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Abstract

Trichloroethylene (TCE) is a chlorinated solvent that has been used widely around the world in the twentieth century for metal degreasing and dry cleaning. Although TCE displays general toxicity and is classified as a human carcinogen, the association between TCE exposure and respiratory disorders are conflicting. In this review we aimed to systematically evaluate the current evidence for the respiratory effects of TCE exposure and the implications for the practicing clinician.

There is limited evidence of an increased risk of lung cancer associated with TCE exposure based on animal and human data. However, the effect of other chlorinated solvents and mixed solvent exposure should be further investigated. Limited data are available to support an association between TCE exposure and respiratory tract disorders such as asthma, chronic bronchitis, or rhinitis. The most consistent data is the association of TCE with autoimmune and vascular diseases such as systemic sclerosis and pulmonary veno-occlusive disease.

Although recent data are reassuring regarding the absence of an increased lung cancer risk with TCE exposure, clinicians should be aware of other potential respiratory effects of TCE. In particular, occupational exposure to TCE has been linked to less common conditions such as systemic sclerosis and pulmonary veno-occlusive disease.

Introduction

Trichloroethylene (TCE) is a non-flammable, volatile, colourless and lipophilic liquid, belonging to the chlorinated aliphatic solvent family. Before the 1990s, TCE was used primarily as an industrial solvent for the cleaning and degreasing of metals. TCE was also widely used as a chemical intermediate and extractant in chemical, dry-cleaning and textile industries, and as a component of many consumer products such as paints, typewriter correction fluids, wood finishes, cleaners, polishes and lubricants [1]. Although there are consistent data to indicate that TCE has kidney and blood toxicity and TCE is currently classified as a human carcinogen by the International Agency for Research on Cancer [7], the association between TCE exposure and respiratory disorders remains unclear. We aimed to review the current knowledge on the adverse respiratory effects of TCE exposure.

Occupational Exposure to TCE

This section briefly presents the main industries and occupations that are involved, or were involved in the past, with exposure to TCE. The major sources of occupational exposure to TCE are provided in Table 1.

A systematic literature review by Bakke et al. published in 2007 highlights the different occupational situations (industries and activities) that are associated with occupational exposure to TCE in the United States (US) and Europe [2]. In the 20th century, the major uses of TCE was degreasing, mainly for cleaning of metal parts but also for other products such as inorganic fibres, glass, and carbon fibres. Degreasing is the process of removing water insoluble substances such as grease or wax from a surface. TCE was first used as a degreaser in the 1910s and became the most common degreasing agent in the 1940s. In 1966, TCE was used for more than 90% of all vapour degreasing processes, and in the 1970s, approximately 12% of all industrial plants used TCE for their cleaning operations. However, in 1971, the

U.S. Environmental Protection Agency issued a warning against the environmental impact of some chlorinated solvents, including TCE. Since then, the use of TCE has declined and by 1980, less than 2% of cold cleaning and only a third of all vapour degreasing continued to use TCE. Metal-working industries are the major users of solvent degreasing in the U.S. and in Europe. In the 1970s, the cleaning of metals accounted for the majority of industrial metal work, and 40 to 65% of plants used solvents for metal degreasing.

While the commercial use TCE began to decrease in the late 1970s in the US and Europe and is currently very limited, its use actually increased in many Asian countries concurrent with the rapid expansion of their industrial sectors. In South Korea, TCE was used commonly in the following industrial sectors (in descending order) [3]: manufacturers of motor vehicle and engine parts and accessories, machinery workers, manufacturers of electric components, computer, radio, television, and communication equipment, and primary metal workers and manufacturers of fabricated metal products. TCE was also used frequently in cleaning activities, with the highest level of TCE exposure reported by manufacturers of non-metallic mineral products, followed by manual cleaning for optic device production, degreasing for rubber good production, and cleaning for transport machineries and equipment production. Similarly, TCE use in China began to increase in the 1990s as its electronic, microelectronics, and telecommunications industries rapidly expanded and required efficient chemical degreasers. TCE use in China increased from 4-5 kilotons between 1980 and 1990 to 40 kilotons in 2000 and 165 kilotons in 2010 [4]. Finally, the highest means of TCE concentrations were found in textile dyeing and printing jobs, and laundry jobs. Other activities with high ambient concentration of TCE were the production of cultural, education, and sports articles, the plate makers, and the workers in surface treatment of metals.

