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Occupational Exposures in the Rubber Tire Industry and Risk of Cancer: a Systematic Review

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Abstract:

Objective: To investigate the association between cancer and the rubber tire industry using indicators used to estimate exposure, such as duration or historical time period of exposure.

Methods: A systematic review using MEDLINE was carried out. The Preferred Reporting Items for Systematic Reviews (PRISMA) statement guided the systematic review. The Risk of Bias in Non-Randomized Studies of Exposures (ROBINS-E) was used to analyze biases in the selected studies.

Results: A total of 240 articles were initially selected. Of these, 17 were included in this systematic review of 15 different cohorts and one case-control study. Five cohorts were composed of rubber industry employees including some who who worked in the rubber tire industry, whereas the other 10 cohorts were composed exclusively of rubber tire industry employees. An increased risk of lung/respiratory cancer is possible in the oldest time periods without duration of exposure showing any association according to the analysis. The work areas of mixing and milling as well as compounding seem to be more specifically associated with this risk, which could be expected because of the exposure to fumes containing carcinogenic agents.

Conclusions: Having worked in the rubber tire industry in the past, especially in milling, mixing as well as compounding may be associated with an increased risk of lung/respiratory cancer.

Keywords: Rubber, Occupational Diseases, Neoplasms, Humans, Cohort Studies, Case-control studies

1 Introduction

Occupational exposures related to rubber industry activities are classified as Group 1 by the International Agency for Research on Cancer (IARC).

The first evaluation by IARC classifying the rubber industry as a carcinogen was in 1982, and it was confirmed in 1987 and 2012 (International Agency for Research on Cancer, 1982, 1987, 2012). There is sufficient evidence of carcinogenicity for lung, bladder, and stomach cancers and also for leukemia and lymphoma. There is limited evidence of carcinogenicity for esophageal, laryngeal, and prostate cancer.

The rubber industry uses hundreds of different chemicals. This wide variety has never allowed IARC to establish the precise role of each individual exposure in the development of cancer. We know that several compounds known to be carcinogens have been used in this industry. On the other hand, carcinogens were formed during the manufacturing processes. Additionally, tools and machines containing asbestos were used in these factories. Although there are common processes among the different branches of the rubber industry, there is some heterogeneity in terms of exposure. In the curing processes, for example, three main techniques are used in the plants: compression/injection, UHF microwaves, and nitrite salt baths. The salt baths expose workers much more to N-nitrosamines than the other techniques (Héry, 2009). Similarly, some plants in the rubber industry have workplaces dedicated to the production of synthetic rubber. Plants producing styrene-butadiene synthetic rubber use 1-3 butadiene as a raw material, sometimes with high exposure, whereas plants supplied with an external source of styrene-butadiene rubber have lower exposure to 1-3 butadiene (Weiland et al., 1998). The European project ExAsRUB highlights higher exposures to different agents for employees working in the general rubber goods (GRG) industry when compared with workers in the tire manufacturing industry (Hidajat et al., 2019). Rubber fume concentrations (Tire geometric mean: 0.17 mg/m³; GRG geometric mean: 0.39 mg/m³; $p < 0.05$) and the sum of n-nitrosamines (Tire geometric mean: 0.24 µg/m³; GRG geometric mean: 1.06 µg/m³; $p < 0.05$) were lower in the tire manufacturing industry than in the GRG industry. These data are consistent with an earlier British study (Dost et al., 2000) where rubber fume concentrations were lower in the tire industry than in the GRG industry (Tire mean: 0.23 mg/m³ ; GRG mean: 0.53 mg/m³).

This heterogeneity in processes and exposures, especially between the GRG industry and the tire manufacturing industry, has led most authors who have conducted studies in this field to identify rubber tire manufacturing plants separately in order to refine the data and obtain a more homogeneous group in terms of exposure.

Alder et al. and Boniol et al. conducted meta-analyses in 2006 and 2017 on the excess risk of cancer in employees of the rubber industry, with an analysis of the tire manufacturing industry (Alder et al., 2006; Boniol et al., 2017) . They did not find any significant increase in risk for different cancers in the tire manufacturing industry. However, neither of the articles addressed the more precise analyses carried out in the included studies, such as risk by work area or years of exposure. No analysis of risk of bias is presented in their work. It appeared, instead, that great disparities were present within the same company. For example, employees assigned to curing had much higher exposure to carcinogens contained in vulcanization fumes. Moreover, N-nitrosamine and aromatic amines exposure, due to technical improvements, dropped as the industry was modernized (Dost et al., 2000; Goutet, 2007).

In order to more fully elaborate on the topic of the meta-analyses of Alder and Boniol (Alder et al., 2006; Boniol et al., 2017) ,we carried out a systematic review on the risk of cancer in the rubber tire manufacturing industry with the aim of presenting the results by type of work area, years of exposure, duration of exposure, and other exposure information. We were interested in cancer site studies associated with sufficient evidence of carcinogenicity in the rubber industry according to IARC.

