloroethylene, perchloroethylene, hexachloroethane, hexachlorobenzene, benzene, toluene, naphtha, n-hexane, and diesel oil have been linked to scleroderma. Haustein and Ziegler [23] reported and reviewed cases of scleroderma in patients exposed to trichloroethylene, benzene, toluene, xylene dieseline, and an amine component of epoxy resins [bis(4-amino-3-methylcyclohexyl)methane]. The postulated mechanisms by which trichloroethylene and related compounds may cause SSc include metabolism to epoxy compounds that subsequently bind to proteins, creating autoantigens [24] and solvent-induced [25] endothelial cell injury that leads to microvascular abnormalities and ultimately target organ fibrosis.

Case reports

Case reports concerning the suspected link between scleroderma and solvents have been reported for more than 30 years. Walder [26] reported seven cases in 1965 (linked to toluene, benzene, and white spirits), and five cases in 1981 (linked to toluene, xylene, white spirits, and dieselene). Zachariae *et al* [27] reported that 13 out of 28 men with SSc reported prior exposure to organic solvents. Garcia-Zamalloa *et al* [28] reported a case of SSc following 23 years of employment in a tire factory where there was potential for exposure to toluene, heptane, dimethylbutylphenyldiamine, and octaphenol formaldehyde. Czirjak *et al* [29] reported a case in a woman who was chronically exposed specifically to trichloroethylene in the workplace. Following 3 years of exposure, she developed Raynaud's phenomenon, acrosclerosis, and joint symptoms. This progressed to esophageal involvement after 7 years of exposure, and ultimately to cardiac and renal involvement after 13 years. One case study by Lockey *et al* [30] suggested that scleroderma can occur as the result of a single acute exposure. Those investigators described the case of a 47-year-old woman who received significant dermal exposure to trichloroethylene over a period of 2.5 h. During the next few days she developed fatigue and a pruritic macular rash over the exposed areas. Four months later, she developed symptoms of fatigue, myalgias, arthralgias, dysesthesias of the hands and feet, and some skin tightness in her hands. Over the course of five more months, she developed increased skin tightness, and systemic involvement including her esophagus, kidneys, and lungs. Ten months after the initial exposure she died as a result of pulmonary failure. Autopsy revealed SSc affecting the esophagus, lungs, skin, and kidneys. Three cases were reported by Flindt-Hansen and Isager [31], two of which were thought to be the result of trichloroethylene and trichloroethane exposure during metal cleaning. Those individuals had been exposed for 12 and 14 years. The third case involved trichloroethylene exposure alone, however; that patient was exposed for only 4 years. Chloroform exposure (in a man repairing carburetors for 13 years) has been implicated as a cause for SSc by Tibon-Fisher [32]. After 15 years of regular hand washing with trichloroethane, xylene, trimethylbenzene, and naphthalene in a foundry, a 41-year-old man developed SSc. Czirjak and Szegedi [33] reported that 17 female patients from a population of 61 patients with SSc had been exposed to chemicals. The development of SSc in a 39-year-old man who used trichloroethylene as a degreaser has been reported [34].

Cases of localized skin scleroderma (morphea) have also been reported. A 26-year-old woman occupationally exposed to a variety of solvent vapors (trichloroethylene, tetrachloroethylene, acetone, benzene, isopropyl alcohol, dimethyl phthalate, methoxyethanol, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, xylene, and phenol) for 1 year developed morphea on her arms and ankles [35]. This resolved after 1 year of treatment. A 45-year-old man exposed to 10–25 parts per million perchloroethylene in the workplace for a period of 1 year developed morphea [36]. Yamakage and Ishikawa [37] reported seven cases of morphea in which the potential for occupational exposure to a variety of solvents might have been present.

The large collection of case studies (of which there are many more reported in the literature than are reviewed here) raises hypotheses that SSc and scleroderma may be caused by any of a large number of chemically unrelated agents under circumstances of exposure that may be brief, prolonged, frequent, or infrequent, and may involve skin contact or inhalation, or both. It is unlikely that all of these observations are correct. In order to determine which of them may be correct, epidemiological studies have been undertaken to determine which solvents and which circumstances of exposure are associated with SSc and scleroderma.

