Raynaud's Phenomenon in Medical Laboratory Workers Who Work with Solvents

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ABSTRACT. ***Objective.*** To investigate whether there is an association between Raynaud's phenomenon (RP) and exposure to organic solvents in laboratory workers.

Methods. Technicians, scientists, and laboratory assistants working in histology, cytology, and transfusion medicine were surveyed about their use of solvents, particularly xylene and toluene, and about symptoms of RP. There were 341 responses. OR for having worked with solvents were calculated with logistic regression adjusted for age and sex.

Results. Laboratory workers who had worked with solvents had higher rates of severe RP, particularly those who had worked with xylene or toluene and either acetone (OR 8.8, 95% CI 1.9–41.1), or chlorinated solvents (OR 8.9, 95% CI 1.9–41.6), xylene or toluene and acetone compared to those who had worked with xylene or toluene but not acetone (OR 4.5, 95% CI 1.2–16.2), and similarly for chlorinated solvents (OR 4.5, 95% CI 1.2–16.3). RP symptoms occurring in the absence of cold exposure were more frequent for those who had worked with any solvent (OR 3.6, 95% CI 1.2–10.5) and just xylene or toluene (OR 2.8, 95% CI 1.1–7.3). Associations were also seen between increasing exposure to xylene or toluene and severe RP (OR 1.7, 95% CI 1.1–2.7, per 10 years) and with symptoms occurring in the absence of cold exposure (OR 1.7, 95% CI 1.2–2.5, per 10 years).

Conclusion. We found that exposure to solvents may be associated with the development of RP, supporting previous work indicating that solvent exposure may be an etiological factor in systemic sclerosis. (J Rheumatol First Release June 15 2011; doi:10.3899/jrheum.101129)

Key Indexing Terms:
RAYNAUD'S PHENOMENON SOLVENTS XYLENES
OCCUPATIONAL EXPOSURE OCCUPATIONAL DISEASES HOSPITAL LABORATORIES

Raynaud's phenomenon (RP) has been defined as peripheral vasoconstriction in response to cold, characterized by color changes, pain, and tautness/fullness in the digits[1]. RP is a common symptom of systemic sclerosis (SSc) and other connective tissue diseases. RP can occur without any disease association (primary RP), or it can occur as a feature of diseases such as systemic lupus erythematosus and SSc (secondary RP). Ten studies, published between 1982 and 1996, of people who consulted a physician because of primary RP were reviewed in a 1998 metaanalysis[2]. After an average followup of 4 years, a related disease was diagnosed in 13% of subjects, with 65% of the related cases being SSc. A 2008 study of 586 patients with no definite connective tissue disease who were referred for evaluation with RP found 13% developed definite SSc and 1% other connective tissue diseases during a median 4-year followup[3].

A 2006 systematic review of solvent exposure and SSc identified 15 epidemiological studies published between 1984 and 2004 and concluded that there was evidence of a link that was probably causal[4]. Another systematic review reported a metaanalysis of 11 of these studies, with a publication-bias adjusted OR of 1.8 (95% CI 1.2–2.5)[5]. Two case-control studies have found increased relative risks of undifferentiated connective tissue disease from solvent exposure[6,7]. A case-control study of 25 patients with primary RP and 61 patients with secondary RP (RP as the sole predominant clinical symptom and either antinuclear antibody positivity, scleroderma capillary pattern, or pitting ulcerations/gangrene, but no internal organ manifestation) found an OR of 2.1 (95% CI 0.9–5.5) for solvent exposure[6]. A population survey found higher rates of simple and more severe RP in people exposed to solvents, with OR of 1.9 (95% CI 1.7–2.2) and 2.7 (95% CI 2.2–3.1), respectively[8]. A case-control study[9] found an increased relative risk of SSc of 2.1 (95% CI 1.2–3.8) and a related study[7] found an increased relative risk of undifferentiated connective tissue disease of 4.5 (95% CI 2.3–9.0) for people working in medical diagnostic or pathology laboratories. Cyanosis of the hands was among the symptoms reported for a histology and cytology laboratory worker exposed to xylene[10], although formal documentation of RP using established criteria was not made.