2 Methods

Research questions

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide this systematic review (Page et al., 2021). This systematic review aimed to answer this question: Is there an increased risk of cancer for rubber tire industry employees if we examine the data characterizing their exposure?

Literature search strategy

Two reviewers searched MEDLINE (via PubMed) for all articles available until the last search date, July 1, 2022. The sequence of terms that was used to search on PubMed was built with the Yale MeSH Analyzer (Grossetta Nardini & Wang, 2022) and validated with five clearly eligible studies (De Vocht et al., 2009; Mirabelli et al., 2012; Pira et al., 2012; Wilczyńska et al., 2001; Wingren & Axelson, 2007) and was: ("Rubber"[Mesh]) AND ("Occupational Diseases"[Mesh] OR "Neoplasms"[Mesh]) AND ("Humans"[Mesh]) AND ("Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Neoplasms/epidemiology"[Majr] OR "Neoplasms/mortality"[Majr]). Reference checking of included articles was done to identify additional studies that were missed. We also examined the reference lists of the two meta-analyses cited above (Alder et al., 2006; Boniol et al., 2017). A complementary search was performed on WEB OF SCIENCE with the algorithm "(tire or tyre) and cancer".

Eligibility criteria

We excluded all articles that were not on human epidemiological cohorts and case-control studies, that did not relate to the rubber tire industry (or in which results for this industry were not reported) as well as studies for which no analysis of statistical significance was performed. We included both incidence and mortality studies and did not specify a minimum duration of follow-up. We did not put any restriction on the year of publication, but they had to be articles published in a scientific journal in English.

Selection process

Two reviewers screened each record, and each report that was retrieved, by working together was shared. Agreement was then reached on which articles would be retained. The first

selection was made on the basis of the title and the abstract, and the second after reading the remaining full-text articles.

Study selection

The search algorithm identified 239 articles. We identified one additional article of interest from the previously cited meta-analyses that was not over-referenced on MEDLINE (Chen et al., 1997). Of these 240 articles, 210 were excluded for not meeting the inclusion criteria or for being identified as an older article from the same study (and were therefore a duplicate). Thus, 30 studies remained to be screened by full-text reading. Finally, 17 articles (Beall et al., 2007; Bernardinelli et al., 1987; Boniol et al., 2016; Chen et al., 1997; Coggon et al., 1990; De Vocht et al., 2009; McElvenny et al., 2018; McMichael et al., 1974; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Sorahan et al., 1989; Veys, 2004; Vlaanderen et al., 2013; Wang et al., 1984; Wilczyńska et al., 2001; Wingren & Axelson, 2007) were included in this systematic review, including two on the same cohort with quite different analyses (De Vocht et al., 2009; Wilczyńska et al., 2001) and only one case-control study (Coggon et al., 1990). Of the 13 articles not included, one did not perform a statistical analysis, one only focused on solvents, and in eleven it was not possible to separate tires from other rubber goods. The search on WEB OF SCIENCE allowed to add a complementary study among the 625 results found, bringing to 18 the number of articles studied (Rubin & Clapp, 2012). The flow chart of the systematic review is described in Fig 1 and data on retained and excluded articles are available as Supplementary data. We did not find any relevant case series.

For each study selected, we examined the results and extracted the data according to the approaches used to estimate the risk (duration of exposure, hiring period, etc.).

Of the eighteen articles, seven were not cited in the last meta-analysis (Boniol et al., 2017). Three were not included (De Vocht et al., 2009; Mirabelli et al., 2012; Wilczyńska et al., 2001) because they overlapped with another article (Boniol et al., 2016), one was an update of a previous study published after the release of the meta-analysis (Fox & Collier, 1976; McElvenny et al., 2018), and three did not appear in the search results of Boniol et al. (Beall et al., 2007; Chen et al., 1997; Rubin & Clapp, 2012).

Assessment of risk of bias in individual studies

A reviewer assessed the risk of bias in the selected studies. The Risk of Bias in Non-Randomized Studies of Exposures (ROBINS-E) tool was used for the risk of bias assessment

(ROBINS-E Development Group, 2022). The seven domains of ROBINS-E were: 1) bias due to confounding, 2) bias in measurement of the exposure, 3) bias in selection of participants into the study, 4) bias due to post-exposure interventions, 5) bias due to missing data, 6) bias in measurement of outcomes, and 7) bias in the selection of the reported results. The 4th domain was not relevant to the studies in the review and was not considered. The judgment for each ROBINS-E item was defined as “Low Risk of Bias”, “Some Concerns”, “High Risk of Bias”, or “Very High Risk of Bias”. For the overall Risk-of-Bias Rating, another judgment was added: “Low Risk of Bias, except for concerns about residual confounding”. In order to be consistent with other publications, we reformulated these judgments to read: “Low”, “Moderate”, “Serious”, or “Critical”. Risk of bias assessment data are available as Supplementary data.

