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Non-malignant respiratory disease among workers in the rubber manufacturing industry: A systematic review and meta-analysis

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Abstract

Background: Non-malignant respiratory disease (NMRD) cases have occurred among rubber manufacturing workers. We examined exposure to rubber manufacturing emissions as a risk factor for NMRD.

Methods: From a systematic literature review, we identified case reports and assessed cross-sectional and mortality studies for strength of evidence of positive association (strong, intermediate, non-significant positive association, none) between exposure to rubber manufacturing emissions and NMRD-related morbidity and mortality, and conducted two meta-analyses.

Results: We analyzed 62 articles. We identified 11 cases of NMRD. Nine (30%) of 30 cross-sectional studies and one (4%) of 26 mortality studies had strong evidence. The summary odds ratio and SMR for the cross-sectional and mortality meta-analyses were 3.83 (95% confidence interval [CI], 2.28–6.51) and 0.90 (95%CI, 0.82–0.99), respectively.

Conclusion: Available evidence supports rubber manufacturing emissions as a potential risk factor for NMRD-related morbidity. Further investigations with longer follow-up periods and

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Nirmala Thapa, MPH – participated in data acquisition, data analysis, manuscript preparation, and manuscript review. Suzanne E. Tomasi, DVM, MPH, DACVPM – participated in study design, data analysis, manuscript preparation, and manuscript review. Jean M. Cox-Ganser, PhD – participated in study design, data analysis, and manuscript review. Randall J. Nett, MD, MPH – participated in study design, data acquisition, data analysis, manuscript preparation, and manuscript review.

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inclusion of short-tenured workers could further define risks for NMRD and identify prevention strategies.

Keywords

chronic bronchitis; chronic obstructive pulmonary diseases; emphysema; eosinophilia; non-malignant respiratory disease; occupational asthma; occupational lung disease; rubber

1 | INTRODUCTION

Several published case reports and cross-sectional epidemiologic studies have reported the occurrence of upper and lower respiratory symptoms and non-malignant respiratory diseases (NMRD) including asthma, bronchitis, emphysema, and chronic obstructive pulmonary disease (COPD) among workers in the rubber manufacturing industry.[1–7] An estimated 725 000 persons are employed in the U.S. plastics and rubber manufacturing industry and potentially exposed to emissions released during rubber manufacturing.[8]

Rubber manufacturing is a complex process that includes mixing and milling, extrusion, molding, and finishing.[9] Approximately 500 ingredients are combined to produce various types of rubber.[5,9,10] During rubber manufacturing, workers are potentially exposed to feedstock materials and reaction products released in the forms of gases, vapors, dusts, mists, and ultrafine particles, collectively referred as rubber manufacturing emissions.[11–13]

Occupational exposure to rubber manufacturing emissions occurs through inhalation or skin contact during the manufacturing process.[7,9,11,14,15] Rubber manufacturing emissions can contain known human carcinogens such as aromatic amines, nitrosamines, and polycyclic aromatic hydrocarbons (PAH), and are associated with an increased risk of cancer among rubber workers.[5,9,16,17] However, the association between exposure to rubber manufacturing emissions and development of NMRD is less clear. A single animal study demonstrated pathologic lung lesions and significant increase in lung mast cells in guinea pigs following inhalation exposure to high concentration of rubber vulcanization fumes;[18] indicating an association between exposure to rubber manufacturing emissions and NMRD.

Work-related respiratory disease is common. Approximately 17% of all adult-onset asthma cases and 15% of COPD cases are attributable to occupational exposures.[19,20] These work-related respiratory diseases have a substantial economic impact related to healthcare cost, absenteeism, and disability.[21] Many of the compounds used in rubber manufacturing are known respiratory hazards (bronchoirritants or sensitizers) that can cause acute or chronic respiratory symptoms.[4,5,15] However, only a small proportion of the numerous chemicals found in rubber manufacturing have occupational exposure limits including: Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs), NIOSH recommended exposure limits (RELs), American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Values (TLV®s), or American Industrial Hygiene Association (AIHA) workplace environmental exposure limits (WEEL®s). Additionally, the combination of chemicals and ultrafine particles could alter the expected health effects.[22]

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Epidemiologic investigations focusing on the carcinogenic risk associated with rubber manufacturing have been well-documented.[9,23,24] However, to our knowledge, a comprehensive literature review of NMRD-related morbidity and mortality among rubber manufacturing workers has not been conducted. A thorough review of existing literature is essential to developing a better understanding of the non-carcinogenic respiratory hazards associated with rubber manufacturing. The purpose of this study was to systematically review the published scientific literature and summarize the evidence for associations between occupational exposure to rubber manufacturing emissions and NMRD-related morbidity and mortality.

2 | MATERIALS AND METHODS

We used the steps Hempel et al recommended for conducting a systematic review of occupational safety and health questions.[25] We conducted a search of Scopus (January 1, 1969 to June 15, 2017), Medline (January 1, 1970 to June 15, 2017), and Embase (January 1, 1970 to June 15, 2017),[a] for the purpose of identifying published studies involving respiratory symptoms, impaired lung function, or NMRD among rubber manufacturing workers.

A total of 1337 unique citations were retrieved (Figure 1). Eleven duplicates were identified and excluded. Additional citations were eliminated because of lack of relevancy following review of title (n = 1193) and abstract (n = 32) by three authors (NT, SET, and RJN). These citations were further classified into case reports, cross-sectional studies, or mortality studies. Articles describing mortality studies were excluded (n = 34) when NMRD-related mortality was not assessed. One article was excluded because the publication was unavailable. Two additional articles were included following a bibliography review of the included studies and review of the author's manuscript collection. During the review process, the authors excluded one article describing an animal study, one article describing non-respiratory symptoms, two articles including non-rubber manufacturing facilities, and two articles describing mortality studies that did not calculate standardized mortality ratios [SMR] for NMRD. A total of 62 articles met the inclusion criteria of the study having an assessment for the presence of respiratory symptoms, impaired lung function, or NMRD among rubber manufacturing workers. During analysis, four articles were combined and analyzed as two cross-sectional studies because the authors described respiratory symptoms and lung function abnormalities for the same cohorts in separate publications.[26–29] One

[a]Search strategy and keywords: **SCOPUS**: TITLE-ABS-KEY (rubber OR "ethylene propylene diene monomer" OR epdm OR neoprene OR polychloroprene OR elastomer* OR "styrene butadiene" OR polybutadiene) AND TITLE-ABS-KEY ("threshold limit value" OR employee* OR facilities OR facility OR industry* OR manufactur* OR "maximum allowable concentration" OR occupation* OR worker* OR workplace*) AND TITLE-ABS-KEY (airway* OR alveol* OR asthma* OR bronch* OR (bronchiolit* W/2 oblit*) OR chest OR respirat* OR expiratory OR fev1 OR (hypersensit* W/2 pneumon*) OR inhal* OR laryng* OR lung OR lungs OR pneumo* OR pulmon* OR respirato* OR spiromet*) AND LANGUAGE (english) AND PUBYEAR>1969 AND NOT TITLE-ABS-KEY (mouse OR mice OR murine OR rats OR swine). **MEDLINE and EMBASE**: TITLE-ABS-KEY (rubber OR "ethylene propylene diene monomer" OR epdm OR neoprene OR polychloroprene OR elastomer* OR "styrene butadiene" OR polybutadiene) AND TITLE-ABS-KEY ("threshold limit values" OR maximum allowable concentration* OR employee* OR worker* OR workplace* OR occupational OR (facility or facilities) OR (industry or industries or industrial) OR manufactur* AND TITLE-ABS-KEY (Respiratory Tract Diseases OR Respiratory system OR Diagnostic Techniques, Respiratory System OR airway* Alveolar Epithelial Cells OR Macrophages, Alveolar OR Pulmonary Alveoli OR (alveolar or alveoli) OR asthma* OR bronchial OR bronchitis OR bronch* OR bronchiolit* adj oblit* OR thorax OR chest OR expiratory OR fev1 OR (hypersensit* adj pneumon*) OR inhalation OR inhal* OR laryng* OR lung* OR pneumo* OR pulmon* OR respirat* OR spiromet* AND LANGUAGE (english) and yr = "1970-Current" AND NOT TITLE-ABS-KEY (mouse OR mice OR murine OR rats OR swine).

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article was considered both as a case series and cross-sectional study.[30] Mortality studies assessing the same cohort during different time periods were grouped together and assigned a corresponding alphabet letter (Table 4). Confidence intervals (CI) not reported in mortality studies were calculated using OpenEpi.[31]

We summarized the study findings regarding exposure to rubber manufacturing emissions, respiratory symptoms or signs, lung function abnormalities, and NMRD diagnoses as defined by the original study. Cross-sectional studies ($n = 30$) and mortality studies ($n = 26$) were evaluated using a grading rubric developed a priori by the authors (Table 1). Each cross-sectional and mortality study was assessed for evidence of association between exposure to rubber manufacturing emissions and NMRD-related morbidity or mortality by three authors (NT, SET, and RJN) and strength of association was characterized as strong, intermediate, non-significant positive, or no association.[b]

We conducted a meta-analysis to analyze the association between exposure to rubber manufacturing emissions and development of respiratory symptoms or NMRD for the cross-sectional and mortality studies using a data analysis guide produced by Neyeloff et al.[32] We modified the guide spreadsheet to account for the use of SMRs and odds ratios. Heterogeneity was evaluated using the I^2 value described by Higgins et al.[33] For the cross-sectional meta-analysis, we included cross-sectional studies that provided odds ratios with confidence intervals for respiratory symptoms, NMRD diagnoses, or sufficient data to calculate odds ratios and confidence intervals. If more than one odds ratio was reported in a study, we chose a lower respiratory outcome with the highest odds ratio. Among the 30 cross-sectional studies, six studies were included in the meta-analysis and 24 were excluded. For the mortality meta-analysis, we included studies that reported overall SMRs for diseases of the respiratory system (ICD code: 427–527) in males. Nineteen mortality studies were included in the meta-analysis and six studies were excluded. For both meta-analyses, each study's weight was calculated by the inverse of the study variance plus the between-studies variance.[32] In the forest plots, each study's weight was represented as a percentage of the sum of the weights. The results of this study were presented at the American Thoracic Society 2018 International Conference.[34]

3 | RESULTS

3.1 | Case reports

Table 2 summarizes five articles describing 11 cases of respiratory illness occurring among workers exposed to rubber manufacturing emissions at five facilities located in the United States ($n = 2$), Canada (1), Korea (1), and Ethiopia (1).[1,2,30,35,36,37] Ten of the cases occurred among males. Of the 10 cases with known age, the median age was 36.5 (range: 21–57) years. Of the 10 cases that reported symptom onset times, the median time from first exposure to symptom onset was 7 weeks (range: 2 weeks-4 years). Five of the 11 workers with respiratory illness used tobacco. Among these 11 cases, symptoms and conditions included rhinorrhea ($n = 1$), nasal congestion (1), sinusitis (1), rhinitis (1), hoarseness (2), chronic laryngitis (1), breathlessness (1), dyspnea (6), wheezing (4), chest congestion (1),

[b]Assigned to studies that did not meet the criteria for the other categories of strength of association.