TCE penetration and metabolism in human

TCE is a lipophilic solvent that can readily cross biological membranes. TCE is taken up by the inhalation, oral or cutaneous route. Metabolism of TCE occurs through two main irreversible pathways: the cytochrome P450 (CYP450)-dependent oxidative pathway and the glutathione (GSH)-conjugation pathway by glutathione S-transferases (GST).[5][6][7]

CYP-dependent oxidative metabolism occurs predominantly in the liver, and to a lesser extent in the lung. The reaction between TCE and CYP450 produces three metabolites: TCE epoxide, chloral, and chloral hydrate. The first one, TCE epoxide, is chemically unstable and spontaneously generates directly oxalic acid or dichloroacetyl chloride transformed to monochloroacetate and dichloroacetyl chloride, then spontaneously transformed to dichloroacetate. The second and the third ones, chloral and chloral hydrate, are quickly transformed to trichloroethanol (TCOH) by alcohol dehydrogenase or CYP450, and trichloroacetic acid by aldehyde dehydrogenase. TCOH is glucuronidated to form TCOH-glucuronide, which undergoes enterohepatic recirculation (excretion in bile with regeneration and reabsorption of TCOH from the gut). Finally, mono, di and trichloroacetate, oxalic acid and TCOH-glucuronide are excreted in urine.

GSH-conjugation occurs in the liver or kidney form dichlorovinyl glutathione, which is further processed in the kidney, forming the *S*-dichlorovinyl-L-cysteine. This Cysteine conjugate may be bioactivated by beta-lyase or flavin-containing monooxygenases to reactive species, or (reversibly) undergo *N*-acetylation to the mercapturate *N*-acetyl dichlorovinyl cysteine, which is then excreted in urine or sulfoxidated by CYP3A to reactive species.

Lung cancer

TCE is classified as a definite carcinogen agent to humans (Group 1) by the International Agency on Research Cancer (IARC) based on the evidence of a causal association between

TCE exposure and kidney cancer [7]. The following section will examine the association between both occupational and environmental exposures of TCE with lung cancer.

Epidemiological studies

Occupational TCE exposure and lung cancer

Most data on the relationship between occupational TCE exposure and lung cancer are based on occupational cohort studies in the US [8-13] and Northern Europe [14, 15]. These cohorts include workers in specific industries (e.g., aircraft/aerospace or metal industry), many of whom were exposed to TCE in the 1950s to 1990s. Standardized Mortality (SMR) or Incidence Ratios (SIR) are reported for many cancer sites, including lung cancer. Most of these studies did not find evidence of an increased risk of lung or respiratory tract cancers associated with TCE exposure. Their results were summarized in a systematic review and meta-analysis of studies on occupational TCE exposure and cancer conducted in 2011 [16, 17]. This meta-analysis found that TCE exposure was not associated with an increased risk of lung cancer (relative risk of 0.96 (95% CI: 0.76-1.21) based on nine cohort studies [16]. Two recent occupational cohort studies on cancer incidence (pooled cohort of 5,553 workers exposed to TCE from three Nordic countries) [18] and death (cohort of 5,535 male workers at a uranium enrichment plant in the US) [19] also did not find an increased risk of lung cancer among TCE-exposed workers compared to the national population. A notable limitation of these occupational cohort studies was the absence of individual data on important confounders such as smoking history and socio-economic status.

More recently, results from relatively large case-control studies on chlorinated solvents (including TCE) and lung cancer risk have been reported [20, 21]. Vizcaya et al. pooled data from two Canadian case-control studies (totaling 2,016 cases and 2,001 controls) conducted in 1980-1986 and 1995-2001, respectively [21]. Exposure to 6 chlorinated solvents was

