# Crystalline Silica Dust and Lung Cancer: A Systematic Review and Meta-Analysis Protocol

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**Background:** Crystalline silica dust is prevalent in mining, construction, and manufacturing. Prolonged exposure is linked to silicosis, COPD, and lung cancer; the International Agency for Research on Cancer classifies crystalline silica as a Group 1 human carcinogen. Yet epidemiological findings vary by region, design, and exposure level. A rigorous synthesis is needed to clarify lung cancer risk.

**Objective:** To conduct a systematic review and meta-analysis quantifying the association between occupational crystalline silica exposure and lung cancer incidence, and to examine heterogeneity by study characteristics, geographic region, and exposure assessment methods.

**Methods:** Following PRISMA, we will search PubMed, Scopus, Web of Science, Embase, and Cochrane Library without date limits. Eligible designs include cohort, case-control, and cross-sectional studies reporting quantitative associations between crystalline silica exposure and lung cancer. Two reviewers will independently screen, extract data, and resolve discrepancies by consensus. Study quality and risk of bias will be appraised using Joanna Briggs Institute tools. Random-effects models will generate pooled effect estimates. Between-study heterogeneity will be assessed using the $I^2$ statistic and Cochran's Q. Prespecified subgroup and sensitivity analyses will evaluate sources of variation, including exposure metrics, industry, sex, smoking adjustment, and confounding by co-exposures. Small-study effects and publication bias will be examined via funnel plots, Egger's regression, Begg's test, and Galbraith plots, with trim-and-fill applied where appropriate. Findings will be reported witforest plots, descriptive tables, and narrative synthesis when pooling is infeasible.

**Discussion:** This review will consolidate the best available evidence on silica-related lung cancer risk, contextualized by mechanistic insights (e.g., inflammation, genotoxicity) and international regulatory standards. Anticipated limitations include exposure misclassification, residual confounding (notably smoking), and variability in study design and adjustment strategies. By providing robust pooled estimates and transparent exploration of heterogeneity, this work aims to inform occupational health policy, risk assessment, and

targeted prevention strategies across diverse workplaces.

# Introduction

## 1. Global Burden of Lung Cancer

Lung cancer remains the foremost cause of cancer mortality worldwide [1]. According to the most recent GLOBOCAN 2020 [2] estimates, there were approximately 2.2 million new lung cancer cases and 1.8 million deaths globally, representing 11.4% of all cancer diagnoses and nearly 18% of all cancer deaths [3]. Despite considerable advances in diagnostic imaging, molecular pathology, surgical techniques, and systemic therapies including immunotherapies and targeted agents the overall prognosis of lung cancer remains poor, with a global five-year survival rate of less than 20% [4].

The incidence of lung cancer varies substantially by sex, geography, and socioeconomic status. Historically, men exhibited higher incidence and mortality, reflecting earlier and heavier adoption of tobacco smoking; however, in many high-income countries, male lung cancer rates have plateaued or declined, while female rates continue to rise [5]. This shifting epidemiology underscores the role of not only tobacco but also other factors including environmental exposures, air pollution, and occupational carcinogens in shaping global lung cancer patterns [6].

Occupational exposures, in particular, have been estimated to account for 10–15% of lung cancer burden in men and up to 5% in women [7], making occupational lung carcinogenesis a substantial but preventable contributor to global cancer mortality [8]. Among occupational carcinogens, crystalline silica dust stands out due to its widespread prevalence across industries, its well-established fibrogenic potential, and increasing evidence of carcinogenicity.

## 2. Crystalline Silica Dust: Properties and Industrial Relevance

Crystalline silica ($SiO_2$) is one of the most abundant minerals in the Earth’s crust. The most common polymorphs relevant to occupational exposure include quartz, cristobalite, and tridymite [9]. These minerals are characterized by a repeating crystal lattice structure, which distinguishes them from amorphous silica (e.g., silica gel), generally considered less toxic [10].