There appear to be no published studies of RP in people occupationally exposed to solvents or exposed to specific solvents. Histology and cytology laboratory workers are exposed

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to solvents, while solvents are not normally used in transfusion medicine. Some laboratory workers also work with frozen specimens. Although a relationship of RP with a cold climate was found in France[11], a study of cryosectioning workers found no significant increase in RP[12]. This paper compares RP rates in solvent-exposed histology, cytology, and transfusion medicine laboratory workers with unexposed medical laboratory workers from transfusion medicine and with the general population with the aim of establishing whether exposure to common laboratory solvents is associated with RP.

MATERIALS AND METHODS

All New Zealand medical laboratories registered with International Accreditation New Zealand for histology, cytology, and transfusion medicine were identified in June 2006. Heads of departments were asked to provide information on the number of technicians, scientists, and laboratory assistants working in their departments and were sent questionnaires to distribute to them. Questionnaires were sent between June and August 2006.

It was estimated that there would be about 210 people working in cytology and histology and a similar number working in transfusion medicine. With a 70% response rate, the study would have an 80% chance of finding a significant difference between those working in cytology or histology and those working in transfusion medicine, at the 0.05% level of significance, if the rates of RP were 20% and 8%, respectively.

RP was assessed using the UK Scleroderma Study Group questionnaire[1] with the following questions: (1) are your fingers sensitive to cold?; (2) do your fingers show unusual colour changes? If Yes, do they become white, blue, red or purple?; (3) have your fingers become numb or had pins and needles in response to cold?; and (4) if applicable, have the color changes or numbness described occurred in the absence of cold exposure, i.e., at normal temperature?

Participants were classified as having possible RP if they answered yes to only 1 color in question (2) or answered yes to question (3), and definite RP if they answered yes to at least 2 colors in question (2). If in addition to 2 colors they answered yes to (3) and (4) then they were classified as having severe RP. People were also asked if they had ever consulted their general practitioner or a specialist concerning their symptoms, and if so, what was the diagnosis?

People were asked their sex, age, when they had worked in medical laboratories, and in what areas they had worked. They were asked whether and when they had worked with frozen specimens, xylene, or toluene. They were also asked how frequently (daily, weekly, or less often) they worked with wet xylene-prepared or toluene-prepared slides, with or without gloves. They were also asked with what other solvents they had worked.

An exposure score for xylene or toluene was calculated as years working with them plus, for those who had worked with wet slides, the product of the years working with wet slides times 25 for daily, 5 for weekly, or 1 for less often, and times 5 when handling wet slides without gloves.

The study was approved by the New Zealand Multi-region Ethics Committee.

Questionnaire data were double-entered. Non-responses to yes or no questions were treated as negative responses. Of the RP questions, (1) was not answered by 2, but they both answered (2) and (3). Fifteen did not answer the first part of (2); all except 1 (who stated she had not noticed it) answered a color-specific question. When answering color-specific questions in (2), 88 of 110 who gave "yes" responses to between 1 and 3 colors left all other colors blank. Two did not answer (3) and 3 did not answer (4) where it was applicable. Fourteen (all from transfusion medicine) did not answer whether they had used xylene or toluene, 107 answering "yes" to xylene did not answer for toluene. Five people did not answer whether they had worked with frozen specimens. The duration of working with xylene or toluene was unknown for 21 people and the exposure score was not calculable for 45. Twelve people did not provide their age. These missing ages were estimated with multiple imputation[13] (10 imputations) from a regression of the log of the age above 14 when people started work, as a function of the year people started working in medical laboratories, the area they worked, whether they had worked in other areas, sex, and RP classification. OR were estimated with logistic regressions adjusted for age and sex, and proportions compared with chi-squared tests.

RESULTS

All laboratory departments agreed to participate in our study and provided data on the total numbers of laboratory workers. There were 301 people working in histology and cytology and 243 in transfusion medicine. The response rate for people working in histology and cytology was 62% (188 questionnaires returned). The response rate for those working in transfusion medicine was 63% (153 questionnaires returned). The response rate was lower for larger departments, both for histology and cytology (Kendall's τ-b correlation coefficient, $\tau = -0.45$, $p = 0.001$) and transfusion medicine ($\tau = -0.39$, $p = 0.008$). The median age of responders was 43 years, and 79% were women.

Among those working in transfusion medicine, 65% worked or had worked in other laboratory areas, with 18% of those working in transfusion medicine having worked in histology or cytology. Fifty-seven percent had worked with frozen specimens. Forty-four percent had worked with solvents, 30% with xylene. Among those working in histology or cytology, 99% had worked with xylene and 60% had worked with other solvents. Fifty-two percent had worked with frozen specimens. The sex distribution, age, and year people first worked in a medical laboratory were similar between departments. A higher proportion of men had worked with other solvents, particularly acetone and chlorinated solvents (Table 1). Those who had used xylene or toluene were older and had started working in medical laboratories earlier.