evaluated by an expert assessment. The overall Odds Ratio (OR) for any TCE exposure was 1.7 (95% CI: 0.9-3.4), with a significant association among non-smokers or light-smokers. However, no dose-response association was observed for the association between TCE exposure and lung cancer; indeed, for higher level of exposure to TCE, the association was close to the null. Associations suggestive of an increased risk of lung cancer were found with exposure to two other chlorinated solvents: perchloroethylene (PCE) and carbon tetrachloride. Mattei et al. reported results of a French case-control study (2,926 cases and 3,555 controls) performed between 2001-2007.[20] Exposure to chlorinated solvents was evaluated by a job exposure matrix. Although a significant trend in the association between TCE cumulative exposure index and lung cancer was observed in women, the association was not significant overall. Furthermore, analyses of mutually exclusive solvent exposure groups revealed no association for workers exposed to TCE only. Similar to the Canadian study, results suggested an association between PCE exposure and lung cancer, although PCE could not be investigated independently of other solvents exposure, and no clear dose-response relationship was observed. These findings suggest a possible effect of mixed exposures, with combination of several solvents. Interestingly, using a more precise analysis of this study with profile regression approach, the author did not observe any significant association between TCE and lung cancer [22]. However, some high-risk clusters identified by the method were related to occupations that are known to be at risk of developing lung cancer, such as painters, construction workers, plumbers and pipe fitters, carpenters, joinery and parquetry workers. Despite their methodological strengths (study design, exposure assessment), the sample size of these two case-control studies and potential exposure misclassification may have resulted in insufficient power to detect modest associations.

Environmental TCE exposure and lung cancer

The effect of environmental exposure to TCE has also been investigated in relation to the risk of lung cancer, although the number of studies is limited. Two studies focused on drinking water contamination with solvents and chemicals in specific US areas caused by industrial leaks and spills [23, 24]. Drinking water contamination results in exposure through ingestion, inhalation and dermal routes, which may equally contribute to overall internal body dose [23]. Groundwater contamination with TCE can also result in volatile organic compounds (VOC) exposure through soil vapor intrusion [1]. In a previous report of drinking water contamination with TCE in the Redlands area (California, USA) a significantly lower risk of lung cancer was actually observed compared to the baseline cancer rate of the state of California [24]. Although no individual data were available, the authors noted that the population under investigation had higher socioeconomic status than the comparison population, suggesting a possible confounding effect of smoking. Similarly, cancer incidence was studied in the Endicott area (New York State, USA), where VOC have been found in soil vapor following TCE, PCE and other solvents contamination [1]. Although an elevated risk of lung cancer was suggested, it was not statistically significant (SIR: 1.28, 95% CI: 0.99-1.62). Similarly the confounding effect of smoking habits was not accounted for, as the population in the contaminated area had a lower socioeconomic status compared to the control population.

Lastly, Bove et al. [23] studied cancer mortality among 154 932 U.S Marines who stayed at Camp Lejeune (North Carolina, USA) during a period when drinking water was contaminated by TCE and PCE (1975-1985). Monthly average contaminant concentrations in the water system were estimated by historical reconstruction and modelling. The control group included other marines at a non-contaminated camp in California. A significantly higher risk for all cancer-related mortality (HR: 1.10, p=0.02) was observed for marines exposed to contaminated water at Camp Lejeune; for lung cancer mortality, the HR was 1.16 (p=0.10).

Overall, the elevated cancer risk only occurred among those with higher cumulative exposure. Based on the finding of an absence of association between exposure to contaminated water and other smoking-related diseases (e.g., COPD: HR<1.10), the authors suggested that confounding by smoking would be limited in this study. However, no increased risk of lung cancer was observed according to estimated exposure concentration in internal comparison analyses. Furthermore, the individual contribution of TCE and PCE exposures to cancer risk could not be ascertained.

Pathobiology of TCE exposure and lung cancer

Regarding the possible association between TCE exposure and lung cancer, there are contradictory data in experimental animal studies depending on the species studied. Indeed, TCE is carcinogenic for mice, but not for rat. Unlike the rat lung, the mouse lung is very rich of Club cells, which contain high CYP450 activity. Chloral hydrate accumulates in Club cells and causes aneuploidy, cell divisions and cytotoxicity. These biological alterations are known to be risk factors of development of cancer and provide a plausible explanation for TCE as a mouse lung carcinogen. Human lung is poor in Club cells (approximately 600-fold less than that in the mouse) [25]. In addition, morphology of Club cells in the human lung differs markedly compared to Club cells in the mouse lung. Hence, extrapolations from rodent findings to human pathobiology must be undertaken with extreme caution.

Moreover, very few data exist on the molecular impact of TCE in pulmonary cells. Most of the available data are from rodent liver and kidney cancers. In this setting, the inability of TCE to induce the formation of premalignant changes or neoplasia, and the absence of carcinogen-specific alteration of genes accepted to be critical for renal tumor development, suggest that TCE mediated carcinogenicity may occur secondary to continuous toxic injury and sustained regenerative cell proliferation [26], and epigenetic mechanisms [27].