The risk associated with silica lies primarily in respirable crystalline silica (RCS) particles those with an aerodynamic diameter below 10 μm, which can penetrate to the alveoli [11, 12]. These particles are generated in high concentrations in numerous industrial settings:

• Mining and quarrying: drilling, blasting, and crushing of rocks.

• Construction: cutting, grinding, drilling, and demolishing stone, concrete, or brick.

• Ceramics and glass industries: handling raw materials containing silica.

• Foundry and metallurgical work: sand casting and abrasive blasting.

• Agriculture: soil disruption, particularly in arid regions.

The ubiquity of these industries means that millions of workers worldwide remain at risk of silica exposure. Indeed, the International Labour Organization (ILO) has estimated that over 30 million workers in developing nations are exposed to silica dust, many with inadequate protective measures [13].

Recognition of silica’s hazards dates back centuries. Reports from the 16th century describe “stonecutter’s disease,” later identified as silicosis, a fibrotic lung disease caused by inhalation of crystalline silica [14, 15]. By the early 20th century, epidemics of silicosis were reported among miners, tunnel workers, and foundry workers. Over time, growing evidence linked silica not only to silicosis but also to chronic obstructive pulmonary disease (COPD), autoimmune disorders, and lung cancer [16]. This prompted the International Agency for Research on Cancer (IARC) to classify crystalline silica as a Group 1 human carcinogen in 1997, a designation reaffirmed in 2012.

## 3. Biological Mechanisms of Silica-Induced Carcinogenesis

The carcinogenicity of crystalline silica is biologically plausible and supported by both in vivo and in vitro studies. Several interrelated mechanisms have been

proposed:

1. Persistent Inflammation

- Silica particles are engulfed by alveolar macrophages but cannot be effectively degraded. This leads to repeated macrophage death, recruitment of additional inflammatory cells, and chronic alveolitis [17].

- The release of cytokines such as TNF-α, IL-1β, and TGF-β creates a pro-inflammatory and pro-fibrotic microenvironment conducive to carcinogenesis [18].

2. Oxidative Stress and DNA Damage

- The crystalline surface of silica particles catalyzes the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [19].

- These reactive molecules induce oxidative DNA damage, DNA strand breaks, and lipid peroxidation, all of which contribute to mutagenesis [20].

3. Genotoxic Effects

- Studies demonstrate that crystalline silica induces micronuclei formation, chromosomal aberrations, and mutations in mammalian cells.

- Unlike silicosis, which requires substantial fibrosis, these genotoxic events may occur even in the absence of overt lung fibrosis.

4. Epigenetic Alterations

- Recent research suggests that silica exposure alters DNA methylation, histone modifications, and microRNA expression patterns, which regulate genes involved in cell cycle control and apoptosis [21].

5. Fibrogenic Microenvironment

- Progressive fibrosis, as seen in silicosis, distorts lung architecture and leads to compensatory hyperplasia of epithelial cells. Chronic injury-repair cycles may promote malignant transformation.

Collectively, these mechanisms underscore that silica is not only a fibrogenic but also a direct carcinogenic agent, with both inflammatory and mutagenic pathways contributing to tumor initiation and progression.

## 4. Regulatory and Public Health Context

Recognition of silica's hazards has led to regulatory action worldwide:

• The Occupational Safety and Health Administration (OSHA) in the United States reduced the permissible exposure limit (PEL) for respirable crystalline silica to 50 μg/m³ in 2016.

• The European Union (EU) similarly enforces an

occupational exposure limit of 100 μg/m³.

• However, in many low- and middle-income countries, enforcement is weak or absent, and exposure levels remain dangerously high.

A clear and updated synthesis of the lung cancer risk associated with silica exposure is thus essential for:

1. Establishing appropriate occupational exposure limits.

1. Guiding workplace safety practices and monitoring.

2. Informing compensation claims for affected workers.

3. Raising awareness in industries where silica exposure is under-recognized.

## 5. Rationale and Knowledge Gaps

Despite abundant research, several uncertainties persist:

• Dose–response relationship: The magnitude of lung cancer risk at low-to-moderate silica exposure remains unclear.

