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Occupational Exposure to Chlorinated Solvents and Lung Cancer: Results of the SYNERGY case-control Study

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Abstract

Objective: The association between occupational exposure to chlorinated solvents and lung cancer remains inconclusive. This study investigated this relationship using data from the internationally pooled SYNERGY study.

Methods: Data from 14 case-control studies conducted in 13 European countries and Canada were pooled, including 28,048 participants (12,329 cases and 15,719 controls). Lifetime occupational exposure to chlorinated solvents was assessed using the ALOHA+ job-exposure matrix. Odds ratios (ORs) and 95% Confidence Intervals (CIs) were estimated using unconditional logistic regression, adjusted for age, sex, study center, smoking (pack-years and cessation), cumulative exposure to five occupational lung carcinogens (asbestos, hexavalent chromium, polycyclic aromatic hydrocarbons, respirable crystalline silica, and diesel engine exhaust), cumulative benzene exposure, and employment in high-risk occupations ("List A" jobs). Associations were estimated across categories of exposure levels, durations, and analyses stratified by smoking status and lung cancer subtypes.

Results: We found no evidence of an association between ever exposure to chlorinated solvents and lung cancer risk (OR 1.03; 95% CI: 0.96–1.10). Among exposed individuals, a positive trend with cumulative exposure was observed (p=0.031), but not when non-exposed individuals were included (p=0.173). Positive trends were found with exposure duration (p=0.048 for exposed; p=0.005 overall); risks were modestly elevated (OR 1.11) in those exposed for 20 or more years. No increased risk was observed across smoking strata or lung cancer subtypes.

Conclusions: This pooled analysis provides limited evidence of an association between occupational exposure to chlorinated solvents and lung cancer, though exposure-response trends were noted among exposed individuals.

Introduction

Workers in various industries are exposed to chlorinated solvents, commonly used in metal degreasing, paint stripping, dry cleaning, and as chemical intermediates [1]. Among these solvents, trichloroethylene (TCE) and tetrachloroethylene (PCE, or perchloroethylene) are the most widely used. In 2012, the International Agency for Research on Cancer (IARC) classified TCE as carcinogenic to humans (Group 1) and PCE as probably carcinogenic to humans (Group 2A) [2]. Regulations had been introduced worldwide to limit or ban several chlorinated solvents due to their known toxicity, as well as their negative environmental impacts such as groundwater contamination and ozone layer depletion [1]. However, high-exposure scenarios persist, for example, in metal product manufacturing in Asia [3,4].

The carcinogenicity of chlorinated solvents has been primarily linked to urinary tract cancers, while evidence for their association with lung cancer remains limited [2]. After the IARC evaluation, several epidemiological studies studied this relationship [5,6], but increased lung cancer risk was not consistently observed across subgroups or lung cancer

subtypes. The evidence remains inconclusive, largely due to small sample sizes, leaving uncertainty about their potential role in lung carcinogenesis. Given that the upper airways are the initial contact point for inhaled chlorinated solvents, their possible role in developing lung cancer warrants further investigation.

In this analysis, we used a large, internationally pooled lung cancer case-control dataset to investigate the association between occupational exposures to chlorinated solvents and lung cancer risk, aiming to provide greater clarity on their carcinogenic potential.

Methods

The SYNERGY project pooled data from 14 lung cancer case-control studies across 13 European countries and Canada, with detailed information published previously [7] and available online (http://synergy.iarc.who.int). Cases and controls were frequency matched by age and sex, with 84% of interviews conducted in person. Lung cancer types were categorized based on World Health Organization guidelines [8], with confirmation by associated hospital pathologists. Ethical approval was obtained in accordance with national regulations and the IARC review board.

We included the same SYNERGY population as in our recent publication on benzene [9], including all participants employed between 1945 to 2009. Occupational exposure to chlorinated solvents was assessed using a general population job-exposure matrix (JEM) called the ALOHA+ JEM (based on the International Standard Classification of Occupations V.1988 (ISCO-88)). The expert-based ALOHA+ JEM was developed using two occupational hygienists' expertise to assess occupational exposure for chronic respiratory and neurodegenerative diseases in community-based studies [10,11]. For every job coded in ISCO-88, the JEM assigns three exposure levels (none, low, high) based on intensity and prevalence of exposure to 10 agents (including dusts, fumes, solvents, metals) and two composite categories [10,11]. Participants' ISCO-68 job records were converted to ISCO-88 for exposure assessment. We did not attempt to assign levels to specific chlorinated solvents as detailed information on occupational exposures and raw materials used was not available. The assigned intensity scores were ordinal (0=no exposure; 1=low exposure; and 4=high exposure). Cumulative exposure (intensity-years) was calculated by summing the products of job duration and intensity score. We only assigned exposure to chlorinated solvents to jobs held after 1960, when the agents became more widely produced and used in Europe and North America [1]. Co-exposures to five lung carcinogens (asbestos, hexavalent chromium [Cr(VI)], polycyclic aromatic hydrocarbons (PAHs), respirable crystalline silica (RCS), and diesel engine exhaust (DEE)); and benzene exposure were assessed with three general population JEMs, following the procedures described elsewhere [9].

