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Occupational exposure to crystalline silica related to lung cancer: scientific evidence synthesis

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Abbreviations and Acronyms:

PS: Primary Study

MA: Meta-analysis

SR: Systematic Reviews

IARC: International Agency for Research on Cancer

RICISST: Red de Institutos y Centros de Investigación en Seguridad y Salud en el Trabajo [Network of Occupational Health and Safety Institutes and Research Centres]

CESSLA: Centro Extremeño de Seguridad y Salud Laboral (Badajoz) del Gobierno de Extremadura [Extremadura Centre for Occupational Health and Safety of the Government of Extremadura (Badajoz)]

IAPRL: Instituto Asturiano de Prevención de Riesgos Laborales [Asturian Institute for the Prevention of Occupational Risks]

ISPLN: Instituto de Salud Pública y Laboral de Navarra [Institute of Public and Occupational Health of Navarra]

ISSGA: Instituto Gallego de Seguridad y Salud Laboral [Galician Occupational Health and Safety Institute]

INSHT: Instituto Nacional de Seguridad e Higiene en el Trabajo [National Institute of Safety and Hygiene at Work]

OSALAN: Instituto Vasco de Seguridad y Salud Laborales [Basque Institute of Occupational Health and Safety]

SGSSL: Subdirección General de Seguridad y Salud Laboral de la Generalitat de Catalunya [Subdirectorate General of Occupational Health and Safety of the Generalitat of Catalunya]

OSTEBA: Servicio de Evaluación de Tecnologías Sanitarias del Gobierno Vasco [Health Technologies Assessment Service of the Basque Government]

AETS: Agencia de Evaluación de Tecnologías Sanitarias [Health Technologies Assessment Agency]

ISSL: Instituto de Seguridad y Salud Laboral de la Región de Murcia [Occupational Health and Safety Institute of the Region of Murcia]

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INTRODUCTION

Silica is a compound made up of silicon and oxygen, in the form of SiO_2 (silicon dioxide or crystalline silica). It appears in nature in the form of sand, granite, clay, etc.

Occupational exposure to silica dust occurs during underground mining and quarry mining activities; construction; smelting; cement manufacturing and aggregate processing; manufacturing, handling, and processing of glass, ceramics; etc.

The inhalation of silica dust may lead to a pneumoconiosis in humans called silicosis. Pneumoconiosis are a group of diseases caused by the accumulation of dust in the lungs and tissue reactions due to its presence, and are included in the group of diffuse interstitial lung diseases (DILD, or EPID in Spanish). Silicosis is recognised as an occupational disease in the European list of occupational diseases as well as in the occupational disease framework of Spain.

In 1997, in a specific monograph[1], the International Agency for Research on Cancer (IARC) classified respirable crystalline silica in the workplace in the form of quartz or cristobalite as a Group 1 carcinogen, meaning there exists sufficient evidence for carcinogenicity in humans. Before and after this statement by the IARC, numerous authors researched the possible carcinogenicity of silica. The method of undertaking these studies has been very diverse: cohorts, case-control studies, job-exposure matrices, populations exposed to silica, workers with silicosis compared to workers without silicosis, etc.

In Spain, following the Commission recommendation of 19 September 2003 concerning the European schedule of occupational diseases, Royal Decree 1299/2006 of 10 November was issued, approving the framework of occupational diseases in the Social Security system and establishing criteria for their notification and registration. The possible carcinogenicity of silica would fit in Annex 2 of this Royal Decree containing a supplementary schedule of diseases with suspected occupational origin and whose inclusion in Annex 1 (table of occupational diseases) might occur in the future as a result of technical and scientific progress.

In this scenario the Red de Institutos y Centros de Investigación en Seguridad y Salud en el Trabajo [Network of Occupational Health and Safety Institutes and Research Centres] (RICISST), which brings together public research organizations in the field of occupational health and safety from across Spain, agreed at its meeting on 26 January 2011 to address the possibility, as RICISST's own initiative, of undertaking a systematic review on the possible carcinogenic effects of occupational exposure to silica. This

[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (vol 68): Silica, some silicates, coal dust and para-aramid fibrils. Lyon: IARC; 1997.

systematic review will help to determine the degree of evidence on the association between exposure to silica dust and the development of lung cancer.