Epidemiological studies

There have been a number of case–control studies that have examined the association between various solvents and SSc [14,38–42]. Czirjak *et al* [42] studied 61 patients with SSc and 61 age-matched and sex-matched referents. The cases were derived from clinical practices

in East Hungary, whereas the control individuals were randomly selected from a single Hungarian village. It does not appear that the source population from which the cases arose was the same as that from which the controls were selected. This raises serious concern about the validity of any comparison between the cases and controls. The authors reported the frequency of solvent exposures (benzene, petroleum distillates, isopropanol, ethyl acetate, turpentine, and trichloroethylene) among the cases, but not among the controls. As a result, this paper provides no information on whether solvents are associated with SSc.

Bovenzi *et al* [14,41] reported a case–control study in Trento, Italy, in which 21 cases and 42 control individuals (matched for sex and age) were identified from hospital records. A statistically significant association was found between solvents and SSc [odds ratio (OR) 9.28, 95% confidence interval (CI) 1.08–243.8] on the basis of four exposed cases and one exposed control individual. Three of the four exposed cases were men. The solvents to which the individuals had been exposed were not identified. This study suggests that solvent exposures are associated with SSc in men, but it gives no information on which chemicals or circumstances of exposure convey this risk. It also provides no support for the conclusion that solvents are associated with SSc in women.

Nietert *et al* [38] reported a case–control study of 178 SSc patients who were identified in rheumatology clinics and 200 controls who had osteoarthritis, fibromyalgia, gout, or localized musculoskeletal pain. The control individuals were not a random sample of the source population from which the cases were selected. Subjects were interviewed regarding their past work histories and their past use of chemicals. Each job and industry reported was assigned an exposure score using a job exposure matrix. Because of concern about the unreliability of self-reported exposures, the exposures claimed by the individuals studied were not used in the analyses. Solvents were associated with SSc in men, but not in women. Among men, there were two statistically significant associations: exposure to any solvent (OR 2.9, 95% CI 1.2–7.1) and exposure to trichloroethylene (OR 3.3, 95% CI 1.0–10.3). Other solvents were associated with SSc in men, but not statistically significantly (benzene exposure OR 2.4, 95% CI 0.8–7.1; trichloroethane OR 2.7, 95% CI not given). The authors also found that the association between solvents and SSc was present only among those subjects who tested positive for anti-Scl-70 antibody, suggesting that solvents may bind to topoisomerase I and trigger an autoimmune response in susceptible individuals. This study provides support for the conclusion that solvent exposure is associated with SSc in men (but not women), and that trichloroethylene specifically is associated with SSc.

Silman and Jones [39] conducted a case–control study of male cases in the UK. Fifty-six cases were recruited from patient registries, 41 control individuals were identified from friends of the cases, and 56 control individuals were recruited from among patients of general practitioners who provided care for the cases. Each study participant completed a mailed questionnaire that ascertained a complete work history. An expert occupational hygienist, who was blinded to disease status, reviewed the jobs and assigned an exposure probability. In addition, individuals were asked about exposures to specific solvents with which they had worked extensively. There were nonsignificant associations between solvent exposure and SSc based on general practitioner controls (OR 1.7, 95% CI 0.7–4.1) and based on friend controls (OR 2.3, 95% CI 0.9–6.2). There was no trend of increasing risk with increasing duration of exposure in either analysis. The authors did not identify any of the solvents to which the subjects were exposed. This paper provides no conclusive evidence of an association between solvents and SSc.

Goldman [40] reported on 279 patients from a rheumatology practice in the USA. Thirty-three people with scleroderma were classified as cases and the remaining 246 individuals were classified as controls. The controls were diagnosed with dermatomyositis, polymyositis, rheumatoid arthritis, mixed connective tissue disease, and SLE. There was no attempt to identify controls who were representative of the source population from which the cases arose. Study subjects completed questionnaires regarding their history of exposure to chemicals and their past occupations. There was no attempt made to blind the investigators to disease status. There was a statistically significant association between solvent exposure and SSc (OR 5.8, 95% CI 2.5–13.4). It is unlikely that the controls are representative of the general population from which the cases arose, and it is possible that selection bias may have altered the apparent association between SSc and solvent exposure.