3 Results

All studies were published from 1974 to 2018. The case-control study took place in England, with 15 cases in the rubber tire industry (Coggon et al., 1990). The cohort sample size varied from 3,425 (Beall et al., 2007) to 17,636 (De Vocht et al., 2009; Wilczyńska et al., 2001). Four studies were performed in Italy (Bernardinelli et al., 1987; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012), four in Great-Britain (Coggon et al., 1990; McElvenny et al., 2018; Sorahan et al., 1989; Veys, 2004), two in China (Chen et al., 1997; Wang et al., 1984), three in the USA (Beall et al., 2007; McMichael et al., 1974; Rubin & Clapp, 2012), one in Germany (Vlaanderen et al., 2013), one in Poland (De Vocht et al., 2009; Wilczyńska et al., 2001), and one in Sweden (Wingren & Axelson, 2007). One publication (Boniol et al., 2016) includes the results of several cohorts (De Vocht et al., 2009; Mirabelli et al., 2012; Wilczyńska et al., 2001) of employees first employed since 1975, and its results are from German, Italian, Polish, Swedish, and English cohorts.

Approaches used to estimate risk

Five studies were conducted in companies that were not all in the rubber tire sector (Boniol et al., 2016; Chen et al., 1997; McElvenny et al., 2018; Sorahan et al., 1989; Vlaanderen et al., 2013), whereas the other twelve were conducted in the rubber tire industry only (Beall et al., 2007; Bernardinelli et al., 1987; Coggon et al., 1990; De Vocht et al., 2009; McMichael et al., 1974; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012; Veys, 2004; Wang et al., 1984; Wilczyńska et al., 2001; Wingren & Axelson, 2007).

Among the twelve studies conducted exclusively in the rubber tire industry, seven did an analysis of risk by duration of employment (Beall et al., 2007; Coggon et al., 1990; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Wilczyńska et al., 2001; Wingren & Axelson, 2007), four by time elapsed since first employment (Beall et al., 2007; Coggon et al., 1990; Mirabelli et al., 2012; Pira et al., 2012), two by the end date of employment and age at the start of employment (Negri et al., 1989; Pira et al., 2012), three by time period at first employment (Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012), and four by work area (Negri et al., 1989; Wang et al., 1984; Wilczyńska et al., 2001; Wingren & Axelson, 2007), and two by sex (Rubin & Clapp, 2012; Wilczyńska et al., 2001). One study used an exposure matrix for aromatic amines and inhalable aerosols (De Vocht et al., 2009).

The characteristics of the eligible studies in this systematic review are shown in Table 1.

Risk of bias

The summary of the risk of bias in the eight included studies is shown in Fig 2. Every study had a serious risk of bias due to confounding factors except one, which focused on digestive cancers (Chen et al., 1997), because none of them took into account the exposure to the major extra-occupational risk factor of smoking or other factors such as exposure to benzene or asbestos for example.

An Italian (Negri et al., 1989), a Chinese (Wang et al., 1984), and an American cohorts (Rubin & Clapp, 2012) and the case-control study (Coggon et al., 1990) had a critical risk of bias due to the selection of the reported results, classification of exposures, a great risk of bias, and a bias due to missing data, respectively. Three studies (Boniol et al., 2016; Chen et al., 1997; De Vocht et al., 2009; Wilczyńska et al., 2001) presented a serious overall risk of bias, and six (Bernardinelli et al., 1987; McMichael et al., 1974; Mirabelli et al., 2012; Pira et al., 2012; Sorahan et al., 1989; Vlaanderen et al., 2013) a moderate risk of bias. In the remaining four studies, the risk of overall bias was low except for confounding factors.

Main findings

Table 1 shows the main findings of the studies, showing the results according to duration of employment, work area, and other results.

Among the twelve studies conducted exclusively in the rubber tire industry, no significant increase in risk was found to be associated with duration of employment, with some exceptions. For example, Wingren et al.'s study of SIR for tracheal, bronchial, and lung cancer in employees exposed from 2.5 to 10 years and for those exposed for more than 10 years, there was an increase (SIR = 1.75 [1.04-2.77], and 1.78 [1.09-2.75, respectively) (Wingren & Axelson, 2007).

No association was found by studying the time elapsed since first employment (Beall et al., 2007; Mirabelli et al., 2012; Pira et al., 2012), the time since last employment, the age at when first employed, and the time period of first employment (Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012).

Four studies have examined the work area of employees. Wilczyńska 2001 et al. (Wilczyńska et al., 2001) did not find any association whereas Wingren et al. (Wingren & Axelson, 2007) found an association between respiratory cancer and compounding, mixing, milling, and maintenance (SIR for tracheal, bronchial, and lung cancers for employees in compounding and

mixing: 2.18 [1.31-3.4]; SIR for tracheal, bronchial, and lung cancers for employees in milling: 2.57 [1.37-4.4]; SIR for tracheal, bronchial, and lung cancers for employees in maintenance: 1.94 [1.03-3.31]). Negri et al. (Negri et al., 1989) found an association between bladder cancer and working in various departments (SMR for bladder cancer for employees in various departments: 3.5, $p < 0.05$). Wang et al. (Wang et al., 1984) found an association between lung cancer and working in mixing and milling (SMR for lung cancer for employees in mixing and milling in the first company: 2.73, $p < 0.05$; SMR for lung cancer for employees in mixing and milling in the second company 5.56, $p < 0.05$).