It is an ambitious project based on a systematic methodology and a thorough quality assessment. To achieve the established objectives, the study has lasted nearly two and a half years since the establishment of the working group, in which the following RICISST members participated: CESSLA, IAPRL, INSHT, ISPLN, ISSGA, OSALAN and SGSSL. The team was multidisciplinary, consisting of hygienists, occupational physicians and general preventionists, which allowed the study to be carried out broadly and from various technical points of view.

The group decided to capture a summary of the key aspects of the methodology, results and discussion of this synthesis of the evidence in a clear and concise report. The detailed descriptions of the methodology, all steps performed and, more importantly, the exhaustive analyses of the studies that allow conclusions to be drawn, are reflected in the annexes. The authors encourage their reading in order to attain a deeper knowledge of the full process and its results.

OBJECTIVES

This study is the result of joint work agreed within the RICISST. The primary objective of this report is to analyse the current scientific evidence regarding the increased risk of lung cancer from occupational exposure to silica, through an evidence synthesis of published systematic reviews and meta-analyses (SR/MA). The secondary objectives of this study include qualitatively analysing high-quality primary studies (PS) taken from all the MAs and SRs and evaluating the possibility of a reanalysis of the data provided by these PSs.

MATERIALS AND METHODS

Although they could have chosen to develop an SR or MA for this study, given the heterogeneity of the studies found, the authors decided on an evidence synthesis.

An evidence synthesis is a way to integrate various types of research findings: quantitative and qualitative, heterogeneous designs, etc... following systematic criteria as developed in a systematic review or a meta-analysis. It provides certain advantages: it allows the handling of a large volume of information, allows the comparison of studies and their results, and provides transparency. It also offers the ability to create evidence tables for each of the studies analysed.

This evidence synthesis focused primarily on SRs and MAs to answer the question of whether lung cancer might be caused by occupational exposure to silica dust. It had a secondary focus of analysing primary studies (PS) contained in the SRs and MAs.

From this starting point, a protocol detailing each of the phases, specifying both the tasks and the working group members in charge of them, was developed. The main steps of the synthesis reflected in the protocol are:

1. Formulation of the question.
2. Search for research studies.
3. Selection of studies.
4. Data compilation and critical appraisal.
5. Primary Study quality evaluation.
6. Critical evaluation of the quality of MA/SR studies.

1. Formulation of the question

Reviewing the scientific literature searching for evidence requires proper definition of the research question and the creation of a logical structure to facilitate and increase the scope of the investigation. A standardized method to proceed to formulate that question is called the PICO strategy, with the acronym spelling out each of the terms that should be included in the question: Population; Intervention; Comparison and Outcome.

A well-structured (well-built) research question allows for the proper definition of what information (evidence) will be necessary to fulfil that aspect of the research[2,3], maximises the recovery of evidence in databases, focuses the purpose of the investigation, and avoids performing unnecessary searches.

In this paper, the PICO strategy has been used as a recognised method to guide the construction of the research question and the search for literature, allowing the research professional, despite their doubts or uncertainties, to locate the best scientific information available carefully and quickly.

The working group agreed upon the following research question:

Are workers at greater risk of suffering from lung cancer due to occupational exposure to silica dust/crystalline silica?

Using the PICO framework, each letter corresponds to:

P: Working population (active and post-employment).
I: Occupational exposure to silica.
C: No occupational exposure to silica.
O: Lung cancer (primary lung tumours).

[2] Flemming K. Critical appraisal. 2 Searchable questions. NT Learn Curve. 1999 Apr 7; 3(2): 6-7.

[3] Bernardo WM, Nobre MR, Jatene FB. Evidence-based clinical practice. Part II-Searching evidence databases. Rev Assoc Med Bras. 2004 Jan-Mar; 50(1): 104-8.

A working population with occupational exposure to silica dust/crystalline silica is defined as all those who, in the course of their occupational activities are or have been exposed to silica, and are active or retired.

This synthesis has not sought to establish the relationship between silicosis and lung cancer, or the existence of a diagnosis of silicosis as a step needed prior to developing lung cancer, but rather, has researched the necessary relationship between exposure to silica dust and the development of lung cancer, with or without the intermediate step of developing silicosis. The starting point is exposure to silica and the end point, lung cancer. This detail is very important when selecting MAs and SRs, as well as the primary studies included therein.