• Role of silicosis: Is lung cancer risk mediated through silicosis, or does silica independently increase cancer risk?

• Effect of co-exposures: Tobacco smoking and asbestos exposure complicate risk estimates.

• Regional differences: Limited data from low-income

countries where exposure is often highest.

• Study quality: Many older studies had incomplete exposure assessment or inadequate confounder control.

These gaps necessitate a rigorous, updated systematic review conducted according to PRISMA standards, integrating high-quality epidemiological evidence and modern approaches to meta-analysis.

## 6. Objectives

Primary Objective:

• To comprehensively assess and quantify the association between occupational crystalline silica exposure and the risk of lung cancer.

Secondary Objectives:

• To investigate potential dose–response relationships.

• To assess heterogeneity by industry type, geographic region, and exposure intensity.

• To evaluate the role of confounders and effect

modifiers, particularly smoking and asbestos.

• To grade the certainty of evidence using transparent methodological frameworks.

• To identify gaps for future research and provide recommendations for occupational health policy.

# Methods

This systematic review and meta-analysis will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines. The objective is to evaluate the association between occupational exposure to crystalline silica dust and the risk of lung cancer in adults. A pre- specified methodological approach has been established to ensure transparency, reproducibility, and scientific rigor throughout the process of literature retrieval, study selection, data extraction, critical appraisal, and statistical synthesis.

## Eligibility Criteria

Eligible studies will include observational epidemiological research involving adult populations (aged 18 years and older) employed in occupations with documented or probable exposure to crystalline silica dust. Such occupations may include, but are not limited to, mining, quarrying, construction, foundry work, ceramics, glass production, and agriculture. Studies will be considered if they provide clear evidence of exposure to respirable crystalline silica (RCS), either through qualitative classification (e.g., based on industry or job title) or quantitative methods (e.g., measured dust concentrations or cumulative exposure indices). The primary outcome of interest will be the incidence or mortality of lung cancer, whether identified through histological confirmation, clinical diagnosis, or linkage with cancer registries or mortality databases.

Studies will be eligible if they employ cohort, case- control, or cross-sectional designs. Both prospective and retrospective cohorts will be included, provided that they report sufficient information to estimate effect measures. Case-control studies must include well-defined cases of lung cancer and appropriate controls from either the general population or occupational groups without silica exposure. Cross-sectional studies reporting lung cancer prevalence in relation to silica exposure will also be considered, though with caution regarding their limitations in causal inference. Excluded studies will include case reports, case series, ecological analyses, reviews, commentaries, and studies that fail to specify crystalline silica exposure. No restrictions will be placed on language or year of publication, and relevant grey literature will also be considered.

## Information Sources and Search Strategy

A comprehensive literature search will be performed in major electronic databases, including PubMed/ MEDLINE, Embase, Web of Science, Scopus, and the Cochrane Library. In addition, grey

literature will be retrieved from OpenGrey and ProQuest Dissertations and Theses. Governmental and regulatory reports, such as those produced by the International Agency for Research on Cancer (IARC), the Occupational Safety and Health Administration (OSHA), and the European Chemicals Agency (ECHA), will also be consulted. Reference lists of relevant reviews and included studies will be screened manually to identify additional records, and citation tracking will be carried out using Google Scholar.

The search strategy will combine Medical Subject Headings (MeSH) and free-text terms for crystalline silica and lung cancer, together with occupational exposure keywords. For example, the PubMed search will include terms such as “crystalline silica,” “quartz,” “cristobalite,” “tridymite,” “lung cancer,” “pulmonary carcinoma,” “occupational exposure,” “miners,” “construction workers,” and “foundry workers,” connected with Boolean operators. This strategy will be adapted for use in other databases to maximize sensitivity and specificity.

## Study Selection

All records identified through the search will be imported into reference management software, and duplicates will be removed. Screening will occur in two stages. In the first stage, two independent reviewers will screen titles and abstracts to exclude studies that clearly do not meet the eligibility criteria. In the second stage, full texts of potentially relevant articles will be retrieved and assessed for inclusion by the same two reviewers. Any disagreements between reviewers will be resolved through discussion, and if consensus cannot be reached, a third reviewer will adjudicate. The process of study selection will be documented in a PRISMA flow diagram, showing the number of records identified, screened, excluded, and ultimately included in the review.