Garabrant *et al* (manuscript submitted for publication) reported on 666 female patients with SSc and 2227 control individuals in Ohio and Michigan in the USA. Controls were drawn from the general population and were frequency-matched with regard to sex, race, age, and geographic region. Individuals were interviewed by telephone regarding possible occupational exposure to solvents and whether they had handled solvents. An expert in exposure assessment, blinded to disease status, reviewed the exposure histories and assigned a probability of exposure. There were statistically significant associations between SSc and paint thinners and removers (OR 1.96, 95% CI 1.46–2.62) and all solvents combined (OR 1.96, 95% CI 1.54–2.49). In addition, there were nonsignificant associations between SSc and trichloroethylene (OR 1.91, 95% CI 0.56–6.56) and xylene (OR 1.92, 95% CI 0.59–6.29).

The self-reported exposures of the individuals were also analyzed and showed similar associations to those based on the expert review. This paper supports the interpretation that there is a weak association between solvent exposure and SSc among women. It contains no information on risk among men. Despite its large size, it did not identify any specific solvent that conveyed risk and the findings were significant only for the least specific solvent products, the identity of which could not be further defined.

Lundberg *et al* [43] carried out a cohort morbidity study of SSc, rheumatoid arthritis, and SLE in 13 counties in Sweden. The cohort included 375 035 men and 140 139 women who had worked for at least 10 years in the same occupation. Of these, 47 males and 24 females had been treated in a hospital for SSc, 896 males and 629 females had been treated in a hospital for rheumatoid arthritis, and 36 males and 57 females had been treated in a hospital for SLE. Exposures were assigned using a job exposure matrix, based on the occupations of the subjects derived from written public records. There was a nonsignificant association between SSc and work with aliphatic hydrocarbons (OR 2.1, 95% CI 0.8–5.5, based on six cases). Other types of solvent exposure, including exposure to gasoline and organic solvents, were ascertained but not reported by the authors (presumably indicating that there were no significant associations). This is an important study because it is population based and it relies entirely on written records rather than the recall of the study subjects. It indicates that there may be a weak association between solvent exposure and SSc, but that chance cannot be excluded as an explanation. This study must be interpreted as providing inconclusive evidence of an association between SSc and solvent exposure.

There have been many cohort mortality studies of solvent-exposed populations, including printers [44–46], dry cleaners [47–50], petroleum refining and gasoline workers [51–71], and painters [72–75]. These studies do not support the conclusion that deaths from SSc or other connective tissue diseases are associated with solvent exposure. It should be emphasized that mortality studies cannot accurately address the risks of diseases that uncommonly cause death. Insofar as SSc has appreciable mortality in severe cases, however, the absence of increased mortality in this large body of epidemiological evidence should appropriately be viewed as providing no evidence that solvent exposure is associated with increased risk of fatal SSc.

Undifferentiated connective tissue disease

There is often overlap in the symptoms and signs of various connective tissue disorders, and in certain cases months or years pass before a specific syndrome becomes apparent. Individuals who have a number of the findings that are consistent with SSc but who do not fulfill the diagnostic criteria for SSc are often diagnosed with UCTD. There is concern that those who have SSc represent only a part of a broader disease entity, and that the causes of UCTD should be studied in addition to focusing on SSc specifically.