2. Search for research studies

With the help of the Health Technologies Assessment Agency (Agencia de Evaluación de Tecnologías Sanitarias, AETS), a specific search strategy was developed for each database, as shown in the annex *Search strategies and results*. All strategies shared a series of common elements, such as the keywords used (silica, silicon dioxide, lung neoplasm, occupational disease, occupational exposure) and the criteria established for both the date of publication of the document (after 1997) and the type of study to be found (MA/SR). The search was conducted without any language restrictions.
The following information sources were consulted: PubMed, Embase, CRD Database, DARE, Cochrane Library, CISDOC, WOK (Web Of Knowledge), NIOSHTIC 2, Up-to-date, Trip database, Scopus, NLM-Gateway, IBSST, IBECS, LILACS, Índice médico español [Spanish Medical Index], Clinical Evidence, Fisterrae, Excelencia clínica [Clinical Excellence], WHO-Health Evidence Network (HEN) and JBI Connect. In addition, specialised occupational health journals were searched, such as the IRSST (Institut de recherche Robert-Sauvé en santé et en sécurité du travail, [Robert-Sauvé Occupational Health and Safety Research Institute]) journal. Furthermore, the web pages of Health and Safety Institutes around the world, and other prestigious organisations, were consulted, such as IFA, IRSST, NIOSH, OSHA, HSE, INRS, INAIL, IOM; as well as silica industry-specific websites: Eurosil (www.eurosil.eu), NEPSI (www.nepsi.eu), RCS (www.crystallinesilica.eu), Sibelco (www.sibelco.com) and IMA-Europe (www.ima-europe.eu).

The last update to the search from among the various sources consulted was performed in July 2013.

After performing the global search, it was necessary to review all of the abstracts of the studies found to determine whether they really pertained to the research question. To aid in this determination, a series of inclusion and exclusion criteria for MA/SR studies had been pre-determined. These criteria are reflected in the following list:

Inclusion and exclusion criteria for MA and SR studies:

Inclusion criteria:

- Type of studies: MA and SR.
- Participants in the study: workers or retired workers exposed during their occupational activities to crystalline silica/silica dust.
- Time period: studies published from 1997 (publication of the IARC) to the present (deadline: July 2013).

Exclusion criteria:

- Not answering the question. Examples: other pathology, such as silicosis; no exposure to silica, etc.
- Type of study: study design other than an MA or SR. Literature reviews or narrative reviews were excluded.
- Subject: exposure not related to work.
- Documentary and bibliographic characteristics: references with no abstract; studies with conflicting results in the abstract and text, incomplete text, etc.

3. Selection of studies

Pre-selection Phase

Given the large number of participants collaborating on the project, two groups of multidisciplinary and homogeneous technicians carried out a pre-selection phase by reading the titles and abstracts resulting from the search.

Both groups reviewed all the abstracts and the discrepancies were resolved by a group of three people (extra group) in a collation or verification phase:

- Group A: LA, CC, OG, GG, AdG, AdV.
- Group B: CD, PH, MI, NL, CP and JR.
- Extra group: CD, AG, AdV.

Selection phase

In the selection phase, participants in group A and group B read the full text of each and every one of the pre-selected MA/SR studies. Each participant presented a list with their proposals for inclusion and exclusion. A common list was decided upon in each group, and then, one common to both groups, A and B. In case of discrepancies

between both groups, the extra group was the one to settle them in the collation phase.

4. Data compilation and critical appraisal

Once the MA and SR studies that would feed the evidence synthesis were selected, it was necessary to study the internal and external quality of the studies. There are several tools available to perform this task. The RICISST team decided, in drafting the protocol, to utilise OSTEBA's (Health Technologies Assessment Service of the Basque Government) tool for the critical appraisal of systematic reviews. This tool is available on a web platform so it is an easy method to manage for a group dispersed across the country. Each appraisal consists of several sections that ask about study characteristics: method, criteria for selection of studies, quality of studies included in the review, conflicts of interest, etc. The appraisal leads the reviewer to delve into the details of the study. Then, with the data that is compiled, evidence tables for each study are constructed.

An OSTEBA systematic review critical appraisal was filled out for each one of the MA/SR studies that had passed the selection phase (Annex *Date compilation and critical appraisal phase*).