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cough (4), sputum production (2), chest pain (1), chest tightness (2), early pneumonia (1), pneumonic infiltrates (1), pneumonitis (1), interstitial fibrosis (1), bilateral interstitial infiltrates (1), acute respiratory distress (1),asthma symptoms (1), nasolaryngotracheobronchitis (1), and chronic bronchitis (2). One case of occupational asthma and one case of acute eosinophilic pneumonia were also identified. Work roles included press operators in the thermo-injection process ($n = 5$), cushion mill operator (1), working in the heat press process (1), tire curing process (1), passenger tire builder (1), and calender operators (2). Six workers had respiratory conditions and eosinophilia; the eosinophil count for five workers was not reported. Nine workers were hospitalized and no workers died.

Bascom et al described five workers who worked as press operators in the thermo-injection process at a single facility.[1] The workers were exposed to heated chloroprene-based rubber that was injected into the metal molds. The onset of respiratory symptoms for all workers occurred 2–6 weeks after an increase in production that resulted in an increase in rubber manufacturing emissions. Two and five workers experienced upper and lower respiratory symptoms, respectively. Two had abnormal spirometry (obstruction = 1; restriction = 1) and one had a decrease in diffusing capacity. Eosinophilia was observed for each press operator. All five workers returned to work after treatment and were transferred to other work areas within the facility.

An article by Kato and Leki reported one case in a 31-year-old male who had the task of pouring raw materials into molds and a heat press.[35] His symptoms began two months after exposure and included dyspnea and fever. He also had bilateral diffuse infiltrates on chest radiographs and eosinophilia. He was diagnosed with acute eosinophilic pneumonia and hospitalized. He was discharged following treatment with oral steroids, at which time he returned to work with no subsequent recurrence of acute eosinophilic pneumonia.

The Korean Occupational Safety and Health Research Institute described a tire curing machine operator in his 30s who developed asthma symptoms after four years of work in a tire manufacturing facility.[36,37] With exposure to rubber manufacturing emissions that ranged from 0.18 to 0.80 mg/m^3, the worker's average peak expiratory flow decreased from 417.1 L/min on a rest day to 361.7 L/min on working day.

Another article by Tarlo reported a case in a 55-year-old male who worked at a rubber tire manufacturing facility as a cushion mill operator where his task was to apply hot rubber coating to rubber strips.[2] His symptoms of rhinitis started one year after exposure to a newly introduced chemical (crude tall oil, heated to 100°C) at the workplace. Three months later, he was hospitalized for asthma. While away from work, his symptoms resolved and lung function results were normal. Following his return to work, he experienced a reoccurrence of respiratory symptoms and a decline in peak expiratory flows. A single-patient blinded specific inhalation challenge was conducted using tall oil resin, with molasses as a control substance. Lung function remained stable following an inhalation challenge with molasses. However, following an inhalation challenge to tall oil resin for 65 min he became dyspneic with a 60% decrease in forced expiratory volume in one second (FEV1), resulting in a diagnosis of occupational asthma.

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One cross-sectional study by doPico et al. described three case reports that occurred among one passenger tire builder and two calender operators.[30] All three workers had worked in the plant for an average of 26 years (range: 15–34 years) and each of them developed upper and lower respiratory symptoms 1–2 months following exposure to the newly introduced thermosetting resin at the workplace. Two of the workers returned to work despite having a chronic productive cough, intermittent wheezing, mild dyspnea, and nasolaryngotracheobronchitis; one calender operator was unable to continue working because of chronic laryngitis and severe bronchitis.

3.2 | Cross-sectional studies

Table 3 summarizes 32 articles describing 30 cross-sectional studies evaluating the presence of respiratory symptoms and NMRD among workers exposed to rubber manufacturing emisssions.[3–7,10–12,14,15,21,26–30,38–53] Occupational cohorts (n = 10 896 workers in total) across studies varied from 34 to 1820 workers, and included facilities from the United States (n = 14), Sweden (6), India (3), Iran (3), Italy (1), Netherlands (1), Poland (1), and Turkey (1). Nineteen studies evaluated both respiratory symptoms/diagnoses and spirometry measurements, eight respiratory symptoms/diagnoses only, and three spirometry measurements only.

All of the 30 cross-sectional studies had non-significant positive or higher evidence of association between exposure to rubber manufacturing emissions and respiratory morbidity. Nine (30%) studies had strong evidence, nine (30%) intermediate, and 12 (40%) non-significant positive association. Compared with controls, exposed workers in 15 (52%), 11 (38%), and 3 (10%) cross-sectional studies had a statistically significant higher prevalence of respiratory symptoms, airflow limitation, or NMRD, respectively. Respiratory symptoms reported among the exposed workers included nosebleed, nasal congestion, shortness of breath, cough, sputum production, dyspnea, wheeze, chest tightness, chest irritation, and chest pain. NMRD diagnoses included sinusitis, pharyngitis, chronic bronchitis, emphysema, COPD, and asthma. Twenty-two studies conducted spirometry measurements; of these, reductions were reported in FEV1 (n = 6), forced vital capacity (FVC) (6), vital capacity (VC) (1), FEV1/FVC (8), forced expiratory flow (FEF) at 75% of FVC (1), FEF at 50% of FVC (1), and FEF at 25% of FVC (1).

Workers included in the cross-sectional studies had known exposures to rubber manufacturing emissions that included suspended dusts, organic and inorganic vapors, respirable and inhalable talc dust, napthalene-diisocyanate (NDI) fumes, respirable particulate matter, polycyclic aromatic hydrocarbons (including benzo(a)pyrene), sulphates, nitrates, thermosetting resin, or carbon black. Twenty-six (87%) of the cross-sectional studies assessed for tobacco use among workers; 19 (63%) of those studies reported respiratory symptoms or lung function associated with smoking. For example, one study described prevalence of lung impairment among exposed non-smokers (odds ratio = 3.45, 95%CI, 1.76–9.50), exposed smokers (12.12, 3.35–37.87), and non-exposed smokers (3.48, 1.42–8.33) compared with non-exposed non-smokers.[14]

For the meta-analysis of cross-sectional studies, odds ratios with confidence intervals from six cross-sectional studies were analyzed using a random effects model (Figure 2). We

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selected the random effects model because of the moderate-to-high I^2 value (67.6%)[33] and the perceived heterogeneity observed during the formal review. The overall odds ratio for the cross-sectional meta-analysis was 3.83 (95% CI, 2.28–6.51).

3.3 | Mortality studies

Table 4 summarizes 26 articles describing 26 mortality studies of 14 occupational cohorts involving 270,408 workers (range: 327–40 867).[16,17,23,54–76] These mortality studies included workers from facilities in the United States (n = 13), Germany (4), United Kingdom (4), Italy (2), Sweden (2), and one study included facilities from five European countries (Germany, Italy, Poland, Sweden, and United Kingdom).

The primary focus of these mortality studies was cancer. For the purpose of our review, NMRD-related mortality was caused by diseases of the respiratory system other than cancer including asthma, bronchitis, chronic airway obstruction, COPD, emphysema, and pneumonia. Median required work tenure was one year (range: 1 day-5 years). Twenty (77%) studies excluded workers with work tenure <1 year and therefore were not designed to assess the relationship between mortality from NMRD and these short-term exposures.

Of the 26 studies addressing NMRD mortality, one (4%) had strong, four (15%) had intermediate, 10 (39%) had non-significant positive association, and 11 (42%) had no evidence of association between exposure to rubber manufacturing emissions and NMRD-related mortality. A mortality study among curing workers, which have a higher exposure to curing fumes compared with other workers,[9] had strong association for NMRD-related mortality; the SMR for pneumonia was 2.2 (95%CI, 1.37–3.38).[61]

Among the four studies demonstrating intermediate association, one reported elevated mortality for COPD (SMR = 1.22, 95%CI, 1.01–1.46) among retired workers in the German rubber industry.[16] Another identified elevated mortality among retired U.S. male rubber manufacturing workers aged 40–64 years from bronchitis, emphysema, and asthma (SMR = 1.84, 95%CI, 1.43–2.40) and other respiratory diseases (SMR = 3.09, 95%CI, 1.8–5.08).[55] A third study among tire manufacturing workers with different work tenures (range: <6 months-10 years) described various NMRD-related mortalities among workers with tenure <6 months, 6 month-2.5 years, >2.5–10 years, and >10 years (SMR = 2.06, 95%CI, 1.36–3.00; 1.92, 1.23–2.85; 1.23, 0.71–1.96 and, 0.59, 0.27–1.12, respectively).[69] Mortality related to NMRD and chronic airway obstruction among workers with 10 years latency was also elevated (SMR = 1.46, 95%CI, 1.15–1.83; 1.67, 1.17–2.31, respectively). Finally, a fourth study reported mortality for bronchitis, emphysema, and asthma (SMR = 1.82, 95%CI, 1.06–2.94) among workers in different sectors (sponge rubber, rubber with plastic, crepe rubber, etc.) of the rubber and cable making industry.[76]

For the meta-analysis of mortality studies, SMRs with confidence intervals from 19 mortality studies were analyzed for the association of rubber manufacturing emissions and NMRD-related mortality (Figure 3). Because I^2 was moderate-to-high (63.2%) and a high heterogeneity was perceived during the formal review,[33] the random effect model was used for the meta-analysis. The overall SMR for the mortality studies meta-analysis was 0.90 (95%CI, 0.82–0.99).

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4 | DISCUSSION

This systematic review identified some evidence that exposure to rubber manufacturing emissions is positively associated with NMRD. Available evidence included: (1) 11 case reports of respiratory conditions occurring among workers in rubber manufacturing facilities, including one case report of occupational asthma that included a positive specific inhalation challenge and one case of acute eosinophilic pneumonia; (2) all 30 cross-sectional studies provided at least non-significant positive association between exposure to rubber manufacturing emissions and development of respiratory symptoms, lung function abnormalities, or NMRD, including nine studies that had strong evidence of association; and (3) the meta-analysis among the six cross-sectional studies that calculated an odds ratio indicated a significant positive association between rubber manufacturing emissions and respiratory symptoms or NMRD. Although 15 of 26 mortality studies had at least non-significant positive association between exposure to rubber manufacturing emissions and NMRD-related mortality, the mortality study meta-analysis found no association. However, one mortality study did indicate strong evidence of association between rubber manufacturing emissions and NMRD-related mortality.

The majority of the cross-sectional and mortality studies included in this review did not conduct a comprehensive exposure analysis. Among the cross-sectional studies, only nine discussed exposure to specific chemicals (Napthalene-diisocyanate, talc dust, hexamethylenetetramine-resorcinol resin, benzo(a)pyrene, carbon disulfide, and carbon black dust) while the other 21 described general rubber manufacturing emissions exposure. Rubber manufacturing workers are exposed to a multitude of natural or anthropogenic chemicals and high concentrations of ultrafine particles through inhalation routes.[9] Evidence has indicated that mixing natural or anthropogenic chemicals with combustion-produced fine and ultrafine particles might increase transfer of chemicals into the respiratory cells; thus, increasing respiratory morbidity and mortality.[22,77] The complexity of rubber manufacturing exposures makes completing an accurate exposure analysis and determining the role rubber manufacturing emissions exposure plays in the development of NMRD difficult.[9] Because of the challenges in attributing specific exposures to health outcomes, animal studies of rubber manufacturing emissions could contribute to a better understanding of the potential respiratory toxicity that occurs from working in rubber manufacturing.