Of those who had worked with solvents, 92% (233) had worked with xylene or toluene. Thirty-five percent of those who had worked with xylene or toluene had worked with other solvents. Most people who had worked with toluene had also worked with xylene (79 of 80). Similarly, most people who had worked with other specific solvents had also worked with xylene or toluene, alcohols 86% (51/59), acetone 92% (22/24), formaldehyde 74% (14/19), and chlorinated solvents (chloroform/trichloroethylene) 95% (21/22). The chlorinated solvent use was mainly chloroform (n = 19), with 4 having used trichloroethylene. Longer duration of working with xylene or toluene was associated with working with other solvents (OR 1.5, 95% CI 1.2–1.9, per 10 years, $p = 0.001$). The median duration of working with xylene or toluene was 12 years [interquartile range (IQR) 4 to 22, ranged from 1 to 48]. Of those who had worked with xylene or toluene, 75% had handled wet slides without gloves and 64% with gloves. Of those who had handled wet slides without gloves, 71% had done so daily for a median of 11 years (IQR range 5 to 20,

Table 1. Characteristics and solvent exposure of subjects.

Characteristics	Women, % (n)	Age, yrs Median (IQR)	Year Started,* Median (IQR)
Histology/cytology (n = 188)	80 (151)	43 (31–51)	1988 (1978–1999)
Transfusion medicine (n = 153)	76 (117)	42 (32–50)	1987 (1976–2000)
No solvents (n = 88)	81 (71)	41 (30–49)	1990 (1979–2000)
Solvents (n = 253)	78 (197)	43 (32–51)	1987 (1977–1999)
No xylene or toluene (n = 108)	80 (86)	40 (30–47)	1990 (1979–2001)
Xylene or toluene (XT; n = 233)	78 (182)	44 (32–52)	1987 (1976–1998)
XT only (n = 132)	84 (111)	43 (30–51)	1988 (1975–2000)
XT and other solvents (n = 101)	70 (71)	45 (35–52)	1986 (1976–1995)
XT and no alcohols (n = 182)	81 (148)	43 (31–52)	1987 (1975–1999)
XT and alcohols Y (n = 51)	67 (34)	44 (35–51)	1987 (1978–1994)
XT and no acetone (n = 211)	81 (170)	44 (32–52)	1987 (1976–1998)
XT and acetone (n = 22)	55 (12)	40 (34–48)	1989 (1977–1995)
XT and no formaldehyde (n = 219)	77 (169)	44 (33–52)	1987 (1976–1998)
XT and formaldehyde (n = 14)	93 (13)	37 (27–43)	1989 (1985–2003)
XT and no chlorinated solvents (n = 212)	80 (170)	43 (32–52)	1987 (1976–1999)
XT and chlorinated solvents (n = 21)	57 (12)	45 (36–46)	1982 (1978–1990)
Worked with frozen specimen (n = 184)	76 (140)	43 (33–51)	1987 (1976–1999)
No frozen specimen work (n = 157)	82 (128)	42 (30–51)	1989 (1979–2001)

* Year first worked in a medical laboratory. IQR: interquartile range.

ranged from 1 to 48). Of those who had used gloves, 64% had done so daily for a median of 6 years (IQR 3 to 12, ranged from 1 to 43).

There were significantly higher rates of severe RP in laboratory workers who had worked with xylene or toluene and either acetone or chlorinated solvents (Table 2). Little association was seen between use of xylene or toluene only (XT only) and definite RP (OR 1.3, 95% CI 0.6–2.5), but there was evidence of a doubling of risk for severe RP (OR 2.3, 95% CI 0.7–7.4). There were higher rates of RP for those who had worked with xylene or toluene and acetone than for those who had worked with xylene or toluene but not acetone (for definite RP, OR 2.1, 95% CI 0.7–6.4; and for severe RP, OR 4.5, 95% CI 1.2–16.2) and higher rates for those who had worked with xylene or toluene and chlorinated solvents than for those who had worked with xylene or toluene but not chlorinated solvents (for definite RP, OR 3.0, 95% CI 1.0–9.0; and for severe RP, OR 4.5, 95% CI 1.2–16.3).

