Clin Rheumatol (2017) 36:569–582
DOI 10.1007/s10067-016-3533-1

ORIGINAL ARTICLE

Occupational and environmental scleroderma. Systematic review and meta-analysis

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Received: 4 May 2016 / Revised: 21 September 2016 / Accepted: 28 December 2016 / Published online: 14 January 2017

Abstract The etiology of systemic sclerosis (SSc) remains unknown; however, several occupational and environmental factors have been implicated. Our objective was to perform a meta-analysis of all studies published on SSc associated with occupational and environmental exposure. The review was undertaken by means of MEDLINE and SCOPUS from 1960 to 2014 and using the terms: "systemic," "scleroderma," or "systemic sclerosis/chemically induced" [MesH]. The Newcastle-Ottawa Scale was used for the qualifying assessment. The inverse variance-weighted method was performed. The meta-analysis of silica exposure included 15 case-control studies [overall OR 2.81 (95%CI 1.86–4.23; $p < 0.001$)] and 4 cohort studies [overall RR 17.52 (95%CI 5.98–51.37; $p < 0.001$)]; the meta-analysis of solvents exposure included 13 case-control studies (overall OR 2.00 [95%CI 1.32–3.02; $p = 0.001$); the meta-analysis of breast implants exposure included 4 case-control studies (overall OR 1.68 (95%CI 1.65–1.71; $p < 0.001$)) and 6 cohort studies (overall RR 2.13 (95%CI 0.86–5.27; $p = 0.10$)); the meta-analysis of epoxy resins exposure included 4 case-control studies (overall OR 2.97 (95%CI 2.31–3.83; $p < 0.001$)), the meta-analysis of pesticides exposure included 3 case-control studies (overall OR 1.02 (95%CI 0.78–1.32; $p = 0.90$)) and, finally, the meta-analysis of welding fumes exposure included 4 studies (overall OR 1.29 (95%CI 0.44–3.74; $p = 0.64$)). Not enough studies citing risks related to hair dyes have been published to perform an accurate meta-analysis. Silica and solvents were the two most likely substances related to the pathogenesis of SSc. While silica is involved in particular jobs, solvents are widespread and more people are at risk of having incidental contact with them.

Keywords Environment · Occupational exposure · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune systemic disease of unknown origin. Although several different etiologic agents have been postulated, chemicals have been the most suggested etiologic agents. Among them, silica [1–27], solvents [5, 6, 17, 19, 21, 22, 24–26, 28–44], silicone breast implants [13, 16, 45–59], epoxy resins [19, 22, 25, 26, 60], welding fumes [21, 22, 25, 41], pesticides [17, 21, 25, 26], and hair dyes [21, 34, 61] have been suspected to be related to SSc development. Besides, scleroderma-like disorders related to other chemical agents such as vinyl chloride [62–64] and toxic oil syndrome [65] have also been reported, and isolated case reports suggesting a chemical-related origin have been published since the early twentieth century. Interestingly, more consistent studies have been published in the last three decades, including case-control studies, cohort studies, and meta-analyses.

Various occupational and environmental exposures are ubiquitous and it is almost impossible to avoid even a single contact. Several occupations are known to be at a higher risk, as workers have intense contact with these substances (Table 1). Accordingly, several reviews [66–81] and meta-analyses have been published so far [4, 30–32, 45–49], a few of which are systematic although incomplete and

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Table 1 Compounds and jobs related to SSc development

- Silica
  1. Silica dust
     - Coal and gold miners
     - Cement, pottery, and foundry workers
     - Stone masons
     - Scouring powder
     - Abrasive powder work
     - Foundry workers
     - Quarrymen
     - Sandblasters
     - Sandstone sculptors
     - Glass grinders
     - Cast polishers
     - Dental mechanics
     - Mechanical plowing and harvesting
     - Jewelry (cutting, grinding, polishing, buffing gems and stones)
     - Steel mills (refractory preparation and furnace repair)
     - Construction (abrasive blasting, tunnel construction, excavation, masonry, concrete work, demolition)
     - Ceramics (mixing, modeling, glazing, enameling and polishing)
     - Cement
     - Boiler scaling (ashes and mineral deposits cleaning of coal fired boilers)
     - Automobile repair (abrasive blasting)
     - Asphalt and roofing felt
     - Agricultural chemicals (handling and crushing of raw materials)
     - Rubber and plastics (materials handling)
     - Ship construction and repair (abrasive blasting)
     - Cosmetics, soaps (abrasive soaps, scouring powders)
  2. Breast implants
     - Silicone
     - Paraffin
- Solvents (workers in dry cleaning, chemicals industry, pump attendants, paint thinners)
  1. Aromatic hydrocarbons
     - Benzene (petroleum derivate)
     - Toluene (tire vulcanization, leather finishings, Hospital laboratory, general manufacturing)
     - Xylene (Hospital laboratory, general manufacturing)
     - Aromatic blends or mixes (White spirit, Diesel)
  2. Aliphatic chlorinated hydrocarbons
     - Vinyl chloride (cleaners of vinyl chloride reactors)
     - Trichloroethylene (non-flammable liquid that dissolves fat, grease, tar or waxes used for cold cleaning; degreasing, typographic correction fluid)
     - Trichloroethane (non-flammable cold cleaning) Trichloroethane (non-flammable cold cleaning)
     - Perchloroethylene (non-flammable liquid for cold cleaning where slow evaporation is desired, degreasing, dry cleaning)
     - Hexachloroethane
     - Hexachlorbenzene
  3. Aliphatic non-chlorinated hydrocarbons
     - Naphta-n-hexane
     - N-hexan
     - Diesel oil
     - Epoxy resins (construction workers)
     - Biogenic amines (metaphenylenediamine)
     - Formaldehyde
     - Varnish and paints (paint thinner)
- Welding fumes
- Pesticides
  - Workers in agriculture, gardeners, chemical industry
- Hair dyes
- Drugs
  - Carbidopa
  - Ethosuximide
  - Penicillamine
  - Ergot methysergide
  - L-5-hydroxytriptophan (against insomnia and depression)
  - Pentazocine
  - Cocaine
  - Appetite supressants (Diethylpropion, amphetamine, phenmetrazine, fenproporex, fenfluramine)
  - D-penicillamine
  - Chemotherapy: Bleomycin and peplomycin, Taxanes (Paclitaxel, Docetaxel), Capecitabine, Adryamicin, cyclophosphamide, Vincristine, doxorubicin, Topotecan, 5-fluorouracil, Uracil-tegafur, Gemcitabine
  - Methysergide
  - Gadolinium
  - Interleukin-2
  - Anti-androgen
  - Interferon-alpha
  - Throtrast
  - Oral contraceptives
  - Phytomenadione
- Toxic oil syndrome (aniline

methodologically often highly debatable. The aim of our study was to perform a systematic review and meta-analysis of all these toxic substances related to scleroderma development.

