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A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases

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ABSTRACT

Objectives Increased risk has been suggested for autoimmune rheumatic diseases following solvent exposure. The evidence for specific solvents is limited, and little is known about exposure–response relations. Styrene is an aromatic, organic solvent and the objective of this study was to analyse the association between occupational styrene exposure and autoimmune rheumatic diseases in men and women.

Methods We followed 72 212 styrene-exposed workers of the Danish reinforced plastics industry from 1979 to 2012. We modelled full work history of styrene exposure from employment history, survey data and historical styrene exposure measurements. We identified cases in the national patient registry and investigated gender-specific exposure–response relations by cumulative styrene exposure for different exposure time windows adjusting for age, calendar year and educational level.

Results During 1 515 126 person-years of follow-up, we identified 718 cases of an autoimmune rheumatic disease, of which 73% were rheumatoid arthritis. When adjusting for potential confounders and comparing the highest with the lowest styrene exposure tertile, we observed a statistically non-significantly increased risk of systemic sclerosis among women (incidence rate ratio (IRR)=2.50; 95% CI 0.50 to 12.50) and men (IRR=1.86; 95 % CI 0.50 to 7.00), based on 9 and 22 cases, respectively. Results were inconsistent for the other autoimmune rheumatic diseases examined.

Conclusion This study suggests an association between occupational styrene exposure and systemic sclerosis in men as well as in women but based on few cases. This is a new finding and has to be replicated before conclusions can be drawn.

Key messages

What is already known about this subject?
- Organic solvent exposure has been associated with systemic sclerosis and other autoimmune rheumatic diseases.

What are the new findings?
- This study suggests an association between occupational styrene exposure and systemic sclerosis.
- No consistent association was seen for rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis or Sjögren's syndrome.

How might this impact on policy or clinical practice in the foreseeable future?
- These findings highlight the possible role of work factors in systemic sclerosis.

Systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome are autoimmune rheumatic diseases for which little is known about environmental risk factors.[1 2] Genetic predisposition is of importance; however, concordance rates among monozygotic twins is low and indicates that environmental factors play an important role in the aetiology of these diseases.[1 3] Smoking is a well-described risk factor for rheumatoid arthritis, and several epidemiological studies have linked occupational exposure to respirable quartz with systemic sclerosis, rheumatoid arthritis, small vessel vasculitis and systemic lupus erythematosus.[1 4]

The occurrence of systemic sclerosis has been associated with occupational exposure to trichloroethylene,[5 6] benzene, toluene or xylene,[7 8] major organic solvent categories[5–10] and unspecified solvents.[11] Exposure assessment has mainly relied on case-by-case expert assessment or job exposure matrices (JEMs) with few exceptions of self-reports.[6 11] Self-reported job tasks and JEM data have indicated associations between unspecified solvent exposure and rheumatic arthritis,[12–14] while the limited evidence for systemic lupus erythematosus is mainly negative.[15–17] Single studies have linked Sjögren's syndrome with aromatic and chlorinated solvents and small vessel vasculitis with unspecified solvent exposure.[18 19]

As it appears, there are little data on specific solvents. Some studies have assessed exposure–response relations based on semiquantitative exposure information, but none has included quantitative exposure information.[7–9 14 15 17 19] Thus, quantitative exposure data based on actual measurements of specific solvents will add significantly to the knowledge base about the suggested association between organic solvent exposure and autoimmune rheumatic diseases.

Styrene is an aromatic solvent with well-documented neurotoxic effects[20] and is possibly associated with lymphohaematopoietic malignancies[21 22] and non-malignant respiratory diseases.[23]

Styrene is a high-production-volume industrial chemical used as a monomer in the production of several plastic polymers and coatings.[20] High levels of styrene exposure are found in the work room air of the reinforced plastics industry during hand lamination of boats, wind mill rotor blades and other reinforced plastics products. Especially high exposure levels were seen before the 1990s.[24]

The aim of this study is to investigate the association between occupational styrene exposure and systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome in men and women.