Bioactivation reactions may also be responsible for TCE toxicity. Glutathione conjugation of TCE followed by metabolism by the enzymes of mercapturic acid pathway produces S-(dichlorovinyl)-l-cysteine (DCVC). DCVC is mutagenic in bacteria and induces mitochondrial toxicity, perturbation of intracellular calcium homeostasis, DNA-repair and DNA strand-breaks in cultured renal cells and in the renal cortex after in vivo administration [28, 29][30][31][32][33]. A transcriptomic profiling of TCE exposure in male mouse liver showed that the expression levels of 431 mRNAs were altered after TCE exposure, of which 291 were up-regulated and 140 were down-regulated [34]. Some of these genes are involved in key signaling pathways including PPAR, proliferation, apoptosis and homologous recombination. Further, alteration in the expression level of a number of vital genes involved in the regulation of DNA methylation (such as Utrf1, Tet2, DNMT3a and DNMT3b) were observed. However, the relevance of these studies for human pathology has to be assessed in human pulmonary tissues and cells.

Conclusion on TCE and lung cancer

In summary, there are very limited evidence of an increased risk of lung cancer associated with TCE exposure based on current epidemiological data from occupational and environmental exposures. Furthermore, cellular studies of the carcinogenic effect of TCE on respiratory epithelium are inconsistent. However, the available data does not completely rule out a modest effect of TCE exposure on lung cancer risk. The association between lung cancer and other chlorinated solvents including mixed solvent exposure requires further study.

Vascular effects of TCE

Epidemiological studies

An increased risk of developing autoimmune diseases is one of the most consistently reported adverse health effects of TCE [5]. In particular, an association between TCE (as well other organic solvents) and systemic sclerosis has been replicated by many studies, and this association has recently been reviewed [35, 36]. Interstitial lung disease appears to be a frequent manifestation of systemic sclerosis in patients exposed to solvents [37].

Occupational exposure to TCE was also recently identified as a risk factor for pulmonary veno-occlusive disease (PVOD), a rare form of pulmonary hypertension [38]. A case-control study was conducted between 2008 and 2010 in patients with a diagnosis of PVOD and patients with idiopathic, anorexigen-induced or heritable pulmonary arterial hypertension (PAH). Occupational exposure was evaluated via questionnaire interview with blinded assessments using both an expert consensus approach and a job exposure matrix. A history of TCE exposure was significantly associated with PVOD and an older age of disease onset.

Pathobiology of TCE and vascular effects

TCE alters endothelial and endothelial nitric oxide synthase (eNOS) function to impair VEGF-stimulated endothelial proliferation [39]. eNOS generation of nitric oxide plays an important role in endothelial cell proliferation, which is considered essential for normal blood vessel growth and development, and vasodilation. In their study, Ou et al [39] demonstrated that TCE alters the balance of nitric oxide and superoxide anion (O_2^-). They showed that TCE alters hsp90 (heat shock protein 90) interactions with eNOS and induces eNOS to shift from nitric oxide to O_2^- generation. Hence, TCE disrupts protein interactions with eNOS to induce endothelial and eNOS dysfunction rather than altering expression of hsp90 or eNOS.

It has also been demonstrated that TCE inhibit uptake and metabolism of serotonin (5-HT) in the rat lung [40] [41]. 5-HT is inactivated in the pulmonary circulation in the endothelial cells

of the capillaries. It is an endogenous vasoactive indoleamine substance, implicated in PAH pathogenesis [42]. In addition to its vasoconstricting effects, 5-HT also exerts mitogenic and comitogenic effects on pulmonary artery smooth muscle (PA-SMC). Hence, the reduced pulmonary clearance of 5-HT related to TCE exposure can theoretically cause cardiovascular side effects such as vasoconstriction, vascular remodeling and thrombosis [43].