Materials and methods

The search was performed by two independent investigators (R-R.M. and M.R.) through the MEDLINE and SCOPUS databases between January 1960 and November 2014, by using the terms: "systemic," "scleroderma," or "systemic sclerosis/ chemically induced" [MesH]. The search was completed by the bibliography review of every paper selected for full-text examination. No restriction related to language was performed initially but eventually a few papers from Eastern Europe and Asia were excluded from the analysis. The first search found 515 articles, of which 447 articles were non-selected assessing the title and/or abstract. Sixty-eight articles were finally selected for full-text review (Fig. 1).

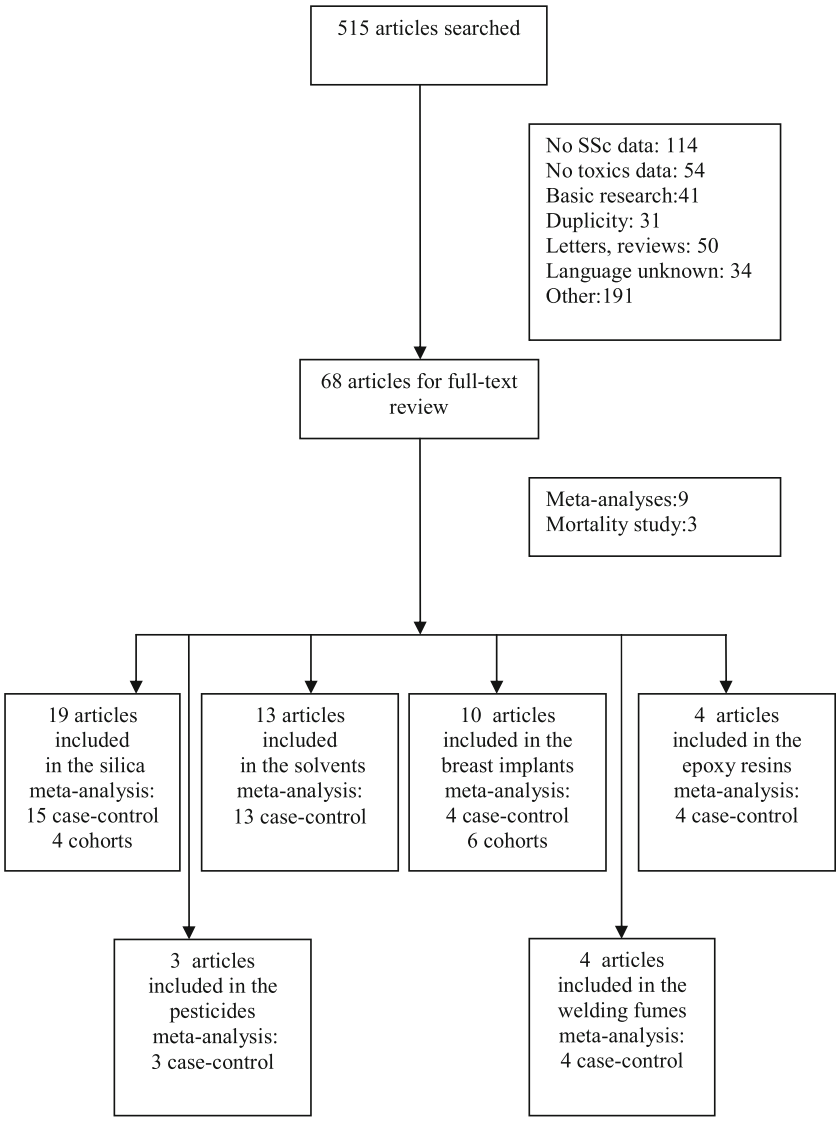

Fig. 1 Flow-chart

In order to perform the meta-analysis, we selected those case-control studies (risk factor described as odds ratio or OR) and cohort studies (risk factor described as risk ratio or RR) separately. Those studies that belonged to other cohorts included in the same meta-analysis were rejected in order to avoid a bias due to data over expression. In such cases, the latest and larger study was selected. In the case of the studies by Bovenzi et al. [5, 6], data belonged to different periods of time, so there was no over expression of data. Eventually, 19 articles were included in the meta-analysis of silica (3 mortality studies were rejected) [5–26], 13 in the meta-analysis of solvents (1 mortality study was rejected) [5, 6, 19, 21, 22, 25, 26, 33, 34, 37–39, 41], 10 in the meta-analysis of breast implants [13, 16, 50–54, 56–59], 4 in the meta-analysis of epoxy resins [19, 22, 25, 26], 4 in the meta-analysis of pesticides [17, 21, 25, 26], and 4 in the meta-analysis of welding fumes [21, 22, 25, 41] (Fig. 1). Not enough studies citing risks related to hair dyes have been published during the study period to perform an accurate meta-analysis [21, 34].

Quality assessment was performed by means of the Newcastle-Ottawa Scale for observational studies [82].

Statistical analysis

Categorical variables were described as absolute number and percentage. Continuous variables were described as mean and standard deviation. A few studies did not publish risk data, but they certainly published raw data enough to calculate the risk factor, so they were included. In those studies reflecting the OR or RR without confidence interval, it was estimated by the formula OR or RR ± 1.96 (OR or RR/$\sqrt{N}$). The study by Sverdrup et al. [43] showed confidence interval without RR, so it was estimated by the formula $\sqrt{}$ lower RR x upper RR [83, 84]. In the study by Thompson et al. [24], there was a

typographical error in the case of silica exposure, and the RR was recalculated in accordance.

The inverse variance-weighted method was initially performed by using the fixed effects model (Fig. 2). Thereafter, between-study variability was measured by Tau^2 parameter and, when confirmed ($p \leq 0.05$), the analysis was completed by using the random effects model. In fact, random effects model assumes that there is an underlying effect for each study which varies randomly across studies, with the resulting overall effect an average of these [84].

Publication bias was ruled out by means of the Begg's method (tau = −0.121 p = 0.547 for silica (case-control) and tau = 0.001 p = 1.000 for silica (cohorts); tau = 0.111 p = 0.677 for solvents; tau = −0.333 p = 0.497 for breast implants (case-control) and tau = 0.467 p = 0.188 for breast implants (cohorts); tau = −0.200 p = 0.624 for epoxy resins; tau = 0.333 p = 0.602 for pesticides; tau = 0.001 p = 1.000 for welding fumes) [85]. Statistical analysis was performed by SPSS 15.0.

Results

All studies included in the present meta-analysis were over 5 points in the Newcastle-Ottawa Scale, reflecting the quality of these papers.

Nineteen studies were included in the meta-analysis of silica (Table 2) [5–26], 4 cohort studies and 15 case-control studies. Three mortality studies were not included (Walsh et al. [14], Calvert et al. [15] and Gold et al. [17]). The 15 case-control studies reported data from 1336 patients (2 studies by Silman et al. [19] were based on the same cases but different controls), 835 (62.5%) were female and 501 (37.5%) were male. The mid-cohort years of every study ranged from 1960 to 2006 and the OR ranged from 0.9 (95%CI 0.2–3.2) to 21 (95%CI 4.7–101). The overall OR was 2.81 (95%CI 1.86–4.23; $p < 0.001$) by means of the random effects model. The overall OR for male gender was 3.06 (95%CI 1.90–4.91; $p < 0.001$) by the random effects model and the overall OR for female gender was 2.10 (95%CI 1.24–3.55; $p = 0.005$) by the fixed effects model. There were 4 cohort studies with risks described as RR. They showed data from 247,563 patients. The mid-cohort years ranged from 1977 to 1995 and RR ranged from 7.8 (95%CI 6.5–9.5) to 37 (95%CI 11.9–86.3). The overall RR was 17.52 (95%CI 5.98–51.37; $p < 0.001$) by means of the random effects model. There were not enough data to analyze by gender.