MATERIALS AND METHODS

Study population

A total of 456 Danish companies producing reinforced plastics products since the early 1960s were identified. In a national pension fund register of mandatory pension saving, all 77 491 workers ever employed in these companies between 1964 and 2007 were identified.[25] To have complete work histories, we excluded those with a registration in 1964 (3496 persons), the year the pension register was established. The Danish civil registration system provided information on vital status. We excluded 25 workers without information on vital status, as well as 1664 who died, disappeared or emigrated before begin of follow-up and 94 diagnosed with a rheumatic autoimmune disease before begin of follow-up as specified later. The study population then included 59 997 men and 12 215 women, in total 72 212 participants. Information on occupation for each year of employment in the study companies was obtained from Statistics Denmark[26] and coded according to the Danish version of the International Classification of Occupations (DISCO-88) into four categories: white collar (DISCO-88 codes 1000 to 5999), skilled blue collar (codes 6000 to 7999), unskilled blue collar worker (codes 8000–9999) and others (eg, student and retired workers).

Autoimmune rheumatic diseases

We identified cases of autoimmune rheumatic diseases in the National Patient Registry 1977–2012.[27] This registry holds information on all inpatient and outpatient contacts with any Danish public or private hospital since 1977. All contacts are registered according to the 8th version (ICD-8: 1977–1993) and 10th version (ICD-10: 1994–2012) of the International Classification of Diseases. Cases were defined as follows: systemic sclerosis: M340, M341, M342, M342A, M342B, M348, M348B, M349, 73400, 73401, 73402, 73408, 73409, 73491; rheumatoid arthritis: M050, M051, M051A-F, M052, M053, M058, M059, M060, M068, M069, 71219, 71229, 71238,71239; seropositive rheumatoid arthritis: M050, M051, M051A-F, M052, M053, M058, M059; seronegative rheumatoid arthritis: M060, M068, M069; systemic lupus erythematosus: M320, M321, M328, M329, 73419; small vessel vasculitis: M301, M310, M310A-B, M311, M311A, M313, M317, M318, M318A, M319, 22709, 44619, 44629, 44649, 44799, 44808, 44809 and Sjögren's syndrome: M350, 73 490.

Approximately 55% of cases were diagnosed at departments of rheumatology, otherwise at departments of dermatology, internal medicine or orthopaedic surgery. We defined incident cases as the first diagnosis of an autoimmune rheumatic disease during the study period with one exception: if different relevant diagnoses were recorded within a year, we selected the last because several hospital contacts may be needed before a confident diagnosis is established.[28] If more diagnoses were registered on the same day, we prioritised them as follows: systemic sclerosis, small vessel vasculitis, lupus erythematosus, Sjögren's syndrome and rheumatoid arthritis.

Exposure assessment

The exposure assessment included three steps: (A) estimation of styrene exposure intensity, (B) estimation of styrene exposure probability and (C) combining A and B into a styrene exposure score.

A. *Styrene exposure intensity* was modelled based on 1122 personal styrene measurements obtained from 133 Danish reinforced plastics companies between 1970 and 2011 and company information on main product, main process and calendar year.
B. *Styrene exposure probability* within the study population was modelled based on information from a job task survey performed 2013–2014 among 11 264 current or former workers in the industry since 1964. Of these, 4996 (43%) reported a job task implying direct styrene exposure. The odds of exposure for different worker characteristics (sex, occupation, year of employment) and company characteristics (main product and main process) were estimated in a mixed-effects logistic regression model.[22]
C. The predicted styrene exposure intensity and the styrene exposure probability were multiplied to get an individual styrene exposure score for each year a worker was employed in a study company.

Cumulated styrene exposure level was computed by adding the annual exposure scores from first to last year of employment during styrene production. For each worker, we also estimated the three components thereof: duration of employment during styrene production, mean styrene exposure intensity and mean styrene exposure probability.

Detailed information on the study population and exposure assessment is described elsewhere.[22 24 29]

Statistical methods

Follow-up started the year after the first year of employment during styrene production, at the earliest in 1979. Because the National Patient Registry began registration in 1977, we included a 2-year washout period (1977 to 1978) to reduce the number of prevalent cases. Follow-up ended at the date of first diagnosis of systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis, Sjögren's syndrome, death, emigration or end of follow-up on 31 December 2012.