Work-related asthma is characterized by asthma symptoms that occur in a previously healthy worker (occupational asthma) or a worker previously diagnosed with asthma whose symptoms are made worse by the workplace (work-exacerbated asthma).[78] There are over 300 known respiratory irritants and sensitizers that can lead to the development of work-related asthma and many are found in dusts, fumes, and vapors from rubber manufacturing.[4,5,15,79,80] Several studies and case reports identified during this systematic review described cases of work-related asthma including a confirmed case of occupational asthma diagnosed following a positive specific inhalation challenge.[2] Additionally, six cross-sectional studies reported a higher prevalence of asthma, a significantly higher number of respiratory symptoms, and a reduction in lung function among workers with higher exposures to rubber manufacturing emissions compared with controls.[7,15,21,26,40,41] Furthermore, four mortality studies that were focused on malignant disease-related mortality reported SMRs for asthma,

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bronchitis, and emphysema including two with statistically significant SMRs[55,76] and two with a non-significant positive association.[54,73] Finally, another mortality study reported a non-significant positive SMR for asthma.[63] Because of the possibility of work-related asthma occurring among rubber manufacturing workers, symptom surveillance, and improving clinician awareness of work-related asthma risks among rubber manufacturing workers might help identify asthma caused by rubber manufacturing emissions sooner.

Six of the 11 case reports included in this review described workers from two rubber manufacturing facilities who had respiratory conditions and eosinophilia.[1,35] Eosinophilia with airway inflammation occurs in a number of respiratory conditions including allergic rhinitis, asthma, bronchitis, and COPD.[81] Allergic airway sensitivity has been associated with inhalational exposure to combustion products,[82,83] and occupational exposures have been associated with eosinophil production.[81] A recent study among professional firefighters who had chronic and prolonged exposure to smoke and numerous ultrafine particulates reported statistically significantly higher percentage of eosinophils on induced sputum and bronchoalveolar lavage fluid testing compared with healthy subjects or firefighter trainees, and demonstrated a significant correlation between the percentage of sputum eosinophils and years of service.[84] Identification of eosinophilic asthma versus non-eosinophilic asthma has important implications for identification of potential causes and for selecting appropriate treatments.[85] Although sputum eosinophilia is the gold standard of diagnosis for eosinophilic asthma, persons with blood eosinophil counts of more than 400 cells/μL can be expected to have increased sputum eosinophils.[85] Therefore, the use of blood eosinophil counts among rubber manufacturing workers who experience respiratory symptoms and the use of non-invasive biomarkers, such as fraction of exhaled nitric oxide (FeNO) that can predict the presence of sputum eosinophilia, can help identify cases of eosinophilic asthma.[86]

The cross-sectional studies included in this review likely underestimated the prevalence of NMRD-related morbidity. Cross-sectional studies are subject to healthy worker bias because ill workers leave the workplace resulting in a healthier workforce.[87] Even so, each of the 30 cross-sectional studies had at least a non-significant positive association between exposure to rubber manufacturing emissions and NMRD-related morbidity. In addition, a meta-analysis of six cross-sectional studies demonstrated a significant positive association of rubber manufacturing emissions and respiratory symptoms or NMRD. Among the 30 cross-sectional studies, 22 incorporated only spirometry to assess lung function changes among rubber manufacturing workers. Although spirometry is commonly used to identify work-related NMRD, baseline lung function testing that includes spirometry combined with other non-traditional testing methods such as impulse oscillometry or FeNO might improve NMRD testing sensitivity. Spirometry, as a single lung function test, has a poor sensitivity for work-related asthma.[88] Identifying work-related asthma in a cross-sectional study includes establishing a relationship between symptoms and work through a medical questionnaire and lung function testing.[89,90] To improve detection of asthma and other work-related lung conditions among rubber manufacturing workers during future cross-sectional studies, consideration should be given to completion of comprehensive studies that include medical questionnaire, spirometry, and other non-traditional testing methods that can aid in the identification of asthma and other airway diseases.[86,91,92] Additionally, repeating

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these comprehensive studies could help identify rubber manufacturing workers with excessive declines in lung function at earlier stages of NMRD.[93,94]

Although 15 of the 26 mortality studies indicated at least a non-significant positive association, the meta-analysis for the mortality studies demonstrated no association between rubber manufacturing emissions and NMRD-related mortality. However, the mortality studies included in this review were likely limited in their ability to detect work-related NMRD-related mortality for multiple reasons. First, the mortality studies were designed to detect cancer-related mortality. Consequently, the studies assessed cumulative exposures over long periods and the majority of studies excluded short-tenured workers, which likely limited the identification of respiratory mortality associated with short-term higher exposures to rubber manufacturing emissions. For example, the case reports included in this study had a median time from exposure to symptom onset of seven weeks. Eight of the 11 mortality studies with no evidence of association between exposure to rubber manufacturing emissions and NMRD-related mortality excluded workers with tenure <1 year. One study of tire manufacturing workers demonstrated a higher mortality for diseases of the respiratory system among workers with a tenure <6 months (SMR = 2.06, 95%CI, 1.36–3.00) compared with workers with tenure 6 months-2.5 years tenure (SMR = 1.92, 95%CI, 1.23–2.85), >2.5–10 years tenure (SMR = 1.23, 95%CI, 0.71–1.96), and >10 years tenure (SMR = 0.59, 95%CI, 0.27–1.12).[69] Second, death certificates are not sensitive for detecting occupational lung diseases,[95] and classification of causes of death reported in death certificates is often inaccurate with frequent discordance with clinical and autopsy information.[96] Third, work-related COPD mortalities might be falsely attributed to tobacco-related mortalities because of the strong causal association with tobacco smoking and the late onset of disease.[97] To improve detection of work-related respiratory disease mortality, future mortality studies of rubber manufacturing worker cohorts should include: NMRD cause of death codes, longer follow-up periods, short-tenured workers, and methods to adjust for confounding of tobacco use such as standardized rate ratios.[98]

This study is subject to several limitations. First, systematic reviews are subject to publication bias of the articles reviewed, which might bias the findings towards a positive association between exposure to rubber manufacturing emissions and development of NMRD-related morbidity or mortality. However, in general, the mortality studies were designed to detect cancer-related mortality and negative findings of NMRD-related mortality would not have precluded their publication. Second, the mortality studies did not assess for a history of tobacco use. Therefore, if the rubber manufacturing workers used tobacco at a higher rate than the general population, the studies might be skewed toward a positive association between employment at a rubber manufacturing facility and NMRD-related mortality. Third, the majority of cross-sectional and mortality studies were lacking detailed exposure information, which limited the ability to compare exposures across studies. Fourth, this review included rubber manufacturing emissions studies from over a span of 42 years. During this period, substantial changes in rubber manufacturing work practices have occurred,[13] which potentially affected the comparability or contemporary relevance of some of the results and conclusions. Finally, our review was restricted to published studies written in the English language, which might have underestimated the occurrence of NMRD among rubber workers and the systematic review results.

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In summary, a systematic review of available case reports, cross-sectional studies, and mortality studies provided some evidence that working in rubber manufacturing is potentially associated with NMRD-related morbidity and mortality, with more evidence for association with morbidity. Conducting detailed exposure assessments during cross-sectional studies that also include traditional (eg, spirometry) and non-traditional testing modalities (eg, FeNO and impulse oscillometry), and associating specific exposures to health outcomes, could help to further describe the association between exposure to rubber manufacturing emissions and respiratory morbidity. Furthermore, future studies assessing mortality among rubber manufacturing workers should include short-tenured workers and use statistical methods that adjust for confounding from tobacco use. Finally, conducting animal studies involving individual and mixed exposures of the predominant chemicals used in rubber manufacturing could help public health professionals better understand the potential respiratory toxicity associated with rubber manufacturing.

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REFERENCES

1. Bascom R, Fisher JF, Thomas RJ, Yang WN, Baser ME, Baker JH. Eosinophilia, respiratory symptoms and pulmonary infiltrates in rubber workers. Chest 1988;93:154–158. [PubMed: 3335147]
2. Tarlo SM. Occupational asthma induced by tall oil in the rubber tyre industry. Clin Exp Allergy 1992;22:99–101. [PubMed: 1551039]
3. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2002;156:738–746. [PubMed: 12370162]
4. Akca ASD, Demircan N, Kart L, Altin R. Evaluation of respiratory symptoms in workers of a rubber factory. Eur J Gen Med 2011;8: 302–307.
5. Governa M, Comai M, Valentino M, Antonicelli L, Rinaldi F, Pisani E. Ventilatory function in rubber processing workers: acute changes over the workshift. Br J Ind Med 1987;44:83–89. [PubMed: 3814549]
6. Jonsson LS, Broberg K, Axmon A, Jonsson BAG, Littorin M. Symptoms and immunologic markers among vulcanization workers in rubber industries in southern Sweden. Scand J Work Environ Health 2007;33:272–279. [PubMed: 17717619]
7. Meijer E, Heederik D, Kromhout H. Pulmonary effects of inhaled dust and fumes: exposure-response study in rubber workers. Am J Ind Med 1998;33:16–23. [PubMed: 9408525]
8. U.S. Bureau of Labor Statistics (BLS). About the Plastics and Rubber Products Manufacturing subsector 2018; https://www.bls.gov/iag/tgs/iag326.htm. Accessed April 09, 2018.
9. International Agency for Research on Cancer. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Occupational Exposures in the Rubber Manufacturing Industry 2012; 100 F:https://www.ncbi.nlm.nih.gov/books/NBK304412/. Accessed August 10, 2017.
10. Gupta P, Banerjee DK, Bhargava SK, Kaul R, Shankara VR. Effect of pollutants on airway resistance in rubber factory workers. Indoor Built Environ 1993a;2:105–110.
11. McMichael AJ, Gerber WS, Gamble JF, Lednar WM. Chronic respiratory symptoms and job type within the rubber industry. J Occup Med 1976;18:611–617. [PubMed: 966093]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