The OR for definite RP for cytology/histology workers vs transfusion medicine workers was 0.9 (95% CI 0.5–1.7) and for severe RP, 1.9 (95% CI 0.7–4.7). For working with frozen specimens, the OR for definite RP was 1.2 (95% CI 0.7–2.1), and for severe RP, 1.8 (95% CI 0.7–4.3). The OR for severe RP for those who had worked with solvents, adjusted for

Table 2. Associations between Raynaud's phenomenon (RP) and solvent exposure among 341 medical laboratory workers.

Type of exposure	Not RP, n = 184, % (n)	Possible RP, n = 100, % (n)	Definite RP		OR* (95% CI) Definite RP	OR* (95% CI) Severe RP
			Not Severe, n = 34, % (n)	Severe, n = 23, % (n)		
No solvents (n = 88)	59 (52)	28 (25)	9 (8)	3 (3)	1.0	1.0
Solvents (n = 253)	52 (132)	30 (75)	10 (26)	8 (20)	1.6 (0.8–3.4)	2.5 (0.7–8.7)
No xylene or toluene (n = 108)	56 (60)	29 (31)	12 (13)	4 (4)	1.0	1.0
Xylene or toluene (XT; n = 233)	53 (124)	30 (69)	9 (21)	8 (19)	1.2 (0.6–2.2)	2.3 (0.8–7.1)
XT only (n = 132)	56 (74)	24 (32)	11 (15)	8 (11)	1.3 (0.6–2.5)	2.3 (0.7–7.4)
XT and other solvents (n = 101)	50 (50)	37 (37)	6 (6)	8 (8)	1.0 (0.5–2.2)	2.5 (0.7–8.6)
XT and no alcohols (n = 182)	54 (98)	28 (51)	10 (18)	8 (15)	1.2 (0.6–2.3)	2.3 (0.7–7.1)
XT and alcohols (n = 51)	51 (26)	35 (18)	6 (3)	8 (4)	1.0 (0.4–2.7)	2.6 (0.6–10.9)
XT and no acetone (n = 211)	55 (117)	28 (59)	9 (20)	7 (15)	1.1 (0.6–2.1)	2.0 (0.6–6.1)
XT and acetone (n = 22)	32 (7)	45 (10)	5 (1)	18 (4)	2.3 (0.7–7.4)	8.8 (1.9–41.1)
XT and no formaldehyde (n = 219)	53 (117)	29 (64)	9 (20)	8 (18)	1.2 (0.6–2.3)	2.4 (0.8–7.3)
XT and formaldehyde (n = 14)	50 (7)	36 (5)	7 (1)	7 (1)	0.8 (0.2–3.7)	1.8 (0.2–17.3)
XT and no chlorinated solvents (n = 212)	54 (114)	30 (64)	9 (19)	7 (15)	1.0 (0.5–2.0)	2.0 (0.6–6.1)
XT and chlorinated solvents (n = 21)	48 (10)	24 (5)	10 (2)	19 (4)	3.2 (1.0–10.0)	8.9 (1.9–41.6)

* Logistic regression adjusted for age and sex. Xylene/toluene (with and without other solvents) OR vs not having worked with xylene or toluene.

working with frozen specimens, was 2.5 (95% CI 0.7–8.6), and for frozen specimens adjusted for solvents, 1.7 (95% CI 0.7–4.3), neither of which were significant. There were no significant associations between definite RP and increasing duration of working with xylene or toluene (OR 1.1, 95% CI 0.8–1.5, per 10 years, p = 0.40) or with xylene or toluene exposure score (OR 1.1, 95% CI 0.8–1.4, per 1000, p = 0.56). There were significant associations between severe RP and increasing duration of working with xylene or toluene (OR 1.7, 95% CI 1.1–2.7, per 10 years, p = 0.018, and adjusted for other solvent use, OR 1.7, 95% CI 1.1–2.7 per 10 years) and with xylene or toluene exposure score (OR 1.6, 95% CI 1.1–2.2, per 1000, p = 0.018). There were no significant associations between duration of working with frozen specimens and definite RP (OR 1.1, 95% CI 0.8–1.5, per 10 years, p = 0.65) or severe RP (OR 1.2, 95% CI 0.8–1.9, per 10 years, p = 0.35).