Associations between styrene exposure and autoimmune rheumatic diseases were analysed with a multivariate logistic regression model with person-year as unit of analysis resulting in incidence rate ratios (IRRs) that we presented with 95% CIs.[30] We stratified all analysis on sex, which was decided a priori due to the higher prevalence of autoimmune rheumatic diseases among women.[31] We adjusted for age (≤39, 40–49, 50–59, 60–69, ≥70 years), education (secondary education, vocational education, short-cycle higher education, medium- or long-cycled higher education, unknown) and calendar year of follow-up (1979, 1980–1989, 1990–1999, 2000–2009, 2010–2012). The cumulated styrene exposure level was grouped in tertiles based on the total person-year exposure distribution of both sexes combined, resulting in three equally sized groups of low exposed (≤17 mg/m^3-years), medium exposed (18–67 mg/m^3-years) and high exposed (≥68 mg/m^3-years). Furthermore, we analysed separately duration of employment, mean styrene exposure probability and mean styrene exposure intensity as well as cumulative styrene exposure accrued during specified time windows

Table 1 Characteristics of person-years (percentages) according to cumulated styrene exposure level among 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

	Men			Women		
	Cumulated styrene exposure level (mg/m^3-years)			Cumulated styrene exposure level (mg/m^3-years)		
	≤17	18–67	≥68	≤17	18–67	≥68
Worker characteristics	367 861 person-years	438 164 person-years	456 872 person-years	137 002 person-years	67 056 person-years	48 171 person-years
Occupation*†						
White collar workers	20	14	16	37	28	25
Skilled blue collar workers	26	32	32	3	2	2
Unskilled blue collar workers	42	35	37	37	40	46
Others/unknown	12	19	15	23	30	27
Education*‡						
Secondary education	41	39	39	49	51	55
Vocational education	41	40	41	34	30	26
Short-cycle higher education	4	3	3	4	3	3
Medium-or long-cycle higher education	8	9	6	8	7	5
Unknown	6	9	11	5	9	11
Age (years by 1 November each year)						
≤39	43	32	28	40	32	26
40–49	28	28	26	29	28	26
50–59	19	23	24	19	23	24
60–69	8	12	15	9	12	16
≥70	2	5	7	3	5	8
Calendar year of follow-up*						
1979	1	2	2	1	2	2
1980–1989	9	21	28	11	23	28
1990–1999	22	32	33	24	30	34
2000–2009	50	35	29	48	35	29
2010–2012	18	10	8	16	10	7

*Age standardised.
†Grouped according to the Danish version of ISCO-88.
‡Highest completed education according to The Populations' Education Register (1981–2011).
ISCO-88, International Standard Classification of Occupations 1988.

(<5, 6–10, 11–15 and ≥16 years prior). In the latter analyses, we treated exposures within each window in separate models and classified styrene exposure outside the window as zero and dichotomised exposure level within the window by the median.[32] We estimated the log-linear relation with the original continuous variables. We used Stata V.13 for all statistical analysis.

RESULTS

The study population accumulated 1 515 126 person-years during follow-up. A total of 718 cases of autoimmune rheumatic diseases were identified between 1979 and 2012: systemic sclerosis (n=31), rheumatoid arthritis (n=527), systemic lupus erythematosus (n=38), small vessel vasculitis (n=80) and Sjögren's syndrome (n=42).

Table 1 shows person-year prevalences, age standardised worker characteristics and age by increasing cumulative styrene exposure for men and women. High cumulative styrene exposure was associated with higher age and follow-up during the 1970s–1980s, as expected. No consistent trends were seen for the other characteristics.

When adjusting for age, calendar year, educational level and comparing highest with lowest cumulative exposure tertile, we observed a non-significantly increased risk of systemic sclerosis among women (IRR=2.50; 95% CI 0.50 to 12.50) and men (IRR=1.86; 95% CI 0.50 to 7.00) (table 2). A trend of 1.19 (95 % CI 1.01 to 1.39) per 100 mg/m^3-years was seen for women, for men this value was 1.03 (95 % CI 0.94 to 1.13). Furthermore, among men, but not among women, we observed a non-significantly increased risk of rheumatoid arthritis when comparing high with low cumulative exposure (IRR=1.28; 95 % CI 0.96 to 1.70), with a trend of 1.02 (95 % CI 1.00 to 1.05) per 100 mg/m^3. We only tabulated the total number of cases to avoid cells with less than four cases.