## Data Extraction

Data extraction will be performed using a standardized form developed specifically for this review. The form will capture information on study characteristics (authors, year of publication, country, funding source, study design, duration of follow-up), population demographics (sample size, age, sex, occupation), exposure assessment methods (qualitative or quantitative), outcome ascertainment (histological confirmation, registry data, mortality records), effect measures (relative risk, odds ratio, hazard ratio, with 95% confidence intervals), variables adjusted for in the analysis (notably smoking and asbestos exposure), and results of quality assessment. Two reviewers will extract the data independently, and discrepancies will be resolved through consensus. When essential data are missing or unclear, study authors will be contacted for clarification.

## Risk of Bias Assessment

The methodological quality and risk of bias of included studies will be assessed independently by two reviewers. For cohort and case-control studies, the Newcastle–Ottawa Scale (NOS) will be applied, evaluating selection of participants, comparability of cohorts or groups, and ascertainment of exposure and outcomes. For cross-sectional studies, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist will be used. Based on these assessments, studies will be categorized as having low, moderate, or high risk of bias. The results of these assessments will be used both descriptively, to comment on the overall quality of the evidence base, and analytically, in sensitivity analyses to evaluate the impact of study quality on pooled estimates.

## Data Synthesis and Statistical Analysis

Effect estimates from individual studies will be harmonized, wherever possible, as relative risks (RRs). Odds ratios (ORs) and hazard ratios (HRs) will be treated as approximations of relative risk,

particularly since lung cancer is a relatively rare outcome in most populations. Pooled effect estimates will be calculated using both fixed-effects models (Mantel–Haenszel method) and random-effects models (DerSimonian and Laird method), with the random-effects model serving as the primary analytic approach due to anticipated heterogeneity in study populations, exposure assessment, and outcome ascertainment.

Statistical heterogeneity across studies will be evaluated using Cochran's Q test, with a significance threshold of $p < 0.10$, and quantified using the $I^2$ statistic, which describes the percentage of variation attributable to between-study heterogeneity rather than chance. Values of $I^2$ below 25% will be considered low, 25–75% moderate, and greater than 75% high. Between-study variance ($\tau^2$) will also be estimated.

Subgroup analyses will be performed to explore sources of heterogeneity. These will include stratification by type of industry (e.g., mining, construction, foundry, ceramics), geographic region (e.g., Asia, Europe, North America), exposure intensity (low, moderate, high, or cumulative exposure metrics), adjustment for smoking (adjusted vs. unadjusted), and the presence or absence of silicosis. Where sufficient data are available, dose–response analyses will be conducted using generalized least-squares trend (GLST) models to evaluate linear and non-linear associations between cumulative silica exposure and lung cancer risk.

Sensitivity analyses will be conducted by excluding studies at high risk of bias, stratifying analyses by study design (cohort vs. case-control), and performing leave- one-out analyses in which each study is sequentially omitted to assess its influence on the pooled estimate.

Publication bias and small-study effects will be examined using both visual and statistical methods. Funnel plots of effect size against standard error will be generated and assessed for asymmetry. The presence of small-study effects will be formally tested using Egger's regression asymmetry test and Begg's rank correlation test. In addition, the trim-and-fill method will be applied to estimate the number and potential effect of unpublished studies. To further evaluate heterogeneity and identify potential outlier studies, Galbraith (radial) plots will be constructed.

The results of the meta-analysis will be presented graphically and numerically. Forest plots will display effect estimates and confidence intervals for individual studies alongside the pooled estimates. Funnel plots will visualize potential publication bias. Where appropriate, dose–response curves will be presented graphically.

All statistical analyses will be performed using STATA version 17 (StataCorp, College Station, TX, USA). Statistical significance will be defined as $p < 0.05$, except in tests of heterogeneity where $p < 0.10$ will be used to indicate significant variation.