At this stage, work was also performed in the same two groups, A and B, established for the article selection phase. First, each participant completed an appraisal for each SR and MA. Second, the participants of group A and group B met separately to discuss each of the questions on the appraisals until compiling a single final joint appraisal for each group. Then, two technicians (CD and AdV) processed the A and B appraisals, and developed a final appraisal with a single table of evidence for each study.

5. Primary Study quality evaluation

As already explained earlier in this report, this study was not intended to exclusively assess the MAs and SRs, but also to investigate the characteristics of the primary studies (PS) forming part thereof. Therefore, this evidence synthesis introduces a novelty compared to other syntheses, in evaluating the Primary Studies that feed the MAs/SRs. In other words, the methodology and the quality of primary research have been evaluated. For this, the literature of each SR/MA was referenced in order to collect the primary studies cited.

The objective of this phase was therefore, to assess the Primary Studies encompassed in the MAs/SRs selected. This quality rating was obtained by filling out a **check-list** specifically created by the working group for this synthesis, and relying heavily on templates for OSTEBA's critical appraisals of case-control studies and cohort studies

(Annex *Primary Study Quality Evaluation Phase*). The questions in the check-list allowed for a maximum rating of 10 points for each PS, as detailed in the Annex.

Four subgroups were formed to apply the check-lists to the Primary Studies included in the high OSTEBA quality MAs/SRs (Annex *Primary Study Quality Evaluation Phase*). In this way, a peer assessment was performed and the evaluation time was reduced. Each member completed a check-list for each PS in order to seek commonalities with the rest of the technicians in the subgroups with which they worked, in order to reach an agreement on a single check-list for each PS.

In cases in which there was no consensus among the subgroups, it was sent to the extra group (CD, AG and AdV) for resolution.

Also using the same check-list, two members of the working team (CD and AdV) analysed the Primary Studies that were only included in the OSTEBA average and low quality MAs/SRs (Annex *Primary Study Quality Evaluation Phase*). The objective of this analysis was to locate all the high quality Primary Studies from the lower quality MAs and SRs. The group considered that to collect and extract all the data from high quality primary research, it could not be guided solely by the methodological quality (OSTEBA) of SRs and MAs, but also by the quality of PSs. It could happen that, for various reasons (time prior to publication, inclusion and exclusion criteria or search strategies different from those established by this synthesis, etc.) there would be certain PS that would not have been taken into account for the authors of high OSTEBA quality MAs/SRs. Therefore, it was decided to include any PS scoring high on the quality check-list.

Once the quality of the PSs were assessed, the so-called **quality check-list** was scored for each of the selected MAs/SRs, determined by the quality of all the primary studies included in each MA/SR. To obtain a number indicative of this quality, the arithmetic mean formula was applied:

Check-list quality = Average score of all primary studies = Sum of the scores of the primary studies / Number of primary studies

Depending on the overall rating that was obtained, the MAs/SRs were grouped into three categories of check-list quality: low, average and high.

Low	0 - <4
Average	4 - <7
High	7 - 10

It is important to emphasise that this formula has an important limitation: if an SR/MA analyses a very small number of PSs, since the formula applied is an arithmetic mean,

the assessment of the quality of those PSs is weighed more heavily in comparison to other SRs/MAs that analyse a large number of PSs.

6. Critical evaluation of the quality of MA/SR studies

In order to generate an overall score for each MA/SR, it was deemed necessary to combine the two previous quality assessments. This was the objective of this phase: integrating the OSTEBA quality of the MA/SR and the check-list quality (assessment of the PSs) and to obtain an overall assessment of the quality, which was designated **RICISST quality.** To assign it, this matrix was referenced:

	High OSTEBA quality	**Average OSTEBA quality**	**Low OSTEBA quality**
High check-list quality	High Quality	Average Quality	Low Quality
Average check-list quality	Average Quality	Average Quality	Low Quality
Low check-list quality	Low Quality	Low Quality	Low Quality

This assessment procedure created by the working group arises from the need to use the highest quality evidence available, both in terms of the content analysed as well as the methodology applied. The systematic nature of the MAs/SRs is essential, as is having good quality primary studies that present an appropriate method and meet the established objectives. The overall rating of the quality enriches the results of the evidence synthesis since it involves a deeper knowledge of the MAs/SRs down to the details of the primary research performed.

The RICISST quality was also gathered in the tables, and allowed, together with other information collected, the assignment of a level of evidence to each MA/SR (Annex *Critical evaluation of the quality of studies phase*).