Analyses of rheumatoid arthritis subclassified into seropositive and seronegative cases (information only available for ICD-10 codes) revealed an increased rate ratio of seropositive rheumatoid arthritis among high exposed women (IRR=1.95; 95 % CI 1.05 to 6.61) but not among high exposed men, and increased rate ratios of seronegative rheumatoid arthritis among high exposed men (IRR=1.52; 95 % CI 0.99 to 2.34) but not among women (table 3).

Risk of systemic sclerosis tended to increase with duration of employment, mean exposure intensity and mean exposure probability among women and less so among men (online supplementary table 1).

Analyses of cumulative styrene exposure accrued within different time windows indicated increasing risk of systemic sclerosis, rheumatoid arthritis and small vessel vasculitis following exposure received >10 years earlier among men. No such pattern was seen among women (online supplementary table 2).

Table 2 Incidence rate ratios with 95% CI for systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, small vessel vasculitis and Sjögren's syndrome by cumulated styrene exposure in 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

		Rate ratio			Rate ratio	
		Men			Women	
Styrene exposure level	n	Crude	Adjusted*	n	Crude	Adjusted*
Systemic sclerosis	22			9		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		2.52 (0.68 to 9.30)	1.90 (0.51 to 7.11)		1.02 (0.19 to 5.58)	1.15 (0.20 to 6.52)
≥68 mg/m^3-years		2.68 (0.74 to 9.75)	1.86 (0.50 to 7.00)		2.13 (0.48 to 9.53)	2.50 (0.50 to 12.50)
Per 100 mg/m^3-years		*1.05 (0.97 to 1.14)*	*1.03 (0.94 to 1.13)*		*1.18 (1.01 to 1.38)*	*1.19 (1.01 to 1.39)*
Reumatoid arthritis	359			168		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		1.32 (0.99 to 1.76)	1.12 (0.83 to 1.49)		0.93 (0.64 to 1.35)	0.83 (0.57 to 1.20)
≥68 mg/m^3-years		1.68 (1.28 to 2.21)	1.28 (0.96 to 1.70)		1.17 (0.80 to 1.71)	0.95 (0.63 to 1.41)
Per 100 mg/m^3-years		*1.04 (1.02 to 1.07)*	*1.02 (1.00 to 1.05)*		*1.05 (0.97 to 1.13)*	*1.01 (0.93 to 1.10)*
Systemic lupus erythematosus	23			15		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		0.94 (0.36 to 2.45)	0.84 (0.32 to 2.24)		1.28 (0.42 to 3.90)	1.50 (0.47 to 4.73)
≥68 mg/m^3-years		0.60 (0.21 to 1.74)	0.55 (0.18 to 1.66)		0.71 (0.15 to 3.35)	0.88 (0.18 to 4.35)
Per 100 mg/m^3-years		*0.70 (0.42 to 1.15)*	*0.68 (0.40 to 1.14)*		*0.65 (0.24 to 1.77)*	*0.71 (0.27 to 1.84)*
Small vessel vasculitis	61			19		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		1.01 (0.51 to 2.00)	0.82 (0.41 to 1.64)		0.79 (0.28 to 2.20)	0.71 (0.25 to 2.01)
≥68 mg/m^3-years		1.50 (0.80 to 2.81)	1.06 (0.55 to 2.04)		0.22 (0.03 to 1.67)	0.18 (0.02 to 1.38)
Per 100 mg/m^3-years		*1.06 (1.01 to 1.11)*	*1.03 (0.99 to 1.09)*		*0.39 (0.10 to 1.60)*	*0.32 (0.07 to 1.47)*
Sjögren's syndrome	18			24		
≤17 mg/m^3-years		1	1		1	1
18–67 mg/m^3-years		0.42 (0.13 to 1.39)	0.40 (0.12 to 1.35)		1.10 (0.44 to 2.76)	1.01 (0.40 to 2.55)
≥68 mg/m^3-years		0.60 (0.21 to 1.74)	0.57 (0.19 to 1.70)		0.88 (0.29 to 2.68)	0.79 (0.25 to 2.52)
Per 100 mg/m^3-years		*0.75 (0.46 to 1.23)*	*0.74 (0.45 to 1.22)*		*0.77 (0.42 to 1.42)*	*0.73 (0.38 to 1.41)*

*Adjusted for age, calendar year of follow-up and educational level.