Thirteen studies were included in the meta-analysis of solvents (Table 3) [5, 6, 19, 21, 22, 25, 26, 33, 34, 37–39, 41]. All of them were case-control studies. The study by Laing et al. [35] belonged to the same cohort than the study by Lacey et al. [34], so we decided to include only the one with the largest number of patients. Czirjak et al. published two case-control studies [36, 39] which belonged to the same cohort, so the oldest was rejected. No study was excluded because of the quality assessment. These 13 case-control studies reported data from 2107 patients. The mid-cohort years ranged from 1983 to 2006 and the OR ranged from 0.56 to 9.28. The overall OR was 2.00 (95%CI 1.32–3.02; $p = 0.001$) by means of the random effects model. The OR for male gender was 2.40 (95%CI 1.44–4.01; $p < 0.001$) and for female gender 2.01 (95%CI 1.66–2.44; $p < 0.001$) with the fixed effects model. There were 2 more cohort studies describing RR of solvents as a risk factor for SSc, but they were not included in the present meta-analysis due to the limited representativeness of the sample [43, 44].

Fig. 2 Forest plots of risk (OR for case-control and RR for cohort studies) for silica, solvents, breast implants, epoxy resins, and welding fumes exposure ▶

Ten studies were included in the meta-analysis of silicone breast implants (Table 4) [13, 16, 50–54, 56–59]. There were 7 cohort studies and 5 case-control studies. No study was excluded because of the quality assessment. Out of the 7 cohort studies the one by Fryzek et al. [55] was excluded since it showed data also reported in that reported by Kjoller et al. [53]. Therefore, the final 6 cohort studies reported data from 23,139 patients. All of them were women. The mid-cohort years ranged from 1978 to 1993 and RR ranged from 0.5 to 27.7. The overall RR was estimated in 2.13 (95%CI 0.86–5.27; $p = 0.10$) by means of the random effects model. Out of the 5 case-control studies, we excluded the one by Goldman et al. [54] since the calculated OR for SSc was zero because no cases of SSC were diagnosed among the 150 patients with breast implants of a representative sample of 721 women with a wide range of connective tissue diseases. Therefore, the final 4 case-control studies reported data from 1615 patients (1551 females and 64 males). The mid-cohort years ranged from 1988 to 1991 and the OR ranged from 1.01 to 1.68. The overall OR was 1.68 (95%CI 1.65–1.71; $p < 0.001$) by means of the fixed effects model.

Four studies were included in the meta-analysis of epoxy resins [19, 22, 25, 26], but the study by Silman et al. [19] included two case-control studies with the same cases but different controls (Table 5). No study was excluded because of the quality assessment. These 4 studies reported data from 264 patients, 147(55.7%) of them were women. The mid-cohort years ranged from 1984 to 2006 and the OR ranged from 0.5 to 4.24. The overall OR was 2.97 (95%CI 2.31–3.83; $p < 0.001$) by means of the fixed effects model. The OR for males was 2.92 (95%CI 2.26–3.78) and for females 1 (95%CI 0.02–12.72).

Three studies were included in the meta-analysis of pesticides (Table 5) [17, 21, 25, 26]. No study was excluded because of the quality assessment. These 3 studies reported data from 264 patients, 147(55.7%) of them were women. The mid-cohort years ranged from 1984 to 2006 and the OR

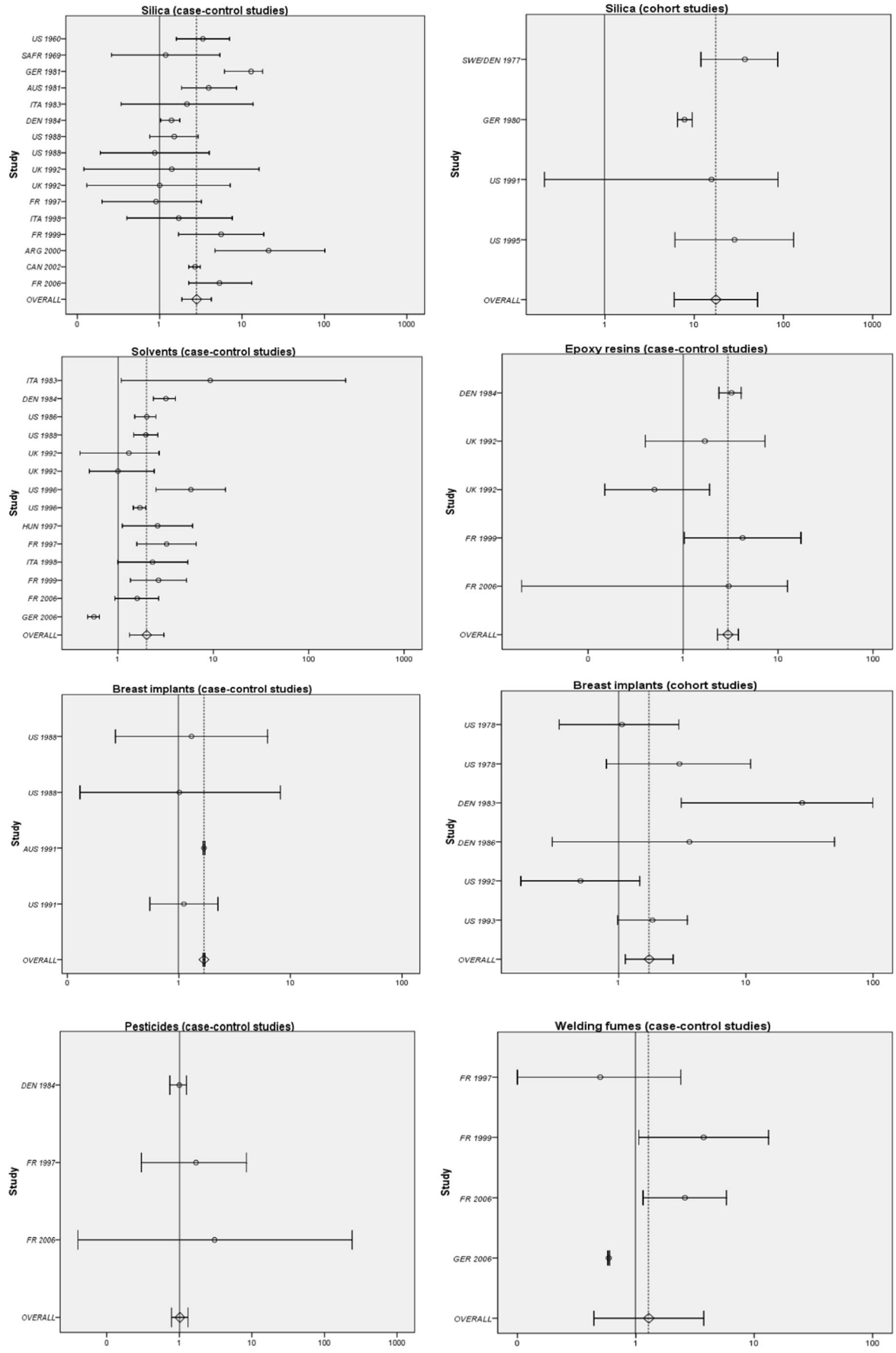
Silica (case-control studies)
US 1960
SAFR 1969
GER 1981
AUS 1981
ITA 1983
DEN 1984
US 1988
US 1988
UK 1992
UK 1992
FR 1997
ITA 1998
FR 1999
ARG 2000
CAN 2002
FR 2006
OVERALL
Study
0
1
10
100
1000
Silica (cohort studies)
SWE/DEN 1977
GER 1980
US 1991
US 1995
OVERALL
Study
1
10
100
1000
Solvents (case-control studies)
ITA 1983
DEN 1984
US 1986
US 1988
UK 1992
UK 1992
US 1996
US 1996
HUN 1997
FR 1997
ITA 1998
FR 1999
FR 2006
GER 2006
OVERALL
Study
1
10
100
1000
Epoxy resins (case-control studies)
DEN 1984
UK 1992
UK 1992
FR 1999
FR 2006
OVERALL
Study
0
1
10
100
Breast implants (case-control studies)
US 1988
US 1988
AUS 1991
US 1991
OVERALL
Study
0
1
10
100
Breast implants (cohort studies)
US 1978
US 1978
DEN 1983
DEN 1986
US 1992
US 1993
OVERALL
Study
1
10
100
Pesticides (case-control studies)
DEN 1984
FR 1997
FR 2006
OVERALL
Study
0
1
10
100
1000
Welding fumes (case-control studies)
FR 1997
FR 1999
FR 2006
GER 2006
OVERALL
Study
0
1
10
100