Color changes or numbness occurring in the absence of cold exposure were significantly more common in those who were working in cytology or histology departments (OR 2.3, 95% CI 1.1–4.8, p = 0.025) and in those who had worked with solvents, xylene or toluene only, or in combination with other solvents (Table 3). There was evidence of close to a trebling of the risk with the use of xylene or toluene only (XT only; OR 2.8, 95% CI 1.1–7.3). The OR for color changes or numbness occurring in the absence of cold exposure for those who had worked with xylene or toluene and acetone compared with those who had worked with xylene or toluene but not acetone was 2.4 (95% CI 0.8–7.5). The OR for those who had worked with xylene or toluene and chlorinated solvents compared with those who had worked with xylene or toluene but not chlorinated solvents was 2.5 (95% CI 0.8–7.8).

There were significant associations between color changes or numbness occurring in the absence of cold exposure and increasing duration of working with xylene or toluene (OR 1.7, 95% CI 1.2–2.5, per 10 years, p = 0.002, and adjusted for other solvent use, OR 1.7, 95% CI 1.2–2.5, per 10 years) and increasing xylene or toluene exposure score (OR 1.6, 95% CI 1.2–2.1, per 1000, p = 0.002).

The OR for color changes or numbness occurring in the absence of cold exposure from having worked with frozen specimens was 1.6 (95% CI 0.8–3.1). There was no significant association between duration of working with frozen specimens and RP (OR 1.0, 95% CI 0.7–1.04, per year, p = 0.94).

Of those giving a positive response to any of the RP symptom questions, 10% (95% CI 6–16; 19/184), all women, had consulted a general practitioner or a specialist concerning their symptoms. There were significant differences in consultation rates between RP classifications (chi-squared = 31.3 df = 3, p < 0.0001) with a consultation rate of 43% (10/23) for severe RP and 6% for both definite (but not severe) and possible RP. Diagnoses reported were arthritis (1), chilblains (1), occupational overuse syndrome (1), poor circulation (2), RP (10), regional pain syndrome (1), rheumatism (1), SSc (1), and 1 reporting that it was not RP. One person with definite RP, who had not consulted about those symptoms, commented that she had been diagnosed with Sjögren's syndrome at a consultation unrelated to RP.

DISCUSSION

There were higher rates of severe RP and symptoms occurring in the absence of cold exposure among laboratory workers who had worked with solvents compared with laboratory workers who had not. Severe RP and symptoms occurring in the absence of cold exposure were associated with increasing duration of exposure to xylene or toluene.

Table 3. Associations between color changes or numbness occurred in the absence of cold exposure and solvent exposure among 341 medical laboratory workers.

Type of Exposure	No Changes, n = 301, % (n)	Changes Occurring in the Absence of Cold, n = 40, % (n)	OR (95% CI)*
No solvents (n = 88)	95 (84)	5 (4)	1.0
Solvents (n = 253)	86 (217)	14 (36)	3.6 (1.2–10.5)
No xylene or toluene (XT; n = 108)	94 (102)	6 (6)	1.0
Xylene or toluene (XT; n = 233)	85 (199)	15 (34)	3.0 (1.2–7.4)
XT only (n = 132)	86 (113)	14 (19)	2.8 (1.1–7.3)
XT and other solvents (n = 101)	85 (86)	15 (15)	3.3 (1.2–9.0)
XT and no alcohols (n = 182)	86 (156)	14 (26)	2.8 (1.1–7.2)
XT and alcohols (n = 51)	84 (43)	16 (8)	3.6 (1.2–11.2)
XT and no acetone (n = 211)	86 (182)	14 (29)	2.7 (1.1–6.8)
XT and acetone (n = 22)	77 (17)	23 (5)	6.6 (1.7–25.3)
XT and no formaldehyde (n = 219)	86 (188)	14 (31)	2.9 (1.2–7.2)
XT and formaldehyde (n = 14)	79 (11)	21 (3)	4.2 (0.9–19.4)
XT and chlorinated solvents (n = 212)	86 (183)	14 (29)	2.7 (1.1–6.8)
XT and chlorinated solvents (n = 21)	76 (16)	24 (5)	6.9 (1.8–26.6)

* Logistic regression adjusted for age and sex. Xylene/toluene (with and without other solvents) OR vs not having worked with xylene or toluene. OR for having symptoms vs not having symptoms.