RESULTS

Search for research studies

In the first search of this evidence synthesis, 197 references were obtained, which ended up as 237 after the last update in July 2013. These data are reflected in the annex *Flowchart*.

Selection of studies

As a result of the pre-selection phase, 219 of the 237 references were eliminated. The primary reason for exclusion was the type of study: they were not MAs/SRs. Below, the remaining 18 references, named in the annex *Pre-selection and selection phases*, were

evaluated in full text in the selection phase. Of these, ten references were admitted, three rejected, and in the remaining five, discrepancies occurred. These latter (IARC, 2009; Birk, 2003; Gamble, 2011; Guha, 2011 and Hu, 2006) were analysed in depth by the extra group. Of these, only Birk, 2003 remained included. Therefore, of the 18 references that reached the selection phase, 7 were excluded for the following reasons:

- Study design other than an MA/SR. IARC, 2009; Gamble, 2011; Guha, 2011; Martínez, 2002. It is particularly important to emphasise that these excluded references, not being an MA/SR, are studies of great value and key to the matter in question, and though they have been considered in the preparation of this evidence synthesis, they did not fulfil the basic inclusion criteria for this review based on study design, and therefore did not pass the selection phase. Specifically, the report by the IARC, 2009 has been a fundamental document for the advancement of knowledge in relation to silica exposure and the development of lung cancer, which has impacted the course of research since that date, as is demonstrated by the fact that it is mentioned by a large number of the references studied.
- Existence of more updated documents from a later date originating from the same source: Bochmann, 2000; Bochmann, 2001 with respect to Birk, 2003. This was confirmed for the working group by the co-authors of the study themselves (BIA).
- Documentary and bibliographic characteristics: Hu, 2006. One of the fundamental requirements of this synthesis was to have the full text of the studies available. In this case, the text provided by the journal was incomplete, and despite the fact that the MA spoke of 27 studies included in its analysis, the bibliography only presented 9 references, for which it was not possible to reference the original studies that provided the primary data.

Data compilation and critical appraisal

The 11 MAs/SRs that were finally selected for inclusion in this evidence synthesis were: Birk, 2003; Checkoway, 2000; Erren, 2009; Erren, 2011; Finkelstein, 2000; Kurihara, 2004; Lacasse, 2005; Lacasse, 2009; Pelucchi, 2006; Steenland, 1997 and Steenland, 2001. For each of them an OSTEBA systematic review critical appraisal was completed, whose result is presented in the tables of evidence annex *Data compilation and critical appraisal phase*.

The evidence tables, along with the rest of the information collected, allow a first level of evidence to be granted for each MA/SR, which we call the **OSTEBA quality.**

It was observed that the 11 MAs/SRs selected presented very different OSTEBA quality ratings. The results are summarised in the following table:

MA/SR (short references)	Final OSTEBA quality rating (merged appraisals by groups A and B)
Birk, 2003	High
Kurihara, 2004	High
Lacasse, 2005	High
Lacasse, 2009	High
Checkoway, 2000	Average
Steenland, 2001	Average
Pelucchi, 2006	Average
Erren, 2009	Average
Erren, 2011	Average
Steenland, 1997	Low
Finkelstein, 2000	Low

Primary Study quality evaluation

Then, the quality of the PSs included in the 11 MAs/SRs was analysed by completing a **check-list** created by the working group for this synthesis. The four subgroups applied the check-lists to the PSs included in the SRs/MAs of high OSTEBA quality (Birk, 2003; Kurihara, 2004; Lacasse, 2005; Lacasse, 2009), and two members of the working team analysed the PSs that were only included in the MAs and SRs of average and low OSTEBA quality (Checkoway, 2000; Erren, 2009; Erren, 2011; Finkelstein, 2000; Pelucchi, 2006; Steenland, 1997 and Steenland, 2001) (Annex *Primary Study quality evaluation phase*).

Of a total of 74 PSs, 31 had a score on the check-list equal to or greater than 7, which indicated a high quality, and 43 scored lower than 7 (Annex *Primary Study quality evaluation phase*).