DISCUSSION

Our analyses suggested an association between styrene exposure and systemic sclerosis in men and women, but based on few observations. No consistent pattern was observed for the other autoimmune rheumatic diseases.

To our knowledge, this is the only study of styrene exposure and the occurrence of autoimmune rheumatic diseases. However, several earlier studies have suggested associations with exposure to aromatic and unspecified solvents. A recent meta-analysis reported an increased risk of systemic sclerosis following exposure to aromatic solvent (OR=2.72; 95% CI 1.21 to 6.09).[10] It has been argued that JEMs are less sensitive for women, resulting in risk estimates biased toward the null.[8 14] However, our styrene assessment provided sex-specific estimates, thus this should not apply to our results.

We relied on national company and pension registries and included a high proportion of all companies of the reinforced plastics industry since the 1960s and all workers ever employed in these companies, hence selection bias related to study population could hardly have affected our findings. The quantitative exposure assessment was based on personal styrene measurements and was independent of individual reporting and should

Table 3 Adjusted incidence rate ratios with 95% CI for seropositive* and seronegative† rheumatoid arthritis by cumulated styrene exposure level in 59 997 male and 12 215 female workers in the Danish reinforced plastics industry, 1979 to 2012

	Rate ratio‡ seropositive				Rate ratio‡ seronegative			
Styrene exposure level	n	Men	n	Women	n	Men	n	Women
	156		60		157		84	
≤17 mg/m^3 years		1		1		1		1
18–67 mg/m^3-years		1.19 (0.79 to 1.81)		0.89 (0.45 to 1.76)		1.17 (0.75 to 1.83)		0.97 (0.59 to 1.58)
≥68 mg/m^3‡-years		1.11 (0.73 to 1.70)		1.95 (1.05 to 6.61)		1.52 (0.99 to 2.34)		0.49 (0.24 to 0.98)
Per 100 mg/m^3-years		*0.98 (0.93 to 1.04)*		*1.11 (1.01 to 1.22)*		*1.04 (1.02 to 1.07)*		*0.87 (0.70 to 1.09)*

*Seropositive cases: ICD-10 codes: M050, M051, M051A-F, M052, M053, M058, M059.
†Seronegative cases: ICD-10 codes: M060, M068, M069.
‡Adjusted for age, calendar year of follow-up and educational level.
ICD-10, International Classification of Diseases, 10th version.

be unaffected by recall bias. Cumulative styrene exposure was a combination of styrene exposure intensity, probability and duration, each estimated with considerable uncertainty and this might have led to non-differential misclassification, underestimation of exposure–response relations and increased the risk of overlooking truly increased risks.

Outcomes were based on hospital register information obtained with a clinical purpose. A recent study showed a positive predictive value of 79% for a diagnosis of rheumatoid arthritis in the Danish National Patient Registry.[33] We had no similar information for systemic sclerosis obtained from the patient registry. Misclassification with 21% false positives will lead to attenuation of the association with styrene exposure. We classified cases by the first recorded diagnosis. Different rheumatic diseases often present with similar symptoms and clinical findings, and the first recorded diagnosis might be temporary[28] and probably often the most prevalent (rheumatoid arthritis). However, the diagnostic procedure is unlikely to be related to styrene exposure; hence the misclassification will be non-differential and most likely result in attenuation of risk estimates. Furthermore, we adjusted for calendar year of follow-up to account for changes in occurrence and diagnostic procedures and criteria over time.

Smoking is a well-documented risk factor for rheumatoid arthritis and possibly also for the other autoimmune rheumatic diseases.[1 34] We had no information on smoking that allowed us to adjust for this, but a previous smoking survey showed declining smoking prevalence with increasing duration of employment in this industry.[29] Thus, the increasing rate ratios seen for systemic sclerosis by cumulative styrene exposure are unlikely to be due to smoking.

In the reinforced plastics industry, acetone, a ketone, is a frequent co-exposure to styrene, but at low intensity.[35] Ketones have been related to systemic sclerosis in a few studies.[5 9] Respirable quartz, a strongly suggested risk factor for autoimmune rheumatic diseases is not found in this industry. Recent studies have suggested wood dust, that may be present in the reinforced plastics industry, as a risk factor for rheumatoid arthritis,[34] but this finding was not supported in another study.[36] Non-occupational styrene exposure from tobacco smoke or food is probably of minor importance.