Cold exposure related to cryosectioning work might be seen as a possible explanation for the increased rates of RP in histology workers compared to transfusion workers; however we found no significant relationships between RP and working with frozen specimens. This is consistent with another study of cryosection workers that also found no significant relationships with RP symptoms[12]. If there is any relationship of RP with cryosectioning work, it is likely to be smaller than detectable in these studies.

We found an increased prevalence of severe RP and symptoms occurring in the absence of cold exposure among those who had worked with solvents. There were increased rates with increased duration and exposure score for working with xylene or toluene. Increased duration and exposure score were associated with working with other solvents and earlier exposures. Exposures may have been higher and workplace practices different in earlier years. The findings are consistent with the increased rates of RP with solvent use found in other studies[6,8]. This study found higher rates of severe RP for those who had worked with xylene or toluene and acetone, a ketone, or chlorinated solvents. The survey did not ascertain whether these exposures were concurrent. The increased risk could be due to the solvents, the combination of solvents, or workplace practices associated with their use. Methyl ethyl ketone has been found to interfere with the metabolism of xylene, increasing the blood concentration of xylene[14]. In rats and mice, blood concentration of xylene was higher with simultaneous acetone exposure and its decline slower than without acetone exposure[15]. Toluene blood concentrations were higher in rats but not mice with simultaneous acetone exposure. A case-control study of SSc found an OR for occupational exposure to ketones of 8.8 (95% CI 1.8–42.4), the highest exposure OR they reported[16]. That study found an OR for occupational chlorinated solvent exposure of 2.6 (95% CI 1.2–5.7). Other case-control studies have found similar[17,18] or smaller[7,9] OR from chlorinated solvent exposure for SSc[9,18] or undifferentiated connective tissue disease[7], and from halogenated solvents for SSc[17].

We found that working with xylene or toluene was associated with severe RP symptoms. Toluene exposure was found to be associated with development of SSc by Diot, *et al* (OR of 3.4, 95% CI 1.1–10.9)[16]. Other case-control studies have found weaker associations with xylene, toluene, and benzene[9,17]. Another study found negative associations between undifferentiated connective tissue disease and exposure to xylene and toluene[7].

Comparative data on the prevalence of RP in the general population, using the same RP symptom questions, were obtained from a postal survey of people from the New Zealand electoral roll in September 2006[19]. There were no significant differences in the rates of definite RP between people selected from the electoral roll and laboratory workers who had not worked with solvents (OR 0.7, 95% CI 0.3–1.5, p = 0.39) or in those who had worked with solvents (OR 1.2, 95% CI 0.7–2.0, p = 0.55), or in the rates of severe RP for those who had not worked with solvents (OR 1.0, 95% CI 0.2–4.4, p = 0.96). The OR for severe RP for laboratory workers who had worked with solvents compared to people selected from the electoral roll was 2.6 (95% CI 1.0–6.9, p = 0.052). Laboratory workers who had color changes were significantly more likely to have 2 or more colors (50%, 57/115) than those on the electoral roll (28%, 27/97; p = 0.001). Compared to people selected from the electoral roll, color changes or numbness occurring in the absence of cold exposure were significantly less frequently reported by laboratory workers who had not worked with solvents (OR 0.2, 95% CI 0.1–0.7, p = 0.006) and not significantly differently reported by those who had (OR 0.8, 95% CI 0.5–1.3, p = 0.38). Among those with color changes and symptoms occurring in the absence of cold exposure, the laboratory workers were significantly (p = 0.0004) more likely to meet the UK Scleroderma Study Group criteria for definite RP (63%, 25/40) than the general population (22%, 8/36). These criteria were developed in a study of subjects selected from a connective tissue disease clinic[1] and may not identify some with vibrating white finger syndrome as definite RP[19]. Vibration syndromes seem unlikely among laboratory workers, leading to lower rates of symptoms in the absence of cold exposure among those not working with solvents. When laboratory workers do experience symptoms in the absence of cold exposure, they are more likely to meet criteria developed for connective tissue disease. Among laboratory workers giving a positive response to any of the RP symptom questions, there was a similar consultation rate to people selected from the electoral roll (women, OR 1.06, 95% CI 0.48–2.37, adjusted for age).

Our study was limited by our failure to obtain ethical approval to ask the heads of departments for the names of individual workers, which would have allowed followup of incomplete and nonresponders, to improve the response rates. The response rate was lower in larger departments. Variation in the response rates between departments may have also been affected by how department heads presented the questionnaire. For example, for some small departments, all questionnaires were returned together. These processes may have been unrelated to the types of solvents used or RP symptoms and hence not have biased the result.