Case reports of atypical scleroderma and undifferentiated connective tissue disease

Several case reports exist concerning solvent exposure and atypical scleroderma. A 50-year-old man employed at a chemical manufacturer for 32 years and apparently exposed to benzene, toluene, toluidine, xylene, xylidene, aniline compounds, and ethanolamine developed a syndrome that involved cold sensitivity, a restrictive lung deficit, peripheral neuropathy, esophageal dysfunction, labile hypertension, and monoclonal paraproteinemia, in addition to skin changes [76]. A 19-year-old man who had been exposed to perchloroethylene in a dry cleaning business for 4 years developed Raynaud's symptoms, weakness, arthralgias, abnormal liver function, and diffusely swollen and thickened skin on his hands [77]. After 10 years of exposure to small quantities of various solvents, a 44-year-old woman developed a scleroderma-like syndrome with cutaneous sclerosis affecting her hands, arms and legs, as well as arthralgias, fever, and fatigue [78]. After 27 years of intermittent exposure to trichloroethylene, a 44-year-old man developed scleroderma as well as Raynaud's phenomenon, malabsorption, lymphadenopathy, peripheral neuropathy, impotence, and gynecomastia [79].

Epidemiological studies

A large epidemiological study of 205 UCTD cases was performed in the USA [80] as a companion study to that of Garabrant *et al* (manuscript submitted for publication), described above. The methods were identical in both studies and the same set of population-based control individuals was used as the referent group for the UCTD cases as was used for the SSc cases. There were statistically significant associations between SSc and paint thinners and removers (OR 2.73, 95% CI 1.80–4.16); mineral spirits, naphtha, or white spirits (OR 1.81, 95% CI 1.09–3.02); and all solvents combined (OR 2.32, 95% CI 1.61–3.34). The self-reported exposures of the individuals were also analyzed and showed similar associations to those based on the expert review. This study supports the interpretation that there is a weak association between solvent exposure and UCTD among women. It contains no information on risk among men.

Other rheumatologic diseases

Although consideration has been given to the role of certain hair dye amines in the development of SLE, organic solvents have not been implicated. It has been suggested, however, that solvents play a role in other rheumatic diseases. Omdal *et al* [81] reported that nine women in a vulcanizing department potentially exposed to

Table 2

Summary of epidemiological studies of scleroderma and solvent exposure

	Men		Women		
Agent/Study	OR	95% CI	OR	95% CI	Comments on exposure assessment
Any solvent					
Lundberg *et al* [43]	NR		NR		JEM
Nietert *et al* [38]	2.9	1.2–7.1	0.6	0.2–1.9	JEM. Maximum intensity of exposure
Silman and Jones [39]	1.7	0.7–4.1	*	*	ER. (General practitioner controls)
Silman and Jones [39]	2.3	0.9–6.2	*	*	ER. (Friend controls)
Garabrant *et al* (manuscript submitted)	*	*	2.0	1.5–2.5	ER
Paint thinners and removers					
Garabrant *et al* (manuscript submitted)	*	*	2.0	1.5–2.6	ER
Aliphatic hydrocarbons					
Lundberg *et al* [43]	2.1	0.8–5.5	NR		JEM. It is not clear that the authors could differentiate aliphatic hydrocarbons from other solvents
Gasoline					
Lundberg *et al* [43]	NR		NR		JEM
Garabrant *et al* (manuscript submitted)	*	*	1.3	0.7–2.6	ER
Benzene					
Nietert *et al* [38]	2.4	0.8–7.1	1.1	0.3–3.9	JEM. Maximum intensity of exposure
Garabrant *et al* (manuscript submitted)	*	*	0.8	0.2–2.6	ER
Trichloroethylene					
Nietert *et al* [38]	3.3	1.0–10.3	0.9	0.3–2.3	JEM. Maximum intensity of exposure
Garabrant *et al* (manuscript submitted)	*	*	1.9	0.6–6.6	ER
Trichloroethane					
Nietert et al [38]	2.7	†	1.4	0.4–4.6	JEM. Maximum intensity of exposure
Garabrant et al (manuscript submitted)	*	*	0.9	0.3–2.8	ER

NR, not reported (presumed non-significant); ER, expert review of self-reported exposure; JEM, Exposures assigned by use of job exposure matrix without self reported exposure; OR, odds ratio. *Not studied; †confidence interval (CI) not given.

trichloroethylene, toluene, ethyl acetate, white spirit, methylene chloride, perchloroethylene, xylene, 1,1,1-trichloroethane, and hexane complained of arthralgias and joint swelling during exposure. The authors postulated a link between solvent exposure and inflammatory joint disease. The cases were not compared with any referent group and the results cannot be interpreted as providing scientific evidence.