Table 2 Risk of SSc after silica exposure. OR: Odds ratio. RR: Risk ratio. PMR: proportional mortality ratio. QA: Newcastle-Ottawa quality assessment. NA : non available

Study	Country	Study design	Number of patients (females)	Years (mid-cohort year)	QA	Risk (95%CI)	Risk for females (95%CI)	Risk for males (95%CI)
Rodnan[7]	US	Case-control	60 (0)	1955–65 (60)	5	OR 3.34 (1.59–7.05)	–	OR 3.34 (1.59–7.05)
Sluis-Cremer[8]	SAFR	Case-control	79 (0)	1955–84 (69)	6	OR 1.18 (0.26–5.38)	–	OR 1.18 (0.26–5.38)
Brown[10]	SWE/DEN	Cohort	2290 (0)	1965–89 (77)	7	RR 37 (11.9–86.3)	–	RR 37 (11.9–86.3)
Mehlhorn[11]	GER	Cohort	103 (0)	1966–95 (80)	7	RR 7.8 (6.5–9.5)	–	RR 7.8 (6.5–9.5)
Ziegler[9]	GER	Case-control	54 (0)	1971–91 (81)	7	OR 12.9 (7.6–22)	–	OR 12.9 (7.6–22)
Englert[12]	AUS	Case-control	160 (0)	1974–88 (81)	7	OR 3.93 (1.84–8.54)	–	OR 3.93 (1.84–8.54)
Bovenzi[5]	ITA	Case-control	21 (16)	1976–91 (83)	6	OR 2.14 (0.34–13.6)	–	OR 5.20 (0.48–74.1)
Zachariae[26]	DEN	Case-control	28 (0)	1974–95 (84)	7	OR 1.39 (1.03–1.75)	–	OR 1.39 (1.03–1.75)
Burns[13]	US	Case-control	274 (274)	1985–91 (88)	8	OR 1.5 (0.76–2.93)	OR 1.5 (0.76–2.93)	–
Walsh[14]	US	Mortality	2920 (2223)	1985–92 (88)	6	PMR 1 (0.8–1.1)	PMR 0.8 (0.6–1.2)	PMR 1 (0.8–1.2)
Calvert[15]	US	Mortality	2875 (NA)	1982–95 (88)	6	OR 2 (0.39–10.31)	–	–
Lacey[16]	US	Case-control	189 (189)	1985–92 (88)	8	OR 0.87 (0.19–4.00)	OR 0.87 (0.19–4.00)	–
Gold[17]	US	Mortality	5642 (NA)	1984–98 (91)	6	RR 1.02 (0.92–1.13)	–	–
Rosenman[18]	US	Cohort	583 (NA)	1987–95 (91)	7	RR 15.65 (0.21–87.03)	–	–
Silman[19]	UK	Case-control	56 (0)	1992 (92)	6	OR 1 (0.13–7.2) OR 1.4 (0.12–16.1)	– –	OR 1 (0.13–7.2) OR 1.4 (0.12–16.1)
Makol[20]	US	Cohort	790 (20)	1985–06 (95)	8	RR 28.3 (6.09–129.98)	–	–
Maitre[21]	FR	Case-control	93 (83)	1995–99 (97)	6	OR 0.9 (0.2–3.2)	–	OR 0.9 (0.2–4.4)
Bovenzi[6]	ITA	Case-control	55 (46)	1997–99 (98)	7	OR 1.7 (0.4–7.6)	OR 2.4 (0.4–15.5)	OR 1.2 (0.1–15.8)
Diot[22]	FR	Case-control	80 (69)	1998–00 (99)	6	OR 5.57 (1.69–18.37)	OR 13.04 (1.54–110.66)	OR 3.62 (0.64–20.4)
Mora[23]	ARG	Case-control	20 (15)	1998–02 (00)	7	OR 21 (4.7–101)	OR 24.6 (3.6–216)	OR 28 (1.4–1200)
Thompson[24]	CAN	Case-control	67 (65)	2002 (02)	7	RR 0.51 (0.43–0.59) OR 2.68 (2.25–3.11)	– –	– –
Marie[25]	FR	Case-control	100 (78)	2005–08 (06)	8	OR 5.32 (2.25–13.09)	OR 3.08 (0.4–23.49)	OR 8.3 (2.58–29.6)
McCormic[4]	AUS	Meta-analysis	1101 (NA)	2010 (10)	–	OR 3.2 (1.89–5.43)	OR 1.03 (0.74–1.44)	OR 3.02 (1.24–7.35)

Table 3 Risk of solvent exposure. OR: Odds ratio. RR: Risk ratio. BTX: benzene, toluene, xylene. QA: Newcastle-Ottawa quality assessment