Classifying nonresponses to yes or no questions as negative responses may have misclassified some people. This seems unlikely for xylene or toluene exposure since all the workers were working in transfusion medicine. They also answered the RP questions in a manner similar to the other questions, leaving only color-specific questions blank; hence any misclassification is likely to be nondifferential and independent, biasing the effects toward unity[20]. For those applicable, 80% left a color-specific question blank, making it the normal response. The UK Scleroderma Study Group did not specify whether the questions used yes or no responses[1].

Xylene and toluene were the only solvents mentioned on

the questionnaire. Reporting the use of other solvents required them to be specified. This could have resulted in misclassification of these exposures. Some people may not think of some of the chemicals they have used as solvents. This would result in nondifferential misclassification, biasing the effects toward unity[20]. With the retrospective reporting there could be differential recall biases, with those reporting RP symptoms being more likely to self-report solvent use, particularly solvents other than those prompted (xylene and toluene), and hence overestimates of the relationships. The healthy worker effect, with workers experiencing symptoms leaving employment, may have caused underestimation of the relationships.

The small number of severe RP cases (n = 23) constrains the number of variables that could reasonably be adjusted for in models[21], in particular individual solvent exposures that were related to other solvent exposures.

Solvents could be causing RP by bringing about peripheral neuropathy, which is associated with hand-arm vibration syndrome[22], a trauma-induced form of RP. Peripheral neuropathy of the radial nerves was found in workers exposed to the combination of white spirit, toluene, xylene, butyl acetate, and ethyl acetate[23]. RP can be trigged by stress, emotion, or anxiety at warm temperatures[24], suggesting a role for the central nervous system in severe RP, and solvent exposure has been shown to cause central neurotoxicity[25]. People with RP were found to have impaired thermoregulation, with low core temperatures after cooling[26]. Evidence for increased hypothalamic dopamine levels was found in toluene-exposed rats[27], which may be associated with hypothermia[28]. Mice fed toluene or benzene had increased hypothalamic norepinephrine[29], which is also associated with hypothermia[30].

Solvents might cause endothelial injury associated with increased levels of vasoconstrictors and decreased vasodilators. Angiotensin II is a vasoconstrictor and nitric oxide (NO) is a vasodilator associated with RP[31]. Angiotensin II levels were increased and NO levels decreased in rats following chronic alcohol consumption[32]. Chronic and high alcohol consumption in humans decreases endothelial cell NO production and increases endothelial cell apoptosis[33].

There could be a causal relationship between solvent exposure and SSc[4]. RP can be an early symptom of SSc[3] and can become severe in SSc. We found that those with severe RP were more likely to consult a physician, and followup studies have found that SSc is the most common connective tissue disease to develop among people who consult physicians regarding RP[2,3]. We did not investigate other symptoms of SSc, but the finding that solvent exposure is associated with severe RP suggests a potential link between solvent exposure and early preclinical SSc.

Several mechanisms have been suggested to explain solvents causing SSc[4,5,9,16,34]. Denaturation of cellular proteins by solvents and the production of antibodies have been suggested[4]. Diot, *et al* noted that after penetration, through the skin and by inhalation, solvents might bind to nucleic acids and proteins, reduce humoral and cell-mediated immune responses, and stimulate the production of fibrogenic proteins and growth factors such as interleukin 1 (IL-1), platelet-derived growth factor, transforming growth factor (TGF)-ß, and fibronectin, which are generated in SSc[16]. After finding some evidence of solvents inducing diffuse cutaneous SSc and pulmonary involvement, and concluding that that action may relate to solvents' double penetration through the skin and lungs, Magnant, *et al* hypothesized that they may amplify the cellular response rather than the humoral response, acting as fibrogenic stimuli in the sites where they are deposited (mainly skin or lungs) by increasing the release of IL-1, IL-6, tumor necrosis factor-α, and TGF-ß[34]. Garabrant, *et al* noted that solvent overexposure is believed to play a role in the formation of autoantibodies to alveolar basement membrane and glomerular basement membrane[9].

Our study has demonstrated that medical laboratory workers who have worked with solvents are more likely to have RP, in particular severe RP, and RP symptoms in the absence of cold exposure, than laboratory workers who have not worked with solvents. These findings are consistent with previous studies indicating a link between exposure to these solvents and development of SSc and highlights the need for careful handling of laboratory solvents.

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