De Vocht et al. (De Vocht et al., 2009) did not find any significant association despite using a matrix of exposure to aromatic amines except for the 3rd quartile of exposure (RR of bladder cancer for the third quartile of exposure to aromatic amines : 7,3 [1.1-51]).

Eleven studies have examined the overall risk of cancer. Of the nine studies that examined respiratory cancer, (Beall et al., 2007; Bernardinelli et al., 1987; McMichael et al., 1974; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012; Wilczyńska et al., 2001; Wingren & Axelson, 2007), two found an increased risk (McMichael et al., 1974; Wingren & Axelson, 2007). For bladder cancer, two (Negri et al., 1989; Veys, 2004) of the ten studies found an increased risk (Beall et al., 2007; Bernardinelli et al., 1987; McMichael et al., 1974; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012; Veys, 2004; Wilczyńska et al., 2001; Wingren & Axelson, 2007). For hematologic diseases and stomach cancer, only the McMichael et al. (McMichael et al., 1974) study found a significant increase in risk among the nine studies investigating it (Beall et al., 2007; Bernardinelli et al., 1987; McMichael et al., 1974; Mirabelli et al., 2012; Negri et al., 1989; Pira et al., 2012; Rubin & Clapp, 2012; Wilczyńska et al., 2001; Wingren & Axelson, 2007).

Among the five studies conducted in companies that were not all in the rubber tire sector (Boniol et al., 2016; Chen et al., 1997; McElvenny et al., 2018; Sorahan et al., 1989; Vlaanderen et al., 2013), two studies (McElvenny et al., 2018; Sorahan et al., 1989) found increased mortality from lung cancer, one study from stomach cancer (Chen et al., 1997), and one from bladder cancer (McElvenny et al., 2018) taking into account that Chen et al. (Chen et al., 1997) studied only digestive cancer.

4 Discussion

We found an increased risk of lung/respiratory cancer associated with a history of having worked in the tire industry across this literature review for several conditions of work.

This is the case for four of the twelve studies investigating overall increased risk or respiratory/lung cancer (McElvenny et al., 2018; McMichael et al., 1974; Sorahan et al., 1989; Wingren & Axelson, 2007). It is of note that for these studies the time periods of exposure are older than those of the studies that did not find any overall associated risk. Manufacturing processes have been improving over the years in the tire manufacturing industry, and carcinogen exposure as well. This result does not surprise us. Although the two studies that performed a analysis by hiring period, they did not find any association with cancer (Negri et al., 1989; Pira et al., 2012), it is possible that exposures in the oldest time periods will have been associated with an increased risk of lung/respiratory cancers. These data are consistent with data on occupational exposure to carcinogens, which show a decline in the intensity of exposure between the 1950s and 1990s in western countries (Boniol et al., 2016; Goutet, 2007).

On the other hand, through the analysis by work area, it appeared that some work areas are associated with an increased risk of developing cancer, specifically compounding, mixing, milling, and for employees who have cross-functional activities, whether in maintenance or in the various departments. Concerning compounding, mixing, and milling, these results are quite logical, as they are certainly the areas most exposed to carcinogens. The fumes released by the heating of raw materials contain PAHs, for example. However, these results should be taken with caution because the methods of classification of the employees into the different work areas are poorly described in the articles and certainly differ. Another work area that could have been found to be associated with some types of cancer is vulcanization, as exposure to fumes are also elevated in the area, but no significant association was found in the different analyses.

The link appears to be weaker for bladder cancer. Only three studies of the sixteen that studied the overall risk found an association (McElvenny et al., 2018; Negri et al., 1989; Veys, 2004). The studies of McElvenny et al. and Veys et al. are considered to have a low risk of overall bias, but the study of Negri is considered to have a critical risk due to multiple analyses and it is thus impossible to conclude which work area could be more at risk. Exposure to aromatic amines is certain in the tire industry. Nevertheless, in the Polish cohort (De Vocht et al., 2009; Wilczyńska et al., 2001) no significant trend was found in the association between the indicator used to estimate exposure to aromatic amines and bladder cancer. However, the study of Veys et al. on

employees exposed to beta naphthylamine before 1949 is in favour of this association. The cessation of the use of beta naphthylamine occurred relatively early in comparison to the time periods examined by the studies in this review (1950s), and this may explain why the association seems weaker. Since then, other aromatic amines have replaced this substance. Concerning stomach cancer, the review does not provide argument supporting an association. Indeed, only two studies found a statistically significant association (Chen et al., 1997; McMichael et al., 1974). One had an overall risk of bias considered serious (Chen et al., 1997) among all the sixteen studies that examined this risk.

With regard to haematological malignancies, the classifications are not comparable between all the studies and the level of precision in the diagnosis is not identical, which makes it impossible to conclude on any precise trend. If we consider hematological diseases overall, only one study of sixteen found a statistically significant association (McMichael et al., 1974).