Unconditional logistic regression models were applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for lung cancer risks associated with various exposure metrics: ever/never exposed, cumulative exposure (>0–10, >10–25, >25–46, and >46 intensity-years), and exposure duration (1–9, 10–19, 20–29, and >29 years). Cumulative exposure levels were categorized into quartiles based on intensity-year scores among exposed controls. We stratified the analyses by smoking status (never, former, and current

smokers). Smokers were mostly defined as those who had smoked more than one cigarette per day for over one year, and former smokers as those who had ceased smoking at least two years prior to diagnosis or interview. Analyses were also stratified by main lung cancer subtypes (adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma). Linear trends were assessed by modelling cumulative exposure (intensity-years) and duration (years) as continuous variables in regression models for all participants and exposed individuals only.

Regression models were adjusted for age group (<45, 45–49, 50–54, 55–59, 60–69, 70–74, >74 years), study center, sex, cigarette pack-years (logarithm of [cigarette pack-years + 1]), time since smoking cessation (current smokers; quitting 2–7, 8–15, 16–25, >25 year before diagnosis/interview; never smokers), cumulative exposure to five lung carcinogens (asbestos, PAHs, RCS, Cr(VI), DEE), and benzene, and whether individuals had ever worked in a “List A” occupation. “List A” comprises jobs and sectors linked to increased lung cancer risk, serving as an adjustment for unmeasured occupational risk factors [9]. We also reported raw ORs adjusted only for age group, sex, and smoking status.

Additionally, we conducted a random-effects meta-analysis of the case-control studies to assess the consistency of the association between ever exposure to chlorinated solvents and lung cancer risk across centers, stratified by control type. We also performed analyses restricted to blue-collar workers and reported sex-specific risk estimates. All analyses were conducted in R (version 4.2.3).

Results

The analysis included 28,048 participants, comprising 12,329 lung cancer cases and 15,719 controls. Participant characteristics were generally similar in both exposed and unexposed groups, although a higher proportion of heavy smokers and individuals ever employed in list-A jobs was observed among exposed subjects (supplemental Table S1). Exposure prevalence among controls ranged from 9.9% to 43.7% across the pooled studies (supplemental Table S2). The most common job title among ever-exposed participants was “Agricultural- or industrial-machinery mechanics and fitters” (n=1,407), followed by “Motor vehicle mechanics and fitters” (n=757) and “Plumbers and pipe fitters” (n=634) (supplemental Table S3).

Chlorinated solvent exposure was reported in 31.7% of cases and 27.4% of controls (Table 1). The raw ORs (adjusted only for age group, sex, smoking status) indicated clear associations with ever/never, cumulative and duration of exposure (Table 1). However, after thorough adjustment of co-exposures to known and potential lung carcinogens, these associations were substantially attenuated. No association was found between ever exposure and lung cancer risk (OR=1.03; 95% CI: 0.96–1.10),Lung cancer ORs across cumulative exposure quartiles ranged from 0.91 (Q1) to 1.13 (Q3). A positive trend was observed among exposed workers (p=0.031) but not in the full population (p=0.173). Analyses by exposure duration showed positive trends in both exposed workers (p=0.005) and the full population (p=0.048), although no elevated risks were identified in any of the four duration categories.

Meta-analysis showed estimates of individual studies were largely centered around an OR of 1 (supplemental Figure S1). Associations between ever exposure and lung cancer risk were generally weaker among former and current smokers; however, a positive exposure-response trend was observed among former smokers across cumulative exposure categories (supplemental Table S4). No elevated risk was found for any of the four major lung cancer subtypes (supplemental Table S5), nor for either sex (Supplemental Table S6) or blue-collar workers (Supplemental Table S7).

Discussion

We examined the association between occupational exposure to chlorinated solvents and lung cancer risk in a large, pooled case-control study. Although no excess risk was observed among ever-exposed participants, there was some evidence of exposure-response trends for cumulative exposure and exposure duration among the exposed participants. Overall, our findings provide limited evidence of an association.