The study by Lundberg *et al* [43] described above also reported results for rheumatoid arthritis. Substantial use of organic solvents was weakly associated (but statistically significantly, nonetheless) with rheumatoid arthritis (OR 1.2, 95% CI 1.0–1.6). Gasoline, aliphatic hydrocarbons, and limited use of organic solvents were not significantly associated with rheumatoid arthritis, however. Lundberg *et al* also reported that male spray painters and lacquer workers were at increased risk for rheumatoid arthritis (OR 2.4, 95% CI 1.1–5.4). Interestingly, launderers and dry cleaners were not at significantly increased risk of rheumatoid arthritis. Lundberg *et al* reported no significant associations between solvents and SLE.

Conclusion

Of the four methodologically sound studies of SSc reviewed above [38,39,43] (Garabrant *et al*, manuscript submitted), one found a statistically significant association with solvents in men [38] and two others found no significant association [39,43] (Table 2). Similarly, one study found a significant association in women (Garabrant *et al*, manuscript submitted) and two others found no significant association [38,42]. Examinations of specific solvent products including paint thinners and removers, gasoline, benzene, trichloroethylene, and trichloroethane in three studies showed only two statistically significant associations [for trichloroethylene in men [38] and for paint thinners and removers in women (Garabrant *et al*, manuscript submitted)] neither of which was confirmed in any other study in men or in women. These studies, on aggregate, do not provide conclusive evidence that solvents (as a group of chemicals) are causally associated with SSc, nor do they provide conclusive evidence that any individual solvent is causally associated with SSc. A very large body of mortality studies among cohorts exposed to paints, dry cleaning solvents, and petroleum distillates provides no

evidence that solvents are associated with fatal SSc. On balance, it should be noted that all four of the morbidity studies [38,39,43] (Garabrant *et al*, manuscript submitted) provide weak evidence of an association between solvents (as a group of chemicals) and SSc in some analyses, but that chance cannot be adequately excluded as an explanation in most. This repeated, suggestive evidence of an association cannot be dismissed as meaningless unless it is refuted by larger, more definitive studies. It is not adequate to conclude that there is a causal association between solvents and SSc at the present time, however. Unless the associations can be found consistently, specific solvents can be identified as conveying risk, and evidence of dose–response is demonstrated, the inconsistent, positive associations that presently exist should be viewed as being inconclusive evidence of a causal association.

Additional morbidity studies of SSc will be necessary to determine whether there is a causal association with solvents. Future studies either must be conducted in populations that have a higher prevalence of solvent exposure, or they must be substantially larger than the previous studies. It is of interest that the study by Garabrant *et al* (manuscript submitted), which included 675 cases and over 2200 control individuals, had marginal power to detect twofold increased risks for specific solvents among women, primarily due to the low prevalence of exposure. The region from which the subjects were drawn is heavily industrialized with automobile, aerospace, pharmaceutical and chemical manufacturing, in which solvent exposure is common. More precise estimates of exposure in terms of the identity of the solvents and the intensity and frequency of exposure will be necessary. Opportunities to conduct such studies are most likely to be fruitful in settings in which exposures can be documented through work records or biologic monitoring and to which morbidity records can be linked.

A single, large epidemiological study of UCTD [80] suggests that solvents are significantly associated with this diagnostic category in women, and that paint thinners and removers and mineral spirits are specifically associated with UCTD. Although that study was methodologically rigorous, replication of the findings is necessary before this association can be accepted as causal.

There is a single study [43] that reported an association between rheumatoid arthritis and solvent use, but which does not identify any specific solvent that conveys this risk. Replication of these findings is necessary before this association can be accepted as causal. There is no scientific evidence that SLE is associated with solvent exposure.

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