The analyses by duration of employment, time since first hired, time since end of exposure, age when hired, or time period of employment do not allow us to conclude that there is a trend between these indicators used to estimate exposure in terms of intensity or duration and the appearance of cancer.

Although the exposures are more homogeneous in the rubber tire industry than in the rubber industry more widely, an important limitation of the assemblage of the different studies is the fact that the level of protection and ventilation in the different companies studied, and even in the different work areas, is certainly not comparable.

There is great heterogeneity in the quality of the articles with regard to the assessment of the risk of bias, with two articles classified as critical. The majority of the studies that found statistically significant associations had a risk of bias assessment classified between low and moderate (McElvenny et al., 2018; McMichael et al., 1974; Sorahan et al., 1989; Veys, 2004; Wingren & Axelson, 2007), which supports our interpretation. However, it should be noted that only one of the authors assessed the risk of bias.

Our systematic review initially relied on the MEDLINE database because it is more accessible to algorithmic searching. However, we cross-referenced our data with the references of the articles, with those of the meta-analyses cited previously (Alder et al., 2006; Boniol et al., 2017) and a search on WEB OF SCIENCE. Two articles emerged from this cross-referencing, which suggests good sensitivity of our method, especially since the overall risk of bias is considered serious (Chen et al., 1997) or critical (Rubin & Clapp, 2012) for these articles.

5 Conclusion

This systematic review has highlighted that, despite the results of meta-analyses that did not find any excess risk of cancer in the rubber tire industry (Alder et al., 2006; Boniol et al., 2017), having worked in this industry, especially in older time periods likely having higher exposure to carcinogens, could be associated with an increased risk of lung cancer. This is particularly true for specific jobs exposing workers to fumes. However, there is no evidence to suggest that this risk is proportional to the duration of exposure.

Future studies on the tire industry should take into account, at minimum, the smoking status of the employees, and at best the major exposures to carcinogens by work area. All the studies reviewed here lacked precision on these points, which limits the conclusions we can draw from the trends described.

Declarations

The authors did not receive support from any organization for the submitted work.

All selected articles are available on the internet and data on their selection and evaluation are available in the supplementary data of the manuscript.

The first author wrote the manuscript, selected the articles and assessed their risk of bias. The second author selected the articles with the first author and corrected the manuscript. The other authors corrected the manuscript.

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Figure 1. Flow chart of literature search for observational studies on occupational exposure in the tire manufacturing industry and risk of cancer.

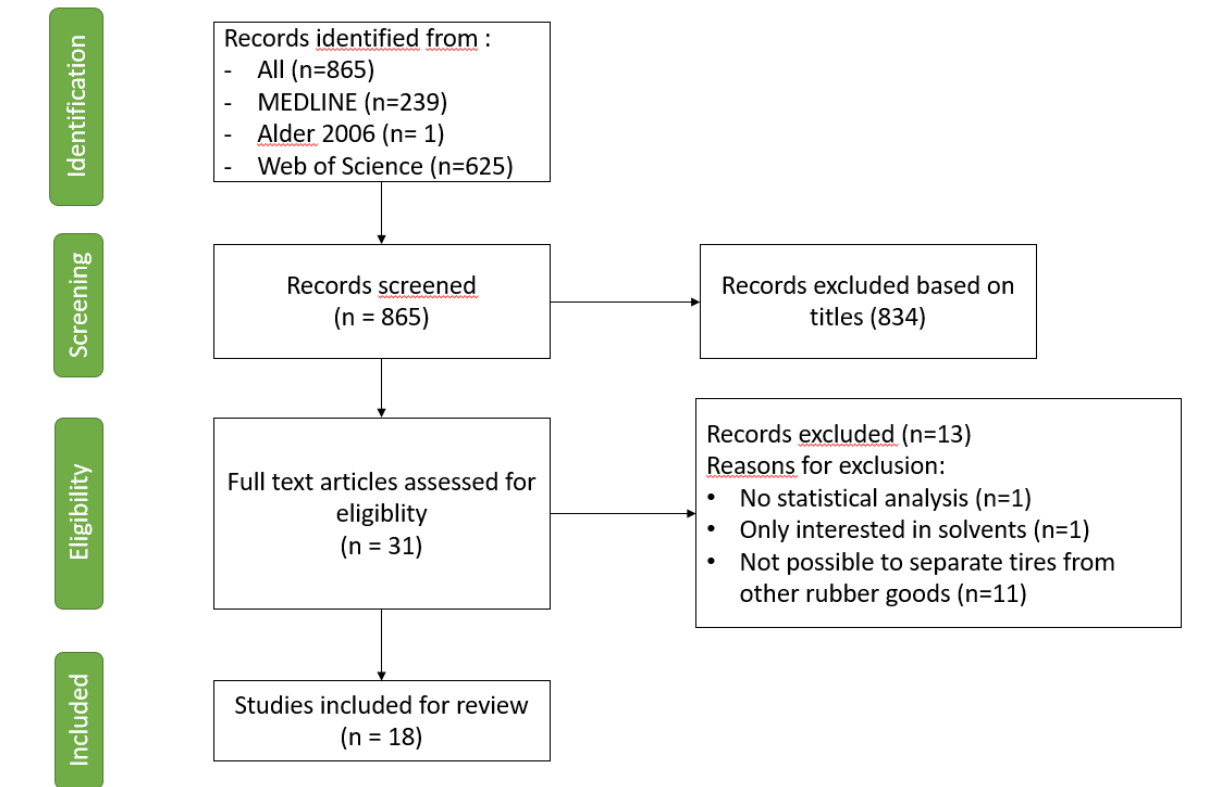


Table 1. Summary of studies from the literature review on occupational exposures in the tire industry and risk of cancer.