Despite a large study population, we had low power to evaluate the association between styrene exposure and other autoimmune rheumatic diseases than rheumatoid arthritis as reflected in the wide CIs.

Our knowledge on the pathogenic mechanism behind autoimmune rheumatic diseases is far from complete. In a mouse model, styrene has been shown to increase levels of interleukins IL-4, IL-5, IL-13 and interferon-γ.[37] In systemic sclerosis IL-4 and IL-13 play a crucial role in differentiating T cells into T helper type 2 (Th2) cells as well as promoting fibrosis.[38] This strong Th2 response seems to be specific for systemic sclerosis and not present for the other autoimmune diseases.[38–40]

Whether our findings for systemic sclerosis can be generalised to other organic solvents than styrene is hard to say, because they comprise a wide range of chemicals with different toxicological profiles. To conclude this study suggests an association between occupational styrene exposure and systemic sclerosis but based on few cases. This is a new finding and has to be replicated before conclusions can be drawn. No consistent associations were observed for the other autoimmune rheumatic diseases.

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Contributors SHB, JMV, MSM conducted the data analysis, and all authors contributed to interpretation of data. SHB drafted the manuscript and all authors contributed to the interpretation of data and critical revision of the manuscript for important intellectual content.

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REFERENCES

1 Miller FW, Alfredsson L, Costenbader KH, *et al*. Epidemiology of environmental exposures and human autoimmune diseases: findings from a national Institute of environmental health sciences expert panel workshop. *J Autoimmun* 2012;39:259–71.
2 Selmi C, Leung PSC, Sherr DH, *et al*. Mechanisms of environmental influence on human autoimmunity: a national Institute of environmental health sciences expert panel workshop. *J Autoimmun* 2012;39:272–84.
3 Selmi C, Lu Q, Humble MC. Heritability versus the role of the environment in autoimmunity. *J Autoimmun* 2012;39:249–52.
4 Gourley M, Miller FW. Mechanisms of disease: environmental factors in the pathogenesis of rheumatic disease. *Nat Clin Pract Rheumatol* 2007;3:172–80.
5 Diot E, Lesire V, Guilmot JL, *et al*. Systemic sclerosis and occupational risk factors: a case-control study. *Occup Environ Med* 2002;59:545–9.
6 Garabrant DH, Lacey JV, Laing TJ, *et al*. Scleroderma and solvent exposure among women. *Am J Epidemiol* 2003;157:493–500.
7 Maître A, Hours M, Bonneterre V, *et al*. Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. *J Rheumatol* 2004;31:2395–401.
8 Nietert PJ, Sutherland SE, Silver RM, *et al*. Is occupational organic solvent exposure a risk factor for scleroderma? *Arthritis Rheum* 1998;41:1111–8.
9 Marie I, Gehanno J-F, Bubenheim M, *et al*. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014;13:151–6.
10 Zhao J-H, Duan Y, Wang Y-J, *et al*. The influence of different solvents on systemic sclerosis: an updated meta-analysis of 14 case-control studies. *J Clin Rheumatol* 2016;22:253–9.
11 Bovenzi M, Barbone F, Pisa FE, *et al*. A case-control study of occupational exposures and systemic sclerosis. *Int Arch Occup Environ Health* 2004;77:10–16.
12 Parks CG, Hoppin JA, De Roos AJ, *et al*. Rheumatoid arthritis in agricultural health study spouses: associations with pesticides and other farm exposures. *Environ Health Perspect* 2016;124:1728–34.
13 Parks CG, Meyer A, Beane Freeman LE, *et al*. Farming tasks and the development of rheumatoid arthritis in the agricultural health study. *Occup Environ Med* 2019;76:243–9.
14 Lundberg I, Alfredsson L, Plato N, *et al*. Occupation, occupational exposure to chemicals and rheumatological disease. *A register based cohort study*. *Scand J Rheumatol* 1994;23:305–10.
15 Cooper GS, Parks CG, Treadwell EL, *et al*. Occupational risk factors for the development of systemic lupus erythematosus. *J Rheumatol* 2004;31:1928–33.
16 Cooper GS, Parks CG. Occupational and environmental exposures as risk factors for systemic lupus erythematosus. *Curr Rheumatol Rep* 2004;6:367–74.
17 Finckh A, Cooper GS, Chibnik LB, *et al*. Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. *Arthritis Rheum* 2006;54:3648–54.