12. Jonsson LS, Jonsson BA, Axmon A, Littorin M, Broberg K. Influence of glutathione-related genes on symptoms and immunologic markers among vulcanization workers in the southern Sweden rubber industries. Int Arch Occup Environ Health 2008a;81: 913–919. [PubMed: 18066575]
13. Forrest M The composition and nature of vulcanisation fumes in the rubber industry-A technical review. Prog Rubber Plast Re 2015;31:219–264.
14. Attarchi M, Dehghan F, Afrasyabi M, Sadeghi Z, Mohammadi S. Combined effect of cigarette smoking and occupational exposures on lung function: a cross-sectional study of rubber industry workers. Workplace Health Saf 2013;61:213–220. [PubMed: 23650896]
15. Zuskin E, Mustajbegovic J, Schachter EN, Doko-Jelinic J, Budak A. Longitudinal study of respiratory findings in rubber workers. Am J Ind Med 1996;30:171–179. [PubMed: 8844047]
16. Weiland SK, Mundt KA, Keil U, et al. Cancer mortality among workers in the German rubber industry: 1981–91. Occup Environ Med 1996;53:289–298. [PubMed: 8673175]
17. Vlaanderen J, Taeger D, Wellman J, Keil U, Schuz J, Straif K. Extended cancer mortality follow-up of a German rubber industry cohort. J Occup Environ Med 2013;55:966–972. [PubMed: 23887703]
18. Rydzynski K, Domanska A, Czerczak S, Krysiak B. The effect of subchronic exposure to the rubber vulcanization fumes on guinea pig lungs. Pol J Occup Med 1990;3:43–50. [PubMed: 2132935]
19. Torén K, Blanc PD. Asthma caused by occupational exposures is common - A systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med 2009;9:7–7. [PubMed: 19178702]
20. Blanc PD. Occupation and COPD: a brief review. J Asthma 2012;49: 2–4. [PubMed: 21895566]
21. Lednar WM, Tyroler HA, McMichael AJ, Shy CM. The occupational determinants of chronic disabling pulmonary disease in rubber workers. J Occup Med 1977;19:263–268. [PubMed: 758090]
22. Penn A, Murphy G, Barker S, Henk W, Penn L. Combustion-Derived ultrafine particles transport organic toxicants to target respiratory cells. Environ Health Perspect 2005;113:956–963. [PubMed: 16079063]
23. Straif K, Keil U, Taeger D, et al. Exposure to nitrosamines, carbon black, asbestos, and talc and mortality from stomach, lung, and laryngeal cancer in a cohort of rubber workers. Am J Epidemiol 2000;152: 297–306. [PubMed: 10968374]
24. Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med 1998;55:1–12. [PubMed: 9536156]
25. Hempel S, Xenakis L, Danz M. Systematic reviews for occupational safety and health questions Santa Monica, CA: RAND Corporation 2016; 1–88. Available at: https://www.rand.org/content/dam/rand/pubs/research_reports/RR1400/RR1463/RAND_RR1463.pdf. Accessed August 18, 2017.
26. Fine LJ, Peters JM. Respiratory morbidity in rubber workers: I. Prevalence of respiratory symptoms and disease in curing workers. Arch Environ Health 1976a;31:5–9. [PubMed: 1244807]
27. Fine LJ, Peters JM. Respiratory morbidity in rubber workers: II. Pulmonary function in curing workers. Arch Environ Health 1976b;31: 10–14. [PubMed: 1244803]
28. Weeks JL, Peters JM, Monson RR. Screening for occupational health hazards in the rubber industry. Part I. Am J Ind Med 1981a;2:125–141. [PubMed: 7349039]
29. Weeks JL, Peters JM, Monson RR. Screening for occupational health hazards in the rubber industry. Part II: health hazards in the curing department. Am J Ind Med 1981b;2:143–151. [PubMed: 7349040]
30. doPico GA, Rankin J, Chosy LW, et al. Respiratory tract disease from thermosetting resins. Study of an outbreak in rubber tire workers. Ann Intern Med 1975;83:177–184. [PubMed: 1147451]
31. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health 2013; https://www.openepi.com/SMR/SMR.htm. Accessed August 30, 2017.
32. Neyeloff JL, Fuchs SC, Moreira LB. Meta-analyses and forest plots using a microsoft excel spreadsheet: step-by-step guide focusing on descriptive data analysis. BMC Res Notes 2012;5:52–52. [PubMed: 22264277]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research ed) 2003;327: 557–560.
34. Thapa N, Tomasi SE, Cox-Ganser JM, Nett RJ. Non-malignant respiratory disease among rubber workers. Am J Respir Crit Care Med 2018;197:A2582.
35. Kato T, Ieki R. A case of acute eosinophilic pneumonia associated with heated rubber fume exposure. Allergol Int 2005;54:491–494.
36. Lee JS, Kwak HS, Choi BS, Park SY. A case of occupational asthma in a plastic injection process worker. Ann Occup Environ Med 2013;25:25. [PubMed: 24472161]
37. >Occupational Safety and Health Research Institute. Occupational disease casebook Republic of Korea Korea Occupational Safety and Health Research Agency; 2013.
38. Alexandersson R, Gustafsson P, Hedenstierna G, Rosen G. Exposure to naphthalene-diisocyanate in a rubber plant: symptoms and lung function. Arch Environ Health 1986;41:85–89. [PubMed: 3718007]
39. Bascom R, Baser ME, Thomas RJ, Fisher JF, Yang WN, Baker JH. Elevated serum IgE, eosinophilia, and lung function in rubber workers. Arch Environ Health 1990;45:15–19. [PubMed: 2317085]
40. Fine LJ, Peters JM. Studies of respiratory morbidity in rubber workers: Part III. Respiratory morbidity in processing workers. Arch Environ Health 1976c;31:136–140. [PubMed: 1275557]
41. Fine LJ, Peters JM, Burgess WA, Di Berardinis LJ. Studies of respiratory morbidity in rubber workers. Part IV. Respiratory morbidity in talc workers. Arch Environ Health 1976;31:195–200. [PubMed: 942261]
42. Gamble JF, McMichael AJ, Williams T, Battigelli M. Respiratory function and symptoms: an environmental-epidemiological study of rubber workers exposed to a phenolformaldehyde type resin. Am Ind Hyg Assoc J 1976a;37:499–513. [PubMed: 1008033]
43. Gupta P, Banerjee DK, Bhargava SK, Kaul R, Ravi Shankar VS. Prevalence of impaired lung function in rubber manufacturing factory workers exposed to benzo(a)pyrene and respirable particulate matter. Indoor Built Environ 1993b;2:26–31.
44. Gupta P, Banerjee DK, Bhargava SK, Kaul R, Shanker VR. Abnormal pattern of lung functions in rubber factory workers. J Indian Med Assoc 1994;92:260–263. [PubMed: 7963614]
45. Jonsson LS, Broberg K, Axmon A, Bergendorf U, Littorin M, Jonsson BAG. Levels of 1-hydroxypyrene, symptoms and immunologic markers in vulcanization workers in the southern Sweden rubber industries. Int Arch Occup Environ Health 2008b;82:131–137. [PubMed: 18425528]
46. Jonsson LS, Lindh CH, Bergendorf U, Axmon A, Littorin M, Jonsson BA. N-nitrosamines in the southern Swedish rubber industries - exposure, health effects, and immunologic markers. Scand J Work Environ Health 2009;35:203–211. [PubMed: 19404559]
47. Jonsson LS, Littorin M, Axmon A, Jonsson BA, Broberg K. Lung function in relation to 2-thiothiazolidine-4-carboxylic acid and genetic effect modification among rubber workers in Sweden. J Occup Environ Med 2008c;50:1006–1012. [PubMed: 18784548]
48. Neghab M, Mohraz MH, Hassanzadeh J. Symptoms of respiratory disease and lung functional impairment associated with occupational inhalation exposure to carbon black dust. J Occup Health 2011;53: 432–438. [PubMed: 21996929]
49. Neghab M, Rahimi E, Emad A, Rajaeei Fard AR. An epidemiological study of talc-related respiratory morbidity among employees of a rubber industry in Shiraz-Iran. Int Arch Occup Environ Health 2007;80: 539–546. [PubMed: 17165065]
50. Sparks PJ, Smith TJ, Fine LJ, Treitman RD, Spiegelman DL. Respiratory morbidity among processing and mill workers. A cross-sectional survey in three tire-manufacturing plants. J Occup Med 1982;24: 690–695. [PubMed: 7131111]
51. Thomas RJ, Bascom R, Yang WN, et al. Peripheral eosinophilia and respiratory symptoms in rubber injection press operators: a case-control study. Am J Ind Med 1986;9:551–559. [PubMed: 3740072]
52. Szubert Z, Szeszenia-Dabrowska N, Sobala W. Sickness absence in a rubber plant in Poland. Int J Occup Med Environ Health 1998;11: 179–188. [PubMed: 9753897]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

53. Gamble J, Liu S, McMichael AJ, Waxweiler RJ. Effect of occupational and nonoccupational factors on the respiratory system of vinyl chloride and other workers. J Occup Med 1976b;18:659–670. [PubMed: 966081]
54. Andjelkovich D, Taulbee J, Blum S. Mortality of female workers in rubber manufacturing plant. J Occup Med 1978;20:409–413. [PubMed: 671118]
55. Andjelkovich D, Taulbee J, Symons M. Mortality experience of a cohort of rubber workers, 1964–1973. J Occup Med 1976;18: 387–394.
56. McMichael AJ, Spirtas R, Kupper LL. An epidemiologic study of mortality within a cohort of rubber workers, 1964–72. J Occup Med 1974;16:458–464. [PubMed: 4842655]
57. Beall C, Corn M, Cheng H, Matthews R, Delzell E. Mortality and cancer incidence among tire manufacturing workers hired in or after 1962. J Occup Environ Med 2007;49:680–690. [PubMed: 17563612]
58. Delzell E, Monson RR. Mortality among rubber workers: V. Processing workers. J Occup Med 1982a;24:539–545. [PubMed: 7119914]
59. Delzell E, Monson RR. Mortality among rubber workers: VI. Men with potential exposure to acrylonitrile. J Occup Med 1982b;24:767–769. [PubMed: 7143123]
60. Delzell E, Monson RR. Mortality among rubber workers: VII. Aerospace workers. Am J Ind Med 1984;6:265–271. [PubMed: 6496477]
61. Delzell E, Monson RR. Mortality among rubber workers: IX. Curing workers. Am J Ind Med 1985a;8:537–544. [PubMed: 4073051]
62. Delzell E, Monson RR. Mortality among rubber workers: X. Reclaim workers. Am J Ind Med 1985b;7:307–313. [PubMed: 3993647]
63. Monson RR, Nakano KK. Mortality among rubber workers. I. White male union employees in Akron, Ohio. Am J Epidemiol 1976;103: 284–296. [PubMed: 1258857]
64. Dost A, Straughan J, Sorahan T. A cohort mortality and cancer incidence survey of recent entrants (1982–91) to the UK rubber industry: findings for 1983–2004. Occup Med (Oxf) 2007;57: 186–190. [PubMed: 17229717]
65. Straughan JK, Sorahan T. Cohort mortality and cancer incidence survey of recent entrants (1982–91) to the United Kingdom rubber industry: preliminary findings. Occup Environ Med 2000;57:574–576. [PubMed: 10896966]
66. Pira E, Pelucchi C, Romano C, Manzari M, Negri E, La Vecchia C. Mortality from cancer and other causes in an Italian cohort of male rubber tire workers. J Occup Environ Med 2012;54:345–349. [PubMed: 22361990]
67. Sathiakumar N, Delzell E, Hovinga M, et al. Mortality from cancer and other causes of death among synthetic rubber workers. Occup Environ Med 1998;55:230–235. [PubMed: 9624276]
68. Sathiakumar N, Delzell E. A follow-up study of mortality among women in the North American synthetic rubber industry. J Occup Environ Med 2009;51:1314–1325. [PubMed: 19858743]
69. Wingren G Mortality in a Swedish rubber tire manufacturing plant: occupational risks or an “unhealthy worker” effect? Am J Ind Med 2006;49:617–623. [PubMed: 16691613]
70. Delzell E, Louik C, Lewis J, Monson RR. Mortality and cancer morbidity among workers in the rubber tire industry. Am J Ind Med 1981;2: 209–216. [PubMed: 7345925]
71. Boniol M, Koechlin A, Swiatkowska B, et al. Cancer mortality in cohorts of workers in the European rubber manufacturing industry first employed since 1975. Ann Oncol 2016;27:933–941. [PubMed: 26884594]
72. Mirabelli D, Cacciatore AM, Ferrante D, Amendola P, Vermeulen R, Merletti F. Cohort study of workers employed in an Italian tire manufacturing plant, 1962–2004. Cancer Causes Control 2012;23: 2023–2029. [PubMed: 23085812]
73. Gustavsson P, Hogstedt C, Holmberg B. Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scand J Work Environ Health 1986;12:538–544. [PubMed: 3823802]
74. Taeger D, Weiland SK, Sun Y, Keil U, Straif K. Cancer and non-cancer mortality in a cohort of recent entrants (1981–2000) to the German rubber industry. Occup Environ Med 2007;64:560–561. [PubMed: 17634250]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