Attached to the article.

Type of industry	N. exposed subjects	Study design	Exposure / follow-up periods	Type of results depending on duration of employment	Main results ^a and Statistical significance	Type of other results	Main results ^a and Statistical significance	Country/Ref
1 tire manufacturing plant	3,425	Exclusion if the employee has worked less than 12 months Vital status known for 96% of employees Comparison to local population (Texas or the 15 county around the plant for incidence)	Exposure : 1962-2003 Mortality : 1963-2003 Incidence : 1995-2003	SIR for bladder cancer for employees exposed more than 10 years (at least 20 years since first employment)	0.78 [0.21-1.99]	SMR for stomach cancer SMR for lung cancer SIR for lung cancer SMR for leukemia SIR for leukemia SMR for NHL SIR for NHL SMR for bladder SIR for bladder	0.97 [0.26-2.48] 0.72 [0.53-0.96] 0.76 [0.53-1.06] 0.95 [0.31-2.23] 0.68 [0.14-1.98] 0.83 [0.27-1.94] 1.38 [0.66-2.53] 1.32 [0.27-3.84] 0.73 [0.29-1.49]	USA/Beall et al. (2007)

Only case-control study in the review, concerning stomach cancer only	15 case in the rubber tire industry, 190 age and sex matched controls	Comparison to local population Taking into account the diet Questionnaire and interview about diet and occupation	Newly diagnosed case during 1985-1987, no other information	RR for stomach cancer for employees exposed 5 years or more at least ten year before the study RR for stomach cancer for employees exposed less than 5 years or shorter than ten year before the study	3.5 [1.1-11] 0.9 [0.2-4.3]	RR for stomach cancer taking account of diet	2.5 [1-6.4]	England/Coggon et al. (1990) et al. (1997)
1 tire manufacturing plant (Overlap with Boniol 2016 (36.4% of workers hired after 1975)	7,017	Vital status known for 99% of employees, cause of death in 96% of cases Comparison to local population (Piedmont) 10 year lag	1962-2000 1962-2004	Multivariate regression ratio (Poisson) for bladder cancer incidence for employees exposed from 5 to 9 years Multivariate regression ratio (Poisson) for bladder cancer incidence for employees exposed from 10 to 19 years Multivariate regression ratio (Poisson) for bladder cancer incidence for employees exposed more than 20 years	1.03 [0.4-2.8] 1.57 [0.7-3.3] 1,74 [0,9-3,6]	SIR for bladder cancer in males	1.15 [0.9-1.4]	Italy/Mirabelli et al. (2012)