18 Chaigne B, Lasfargues G, Marie I, *et al*. Primary Sjögren's syndrome and occupational risk factors: a case-control study. *J Autoimmun* 2015;60:80–5.
19 Lane SE, Watts RA, Bentham G, *et al*. Are environmental factors important in primary systemic vasculitis? A case-control study. *Arthritis Rheum* 2003;48:814–23.
20 Rosemond Z, Chou S, Wilson J, *et al*. US department of health and human services, agency for toxic substances and disease registry; toxicological profile for styrene, 2010. Available: https://www atsdr cdc gov/toxprofiles/tp53 pdf/ [Accessed 24 Sep 2019].
21 IARC Monographs Vol 121 Group. Carcinogenicity of quinoline, styrene, and styrene-7,8-oxide. *Lancet Oncol* 2018:30316–4.
22 Christensen MS, Vestergaard JM, d'Amore F, *et al*. Styrene exposure and risk of lymphohematopoietic malignancies in 73,036 reinforced plastics workers. *Epidemiology* 2018;29:342–51.
23 Nett RJ, Cox-Ganser JM, Hubbs AF, *et al*. Non-Malignant respiratory disease among workers in industries using styrene-A review of the evidence. *Am J Ind Med* 2017;60:163–80.
24 Kolstad HA, Sønderskov J, Burstyn I. Company-level, semi-quantitative assessment of occupational styrene exposure when individual data are not available. *Ann Occup Hyg* 2005;49:155–65.
25 Hansen J, Lassen CF. The supplementary pension fund register. *Scand J Public Health* 2011;39:99–102.
26 Thygesen LC, Daasnes C, Thaulow I, *et al*. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health* 2011;39:12–16.
27 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
28 Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. *Lancet* 2013;382:797–808.
29 Christensen MS, Hansen J, Ramlau-Hansen CH, *et al*. Cancer incidence in workers exposed to styrene in the Danish-reinforced plastics industry, 1968-2012. *Epidemiology* 2017;28:300–10.
30 Richardson DB. Discrete time hazards models for occupational and environmental cohort analyses. *Occup Environ Med* 2010;67:67–71.
31 Whitacre CC. Sex differences in autoimmune disease. *Nat Immunol* 2001;2:777–80.
32 Checkoway H, Pearce N, Hickey JL, *et al*. Latency analysis in occupational epidemiology. *Arch Environ Health* 1990;45:95–100.
33 Ibfelt EH, Sørensen J, Jensen DV, *et al*. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish national patient registry. *Clin Epidemiol* 2017;9:627–32.
34 Blanc PD, Järvholm B, Torén K. Prospective risk of rheumatologic disease associated with occupational exposure in a cohort of male construction workers. *Am J Med* 2015;128:1094–101.
35 Jensen AA, Breum NO, Bacher J, *et al*. Occupational exposures to styrene in Denmark 1955-88. *Am J Ind Med* 1990;17:593–606.
36 Gold LS, Ward MH, Dosemeci M, *et al*. Systemic autoimmune disease mortality and occupational exposures. *Arthritis Rheum* 2007;56:3189–201.
37 Ban M, Langonné I, Huguet N, *et al*. Inhaled chemicals may enhance allergic airway inflammation in ovalbumin-sensitised mice. *Toxicology* 2006;226:161–71.
38 O'Reilly S, Hügle T, van Laar JM. T cells in systemic sclerosis: a reappraisal. *Rheumatology* 2012;51:1540–9.
39 Magyari L, Varszegi D, Kovesdi E, *et al*. Interleukins and interleukin receptors in rheumatoid arthritis: research, diagnostics and clinical implications. *World J Orthop* 2014;5:516–36.
40 Ohl K, Tenbrock K. Inflammatory cytokines in systemic lupus erythematosus. *J Biomed Biotechnol* 2011;2011:1–14.