75. Fox AJ, Lindars DC, Owen R. A survey of occupational cancer in the rubber and cablemaking industries: results of five-year analysis, 1967–71. Br J Ind Med 1974;31:140–151. [PubMed: 4830765]
76. Fox AJ, Collier PF. A survey of occupational cancer in the rubber and cablemaking industries: analysis of deaths occurring in 1972–74. Br J Ind Med 1976;33:249–264. [PubMed: 999799]
77. Schwartz J, Dockery DW, Neas LM. Is daily mortality associated specifically with fine particles? J Air Waste Manag Assoc 1996;46: 927–939.
78. Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest 2008;134:1s–41s. [PubMed: 18779187]
79. Williams TM, Harris RL, Arp EW, Symons MJ, Van Ert MD. Worker exposure to chemical agents in the manufacture of rubber tires and tubes: particulates. Am Ind Hyg Assoc J 1980;41:204–211. [PubMed: 7395731]
80. Karr RM, Davies RJ, Butcher BT, et al. Occupational asthma. J Allergy Clin Immunol 1978;61:54–65. [PubMed: 618946]
81. Quirce S Eosinophilic bronchitis in the workplace. Curr Opin Allergy Clin Immunol 2004;4:87–91. [PubMed: 15021059]
82. Wyler C, Braun-Fahrländer C, Künzli N, et al. Exposure to motor vehicle traffic and allergic sensitization. Epidemiology 2000;11:450–456. [PubMed: 10874554]
83. Diaz-Sanchez D, Penichet-Garcia M, Saxon A. Diesel exhaust particles directly induce activated mast cells to degranulate and increase histamine levels and symptom severity. J Allergy Clin Immunol 2000; 106:1140–1146. [PubMed: 11112898]
84. Gianniou N, Katsaounou P, Dima E, et al. Prolonged occupational exposure leads to allergic airway sensitization and chronic airway and systemic inflammation in professional firefighters. Respir Med 2016; 118:7–14. [PubMed: 27578465]
85. Carr TF, Zeki AA, Kraft M. Eosinophilic and noneosinophilic asthma. Am J Respir Crit Care Med 2018;197:22–37. [PubMed: 28910134]
86. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602–615. [PubMed: 21885636]
87. Shah D Healthy worker effect phenomenon. Indian J Occup Environ Med 2009;13:77–79. [PubMed: 20386623]
88. MacNeil J, Loves RH, Aaron SD. Addressing the misdiagnosis of asthma in adults: where does it go wrong? Expert Rev Respir Med 2016;10:1187–1198. [PubMed: 27677224]
89. Chan-Yeung M, Malo J-L. Occupational asthma. New Eng J Med 1995;333:107–112. [PubMed: 7777015]
90. Vermeulen R, Heederik D, Kromhout H, Smit HA. Respiratory symptoms and occupation: a cross-sectional study of the general population. Environ Health 2002;1:5–5. [PubMed: 12537592]
91. Galant SP, Komarow HD, Shin H-W, Siddiqui S, Lipworth BJ. The case for impulse oscillometry in the management of asthma in children and adults. Ann Allergy Asthma Immunol 2017;118:664–671. [PubMed: 28583260]
92. Shirai T, Kurosawa H. Clinical application of the forced oscillation technique. Intern Med 2016;55:559–566. [PubMed: 26984069]
93. Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. Thorax 2006;61:472–477. [PubMed: 16517577]
94. Buist AS, Vollmer WM. The use of lung function tests in identifying factors that affect lung growth and aging. Stat Med 1988;7:11–18. [PubMed: 3353600]
95. Selikoff IJ, Seidman H. Use of death certificates in epidemiological studies, including occupational hazards: variations in discordance of different asbestos-associated diseases on best evidence ascertainment. Am J Ind Med 1992;22:481–492. [PubMed: 1442783]
96. Selikoff IJ. Use of death certificates in epidemiological studies, including occupational hazards: discordance with clinical and autopsy findings. Am J Ind Med 1992;22:469–480. [PubMed: 1442782]

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97. De Matteis S, Heederik D, Burdorf A, et al. Current and new challenges in occupational lung diseases. Eur Respir Rev 2017;26:170080. [PubMed: 29141963]

98. Richardson DB. Occupational exposures and lung cancer: adjustment for unmeasured confounding by smoking. Epidemiology 2010;21: 181–186. [PubMed: 20081541]

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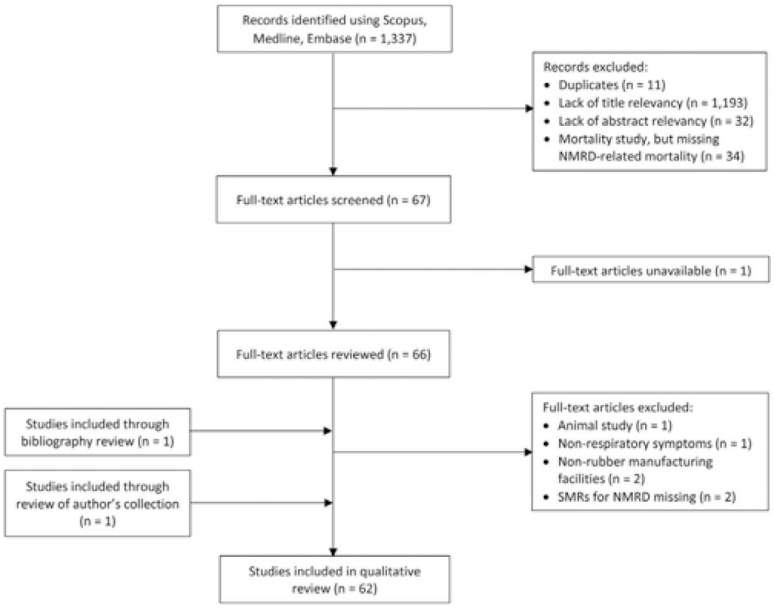

FIGURE 1.

Flow diagram illustrating process for inclusion of studies analyzing the association between occupational exposure to rubber manufacturing emissions and non-malignant respiratory disease. NMRD, non-malignant respiratory disease; SMR, standardized mortality ratio

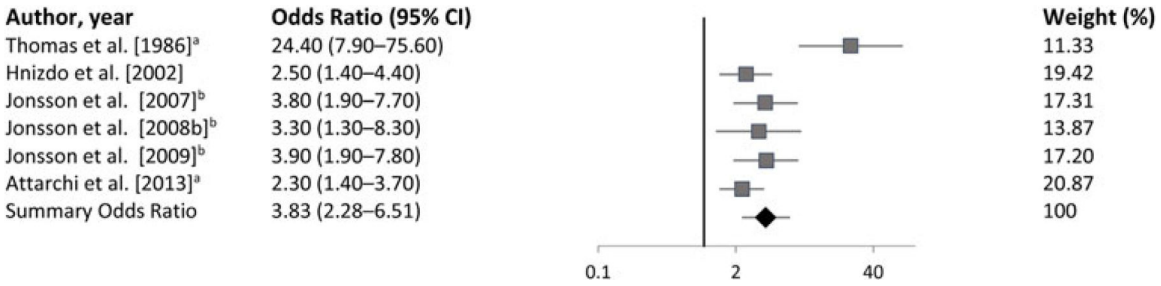

FIGURE 2.

Forest plot of cross-sectional studies[c] for the association between occupational exposure to rubber manufacturing emissions and development of respiratory symptoms or non-malignant respiratory disease. [a]Caluculated odds ratios and CI from values reported in manuscripts. [b]Study included multiple odds ratio values so selected highest odds ratio value for a lower respiratory symptom. [c]Cross-sectional studies included in the meta-analysis were studies that reported odds ratios with CI for respiratory symptoms or NMRDs, or reported data to calculate odds ratios and CI. CI, Confidence Interval; NMRD, non-malignant respiratory disease

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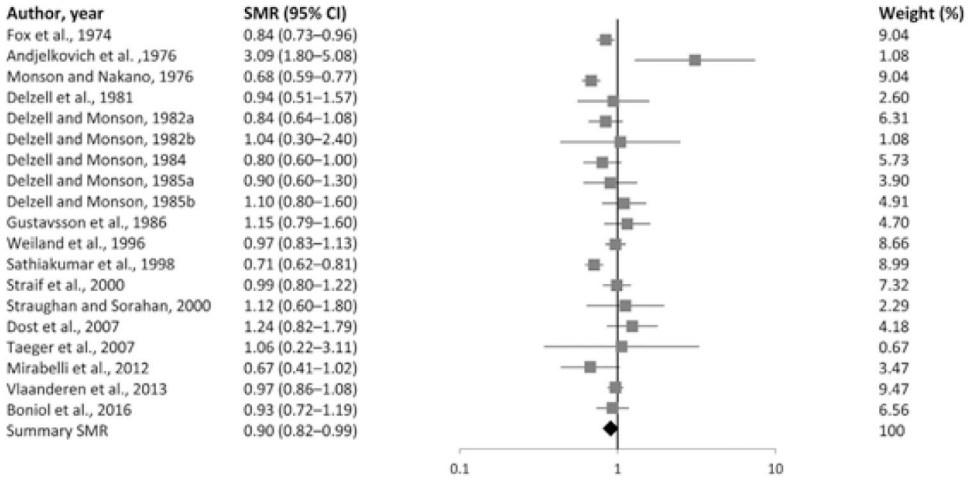

FIGURE 3.