Check-list score	≥ 7	<7
No. of primary studies	31	43

Once the quality of the PS was evaluated, the **check-list quality** of the selected MAs/SRs was calculated. Two MAs/SRs obtained high quality ratings, and the remaining nine MAs/SRs, average quality. The check-list quality for each selected MA/SR is presented in the following table:

MA/SR (short references)	Evaluation of the quality check-list
Finkelstein, 2000	High (7.3)
Lacasse, 2009	High (7.0)
Birk, 2003	Average (6.6)
Lacasse, 2005	Average (6.6)
Steenland, 1997	Average (6.5)
Checkoway, 2000	Average (6.1)
Erren, 2009	Average (6.1)
Erren, 2011	Average (6.1)
Steenland, 2001	Average (6.0)
Pelucchi, 2006	Average (6.0)
Kurihara, 2004	Average (5.9)

As mentioned above, the formula that calculates the check-list quality presents a significant limitation when the SR/MA includes a very low number of PSs. This is the case of Finkelstein, 2000 which presents in its research three PSs with check-list scores equal to or greater than 7, which makes it obtain a score of 7.3 in the check-list quality.

Critical evaluation of the quality of MA/SR studies

The weakness arising from the check-list quality formula is resolved by combined evaluation of the PS quality (quality check-list) and the SR/MA methodology (OSTEBA quality), prioritising the latter in the final evaluation of the SR/MA, as reflected in the table below. The result of this combination is the **RICISST quality** which was also gathered in the evidence tables and allowed, together with the rest of the information compiled, the assignment of a level of evidence to each MA/SR (Annex *Critical evaluation of the quality of studies phase*).

RICISST quality result:

	High OSTEBA quality	Average OSTEBA quality	Low OSTEBA quality
High check-list quality	Lacasse, 2009		Finkelstein, 2000
Average check-list quality	Lacasse, 2005 Birk, 2003 Kurihara, 2004	Erren, 2009 Erren, 2011 Checkoway, 2000 Pelucchi, 2006 Steenland, 2001	Steenland, 1997
Low check-list quality			

Four of the eleven SRs/MAs (Birk, 2003; Kurihara, 2004; Lacasse, 2005 and Lacasse, 2009), shaded in green in the table above, met the criteria for high OSTEBA quality, and only one attained the category of high RICISST quality (Lacasse, 2009).

The following briefly describes these four SRs/MAs (Annex *Data compilation and critical appraisal phase* for more information):

Birk, 2003 analyses workers exposed to silica who perform their work in a variety of occupations and occupational sectors. It studies 78 articles, including a total of 35 cohorts. Similarly, it analyses the quality of the primary studies included in exhaustive detail. As a result of this search for high quality, the authors consider that only six of them were of adequate quality (Cherry, 1998; Hughes, 2001; Steenland, 2001; Steenland, 2001; Hnizdo, 1997, Checkoway, 1997 and Checkoway, 1999). They provide a good, detailed description of confounding factors and selective survival biases. They argue, moreover, that it is difficult to make comparisons between the exposure values estimated in the various primary studies, as they differ greatly both in quantity and quality, and also do not use a consistent method for measuring exposure to silica.

They conclude that, in general, high-quality studies included in the systematic review demonstrate an increased risk of lung cancer among groups of workers with higher exposure to crystalline silica, primarily if it is above the current exposure limits. They also note the potential influence of smoking and the presence of silicosis. However, another clear conclusion of this systematic review is that due to the lack of reliable data on exposure to crystalline silica, at the time of the publication of the SR, it is not possible to establish a threshold value below which there is no risk of developing lung cancer in exposed workers.

Kurihara, 2004 investigates the potential causality between silica exposure and silicosis, and between suffering from silicosis and developing lung cancer. It analyses a total of 30 studies. On the one hand, it studies the overall risk of lung cancer from

exposure to silica. This value, according to the authors, may be overestimated because some of the studies considered did not exclude workers with silicosis. On the other hand, it analyses the risk of lung cancer among workers with and without silicosis separately. The authors do not place special emphasis on the heterogeneity of the primary studies, in contrast to the rest of the SRs/MAs.

By measuring the risk of lung cancer among workers exposed to silica who have not developed silicosis, a Relative Risk (RR) of 0.96 is obtained with a 95% Confidence Interval (CI) between 0.81 and 1.15. However, when the analysis is done together with exposure to silica, whether suffering from silicosis or not, the RR increases to 1.32 (95% CI: 1.23-1.41). And this risk rises considerably when taking into account only workers with silicosis (RR: 2.37, 95% CI: 1.98-2.84). Therefore, the authors conclude that silicosis is a risk factor for lung cancer. They also consider that there is a small risk of lung cancer in subjects exposed to silica. The authors also reflect on the importance of smoking as enhancing the risk of developing lung cancer among workers with silicosis. All these data make them suggest that crystalline silica can induce lung cancer indirectly.