Study	Country	Study design	Patients (females)	Years (mid-cohort)	QA	Toxic	Risk (95%CI)	Risk for females (95%CI)	Risk for males (95%CI)
Sverdrup[43]	SWE	Cohort	9 (0)	1970–75 (73)	6	Solvent	RR 7.28 (6.86–7.72)	–	RR 7.28 (6.86–7.72)
Lundberg[44]	SWE	Cohort	71 (24)	1981–83 (82)	8	Aliphatics	RR 2.1 (0.8–5.5)	–	RR 2.1 (0.8–5.5)
Bovenzi[5]	ITA	Case-control	21 (16)	1976–91 (83)	6	Solvent	OR 9.28 (1.08–243.8)	OR 2.03 (0.05–83)	–
Zachariae[26]	DEN	Case-control	28 (0)	1974–95 (84)	7	Solvent	OR 3.18 (2.35–4.01)	–	OR 3.18 (2.35–4.01)
Garabrant[33]	US	Case-control	660 (660)	1980–92 (86)	7	Solvent	OR 2 (1.5–2.5)	OR 2 (1.5–2.5)	–
						Paint thinners	OR 2.0 (0.5–2.6)	OR 2.0 (0.5–2.6)	–
						Gasoline	OR 1.3 (0.7–2.6)	OR 1.3 (0.7–2.6)	–
						Toluene	OR 1.7 (0.7–4.1)	OR 1.7 (0.7–4.1)	–
						Xylene	OR 1.9 (0.6–6.3)	OR 1.9 (0.6–6.3)	–
						Benzene	OR 0.8 (0.2–2.6)	OR 0.8 (0.2–2.6)	–
						Trichloroethylene	OR 1.9 (0.6–6.6)	OR 1.9 (0.6–6.6)	–
						Perchloroethylene	OR 1.1 (0.4–2.9)	OR 1.1 (0.4–2.9)	–
						Trichloroethane	OR 0.9 (0.3–2.8)	OR 0.9 (0.3–2.8)	–
						Mineral spirits, naphta, white spirits	OR 1.2 (0.9–1.8)	OR 1.2 (0.9–1.8)	–
Lacey[34]	US	Case-control	472 (NA)	1985–92 (88)	6	Solvent	OR 1.96 (1.46–2.62)	–	–
						Paint thinners	OR 1.82 (1.32–2.51)	–	–
						Trichloroethylene	OR 2.29(0.92–5.71)	–	–
						Gasoline	OR 1.78 (1.01–3.16)	–	–
Laing[35]	US	Case-control	274 (274)	1985–92 (88)	6	Solvent	OR 3.55 (1.69–7.47)	–	–
Czirjak[36]	HUN	Case-control	61 (60)	1989 (89)	6	Solvent	OR 23.28 (17.44–29.12)	–	–
Gold[17]	US	Mortality	5642 (NA)	1984–98 (91)	6	Solvent	RR 0.96 (0.90–1.03)	–	–
						Benzene	RR 1.03 (0.94–1.12)	–	–
Silman[19]	UK	Case-control	56 (0)	1992 (92)	6	Solvent	OR 1.3 (0.4–2.7)	–	OR 1.3 (0.4–2.7)
						Formaldehide	OR 1.0 (0.5–2.4)	–	OR 1.0 (0.5–2.4)
							OR 0.8 (0.2–3)	–	OR 0.8 (0.2–3)
							OR 0.9 (0.2–4.4)	–	OR 0.9 (0.2–4.4)
Goldman[37]	US	Case-control	33 (30)	1996 (96)	7	Solvent	OR 5.82 (2.5–13.4)	–	–
						Perchloroethylene	OR 12.20 (8.04–16.36)	–	–
						Trichloroethane	OR 15.87 (10.46–21.28)	–	–
Nietert[38]	US	Case-control	178 (141)	1995–97 (96)	8	Solvent	OR 1.70 (1.45–1.95)	OR 1.1 (0.5–2.2)	OR 2.9 (1.1–7.6)
						Trichloroethylene	OR 1.63 (1.39–1.87)	OR 1.2 (0.5–2.69	OR 2 (0.7–5.3)
						Trichloroethane	OR 1.84 (1.57–2.11)	OR 1.5 (0.6–3.7)	OR 2 (0.7–5.2)
						Benzene	OR 1.28 (1.09–1.47)	OR 2 (0.7–5.5)	OR 1.5 (0.6–3.8)
						Carbon tetrachloride	OR 1.75 (1.49–2.01)	OR 1.0 (0.4–2.6)	OR 2.0 (0.8–5.3)
Czirjak[39]	HUN	Case-control	63 (63)	1995–00 (97)	6	Solvent	OR 2.60 (1.11–6.06)	OR 2.60 (1.11–6.06)	–
Maitre[21]	FR	Case-control	93 (83)	1995–99 (97)	6	Solvent	OR 3.23(1.58–6.63)	OR 2.8 (1.2–6.1)	OR 8.4 (0.9–78.6)
						Halogenated	OR 2.5 (0.8–7.3)	OR 1.8 (0.5–6.6)	OR 6.2 (0.6–64.2)
						BTX	OR 1.3 (0.5–3.2)	OR 1.3 (0.4–3.8)	OR 1.4 (0.3–6.5)

Table 3 (continued)

Study	Country	Study design	Patients (females)	Years (mid-cohort)	QA	Toxic	Risk (95%CI)	Risk for females (95%CI)	Risk for males (95%CI)
						Aliphatic	OR 1.4 (0.2–9.7)	–	–
						Formaldehyde	OR 1.5 (0.6–3.9)	OR 1.7 (0.6–5)	–
Arnaud[40]	FR	Case-control	93 (83)	1995–99 (97)	6	Solvent	OR 4 (1.91–8.39)	OR 3.10 (1.41–6.82)	–
Bovenzi[6]	ITA	Case-control	55 (46)	1997–99 (98)	7	Solvent	OR 2.3 (1.0–5.4)	OR 1.7 (0.6–4.6)	OR 17 (1.3–218)
Diot[22]	FR	Case-control	80 (69)	1998–00 (99)	6	Solvent	OR 2.66 (1.35–5.23)	OR 2.25 (1.01–5.05)	OR 7.11 (1.4–36.12)
						Aromatics	OR 2.67 (1.06–6.75)	OR 2.48(0.8–7.7)	OR 3.62(0.64–20.41)
						Toluene	OR 3.44 (1.09–10.9)	OR 3.51(0.81–15.17)	OR 3.75(0.52–26.84)
						Chlorides	OR 2.61 (1.2–5.66)	OR 2.44(0.9–6.63)	OR 4.67(0.99–21.89)
						Trichloroethylene	OR 2.39 (1.04–5.22)	OR 2.1(0.65–6.75)	OR 4.67 (0.99–21.89)
						White spirits	OR 3.46 (1.48–8.11)	OR 5.9(1.51–23.01)	OR 3.75(0.82–17.17)
						Cetones	OR 8.78 (1.48–42.38)	OR 7.68(1.55–38.02)	–
Thompson[24]	CAN	Case-control	67 (65)	2002 (02)	7	Toluene	RR 0.76 (0.37–4.76)	–	–
						Benzene	RR 0.8 (0.44–3.719	–	–
						White spirit	RR 0.67 (0.12–3.71)	–	–
						Perchloroethylene	RR 0.91 (0.14–5.48)	–	–
						Trichloroethylene	RR 0.91(0.14–5.48)	–	–
						Trichloroethane	RR 0.65 (0.06–7.6)	–	–
						Vinyl chloride	RR 0.22 (0.02–1.8)	–	–
						Formaldehyde	RR 1.67 (0.67–4.84)	–	–
						Aromatics	RR 1.35 (0.33–5.66)	–	–
						Aliphatics	RR 0.65 (0.06–7.48)	–	–
Aryal[30]	US	Meta-analysis	722 (NA)	2002 (02)	–	Solvent	OR 2.91 (1.6–5.3)	–	–
Marie[25]	FR	Case-control	100 (78)	2005–08 (06)	8	Solvent	OR 1.59 (0.93–2.67)	OR 1.86 (0.98–3.48)	OR 1.10 (0.37–3.24)
						Chlorinated	OR 2.46 (1.12–5.32)	OR 1.72 (0.44–5.92)	OR 4.01 (1.23–13.37)
						Trichloroethylene	OR 2.26 (0.95–5.26)	OR 1.36 (0.30–5.04)	OR 2.77 (0.80–9.35)
						Toluene	OR 2.04 (0.41–8.79)	OR 3.07 (0.22–42.96)	OR 1.52 (0.13–11.53)
						Xylene	OR 1.56 (0.14–11.06)	–	OR 2.05 (0.16–19.23)
						Aromatic	OR 8.17 (2.29–36.5)	OR 26.4 (3.45–1183)	OR 2.05 (0.60–19.22)
						Cetones	OR 3.37 (1.51–7.53)	OR 5.52 (1.76–19.37)	OR 2.04 (0.53–7.41)
Kütting[41]	GER	Case-control	175 (141)	2006 (06)	6	Solvent	OR 0.56 (0.48–0.64)	OR 0.48 (0.09–2.64)	OR 4.79 (0.46–69.90)
Kettaneh[31]	FR	Meta-analysis	1291 (1102)	2007 (07)	–	Solvent	OR 2.41 (1.73–3.37)	OR 1.89 (1.60–2.23)	OR 2.96 (1.89–4.64)
Barragán[32]	COL	Meta-analysis	635 (NA)	2012 (12)	–	Solvent	OR 2.52 (1.24–5.14)	–	–