Forest plot of mortality studies[a] for the association between occupational exposure to rubber manufacturing emissions and NMRD-related mortality. [a]Mortality studies that reported summary standardized mortality ratios for male employees who died of NMRDs (ICD code: 427–527). CI, Confidence Interval; NMRD, non-malignant respiratory disease

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TABLE 1

Criteria used for evaluating strength of evidence for a positive association between exposure to rubber manufacturing emissions and NMRD-related morbidity or mortality

	Strong (+++)	**Intermediate (++)**	**Non-significant positive (+)**
Cross-sectional studies	(1) Inclusion of rubber manufacturing emissions exposed and comparison groups[a], AND	(1) Inclusion of rubber manufacturing emissions exposed and comparison groups[a], AND	(1) Inclusion of rubber manufacturing emissions exposed and comparison groups[a] and non-statistically significantly[b] higher prevalence of ≥1 respiratory symptoms[c] or ≥1 NMRD, or airflow limitation on spirometry, OR
	(2) Exposed group had statistically significantly[b] higher prevalence of ≥1 respiratory symptoms[c] or ≥1 NMRD, AND	(2) Exposed group had statistically significant[b] higher prevalence of ≥1 respiratory symptoms[c] or ≥1 NMRD, or airflow limitation on spirometry	(2) No comparison groups[a] and presence of exposed workers with respiratory symptoms[c] or ≥1 NMRD, or airflow limitation on spirometry
	(3) Exposed group had statistically significantly[b] higher prevalence of airflow limitation on spirometry		
Mortality studies	(1) Analysis of workers by level of rubber manufacturing emissions exposure, AND	(1) All workers or a subset of workers had statistically significantly[b] higher SMR for ≥1 NMRD	(1) All workers or a subset of workers had non-statistically significantly[b] higher SMR for ≥1 NMRD
	(2) Workers with higher exposure had statistically significantly[b] higher SMR for ≥1 NMRD		

NMRD, non-malignant respiratory disease; SMR, standardized mortality ratio.

[a] Comparison groups determined by environmental exposure data at factories and include groups with either no or comparatively lower exposure to rubber manufacturing emissions.

[b] $P < 0.05$.

[c] Upper and lower respiratory symptoms.

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TABLE 2

Cases of respiratory illness associated with exposure to rubber manufacturing emissions

References	Age/sex	Job title	Symptom onset[a]	Symptoms/diagnosis	Laboratory values	PFT	Outcome
Bascom et al. [1988][1]	36 F	Thermoinjection press operator	2 weeks	Fever, delirium, rhinorrhea, bilateral interstitial infiltrates, acute respiratory distress	WBC = 12 000/μL with 35% eosinophils[b]	Spirometric and diffusing capacity measurements within normal limits[c]	Transferred to clerical position with chronic productive daytime cough
	28 M	Thermoinjection press operator	3 weeks	Dyspnea, wheezing, early pneumonia	WBC = 16 300/μL with 4% eosinophils[d]	[e]FEV1/FVC = 0.73	Transferred to another part of plant with chronic productive cough
	37 M	Thermoinjection press operator	6 weeks	Dizziness, dyspnea, wheezing, chest congestion	WBC = 11 600/μL with 37% eosinophils[f]	[g]FEV1/FVC = 0.62	Transferred to another part of plant
	27 M	Thermoinjection press operator	1 month	Rhinorrhea, nasal congestion, productive cough, chest pain	Eosinophils = 774/μL	FEV1 = 2.70 L (59% predicted) and FVC = 3.37 L (59% predicted)[h]	Transferred to another part of plant with slight improvement in spirometric data
	21 M	Thermoinjection press operator	2 months	Chest tightness	Eosinophils = 3696/μL	Normal spirometry and diffusing capacity[i]	Transferred to another part of plant
doPico et al. [1975][30]	43 M	Passenger tire builder	2 months	Rhinorrhea, hoarseness, wheezing breathlessness, cough, dyspnea, chest tightness	NR	FEV1 = 1.40 L and FVC = 2.20 L; FEV1/FVC = 64%	Returned to work with productive cough, intermittent wheezing, and mild dyspnea
	56 M	Calender operator	1 month	Hoarseness, cough, sputum production, dyspnea, wheezing, interistitial fibrosis, chronic bronchitis	NR	FEV1 = 1.64 L and FVC = 3.58 L; FEV1/FVC = 46%	Unable to return to work; developed residual interstitial fibrosis, chronic laryngitis, and chronic bronchitis
	57 M	Calender operator	NR	Cough, sputum production, pnemonic infiltrates, pnemonitis, chronic bronchitis, sinusitis	NR	FEV1 = 1.81 L and FVC = 2.80 L; FEV1/FVC = 65%	Returned to work with severe nasolaryngotracheobronchitis
Kato and Leki [2005][35]	31 M	Heat pressing	2 months	Fever, dyspnea, acute eosinophilic pneumonia (AEP)	WBC = 7900/μl with 18.2% eosinophils	NR	Returned to work after his hospitalization with no recurrence of AEP
Occupational Safety and Health Research Institute [2003][37]	30–39 age category M	Curing tires	4 years	Asthma symptoms	NR	PEF decreased from 417.1 L/min on a rest day to 361.7 L/min on a work day; 15% decrease in PEF observed between work and rest	NR

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References	Age/sex	Job title	Symptom onset[a]	Symptoms/diagnosis	Laboratory values	PFT	Outcome
						periods in the same 24 h Lee et al. [2013][36]	
Tarlo [1992][2]	55 M	Cushion mill operator	1 year	Rhinitis, occupational asthma	NR	Peak flow and FEV1 reduction	Returned to work multiple times with unstable pulmonary function

F, female; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; L, liter; L/min, liter/minute; M, male; NR, not reported; PEF, peak expiratory flow, PFT, pulmonary function testing; WBC, white blood cell; μL, miroliter. Upper respiratory symptoms (rhinorrhea, nasal congestion, and hoarseness) and lower respiratory symptoms (bilateral interstitial infiltrates, acute respiratory distress, dyspnea, wheezing, breathlessness, early pneumonia, pnemonic infiltrates, chest congestion, productive cough, sputum production, chest pain, and chest tightness).

[a]Time from initial exposure to symptom onset.

[b]Estimated total count of 4200/μL.

[c]Seven months after the worker was moved to a clerical position.

[d]Estimated total count of 652/μL.

[e]Three months after the worker was transferred to another part of plant.

[f]Estimated total count of 4292/μL.

[g]Three and half months later after acute illness.

[h]Evaluation after 4 years.

[j]Evaluation after 10 months.

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TABLE 3

Cross-sectional prevalence of respiratory symptoms and non-malignant respiratory disease among rubber manufacturing workers

References	No. of workers	Symptoms/diagnosis	PFT	Findings[a]	Strength of evidence[b]
Akca et al. [2011][4]	141	Cough, sputum production, dyspnea, wheezing	Yes	(i) Respiratory symptoms among all workers: cough = 16.3%; sputum production = 29.8%; dyspnea = 14.2%; wheezing = 5.0%; (ii) FEV1/FVC = 86.90 ± 6.60 (exposed); 92.00 ± 6.40 (low or non-exposed), ($P < 0.05$)	++
Alexandersson et al. [1986][38]	34	Cough, dyspnea on exertion, chronic bronchitis	Yes	(i) Productive cough = 35.0% (exposed) and 5.8% (controls); dyspnea on exertion = 35.0% (exposed) and 0% (controls); chronic bronchitis = 11.8% (exposed) and 0% (controls); (ii) no significant difference in pulmonary function between exposed and controls	+
Attarchi et al. [2013][14]	631	Dyspnea, cough, wheezing, sputum	Yes	(i) Dyspnea = 27.8% (exposed) and 10.7% (controls); cough = 19.4% (exposed) and 10.7% (controls), ($P < 0.05$); wheezing = 8.3% (exposed) and 1.7% (controls); sputum = 16.1% (exposed) and 8.4 % (controls), ($P < 0.05$); (ii) FEV1/FVC (%) = 87.06 ± 11.09 (exposed) and 89.34 ± 7.22 (controls), ($P < 0.05$)	+++
Bascom et al. [1990][39]	63	Cough, chest tightness, dyspnea, wheezing	Yes	(i) Sore throat = 74.0% (exposed) and 40.0% (controls), ($P < 0.05$); (ii) no significant difference in pulmonary function between exposed and controls	++
doPico et al. [1975][30]	210	Cough, dyspnea	Yes	(i) Cough = 95.2% (exposed); dyspnea = 86.7% (exposed); sore throat = 66.0% (exposed); (ii) FEV1/FVC (%) = 71.90 ± 13.10 (actual) and 83.00 ± 18.00 (predicted)	+
Fine and Peters [1976a][26]; Fine and Peters [1976b][27]	310	Cough, phlegm, wheezing, dyspnea, asthma	Yes	(i) Cough = 19.2% (exposed) and 7.4% (controls), ($P = 0.002$); phelgm = 25.0% (exposed) and 12.7% (controls), ($P = 0.005$); wheezing = 8.3% (exposed) and 5.3% (controls); dyspnea = 1.7% (exposed) and 0% (controls); asthma = 5.8% (exposed) and 2.1% (controls); (ii) FEV1/ FVC (%) = 78.80 ± 6.80 (exposed) and 79.20 ± 6.90 (controls); residual FEV1 (ml) = −169 ± 471 (exposed) and +27 ± 523 (controls), ($P = 0.05$); residual FVC (ml) = −266 ± 675 (exposed) and +48 ± 596 (controls), ($P = 0.01$)	+++
Fine and Peters [1976c][40]	254	Cough, dyspnea, wheezing, past history of asthma	Yes	(i) Cough = 20.0% (exposed) and 7.4% (controls), ($P = 0.007$); Phlegm = 38.5% (exposed) and 12.7% (controls), ($P = 0.001$); wheezing = 6.2% (exposed) and 5.3% (controls); past history of asthma = 1.6 % (exposed) and 2.1% (controls); (ii) FEV1/FVC (%) = 76.50 ± 8.00 (exposed) and 79.20 ± 6.90 (controls), ($P = 0.03$); workers >10 years exposure, FEV1/FVC (%) = 71.90% (exposed) and 78.20% (controls), ($P = 0.003$)	+++
Fine et al. [1976][41]	269	Cough, phlegm, wheezing, dyspnea, past history of asthma	Yes	(i) Cough = 20.0% (exposed) and 7.4% (controls), ($P = 0.004$); wheezing = 16.3% (exposed) and 5.3% (controls), ($P = 0.005$); phlegm = 31.3% (exposed) and 12.7 % (Controls), ($P = 0.001$); past history of asthma = 2.7% (exposed) and 2.1% (controls) (ii) >10 years duration, residual FEV1 (mL) =−211 (exposed) and +64 (controls), ($P = 0.02$)	+++
Gamble et al. [1976a][42]	52	Cough, phlegm, chest pain, chronic bronchitis	Yes	(i) Cough = 30.0% (exposed); breathing better away from the work = 70.0% (exposed), ($P < 0.05$); chest tightness = 27.0% (exposed); (ii) cross-shift mean percent change in FEF50 (liters/s) = −6.20% (exposed) and −2.80% (controls), ($P < 0.025$); FEF75 (liters/sec) = −17.10% (exposed) and −5.70% (controls), ($P < 0.005$)	+
Gamble et al. [1976b][53]	136	Cough, phlegm, breathlessness	Yes	(i) Cough = 10.3% (exposed); phlegm = 15.1% (exposed); persistent cough and phlegm = 5.9% (exposed); breathlessness = 20.6% (exposed); (ii) prevalence of impaired lung function (FEV/FVC < 0.75) = 41.30% (exposed)	+++
Governa et al. [1987][5]	79	Cross-shift change in pulmonary function	Yes	(i) ≤5 years exposure: FVC (% predicted) = 106 ± 14 (end of work shift) and 111 ± 14 (beginning of work shift); FEV1 (% predicted) = 107 ± 18 (end of work shift) and 111 ± 18 (beginning of	+
Gupta et al. [1993a][10]	626	Coughing with sputum, chest pain, breathlessness	Yes	(i) Coughing with sputum = 6.0% (packaging and loading workers), 7.0% (vulcanization workers), and 3.0% (compounding workers); chest pain = 17.0% (packaging and loading), 22.0 % (vulcanization workers), and 25.0% (compounding workers); breathlessness: 6.0% (packaging and loading), 3.0% (vulcanization workers), and 5.0% (compounding); vomiting with blood: 4.0% (packaging and loading), 2.0% (vulcanization workers), and 4.0% (compounding workers); (ii) Raw (airway resistance) mean ± SD = 1.51 ± 0.45 (packaging and	+