Lacasse, 2005 examines the relationship between workers with silica exposure and lung cancer, as well as that between those suffering from silicosis and the development of lung cancer. It includes 8 studies on the relationship between silica and lung cancer, and 32 studies on the relationship between silicosis and lung cancer. An important characteristic of this study is that it provides effect data based on the concentrations of silica exposure in mg/m^3*year, with the idea of performing dose-response analysis.

Of the eight studies involving this evidence, four of them considered a latency period of 15 years (Hughes, 2001; Steenland, 2001; Checkoway, 1997 and Attfield, 2004) and four did not (Ulm, 1999; Bruske-Hohlfeld, 2000; Cocco, 2001 and Westeberg, 2003). The authors state that there is a high heterogeneity between the PSs included in the review, and also reflect on the lack of adjustment of the results for smoking in any of the PSs, making it difficult to draw clear conclusions.

Lacasse, 2005 determined that for each unit of silica exposure (in mg/m^3*year), the risk of lung cancer is RR: 1.08 with a 95% CI: 1.02-1.15, such that for each unit of silica exposure, the risk of lung cancer increases by 8%. Additionally, when considering a latency period of fifteen years, the RR increased slightly to 1.15 with a 95% CI between 1.10 and 1.20. Or similarly, for each unit of silica exposure, the risk of lung cancer increases by 15%.

The authors conclude that there is a weak dose-response relationship between silica exposure and the risk of lung cancer. They also consider that occupational exposure to

silica represents a low risk factor for developing lung cancer, even at high exposure levels above the allowable limits.

Lacasse, 2009 is the only SR/MA that obtained a high RICISST quality score in this evidence synthesis, in addition to a high OSTEBA quality, which implies that the PSs included in this SR obtained good check-list scores. The objective of this SR/MA was to examine the association between occupational exposure to silica and the development of lung cancer, with special emphasis on the methodological quality of observational studies. The authorship analysed ten studies: four cohort and six case-control. It also represents the concentration of silica in mg/m^3 in order to conduct a dose-response analysis, without a latency period. The heterogeneity between studies is emphasised.

Lacasse, 2009 presents results at two levels of crystalline silica exposure. When the silica level is at 1 mg/m^3 each year, the RR is 1.22, with a 95% CI between 1.01 and 1.47. And at a concentration greater than 6 mg/m^3 per year, the RR increases to 1.84 with a 95% CI between 1.48 and 2.28. The authors conclude that there is a relationship between exposure to silica and lung cancer development above a threshold level of 1.84 mg/m^3*year. Similarly, they discuss that the PSs present a wide range of exposures to silica and that silicosis acts as a confounding factor that can not be evaluated completely.

To summarise the quality of evidence for these four SRs/MAs, as extracted from the OSTEBA tool, the following should be highlighted: the clarity with which the questions are defined, a well-described and appropriate methodology, conclusions that are justified and useful, as well as results that are correctly synthesised, described, and generalisable to the population and the context. Furthermore, these results are free of influences arising from conflicts of interest, except in the case of Birk, 2003 where the parameters relating to this aspect were unable to be studied due to a lack of information.

DISCUSSION

In 1997, in monograph volume 68, the IARC classified silica as carcinogenic in humans. This decision generates a lot of controversy within the scientific community and many studies appear related to exposure to silica, which in turn give rise to many questions regarding both the carcinogenicity of silica as well as the methodology used in the studies.

Between 2003 and 2005 a series of systematic reviews and meta-analyses were published that echoed the disputes surrounding the relationship between exposure to

silica and lung cancer. Those questions attempt to be answered by the SRs/MAs included in this evidence synthesis.

Kurihara, 2004 in Japan, based on studies published until 2001, estimates the magnitude of the relationship between exposure to silica and lung cancer. To do so, 30 studies were selected, 17 cohort and 13 case-control, and a meta-analysis was performed with their results. It considers that all those exposed to silica have a 32% higher risk of developing lung cancer than those not exposed. This data supports the conclusion of the IARC, providing a quantification of risk, but does not provide a dose-response gradient that would contribute to strengthening it as causation criteria.