1 tire manufacturing plant	6,629	Exclusion if the employee has worked less than 12 months Comparison to national population (Italy) Analyse by duration of exposure, time since last exposure, age at first exposure, time period at first employment and by job title	1906-1981 1946-1981	SMR for lung cancer for employees exposed more than 20 years	0.97	SMR for lung cancer SMR for lung cancer for employees in various services ^b SMR for lung cancer for employees hired between 1906 and 1939 SMR for bladder cancer SMR for bladder cancer for employees in various services ^b SMR for stomach SMR for leukemia	1.01 [0.79-1.29] 2.25* 1.27 1.83 [1.05-2.96] 3.5* 0.78 [0.54-1.08] 0.91 [0.39-1.79]	Italy/Negri et al. (1989)
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1 tire manufacturing plant	6,246	Exclusion if the employee has worked less than 3 months or is over 85 years old Vital status known for 95% of employees, cause of death in 94% of cases Comparison to local population (Piedmont) Analyse by duration of employment, time since first employment, time since last employment and time period at first employment	1954-2008 1954-2008	SMR for bladder cancer for employees exposed less than 10 years SMR for bladder cancer for employees exposed from 10 to 19 years SMR for bladder cancer for employees exposed more than 20 years	0.81 [0.29-1.76] 1.83 [0.79-3.6] 1.27 [0.55-2.51]	SMR for lung cancer SMR for lung cancer for employees hired before 1965 SMR for stomach cancer SMR for all lymphatic and hematopoetic cancers	0.8 [0.6-0.9] 0.7 [0.57-0.97] 1 [0.7-1.4] 1 [0.7-1.4]	Italy/Pira et al. (2012)
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1 tire manufacturing plant, Overlap with Boniol 2016 (~60% of workers hired after 1970)	17,636	Exclusion if the employee has worked less than 3 months Vital status known for 97% and cause of death for 88%. Comparison to national population (Poland) Use Exposure Matrix for aromatic amines and inhalable aerosols Latency period of 5 years	1950-1995 1950-2001	SMR for bladder cancer for employees exposed less than 5 years SMR for bladder cancer for employees exposed more than 5 years	0.56 [0.07-2.02] 0.64 [0.17-1.64]	SMR for lung cancer SMR for bladder in males SMR for bladder in males in preparation of materials ^b RR of bladder cancer for the third quartile of exposure to aromatic amines RR of bladder cancer for the fourth quartile of exposure to aromatic amines SMR for tumors of lymphoid and hematopoietic tissues in males RR for tumors of lymphoid and hematopoietic tissues in males for the second quartile of exposure to aromatic amines RR for tumors of lymphoid and hematopoietic tissues in males for the third quartile of exposure to aromatic amines RR for tumors of lymphoid and hematopoietic tissues in males for the fourth quartile of exposure to aromatic amines	0.7 [0.6-0.9] 0.6 [0.2-1.3] 1.3 [0.3-3.8] 7,3 [1.1-51] 8.3 [1-66.3] 0.6 [0.4-1.1] 2.1 [0.5-7.9] 1.3 [0.2-7.2] 3 [0.8-11.1]	Poland/ de Vocht et al. (2009) and Wilczyńska et al. (2001)
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1 tire manufacturing plant	5,745	Exclusion if the employee has worked less than 12 months Comparison to national population (Sweden) Latency period of 10 years	1938-1981 1958-2001	SIR for trachea, bronchus, and lung cancers for employees exposed from 2,5 to 10 years SIR for trachea, bronchus, and lung cancers for employees exposed more than 10 years	1.75 [1.04-2.77] 1.78 [1.09-2.75]	SIR for trachea, bronchus, and lung cancers SMR for trachea, bronchus, and lung cancers SIR for trachea, bronchus, and lung cancers for employees in compounding and mixing ^b SIR for trachea, bronchus, and lung cancers for employees in miling ^b SIR for trachea, bronchus, and lung cancers for employees in maintenance ^b	1.62 [1.28-2.02] 1.54 [1.21-1.94] 2.18 [1.31-3.4] 2.57 [1.37-4.4] 1.94 [1.03-3.31]	Sweden/Wingren et al. (2007)
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2 tire manufacturing plants	not find	Included if the employee is over 30 years old Comparison to local population (Shangai)	1971-1980 and 1976-1980 (difference between exposure and follow-up periods not clear)			SMR for lung cancer for employees in mixing and milling in the first plant SMR for lung cancer for employees in mixing and milling in the second plant ^b SMR for stomach cancer for employees in mixing and milling in the first plant ^b SMR for stomach cancer for employees in mixing and milling in the second plant ^b	2.73* 5.56* 1.59 1.84	China/Wang et al. (1984)
1 tire manufacturing plant	4,917	Exclusion if the employee has worked less than 12 months Vital status known for 99% of employees Comparison to local population (Cuneo province) Only males	1962-1983 1962-1983			SMR for stomach cancer SMR for bronchus, trachea or lung cancers SMR for bladder cancer SMR for Hodgkin lymphoma SMR for myeloid leukemia SMR for other leukemia	1.4 0.7 1.4 1.7 3.6 1.1	Italy/Bernardinelli et al. (1987)

1 tire manufacturing plant	6,678	Inclusion of active and retired employees aged 40 to 84 at 1/1/1964 Vital status known for 99% of employees, cause of death in 99.5% of cases Only male	Until 1972 (no information on the opening date of the plant) 1964-1972			SMR for stomach cancer 1.87* SMR for respiratory system cancer 0.84* SMR for bladder cancer 0.73 SMR for lymphosarcoma 2.26* SMR for leukemia 1.28		USA/Mc Michael et al. (1974)
1 tire manufacturing plant	5,128	Vital status known for 99,8% of employees Comparison to local national (England and Wales) and local (Birmingham) population	1945-1949 1951-1995			SIR for bladder 1.23 [1.02-1.48] SIR for bladder for employees exposed to beta-naphtylamine between 1946 and 1949 1.71 [1.3-2.21] SMR for bladder 0.97 [0.55-1.57] SMR for bladder for employees exposed to beta-naphtylamine between 1946 and 1949 0.85 [0.6-1.18]		Great Britain/Veys et al. (2004)