Table 4 Risk of SSc after breast implants exposure. In brackets cases of SSc in the cohort studies. OR: Odds ratio. RR: Risk ratio. HR: Hazard ratio. NA: non available. QA: Newcastle-Ottawa quality assessment

Study	Country	Study design	Number of patients (SSc cases)	Female / male	Years (mid-cohort)	QA	Risk (95%CI)
Gabriel[50]	US	Cohort	749 (1)	749/0	1964–91(78)	8	RR 1.06 (0.34–2.97)
Brinton[51]	US	Cohort	7234(23)	7234/0	1960–96(78)	6	RR 3 (0.8–10.9)
McLaughlin[52]	DEN	Cohort	824 (2)	824/0	1977–89(83)	6	RR 27.7 (3.1–99.8)
Kjoller[53]	DEN	Cohort	2761(2)	2761/0	1977–96(86)	8	RR 3.6 (0.3–49.7)
Goldman[54]	US	Case-control	64	64/0	1982–92(87)	8	OR 0 (0–2.05)
Burns[55]	US	Case-control	274	274/0	1985–91(88)	8	OR 1.30 (0.27–6.23)
Lacey[56]	US	Case-control	189	189/0	1985–92(88)	8	OR 1.01 (0.13–8.15)
Fryzek[57]	DEN	Cohort	2761(3)	2761/0	1977–01(89)	8	HR 1.7 (0.4–7.7)
Englert[58]	AUS	Case-control	315	251/64	1989–93(91)	9	OR 1.68 (1.65–1.71)
Hochberg[59]	US	Case-control	837	837/0	1990–93(91)	7	OR 1.11 (0.55–2.24)
Wigley[60]	US	Retrospective cohort	741	741/0	NA-92(92)	6	RR 0.5 (0.17–1.46)
Hennekens[61]	US	Retrospective cohort	10,830(324)	324/0	1992–95(93)	6	RR 1.84 (0.98–3.46)
Hochberg[46]	US	Meta-analysis	1426	1362/64	1995	–	OR 1.04 (0.58–1.88)
Perkins[45]	US	Meta-analysis	3242	3242/0	1995	–	RR 0.98 (0.57–1.64)
Wong[47]	US	Meta-analysis	2232	2168/64	1996	–	OR 0.82 (0.50–1.35)
Whorton[48]	US	Meta-analysis	1426	1362/64	1997	–	OR 1.02 (0.56–1.84)
Janowsky[49]	US	Meta-analysis	12,445	12,381/64	2000	–	RR 1.30 (0.86–1.96)

ranged from 1 to 3.06. The overall OR was 1.02 (95%CI 0.78–1.32; $p = 0.90$) by means of the fixed effects model. The OR for males was 1.02 (95%CI 0.79–1.33; $p = 0.86$) and for females 3.06 (95%CI 0.22–43.34).

Four studies were included in the meta-analysis of welding fumes (Table 5) [21, 22, 25, 41]. All of them were case-control studies. No study was excluded because of the quality assessment. The study by Kutting et al. [41] reported OR for genders but did not report overall OR. However, it could be easily calculated. Inversely, the study by Maitre et al. [21] reported overall OR and we calculated those OR by genders. These 4 studies reported data from 448 patients, 371 (82.81%) of them were women. The mid-cohort years ranged from 1997 to 2006 and the OR ranged from 0.5 to 3.74. The overall OR was 1.29 (95%CI 0.44–3.74 $p = 0.64$) by means of the random effects model. The OR for males was 5.87 (95%CI 2.49–13.86) and for females 1.52 (95%CI 0.36–6.49).

Discussion

The present study constitutes the largest meta-analysis ever done before in occupational and environmental SSc. To date, only 8 meta-analyses had previously focused on this matter in medical literature: 1 on silica-related SSc, 3 on solvent-related SSc, 4 on silicone breast implant-related SSc, and none assessing epoxy resins nor pesticides nor welding fumes-related SSc. Differences between overall RR and OR were notorious, probably due to cohort studies just including a relatively small number of SSc cases and this fact can bias the results. Thus, in our opinion, case-control studies are a more appropriate method to study such low incidental disease.

Silica

Silica was the best and first well-known exposure related to SSc development [1, 2]. Silicon exists primarily in the form of silica dioxide (SiO2) and its three principal crystalline forms: quartz, tridymite, and cristobalite. Symptoms are undistinguishable from those recognized in the classical scleroderma, and autoimmune spectrum is similar as well. Antinuclear antibodies and anti-topoisomerase have been described in the majority of patients [3]. Only 1 meta-analysis has been reported by McCormic et al. [4], including 16 studies of different nature (case-control, cohort and mortality studies), initially evaluated all together and, thereafter, separately. Data were expressed as estimator of RR (CERR) but certainly the source risk was heterogenous. They estimated an overall CERR of 3.2 (95%CI 1.89–5.43) and of 2.24 (95%CI 1.65–3.31) for just the case-control studies. In the present meta-analysis, we showed data from 19 studies, 15 of which were case-control studies with an overall OR of 2.81 (95%CI 1.86–4.23; $p < 0.001$). The exposure levels differ from one patient to another and these differences were not taken into account in these studies.