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References	No. of workers	Symptoms/diagnosis	PFT	Findings[a]	Strength of evidence[b]
				loading workers), 1.82 ± 0.86 (vulcanization workers), and 2.12 ± 0.86 (compounding workers); changes in lung function typical of obstruction leads to an increase in raw value	
Gupta et al. [1993b][43]	667	Breathing problems, chest pains, chest irritation, cough, sputum, blood vomiting	Yes	(i) Breathing problems, chest pain (packaging and loading workers), vomiting blood, breathing problems, chest pain, cough and sputum with blood (vulcanizing workers), and breathing problems, chest pain, chest irritation, cough and sputum with blood, throat irritation (compounding workers): specific numbers were not provided; (ii) FEV1/ FVC (%) (Length of employment >6 years) = 91.50 ± 7.50 (packaging and loading workers), 89.90 ± 12.30 (vulcanization workers), and 89.10 ± 17.10 (compounding workers)	+
Gupta et al. [1994][44]	667	Lung obstruction and restriction	Yes	(i) RV(l) = 1.08, TLC(l) = 3.73, RV/TLC ratio = 28.95, and FRC(l) = 2.00 (packaging and loading workers), RV(l) = 1.09, TLC(l) = 3.64, RV/TLC = 29.95,and FRC(l) = 2.01 (vulcanizing workers), and RV(l) = 1.22, TLC(l) = 3.31, RV/TLC = 36.86, FRC(l) = 2.12 (compounding workers)	+
Hnizdo et al. [2002][3]	71	COPD	No	(i) COPD, OR (95%CI) = 2.5 (1.4–4.4)	++
Jonsson et al. [2007][6]	283	Throat burning, cough, dyspnea, wheezing, chest tightness	No	(i) Cough, OR (95%CI) = 3.8 (1.9–7.7) (exposed), 3.6 (1.5–8.7) (low TTCA level exposed), 5.1 (2.2–12.0) (intermediate TTCA level exposed), and 3.0 (1.3–7.2) (high TTCA level exposed), ($P \leq 0.05$); dyspnea, wheezing, or chest tightness, OR (95%CI) = 1.2 (0.6–2.2) (exposed), 1.2 (0.5–2.6) (low TTCA level exposed), 0.9 (0.3–2.2) (intermediate TTCA level exposed), and 1.3 (0.6–2.8) (high TTCA level exposed)	++
Jonsson et al. [2008a][12]	262	Nosebleed, hoarseness	No	Nosebleed, OR (95%CI) = 2.9 (1.0–8.3) (exposed workers)	+
Jonsson et al. [2008b][45]	269	Throat burning, cough, dyspnea, wheezing, chest tightness	No	(i) Cough, OR (95%CI) = 3.3 (1.3–8.3) (low 1-HP level exposed), 3.6 (1.5–9.0) (intermediate 1-HP level exposed), and 6.9 (2.9–17.0) (high 1-HP level exposed); dyspnea, wheeze, or chest tightness, OR (95%CI) = 1.5 (0.6–3.3) (low 1-HP level exposed), 1.1 (0.4–2.4) (intermediate 1-HP level exposed), and 1.3 (0.5–2.8) (high 1-HP level exposed)	++
Jonsson et al. [2008c][47]	277	Lung impairment	Yes	(i) FVC (%), (mean, range) = 95, 57–129 (exposed) and 97, 50–129 (controls)	+
Jonsson et al. [2009][46]	290	Throat burning and dryness, hoarseness, severe dry cough, dyspnea, wheezing, chest tightness	No	(i) Throat burning and dryness, OR (95%CI) = 3.2 (1.7–6.1) (exposed), 3.7 (1.7–7.7) (low N-nitrosamines level exposed), 3.4 (1.5–7.4) (intermediate N-nitrosamines level exposed), and 2.6 (1.1–5.9) (high N-nitrosamines level exposed), ($P \leq 0.05$); cough, OR (95%CI) = 3.9 (1.9–7.8) (exposed), 4.0 (1.8–9.2) (low N-nitrosamines level exposed), 5.1 (2.2–12) (intermediate N-nitrosamines level exposed), and 2.7 (1.1–6.7) (high N-nitrosamines level exposed), ($P \leq 0.05$); dyspnea, wheezing and/or chest tightness, OR (95%CI) = 1.2 (0.6–2.2) (exposed), 1.1 (0.4–2.3) (low N-nitrosamines level exposed), 1.5 (0.7–3.3) (intermediate N-nitrosamines level exposed), and 1.2 (0.5–2.8) (high N-nitrosamines level exposed)	++
Lednar et al. [1977][21]	73	Emphysema, asthma	No	(i) Total retirees due to pulmonary disability, emphysema = 53.4%, asthma = 11.0%, and other pulmonary conditions = 21.9%	+
McMichael et al. [1976][11]	1820	Cough, phlegm, chest illness	Yes	(i) Cough = 16.3% (rubber workers) and 10.9% (postal workers); phlegm = 21.9% (rubber workers) and 10.0% (postal workers); persistent cough, phlegm and chest illness = 8.1% (rubber workers) and 4.1% (postal workers); (ii) Workers reporting respiratory symptoms had lower FEV1 than asymptomatic workers	+
Meijer et al. [1998][7]	179	Cough, phlegm, dyspnea, wheeze, asthmatic attack	Yes	(i) Cough and/or phlegm = 3.0% (exposed non/ex-smoker), 13.0% (exposed smoker), 8.0% (non/ex-smoker controls), and 16.0% (smoker controls); dyspnea and/or wheeze = 19.0% (exposed non/ex-smoker), 21.0% (exposed smoker), 13.0% (non/ex-smoker controls), and 19.0% (smoker controls); asthmatic attack = 13.0% (exposed non/ex-smoker), 5.0% (exposed smoker), 8.0% (non/ex-smoker controls), and 13.0% (smoker controls); (ii) FEV1/ FVC (%) = 79.90 (exposed) and 81.90 (controls), ($P < 0.05$)	++
Neghab et al. [2011][48]	141	Cough, phlegm, wheezing, dyspnea	Yes	(i) Cough = 23.6% (exposed) and 1.4% (controls); phlegm = 41.6% (exposed) and 5.7% (controls); productive cough = 25.0% (exposed) and 2.8% (controls); wheezing = 25.0 % (exposed) and 1.4% (controls); dyspnea = 31.9 % (exposed) and 0% (controls), ($P = 0.0001$); (ii) FEV1/ FVC (%) = 98.30 ± 12.33 (exposed) and 101.92 ± 9.71 (controls), ($P < 0.05$)	+++

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References	No. of workers	Symptoms/diagnosis	PFT	Findings[a]	Strength of evidence[b]
Neghab et al. [2007][49]	207	Cough, phlegm, breathlessness, wheezing	Yes	(i) Cough = 15.6% (exposed non-smokers), 42.4% (exposed smokers), 5.4% (non-smokers controls), and 13.5% (smoker controls); phlegm = 17.1% (exposed non-smokers), 48.4% (exposed smokers), 8.2% (non-smokers controls), and 18.9% (smoker controls); productive cough = 6.2% (exposed non-smokers), 27.3% (exposed smokers), 2.7% (non-smokers controls), and 5.4% (smoker controls); breathlessness = 10.9% (exposed non-smokers), 36.3% (exposed smokers), 8.2% (non-smokers controls), and 10.8% (smoker controls), ($P < 0.001$); (ii) VC (%) = 79.78 (exposed) and 90.65 (unexposed), ($P < 0.0001$); FVC (%) = 80.30 (exposed) and 91.90 (unexposed) ($P < 0.0001$); FEV1 (%) = 79.87 (exposed) and 91.41 (unexposed), ($P < 0.0001$)	+++
Sparks et al. [1982][50]	370	Wheezing, dyspnea, cough, chest tightness, chronic bronchities	Yes	(i) Chronic bronchitis = 13.3% (high dust exposed), 32.5% (medium dust and fumes exposed), and 19.0% (low dust exposed), ($P < 0.05$); loose or productive cough = 35.5% (high dust exposed), 42.5% (medium dust and fumes exposed), and 29.3% (low dust exposed) ($P < 0.05$); wheezing = 4.5% (high dust exposed), 2.7% (medium dust and fumes exposed), and 4.8% (low dust exposed); chest tightness = 23.9% (high dust exposed); 22.7% (medium dust and fumes exposed), and 16.7% (low dust exposed) (ii) mean ratio of FEV1/±SE: 0.795 ± 0.001 (high dust exposed), 0.786 ± 0.001 (medium dust and fumes exposed), and 0.790 ± 0.001 (low dust exposed)	++
Szubert et al. [1998][52]	973	NR	No	(i) Sickness absence among all workers (respiratory disease) = 17.2%; difference in lost time rate between manufacturing and other department workers with respect to respiratory diseases = 75.0%	+
Thomas et al. [1986][51]	217	Nasal congestion, pharyngitis, cough, wheezing, dyspnea	No	(i) ≤25 age, symptomatic = 14 (thermoinjection workers) and 3 (other); asymptomatic = 15 (thermoinjection workers) and 52 (other), OR (95%CI) = 16 (4.1–63.0); >25 age, symptomatic = 7 (thermoinjection workers) and 1 (other); asymptomatic = 19 (thermoinjection workers) and 106 (other), OR (95%CI) = 39 (3.7–414.0)	++
Weeks et al. [1981a][28]; Weeks et al. [1981b][29]	744	Shortness of breath, cough, sputum, wheeze, chest tightness	Yes	(i) Shortness of breath, CI = 0.4–1.8 (curing workers); wheeze, CI = 1.1–2.5 (curing workers) and O/E = 1.3 (milling workers); cough, CI = 0.8–2.1 (curing workers) and O/E = 1.4 (milling workers); sputum, CI = 0.9–3.1 (curing workers); chest tightness, CI = 1.8–5.2 and O/E = 1.5 (milling workers); sputum, O/E = 1.7 (milling workers), ($P < 0.05$); (ii) loss of FEV1 at about 12 mL per curing year (curing workers), ($P = 0.036$) and loss of FVC at about 12 mL per curing year (curing workers), ($P = 0.042$); FEV1, O/E = 1.30 and FVC, O/E = 1.00 (milling workers), ($P < 0.05$)	+++
Zuskin et al. [1996][15]	581	Sinusities, cough, phlegm, dyspnea, chronic bronchities, occupational asthma	Yes	(i) Sinusities = 23.7% (exposed) and 2.9% (controls), ($P < 0.01$); cough = 52.6% (exposed) and 26.2% (controls), ($P < 0.01$); phlegm = 51.8% (exposed) and 35 % (controls) ($P < 0.01$); dyspnea = 63.6% (exposed) and 29.1% (controls), ($P < 0.01$); chronic bronchitis = 48.9% (exposed) and 23.3% (controls), ($P < 0.01$); occupational asthma = 5.1% (exposed) and 0% (controls); (ii) FVC (%) = Difference before-after shift: −3.7 (exposed smoker), −1.80 (exposed non-smoker), −0.40 (smoker controls), and −0.60 (non-smoker controls), ($P < 0.01$)	+++