Animal studies have shown sufficient evidence of carcinogenicity for several commonly used chlorinated solvents; however, epidemiological evidence for lung cancer remains limited and inconclusive, with concerns about residual confounding from smoking and co-exposure to known lung carcinogens [2]. Two studies conducted after the IARC evaluation addressing those concerns have yielded suggestive but inconsistent evidence. Vizcaya et al. reported a potential increased lung cancer risk among men exposed to perchloroethylene and carbon tetrachloride in two Canadian case-control studies, but this was not evident among non/light smokers or for other chlorinated solvents [5]. Similarly, a French case-control study found weak associations for five individual chlorinated solvents, but stronger association for combined exposure to PCE, TCE, and dichloromethane (DCM) [6].

The two studies, separately conducted in Canada and France, used more detailed, country-specific exposure assessments for chlorinated solvents than in this study [5,6]. Their population were subsequently included in the current analysis which pooled data also from other SYNERGY centers, leading to a substantially larger sample size. Despite the large study population and more comprehensive adjustments for residual confounding by including quantitative estimates of co-exposures, our findings similarly showed very limited evidence to support a positive association. The identified attenuation of the risk estimates relative to the unadjusted ones further demonstrates the importance to account for co-exposures confounding (Table 1).

However, the exposure assessment was limited in this analysis by applying a generic population JEM. Due to the absence of an international JEM for assessing specific chlorinated solvents, we were unable to assign levels of individual chlorinated solvents (e.g. TCE, PCE, DCM) to the SYNERGY population. Such limitation in exposure assessments, as discussed elsewhere [12], may have contributed to imprecise estimates due to uncertainty in exposure assignments.

Overall, our study provides valuable insights, but future research in countries where chlorinated solvents are still used could refine exposure assessment through detailed task-

specific data. Triangulating evidence from diverse study designs, such as industrial cohort studies, may further clarify the relationship between chlorinated solvents and lung cancer risk, particularly for specific solvents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The data are currently not publicly available.

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Box 1

What is already known on this topic

Occupational exposure to some chlorinated solvents has been associated to increased lung cancer risk, though evidence is inconclusive and inconsistent across studies.

What this study adds

This large pooled analysis provides limited evidence of an association between occupational exposure to chlorinated solvents and lung cancer risk, though exposure-response trends observed among exposed individuals suggest a need for further investigation despite inconsistent findings.

How this study might affect research, practice or policy

This study highlights the need for further research on chlorinated solvents and lung cancer risk. If associations are corroborated this would ask for stricter occupational safety measures and regulations.

Table 1

Association between lung cancer and different metrics of occupational exposure to chlorinated solvents

Occupational chlorinated solvent exposure	N Cases (%)	N controls (%)	Raw OR (95% CI)	OR (95% CI)
Never	8,418 (68.3)	11,418 (72.6)	Referent	Referent
Ever exposure	3,911 (31.7)	4,301 (27.4)	1.16 (1.09 – 1.23)	1.03 (0.96–1.10)
Cumulative exposure, intensity-years *				
>0.01–10.00	908 (7.4)	1,139 (7.2)	1.00 (0.90 – 1.10)	0.91 (0.81–1.01)
[10.01–25.00]	947 (7.7)	1,033 (6.6)	1.18 (1.06 – 1.30)	1.08 (0.96–1.20)
[25.01–46.00]	987 (8.0)	1,057 (6.7)	1.21 (1.09 – 1.34)	1.13 (1.00–1.27)
> 46	1,069 (8.7)	1,072 (6.8)	1.26 (1.15 – 1.39)	1.07 (0.95–1.20)
Test for trend (exposed only), *p* value			0.006	0.031
Test for trend (all subjects), *p* value			<0.001	0.173
Duration, years				
1–9	1,377 (11.2)	1,578 (10.0)	1.09 (1.00 – 1.19)	0.98 (0.90–1.08)
10–19	774 (6.3)	879 (5.6)	1.13 (1.01 – 1.26)	1.01 (0.90–1.14)
20–29	811 (6.6)	892 (5.7)	1.20 (1.08 – 1.34)	1.11 (0.98–1.25)
>29	949 (7.7)	952 (6.1)	1.26 (1.13 – 1.39)	1.11 (0.98–1.26)
Test for trend (exposed only), *p* value			0.006	0.005
Test for trend (all subjects), *p* value			<0.001	0.048

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

P values for trend test were obtained by using the exposure metrics as continuous variables in the logistic regression model.

Raw ORs only adjusted for age group, sex, smoking status.

OR adjusted for study, age group, sex, smoking (pack-years, time since quitting smoking), list A jobs, cumulative exposures of asbestos, hexavalent chromium, polycyclic aromatic hydrocarbons, silica, benzene, and diesel engine exhaust.

*Cumulative exposure was calculated by summing the product of intensity and duration (years) for all recorded occupations. Cumulative exposure levels were categorized into quartiles based on the intensity-year scores among the exposed controls.