1 tire manufacturing plant	2,924	Exclusion if the employee has worked less than 12 months Comparison to local population (Winsconsin) Latency period of 5 years	1932-1992 No information			PCMR for lung cancer in males PCMR for bladder cancer in males PCMR for stomach cancer in males PCMR for leukemia cancer in males PCMR for leukemia cancer in males hired between 1932 and 1950	0.9 [0.64-1.22] 0.46 [0.06-1.67] 1.21 [0.39-2.82] 0.98 [0.36-2.13] 3.32 [0.68-9.7]	USA/Rubin et al. (2012)
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Rubber industry, 64 plants	17,389 in tire manufacturing plants	Pooled analysis of 5 European cohorts Exclusion if the employee has worked less than 12 months Only first employed at 1 January 1975 or later Comparison with national population according to WHO data, except in Italy Overlap with de Vocht et al. (2009) and Wilczyńska et al. (2001) with & Mirabelli et al. (2012)	1975-(max 2013)1975-(max 2013)			SMR for lung cancer in tire plants SMR for bladder cancer in tire plants SMR for stomach cancer in tire plants SMR for leukemia cancer in tire plants	0.71 [0.56-0.90] 0.97 [0.46-2.08] 0.92 [0.59-1.44] 0.96 [0.52-1.78]	Germany, Italy, Poland, Sweden and Great Britain/Boniol et al. (2016)
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3 tire and other rubber goods manufacturing plants	7,808, number of employees working in tire manufacturing not specified	Exclusion if the employee has worked less than 12 months Comparison to local population (Shanghai) Taking into account the smoking status Latency period of 5 years	1920s (max) -1972 1967-1988			SIR for stomach cancer in non-smokers males in miling and smelting for tire SMR for stomach cancer in males in material handling for tire	2.3* 2*	China/Chen et al. (1997)
Rubber industry	14,906 in tire manufacturing plants	Employee younger than 35 years of age were excluded Comparison to local population (England and Wales)	Recruitment in 1967 but could have worked since 1950 or before 1967-2015			SMR for trachea, bronchus, and lung cancers in tire plants SMR for bladder cancer in tire plants	1.25 [1.19-1.32] 1.38 [1.23-1.53]	Great Britain/McElvenny et al. (2018)

Rubber industry, 13 plants	36,445, number of employees working in tire manufacturing not specified	Exclusion if the employee has worked less than 12 months Vital status known for 93% of employees Comparison to local population (England and Wales)	1946-1960 1946-1985			SMR for stomach cancer for employees hired between 1946 and 1950	1.12	Great Britain/Sorahan et al. (1989)
						SMR for stomach cancer for employees hired between 1951 and 1955	0.97	
						SMR for stomach cancer for employees hired between 1956 and 1960	1.29	
						SMR for lung cancer for employees hired between 1946 and 1950	1.32	
						SMR for lung cancer for employees hired between 1951 and 1955	1.16	
						SMR for lung cancer for employees hired between 1956 and 1960	1.33	

Rubber industry, 5 plants	13,495 in these 5 plants	Exclusion if the employee has worked less than 12 months No analyse by duration of employment in tire industry Comparison with local population (Western Germany) Vital status known for 99% of employees, , cause of death in 93% of cases (males) Multivariate analyses by duration of employment and time since first employment	Recruitment in 1981 but could have worked before 1981-2000			SMR for lung cancer in production of tire SMR for bladder cancer in production of tire SMR for stomach cancer in production of tire SMR for leukemia cancer in production of tire	1.09 [0.87-1.36] 1.31 [0.7-2.23] 1.17 [0,75-1.72] 0.39 [0.08-1.15]	Germany/Vlaanderen et al. (2013)
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* p<0,05

^a only for a priori important causes of death based on the IARC monograph conclusions for rubber industry

^b analysis by work area

Figure 2. Risk of bias summary : reviewers' judgement regarding each risk of bias domain foe each included study.

First author (year)	D1	D2	D3	D5	D6	D7	Overall
McElvenny (2018)	Red	Green	Green	Green	Green	Green	Green
Boniol (2016)	Red	Green	Green	Red	Red	Green	Red
Vlaanderen (2013)	Red	Green	Green	Green	Yellow	Green	Yellow
Mirabelli (2012)	Red	Yellow	Green	Green	Yellow	Green	Yellow
Pira (2012)	Red	Green	Green	Green	Yellow	Green	Yellow
de Vocht (2009)	Red	Yellow	Green	Red	Green	Red	Red
Wingren (2007)	Red	Green	Green	Green	Green	Green	Green
Veys (2004)	Red	Green	Green	Green	Green	Green	Green
Beall (2007)	Red	Green	Green	Green	Green	Green	Green
Negri (1989)	Red	Yellow	Red	Red	Red	Black	Black
Sorahan (1989)	Red	Green	Green	Green	Green	Yellow	Yellow
Bernardinelli (1987)	Red	Green	Green	Green	Yellow	Yellow	Yellow
Wang (1984)	Red	Black	Green	Red	Red	Green	Black
Mc Michael (1974)	Red	Green	Green	Green	Yellow	Green	Yellow
Chen (1997)	Green	Green	Red	Green	Green	Red	Red
Coggon (1990)	Red	Red	Yellow	Red	Red	Red	Black
Rubin & Clapp (2012)	Red	Green	Green	Black	Yellow	Yellow	Black

Domains: D1: Bias due to confounding, D2: Bias in measurement of the exposure, D3: Bias in selection of participants into the study, D5: Bias due to missing data, D6: Bias in measurement of outcomes and D7: Bias in the selection of the reported results.

Judgement:

: Critical
 : Serious
 : Moderate
 : Low