Inflammation is important for the initiation and the maintenance of vascular remodeling in most animal models of pulmonary hypertension, and therapeutic targeting of inflammation in these models blocks pulmonary hypertension development. In humans, pulmonary vascular lesions of PAH are the source of cytokine and chemokine production, related to inflammatory cell recruitment and lymphoid neogenesis [44], [45]. There is a suppression of pulmonary host defenses and enhanced susceptibility to respiratory bacterial infection in mice following inhalation exposure to trichloroethylene [46]. If relevant to human, this may favour chronic inflammation after lung infection and boost an underlying pulmonary vascular disease. Circulating autoantibodies (Ab) to endothelial cells and to fibroblasts have been reported in 10 to 40% of patients with idiopathic PAH, suggesting a possible role for autoimmunity in the pathogenesis of pulmonary vascular lesions [47]. Relevant to autoimmunity and inflammation is the established relationship between TCE exposure and autoimmune disease. In this regard, Cooper et al. [36] systematically assessed the immune-related effects of TCE toxicity. They reported that $MRL^{+/+}$ lupus-prone mice exhibit an accelerated autoimmune response when exposed to TCE or its metabolites. This included an increased production of anti-nuclear antibodies and interferon-γ (IFN-γ) and decreased secretion of interleukin-4 (IL-4), consistent with an inflammatory response. Mechanistic experiments in mice demonstrated the activation of a specific antibody response directed against dichloroacetylated proteins that were detected in the liver and, relevant for PVOD, in the lungs [48]. The covalent modification of cellular proteins in the lung by TCE may play a role in the acceleration of pulmonary autoimmunity

(hapten-specific immune response). Moreover, TCE is known to generate free radicals and to causes increased lipid peroxidation both *in vivo* and in *vitro* [49]. Several lines of evidence in lupus-prone mice showed that increased reactive oxygen species generation was associated with increased formation of autoantibodies, suggesting a potential role of oxidative stress in TCE-induced autoimmune response. TCE was also showed to induce an IL17 mediated (Th17) immune response [49], in TCE-exposed mice; an immune polarization implicated in the pathogenesis of autoimmune diseases. Interestingly, n-acetylcysteine (a cell-permeable antioxidant) supplementation attenuated not only the TCE-induced oxidative stress, IL-17 release and mRNA expression, but also markers of autoimmunity, as evident by decreased levels of ANA, anti-dsDNA and anti-Smith antibodies in the sera [49]. Since both Th17 [50] and oxidative stress ([51], [52] are related to pulmonary hypertension pathophysiology, these mechanisms may also be relevant of TCE-induced PVOD.

Conclusion on TCE and vascular effects

Recent studies demonstrate an association between TCE exposure with autoimmune and vascular diseases like systemic sclerosis and pulmonary veno-occlusive disease. This association is supported by plausible mechanistic studies from animal models of TCE exposure.

Other chronic respiratory diseases

Epidemiological studies

Very few studies have investigated TCE exposure as a risk factor for chronic respiratory diseases such as asthma, COPD or related respiratory symptoms in occupational settings. Cases of hypersensitivity pneumonitis [53], acute pulmonary injury [54], and development of pulmonary oedema and chronic dyspnoea [55] have been described in case reports. Some

surveillance programmes for work-related asthma found that solvents were among the main causative agents for occupational asthma or work-exacerbated asthma [56, 57]. However, individual types of solvents were not specified, but were likely to include primarily solvents other than TCE. Some occupational cohort studies have reported an association between TCE exposure and death from non-malignant respiratory diseases. Two U.S. studies of aircraft manufacturing [12] or maintenance [13] workers exposed to TCE found significantly elevated standardised mortality rate for non-malignant respiratory diseases (bronchitis, emphysema and/or asthma, or non-specified), but did not reveal a dose-response effect according to exposure levels. The authors suggested that the increase in asthma mortality, for example, was unlikely to be causally related to TCE exposure, as death occurred many years after TCE exposure. Two other studies examining death from non-malignant respiratory diseases did not report a significantly elevated risk associated with TCE exposure [10, 11].