Recently, Freire et al. reported clinical peculiarities in those patients with scleroderma exposed to silica [27]. Thus, these patients tended more often to be male and presenting with

Table 5 Risk of SSc after different exposures. OR: Odds ratio. RR: Risk ratio. NA : non available. QA: Newcastle-Ottawa quality assessment

Study	Country	Study design	Number of patients (females)	Years (mid-cohort year)	QA	Toxic	Risk (95%CI)	Risk for females (95%CI)	Risk for males (95%CI)
Zachariae[26]	DEN	Case-control	28 (0)	1974–95 (84)	7	Epoxy resins	OR 3.24 (2.39–4.09)	–	OR 3.24 (2.39–4.09)
Silman[19]	UK	Case-control	56 (0)	1992 (92)	6	Epoxy resins	OR 1.7 (0.4–7.3)	–	OR 1.7 (0.4–7.3)
							OR 0.5 (0.15–1.9)	–	OR 0.5 (0.15–1.9)
Diot[22]	FR	Case-control	80 (69)	1998–00 (99)	6	Epoxy resins	OR 4.24 (1.03–17.44)	–	OR 2.37(0.39–14.38)
Marie[25]	FR	Case-control	100 (78)	2005–08 (06)	8	Epoxy resins	OR 3.03 (0.02–12.6)	OR 1 (0.02–12.72)	–
Maitre[21]	FR	Case-control	93 (83)	1995–99 (97)	6	Welding fumes	OR 0.5 (0.1–2.4)	–	–
Diot[22]	FR	Case-control	80 (69)	1998–00 (99)	6	Welding fumes	OR 3.74 (1.06–13.18)	OR 4.09(0.36–45.9)	OR 5.28(0.96–28.9)
Marie[25]	FR	Case-control	100 (78)	2005–08 (06)	8	Welding fumes	OR 2.6 (1.15–5.81)	OR 3.17 (0.82–12.24)	OR 8.62(2.64–32.04)
Kütting[41]	GER	Case-control	175 (141)	2006 (06)	6	Metallic fumes	OR 0.59 (0.58–0.60)	OR 0.58 (0.47–0.71)	OR 3.32 (0.71–19.19)
Maitre[21]	FR	Case-control	93 (83)	1995–99 (97)	6	Dyes	OR 2(0.3–10.5)	OR 2 (0.3–10.5)	–
Lacey[34]	US	Case-control	472 (NA)	1985–92 (88)	6	Dyes	OR 1.64 (0.98–2.74)	OR 1.64 (0.98–2.74)	–
Zachariae[26]	DEN	Case-control	28 (0)	1974–95 (84)	7	Pesticides	OR 1 (0.74–1.26)	–	OR 1 (0.74–1.26)
Gold[17]	US	Mortality	5642 (NA)	1984–98 (91)	6	Pesticides	RR 0.99 (0.90–1.10)	–	–
Maitre[21]	FR	Case-control	93 (83)	1995–99 (97)	6	Pesticides	OR 1.7 (0.3–8.4)	–	–
Marie[25]	FR	Case-control	100 (78)	2005–08 (06)	8	Pesticides	OR 3.06 (0.04–241.94)	OR 3.09 (0.22–43.34)	OR 2.63 (0.47–13.72)

diffuse subset, topoisomerase antibodies, and interstitial lung disease.

Solvents

There is a very broad spectrum of different solvents potentially involved in the genesis of SSc related to chemical industry. Since its first description in 1957 [28], there have been many case reports and case series described [29]. Symptoms are also similar to those of classical SSc. Antinuclear antibodies with speckled pattern have been described and angiography reveals digital arterial narrowing.

There were 3 prior meta-analyses published in the last decades [30–32]. In 2002, Aryal et al. [30] reported the first systematic review focused on solvent exposure including 7 case-control studies and one cohort study, with an overall RR of 2.91 (95%CI 1.60–5.30). This review was done with only one database and data included were heterogenous, including both OR and RR in the same analysis. In 2007, Kettaneh et al. [31] reported a brilliant meta-analysis assessing 11 case-control studies with an overall OR of 2.41 (95%CI 1.73–3.37). Data were homogeneous and methodology was impeccable. Finally, in 2012, Barragán et al. [32] published the most recent meta-analysis from 4 different databases which included 8 case-control studies with an overall OR of 2.52 (95%CI 1.24–5.14). Among the revised studies, the one by Thompson et al. [24] showed data from different kinds of solvents but there was no category called "any solvent." In the present meta-analysis, the representative sample of 13 case-control studies was larger and homogeneous, and data were expressed as OR in every study. Our overall OR was OR 2.00 (95%CI 1.32–3.02; $p = 0.001$), clearly reaffirming the results observed in previous studies. Again, the exposure levels differ from one patient to another and these differences were not taken into account in these studies.

Silicone breast implants

Early after the introduction of this surgical procedure, concern grew about the risk of induction and development of associated connective tissue diseases. In early 60's, paraffin, silicone, and petroleum jelly injections for augmentation mammoplasty (a technique widely used in Japan at that time) were related to SSc. Presence of antinuclear antibodies were described as well as improvement of the connective tissue disorder after implant removal.

Five meta-analyses [45–49] were reported in the medical literature prior to the present study. Perkins et al. [45] published the first meta-analysis in 1995, showing data from 7 studies (4 case-control and 3 cohort) from 4 databases. They found an overall RR of 0.98 (95%CI 0.57–1.64). However, these authors analyzed all these heterogenous studies together and did not reject any one of them with 0 cases reported.

Hochberg et al. [46] published in 1995 a meta-analysis from 3 case-control studies by reviewing just one database (Medline), with an overall OR of 1.04 (95%CI 0.58–1.88). Publication bias was not assessed. Wong et al. [47] published in 1996 a meta-analysis including only 3 case-control studies from 2 databases, with an overall OR of 0.82 (95%CI 0.50–1.35). Whorton et al. [48] published their study in 1997. They did not specify the method for research and publication bias was not assessed. They showed data from 3 case-control studies with an overall OR of 0.82 (95%CI 0.50–1.35). Janowsky et al. [49] published in 2000 the most recent meta-analysis including 5 studies (4 case-control and 1 cohort) from 4 databases. They showed a summary RR of 1.30 (95%CI 0.86–1.96) but they certainly did not analyze homogenous studies. In our meta-analysis, the overall RR for cohort studies was 2.13 (95%CI 0.86–5.27; $p = 0.10$) and the overall OR for case-control studies was 1.68 (95%CI 1.65–1.71; $p < 0.001$). Although previous studies could not demonstrate a possible role of silicone breast implants inducing SSc, this possibility cannot be ruled out in our meta-analysis, in which results reached statistical significance when analyzing case-control studies. Another point of discussion would be the fact that the breast augmentation surgery has been changing over time and materials used today differ from those used in the past. They are expected to be safer, but unfortunately, the short number of studies performed and their heterogeneity does not allow identifying this progression over time.