### Certainty of Evidence

Finally, the certainty of the body of evidence will be evaluated according to the GRADE framework. The assessment will consider risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence will be classified as high, moderate, low, or very low certainty. This grading will inform the strength of conclusions and recommendations arising from the review.

## Results (Planned Presentation)

The results of this systematic review and meta-analysis will be presented in accordance with the PRISMA guidelines. A PRISMA flow diagram will illustrate the process of study identification, screening, eligibility assessment, and final inclusion, ensuring transparency of the selection process. Descriptive summaries will be provided for all included studies, detailing their design,

geographic location, study population characteristics, type and level of crystalline silica exposure, duration of follow-up (for cohort studies), and the method of lung cancer diagnosis or confirmation.

Quantitative synthesis will include pooled estimates of the association between crystalline silica dust exposure and lung cancer risk. These will be expressed as relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs), depending on the effect measure reported in the original studies. When possible, standardized effect measures will be derived to allow comparability. Forest plots will be used to display individual study estimates alongside pooled results.

Assessment of heterogeneity will be central to the results. The $I^2$ statistic, $\tau^2$, and Cochran's Q test will be reported for each meta-analysis to quantify inconsistency across studies. Subgroup analyses will be presented to explore sources of heterogeneity, such as occupational sector (e.g., mining, construction, foundry work), geographic region, study design, degree of exposure, and whether smoking adjustment was included in the analysis. Sensitivity analyses will be conducted by excluding studies at high risk of bias or those with extreme effect estimates to evaluate the robustness of the pooled results. Publication bias and small-study effects will be evaluated using funnel plots, which will be visually inspected for asymmetry, and formally tested with Egger's regression test and Begg's rank correlation test. A Galbraith plot will also be generated to visually identify studies that contribute to heterogeneity or deviate significantly from the pooled estimate. Where evidence of publication bias is observed, the trim-and-fill method will be applied to assess its potential influence on the overall effect size.

Where meta-analysis is not feasible due to heterogeneity in study design or outcome measures, findings will be synthesized narratively. This will involve grouping studies by exposure type, region, or methodological approach, and summarizing consistent themes and patterns across the evidence base.

# Discussion (Planned Approach)

The discussion section of this protocol outlines how the results, once obtained, will be interpreted and contextualized. The primary focus will be on assessing whether crystalline silica dust exposure is associated with an increased risk of lung cancer across occupational groups. The magnitude and consistency of the association will be evaluated, along with the quality of the evidence base.

Potential biological mechanisms, such as silica- induced chronic inflammation, genotoxicity, and impaired clearance of dust particles in the lung parenchyma, will be integrated into the interpretation of results. Findings will also be compared against existing evaluations, such as those from the International Agency for Research on Cancer (IARC), which has classified crystalline silica as a Group 1 human carcinogen.

The discussion will also address limitations expected to arise in the review. These may include heterogeneity in exposure assessment methods across studies (e.g., self-reports, job-exposure matrices, direct measurement), differences in outcome ascertainment, residual confounding (particularly smoking and co-exposures such as radon or asbestos), and potential publication bias. The influence of these limitations on the reliability of the pooled estimates will be critically evaluated.

Implications for occupational health and policy will form an essential part of the discussion. If the findings demonstrate a strong and consistent association, this would support stricter workplace exposure limits, improved monitoring, and implementation of protective measures for workers in high-risk industries. Conversely, if substantial uncertainty remains, the discussion will highlight the need for further well-designed epidemiological studies, particularly in low- and middle-income countries where silica exposure remains poorly studied but highly prevalent.

Finally, the discussion will outline how this systematic review and meta-analysis can contribute to the broader field of occupational cancer epidemiology, providing an evidence base for policymakers, clinicians, and researchers. The integration of quantitative synthesis, subgroup analyses, and bias assessments is expected to strengthen the conclusions and provide a reliable resource for guiding both preventive strategies and future investigations.

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*Statement of Transparency and Principals:*

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request.

• All authors have contributed to implementation of this research.

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