Two studies have been conducted in workers of a Turkish gun factory in order to evaluate the associations of solvents exposures with chronic respiratory symptoms and lung function [58, 59]. In this industry, TCE and many other solvents were used to clean gun pieces. In the first study (n=1,091), a higher prevalence of asthma-related symptoms was reported in the solvents exposed group. In the second study performed 5 years later and in a smaller group of workers (n=393), this association was no longer observed when a more stringent definition of asthma was used. No association was seen between solvent exposure and lung function parameters in both studies. In another study of 244 workers in a clock manufacturing factory in Bangkok (Thailand), associations between TCE exposure and various health outcomes including skin, respiratory and allergy symptoms were evaluated by self-administered questionnaire [60]. Workers were classified as exposed to TCE or non-exposed based on their type of job. Exposure measurements showed higher levels of airborne TCE concentrations and urinary trichloroacetic acid (TCA) in exposed compared to non-exposed workers, although TCE

levels were below permissible exposure limits recommended by US Occupational Safety and Health Administration. A significantly higher prevalence of skin and respiratory symptoms (cough, frequent phlegm, sinusitis, bronchitis, irritation of throat, wheezing or breathlessness), but a lower prevalence of allergy were reported among exposed workers. However, adjustment for potentially important confounders (e.g. smoking) were not reported, which limited the conclusion of the findings.

A few studies on health effects of indoor air pollution, in particular those focused on volatile organic compounds (VOCs) exposure in households, have also reported data on the association between TCE concentrations and respiratory illnesses. In a subsample of the US National Health and Nutrition Examination Survey participants (n=550 adults), personal exposures to 10 VOCs were measured [61]. Because indoor air pollutants are multiple and often correlated, exploratory factor analysis of VOC exposures was used to identify two main exposure factors, labelled "aromatic compounds" (eg, ethylbenzene, o-xylene) and "chlorinated hydrocarbon" (PCE and TCE). While exposure to aromatic compounds was associated with physician-diagnosed asthma, chlorinated hydrocarbons exposure was not. An association was observed between chlorinated hydrocarbons exposure and attacks of wheezing among non-asthmatic subjects, but no dose-response relationship according to the number of attacks in the past year was evidenced. Asthma and rhinitis outcomes were also of interest in a study of 567 French dwellings (n=1012 adults, 2003-2005) with VOC measurements [62]. Current asthma and rhinitis, evaluated by standardized questionnaires, were associated with a score representing the combined effect of the 20 measured VOCs. In single VOC models, a significant association was reported between TCE exposure and rhinitis (OR: 1.54, 95% CI: 1.07-2.21) but not current asthma. In another analysis in the same population [63], associations of VOC exposures with breathlessness and chronic bronchitis were evaluated in the elderly (≥65 years, n=144). Elevated concentrations of some pollutants

(toluene, o-xylene), but not the global VOC score, were associated with breathlessness at night. Higher TCE concentration was also associated with breathlessness at night among the elderly (OR=2.81), but the confidence interval was wide (1.02-7.76) and the interaction with age (<65 years vs. ≥65 years) was not significant.

Pathobiology of TCE and other chronic respiratory diseases

TCE is an irritant molecule for lung tissue, as previously described for skin. Upon combustion, TCE produces also irritants and toxic gases and may cause an acute or sub-acute chemical pneumonitis [64]. TCE can also cause arterial hypoxemia by increasing ventilation-perfusion mismatching via impairing vasoconstriction in hypoxic areas of lung [65].

In mice, TCE elicits acute pulmonary cytotoxicity [66], which involves Club cells of bronchioles. In this animal model, an acute dose of TCE induced pulmonary fibrosis that was detected at 15 days after exposure and was progressive during the 90 days of follow up. Diffuse interstitial fibrosis was observed in the alveolar zone, resulting in thickening of alveolar septa and distortion of lung structure. The fibrosis became most pronounced at 90 days after treatment, resulting in deposition of connective tissue in the alveolar septa mirrored by high levels of total lung hydroxyproline. The increase in collagen deposition at 90 days coincided with a significant increase in lung elastic recoil. In summary, TCE can cause progressive structural and functional abnormalities of the lungs compatible with chronic respiratory disease presentation in animal models of TCE exposure.

Conclusion on TCE and other chronic respiratory diseases

A limited number of epidemiological studies have suggested an association between TCE exposure and respiratory symptoms indicative of asthma, chronic bronchitis, or rhinitis. However, these studies were all cross-sectional, and were limited by either poorly defined

outcomes, lack of control for confounders, small population size, or multiple correlated exposures preventing a clear identification of the specific effect of TCE. A potential causal role of TCE in any of these respiratory illnesses needs to be addressed in studies with stronger design.