Epoxy resins

These compounds are commonly used in construction. Their association with SSc was first described in 1980 by Yamakage et al. in 6 patients engaged in the polymerization process of epoxy resins, probably due to exposure to bis-(4-amino-3-methyl-cyclohexyl) methane [60]. These patients demonstrated skin sclerosis, telangiectasias, hyperpigmentation, muscle weakness, fatigue, pruritus, total loss of body hair, arthralgias, flexion contractures, diminished vital capacity in pulmonary function tests. Unlike scleroderma, neither Raynaud's phenomenon nor antinuclear antibodies were detected. Angiography revealed narrowing and irregularity of the lumen in the left ulnar and interosseous arteries.

Since there were no prior systematic reviews on epoxy resins-induced SSc, the present study constitutes the first meta-analysis published to date. An overall OR of 2.97 (95%CI 2.31–3.83; $p < 0.001$) was found.

Welding fumes, pesticides and hair dyes

Few studies have focused on welding or metallic fumes as a causative agent of SSc. In particular, there were only 4 case-control studies previously published to our knowledge. Since the first detection of pesticides as a potential causative agent in 1996 [26], there have been only three case-control studies and one mortality study. Moreover, three case-control studies have focused on hair dyes as a causative agent to date. Thus, no previous meta-analyses have focused on welding fumes, pesticides or dyes exposure. Interestingly, and despite the low number of studies included, the present study constitutes the first meta-analysis evaluating pesticides and welding fumes-related SSc, with an overall OR of 1.02 (95%CI 0.78–1.32; $p = 0.90$) for the former and OR of 1.29 (95%CI 0.44–3.74; $p = 0.64$) for the latter. Conversely, it was considered that there were not enough published studies citing risks related to hair dyes to perform an accurate meta-analysis.

Drugs

A few drugs have been described as a case report or case series as potentially related to SSc or SSc-like development, namely some chemotherapy agents, appetite suppressants and L-5-hydroxytriptophan. Other drugs are reported as suspiciously related and in a few cases there is just an isolated case report so no conclusions can be made. In all these cases, symptoms are similar to those found in SSc, but autoimmunity is absent, so we should assume these cases are scleroderma-like disorders.

Vinyl chloride disease or occupational acro-osteolysis

Polymerized vinyl chloride is used by the plastic industry to produce manufactured goods and it was related to SSc from the beginning mainly to long-term reactor cleaning [62]. In the 1960s, first cases described presented with Raynaud's phenomenon, acro-osteolysis on X-rays, clubbing, and scleroderma-like skin changes involving the hands, forearms and face, fatigue, artharlgias, myalgias, decreased grip, upper abdominal symptoms, dizziness and impotence and increased perspiration, carpal tunnel syndrome, hepatomegaly or splenomegaly, vasculitic purpura, abnormal liver function tests, thrombocytopenia, and leucopenia [63]. Non-cirrhotic portal hypertension and liver angiosarcoma appeared as late complications. All the patients were males. Lesions healed after withdrawal from vinyl chloride exposure [62]. Unlike scleroderma, calcinosis, telangiectasias, and esophageal, intestinal, cardiac or pulmonary involvement were not detected. Capillaroscopy revealed dilated capillary loops and avascular areas similar to those described in scleroderma. Antinuclear antibodies have been found in these patients [64]. Although there was evidence of similarities to SSc, there were differences in the presence of paresthesia, thrombocytopenia, splenomegaly, reticulocytosis, central nervous system involvement, leukopenia, angiosarcoma of the liver, absence of calcinosis and autoantibodies, so we should assume this entity as a scleroderma-like disorder.

Toxic oil syndrome

A worrisome circumscribed and extremely rare epidemic appeared in Spain in 1981 [65]. In its early stage, it appeared as an atypical pneumonia with fever, myalgia, rash, pruritus, arthralgia, headache, encephalopathy, thrombocytopenia, nausea, abdominal pain, purpura, lymphadenopathy, hepatomegaly, pancreatitis, pericardial effusion cough, shortness of breath, pleuritic chest pain with transudative pleural effusion, hemoptysis, and eosinophilia. The intermediate phase was characterized by myalgia, paraesthesias in lower extremities, pulmonary hypertension, severe thrombocytopenia, lymphocytosis, thromboembolic events, disseminated intravascular coagulation, dark yellow papoles on the skin, edema in the face and limbs. Finally, the late phase was characterized by scleroderma-like skin thickening with hyperpigmentation, Raynaud's phenomenon, flexion contractures, dysphagia and sicca symptoms, acro-osteolysis, acro-osteosclerosis or osteopenia on X-rays, myalgia, dysesthesia, muscle atrophy, polyneuropathy, difficulty in swallowing, malabsorption, improving pulmonary hypertension. Most patients had positive antinuclear antibodies. Despite evident similarities to SSc, it differed on the presence of rash, pruritus, neuropathy, adenomegalies, eosinophilia, thrombocytopenia, lymphocytosis, so we should also assume this entity is a scleroderma-like disorder. Epidemiologic studies revealed cooking oil from toxic unlabelled plastic containers as the source of the disease. They contained a mixture of rapeseed oil (90%), liquefied aniline, and acetanilide. Initially, denaturalized with aniline and legally introduced in Spain for industrial use, the removal of aniline was attempted but unfortunately part of it was left behind, as well as acetanilide and oleoanilide.

In our opinion, there is enough data to step forward in our research. If we could measure these substances, we would be able to try to correlate these results with disease occurrence and even with clinical features according to the chemical involved. Safe levels of exposure could then be suggested by occupational hygienists and physicians.

As limitations of our study, there is between-study variability so random effects model was chosen for the assessment of risk in the case of silica, solvents, breast implants and welding fumes. All these studies are based on self-reported surveys and it is difficult to quantify—even by experts—the contact of any of these substances. Thus, since the exposure is difficult to quantify, this would be a good opportunity to perform a prospective cohort study based on particular jobs with a known exposure burden. Another limitation is the variable nature of the exposures over time as ALARA (as low as reasonably achievable) exposure levels that are increasingly brought into industry. Moreover, exposures in the non-occupational environment have not been taken into account in those studies.

Conclusion

In conclusion, the present study constitutes the largest meta-analysis ever done to date and concerning occupational and environmental SSc. We hereby reported a significant increased overall OR after exposure to silica, solvents, silicone breast implants, epoxy resins, pesticides, and welding fumes. These data support the suspicion that a chemical might be behind the diagnosis of scleroderma. Moreover, these chemicals can be present in many different occupations but widespread as well in our daily lives. In accordance, more efforts should be done to reveal these compounds in tissue samples of SSc patients and comparing with controls. It is hard work to make recommendations regarding occupations potentially related to SSc but, in our opinion, a change of job might be suggested after diagnosis. There are a few scleroderma-like disorders described so far, exhibiting common signs such as skin thickening, Raynaud's phenomenon or even interstitial lung disease. Unlike SSc, they do not exhibit specific antibodies or other visceral involvements and, in contrast, they do exhibit atypical ancillary findings such as eosinophilia, rare cancers (angiosarcoma), or neuropathy.

Acknowledgements Special acknowledgment is given to Sandra Stroo from Dallas, Texas (USA), for the revision of the present study.

Compliance with ethical standards

Conflict of interest There is neither financial support nor conflict of interest.

The authors declare no conflict of interest, no source of funding or sponsors or any relationship to organizations that could potentially influence the present work.

Financial support None

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