CI, confidence interval; COPD, Chronic Obstructive Pulmonary Disease; FEV1, forced expiratory volume in 1 secs; FEF50, forced expiratory flow at 50% of FVC; FEF75, forced expiratory flow at 75% of FVC; FVC, forced vital capacity; FRC, functional residual capacity; ml, milliliters; NR, not reported; NS, non-significant ($P \geq 0.05$); OR, odds ratio; O/E, observed/ expected; PM, particulate matter; PAHs, polyaromatic hydrocarbons; PFT, pulmonary function testing; PVC, polyvinyl chloride; RV, residual volume; SD, standard deviation; SE, standard error; TLC, total lung capacity; VC, vital capacity; 1-HP, 1-hydroxypyrene; TTCA, 2-thiothiazolidine-4-carboxylic acid. Residual, difference between the predicted and the actual value of a pulmonary function test; residual FEV1 and FVC, based on a multiple regression equation derived from the non-black control rubber workers over 24 years of age, adjusted for the major confounding variables: age, height, and years of cigarette smoking between the two groups of exposed and control workers. Upper respiratory symptoms (nosebleed, nasal congestion, throat burning and dryness, hoarseness, pharyngitis, and sinusitis) and lower respiratory symptoms (cough, sputum production, dyspnea, wheezing, chest tightness, phlegm, chest irritation, chest pain, breathlessness, and shortness of breath).

[a] Findings reported in publications.

[b] Strength of evidence for positive association: +++, strong; ++, intermediate; +, non-significant positive association; NA, no association; definitions-Table 1.

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TABLE 4

Non-malignant respiratory disease-related mortality among rubber manufacturing cohorts

Cohort and reference	No. of workers	Required tenure	Findings	Strength of evidence[a]
A—Andjelkovich et al. [1978][54]	1649	Employed or retired	(i) White females, 40–84 years age category, 1964–1973; (ii) pneumonia[b], SMR, 0.66 (95%CI, 0.24–1.47); (iii) bronchitis, emphysema, and asthma, SMR, 1.05 (95%CI, 0.26–2.86); (iv) NMRD, SMR, 1.96 (95%CI, 0.50–5.40)	+
A—Andjelkovich et al. [1976][55]	2373	Employed or retired	(i) White males, retired group, 40–64 years age category, 1964–1973; (ii) pneumonia[b], SMR, 0.88 (95%CI, 0.22–2.40) (iii) bronchitis, asthma, and emphysema, SMR, 1.84 (95%CI, 1.43–2.40); (iv) NMRD, SMR, 3.09 (95%CI, 1.80–5.08)	++
A—McMichael et al. [1974][56]	6678	Employed or retired	(i) White males, 40–64 years age category, 1964–1972; (ii) chronic respiratory diseases, SMR, 0.96 (95%CI, 0.53–1.59)	NA
B—Beall et al. [2007][57]	3425	≥1 year	(i) Total employees hired in or after 1962; (ii) NMRD, SMR, 0.51 (95%CI, 0.30–0.80) (total employees) and 0.52 (95%CI, 0.31–0.83) (male)	NA
C—Delzell and Monson [1982a][58]	2666	≥2 years	(i) White males, processing workers, 1940–1971; (ii) NMRD, SMR, 0.84 (95% CI, 0.64–1.08); (iii) emphysema, SMR, 1.18 (95%CI, 0.75–1.77)	+
C— Delzell and Monson [1982b][59]	327	≥2 years	(i) White males, exposed to acrylonitrile, 1940–1971; (ii) NMRD, SMR, 1.04 (95%CI, 0.30–2.40)	+
C—Delzell and Monson [1984][60]	3161	≥2 years	(i)) White males, aerospace workers, 1940–1971; (ii) NMRD, SMR, 0.80 (95% CI, 0.60–1.00)	NA
C—Delzell and Monson [1985a][61]	1790	≥2 years	(i) White males, reclaim division workers, 1940–1971; (ii) NMRD, SMR, 0.90 (95%CI, 0.60–1.30); (iii) emphysema, SMR, 1.30 (95%CI, 0.60–2.40)	+
C—Delzell and Monson [1985b][62]	1152	≥2 years	(i) White males, curing workers, 1940–1971;(ii) emphysema, SMR, 0.80 (95% CI, 0.30–1.70); (iii) NMRD, SMR, 1.10 (95%CI, 0.80–1.60); (iii) pneumonia (curing workers compared to non-curing workers), SMR, 2.20 (95%CI, 1.37–3.38)	+++
C—Monson and Nakano [1976][63]	13571	≥5 years	(i) White males, 1940–1974; (ii) NMRD, SMR, 0.68 (0.59–0.77); (iii) asthma, SMR, 1.60 (95%CI, 0.82–2.73); (iv) pneumonia, SMR, 1.60 (95%CI, 0.84–2.64)	+
D—Dost et al. [2007][64]	8651	≥1 year	(i) Total employees, 1983–2004; (ii) NMRD, SMR, 1.24 (95%CI, 0.82–1.79) (male) and 1.70 (95%CI, 0.55–3.97) (female)	+
D—Straughan and Sorahan [2000][65]	8651	≥1 year	(i) Total employees, 1983–1998; (ii) NMRD, SMR, 1.12 (95%CI, 0.60–1.80) (male) and 0.81 (95%CI, 0.04–4.01) (female)	+
E—Pira et al. [2012][66]	6251	≥6 months	(i) Males, 1954–2008; (ii) COPD, SMR, 0.63 (95%CI, 0.39–0.95)	NA
F—Sathiakumar et al. [1998][67]	15649	≥1 year	(i) Males, 1943–1991; (ii) NMRD, SMR, 0.71, (95%CI, 0.62–0.81)	NA
F— Sathiakumar and Delzell [2009][68]	4863	≥1 year	(i) Females, 1943–2003; (ii) NMRD, SMR, 0.97, (95%CI, 0.79–1.18)	NA
G—Weiland et al. [1996][16]	11663	≥1 year	(i) Males, 1981–1991; retired and employed workers; (ii) NMRD, SMR, 0.97 (95%CI, 0.83–1.13) (combined), 1.03 (95%CI, 0.87–1.21) (retired), and 0.72 (95%CI, 0.46–1.08) (employed) (ii) COPD, SMR, 1.15 (95%CI, 0.96–1.35) (combined), 1.22 (95%CI, 1.01–1.46) (retired), and 0.85 (95%CI, 0.52–1.31) (employed)	++
G—Straif et al. [2000][23]	8933	≥1 year	(i) Males, 1981–1991 (ii) NMRD, SMR, 0.99 (95%CI, 0.80–1.22)	NA

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Cohort and reference	No. of workers	Required tenure	Findings	Strength of evidence[a]
G—Vlaanderen et al. [2013][17]	13395	≥1 year	(i) Total employees, 1981–2000 (ii) NMRD, SMR, 0.97 (95%CI, 0.86–1.08) (male) and 1.13 (95%CI, 0.65–1.83) (female)	+
H—Wingren [2006][69]	5745	>1 month	(i) Males, 1958–2001; (ii) NMRD, SMR, 2.06, (95%CI, 1.36–3.00) (< 6 months tenure), 1.92 (95%CI, 1.23–2.85) (6 months—2.5 years tenure), 1.23 (95% CI, 0.71–1.96) (>2.5–10 years tenure), 0.59 (95%CI, 0.27–1.12) (>10 years tenure), and 1.46 (95%CI, 1.15–1.83) (10 years latency); (iii) pneumonia[b], SMR, 1.23 (95%CI, 0.83–1.75) (10 years latency); (iv) chronic airway obstruction, SMR, 1.67 (95%CI, 1.17–2.31) (10 years latency)	++
I—Delzell et al. [1981][70]	1792	≥2 years	(i) Males, 1954–1976; (ii) NMRD, SMR, 0.94 (95%CI, 0.51–1.57)	NA
J—Boniol et al. [2016][71]	38457	≥1 year	(i) Total employees, working since 1975; (ii) Respiratory diseases excluding pneumonia, SMR, 0.93 (95%CI, 0.72–1.19) (male), 0.74 (95%CI, 0.38–1.42) (female), and 0.90 (95%CI, 0.71–1.13) (combined)	NA
K— Mirabelli et al. [2012][72]	9501	Observation started at the date of hire	(i) Total employees, 1962–2000; (ii) NMRD, SMR, 0.67 (95%CI, 0.41–1.02) (male)	NA
L— Gustavsson et al. [1986][73]	8734	≥1 year	(i) Total employees, 1952–1981; (ii) NMRD, SMR, 1.15 (95%CI, 0.79–1.60) (male); (iii) asthma, bronchitis, and emphysema, SMR, 1.26 (95%CI, 0.72–2.04) (male)	+
M— Taeger et al. [2007][74]	9597	≥1 year	(i) Total employees, 1981–2000; (ii) NMRD, SMR, 1.06 (95%CI, 0.22–3.11) (male); (ii) COPD, SMR, 1.37 (95%CI, 0.17–4.93) (male)	+
N— Fox et al. [1974][75]	40867	≥1 year	(i) Males, 1968–1971; (ii) NMRD, SMR, 0.84 (95%CI, 0.73–0.96) (all sectors) and 0.55 (95%CI, 0.35–0.80) (tire sector); (ii) bronchitis, SMR, 0.86 (95%CI, 0.72–1.02) (all sectors) and bronchitis and emphysema, SMR, 0.82 (95%CI, 0.60–1.09) (tire sector)	NA
N—Fox and collier. [1976][76]	40867	≥1 year	(i) Males, 1972–1974; (ii) NMRD, SMR, 1.02 (95%CI, 0.89–1.15) (all sectors) and 1.51 (95%CI, 0.98–2.23) (sector: sponge rubber, rubber with plastic, crepe rubber, etc) (ii) bronchitis, SMR, 1.14 (95%CI, 0.96–1.34) (all sectors) and bronchitis, emphysema, and asthma, SMR, 1.82 (95%CI, 1.06–2.94) (sector: sponge rubber, rubber with plastic, crepe rubber, etc)	++

CI, confidence interval; COPD, chronic obstructive pulmonary disease; NA, no association; NMRD, non-malignant respiratory diseases; SMR, standardized mortality ratio.

[a]Strength of evidence for positive association: +++, strong; ++, intermediate; +, non-significant positive association; definitions located in Table 1.

[b]SMR for pneumonia includes deaths from influenza as well.