Practical considerations for clinicians and conclusions

Organic solvents, particularly TCE, have been widely used in the past decades; although its use started to decrease from the 1970s and is currently limited in Europe and in the US, it remains common nowadays in Asian countries. Thus, TCE represent an important source of past or current occupational exposure for industrial workers worldwide. Exposure to TCE may induce respiratory toxicity and physicians should develop an awareness of the possible acute and chronic complications of TCE exposure. Although chlorinated solvents have been implicated in the development of lung cancer, the specific association between TCE and lung cancer is weak and inconclusive. Exposure to TCE may potentially be associated with respiratory diseases such as asthma, hypersensitivity pneumonitis and rhinitis, but the evidence supporting this association is also low. The best evidence to date is the association of TCE exposure with the development of autoimmune and systemic vascular disorders. Although further studies are needed, there are consistent studies that demonstrate an increased risk of systemic sclerosis with TCE exposure. More recently, occupational TCE exposure has also been associated with PVOD, a rare form of pulmonary hypertension characterized by pulmonary venular and capillary remodeling.

In conclusion, exposure to TCE may be associated with a potential range of adverse respiratory effects but further studies are needed before firm conclusions can be made. Although TCE is classified as a carcinogen, there is currently no data to support an association with lung cancer. Clinicians should be encouraged to take a detailed occupational

history in patients presenting with rarer conditions such as systemic sclerosis and PVOD, where an association with TCE exposure has been demonstrated in recent studies.

Figure/Tables

Box 1

Search strategy for the epidemiologic literature

Published studies were identified from PubMed using the key words "occupational AND trichloroethylene", published from 1980 through December 2015. We made a critical selection of studies relevant for the topic (respiratory disorders). To identify potential studies not retrieved from the initial search, we performed additional searches on specific disorders (e.g., using keywords "asthma trichloroethylene", "solvents occupational asthma", or "chlorinated solvents asthma"; and similar searches replacing "asthma" by "respiratory", "lung", "pulmonary" or "COPD"). We also reviewed all selected papers for reference citations that had not been otherwise identified in the initial search.

Table 1. Major exposure sources of TCE

Industry	Type of exposure
Metal-working industries: manufactoring of primary metals	Solvent degreasing product: metal furniture, fabricated products, non-electric machinery, electric and transportation equipment's, instruments and clocks
Metal-working industries: maintenance and service operations	Solvent degreasing products: automotive repair, railroad transportation maintenance and aircraft maintenance (still used).
Dry cleaning et dyeing / other fabric cleaning	Solvent: Batch process cleaning large quantities of textiles or spot remover on individual pieces, with use of TCE between 1910 and early 1960s, very rare after
Textile Mill products and apparel	Solvents including TCE: Scouring, sizing or desizing textiles, removing foreign substances.
Leather and leather products	Removing fat from hides in the processing of leather (until the 1960s) and disinfecting hides and skins
Electronic components and accessories	Manufacturing of semiconductor substrates and integrated circuits / manufacturing of printed circuit boards. Use small in 1984.
Rubber and miscellaneous plastic products	Binding and cementing materials (treads, tire, and bead building) TCE still used in the 1970s but probably rarely.
Agricultural production and chemicals	Fumigant in grain storage and related industries and solvent for insecticides / component of fungicides / aerosolized insecticides from 1930s through 1970s at least
Food and kindred products	Extractant in two processes: decaffeination of coffee and spice oleoresins. Uses stopped in 1977 after banishment of TCE as a food additive by the Environmental Protection Agency (EPA)
Heath services	- Anesthetic (dental extractions, orthopedic manipulations, cystoscopy, obstetrics, burn dressing, and similar short surgical procedures). use decline in the 1970s - Analgesics, detergent for skin, veterinary medicine
Chemicals and allied products	- Extracting resin from wood and production of pulverized sulphur.

	- Dye manufacturing (use rare in the 1970s) - Vehicle in glues, adhesives, and cements in the shoe, foam, and rubber industries. Since the 1930s, rare in the 1970s
Paints, varnishes, lacquers, enamels, and allied products	Thinner for paints and varnishes
Transportation by air	Aircraft maintenance industry (including parachute cleaning). Introduction in 1955, use apparently ended before the 1980s.
Papers and allied products	Pulp and papermaking industry in impregnating cardboard and paper board boxes. use rare in the 1970s
Perfumes, cosmetics, and other toiletry preparations	Component in dry shampoo / cleaner for false eyelashes / perfumes. Use banned in the cosmetics by the Federal Drug Administration (FDA) in 1977.

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