In this same period, Birk, 2003 in Germany and Lacasse, 2005 in Canada, including more recent evidence, until 2004, take a step further and address the issue of quantifying the dose-response relationship of the association between silica exposure and lung cancer from different perspectives. Birk, 2003 focuses on key methodological issues such as the evaluation of exposure to silica in the existing evidence and the methodological rigour of those studies published before 2004. On the other hand, Lacasse, 2005 prioritises the possibility of a meta-analysis, seeking to quantify the dose-response relationship based on published evidence. In this sense, according to their inclusion criteria, they only include studies in which the exposure is in the form of mg/m^3*year, being less stringent about the quality of any of the included studies.

Birk, 2003 indicates that the lack of reliable data on exposure to crystalline silica prevents the establishment of a threshold value below which there is no risk of developing lung cancer. The study further considers that, for the sake of thoroughness, a systematic and careful review of the evidence shows that the number of studies that demonstrate sufficient quality to address this issue is reduced. It argues that the main problem of the studies conducted to date is in the exposure assessment, given the absence of measurements of silica concentrations and the variety of assessment methods for them. Given the historical lack of measurements, especially in times when the exposure was predictably higher, judgements and extrapolations were made from data derived from different types of measurements and analytical methods, such that the estimate of exposure contains many uncertainties and could be distant from the actual values. Over time, the total powder, respirable fraction, and the silica content in powder have been measured, and various measurement methods have been used, so that comparisons between the levels estimated for different studies might not be valid. For cumulative exposures, the data from the extrapolated estimates are summed for each time period, with the risk of multiplying the estimation errors. The study claims, therefore, that the relative risk estimates based on these assessments of exposure should be interpreted with caution and, therefore, cannot be used to quantify risk.

Despite these limitations and based on a qualitative systematic review, it considers that high quality studies indicate an excess risk among the most exposed groups, both

when discussing cumulative exposures as well as average exposures. It concludes affirming that there is a higher risk of lung cancer among groups of workers with high exposure to crystalline silica, estimating that it would be found above the limits of current exposure. However, it indicates that with the data available, it is not possible to establish a threshold value below which there is no risk of developing lung cancer.

Lacasse, 2005, unlike Birk, 2003, considers that it is possible to quantify the dose-response relationship between silica exposure and lung cancer. For this, the study draws exclusively from those studies that include a quantitative estimate of silica exposure in terms of mg/m^3*year, as it is understood that studies in which exposure is not quantified do not provide information regarding the real risk of this exposure and do not allow for comparison between them. Lacasse, 2005, therefore, includes in its search observational studies (case-control or cohort) that report a dose-response analysis of the relationship between the occupational exposure to silica and the risk of lung cancer. To avoid confounding bias, it excludes studies involving concomitant exposures to that of silica, such as arsenic, uranium or radon, unless the outcome has been adjusted for these factors. It also excludes autopsy studies to avoid selection bias. It finally selected 8 studies. In this meta-analysis, results of cohort and case-control studies are combined, based on the fact that the small number of events allows the measurements of effect to take on similar values (RR for cohort and OR for case-control). The authors assume a linear relationship between log (RR) and the level of exposure and build a linear regression model for each study, taking for each exposure interval a value that will generally be the midpoint of the interval. The slope of the lines that are obtained show how the risk of developing cancer increases when exposure increases 1 mg/m^3*year. Finally, a meta-analysis is conducted of the slopes calculated for each study, obtaining the combined measure of how much the risk increases as a function of increasing exposure. Lacasse, 2005 indicates that their results are consistent with those published in Steenland, 2001 in their combined analysis of 10 cohorts exposed to silica and concludes that occupational exposure to silica represents a low risk factor for the development of lung cancer, even at high exposure levels above the allowable limits. The authors suggest that these results should be interpreted with caution due to the heterogeneity of the studies analysed.

These authors in 2009, aware, like Birk, 2003, that their results do not allow for the establishment of a threshold of exposure from which a dose-response relationship is established, conducted a new meta-analysis, which updates the previous one and tries to answer this last question. This meta-analysis (Lacasse, 2009) includes 5 studies published after the 2005 one was conducted, with similar inclusion criteria. However, this time the authors do not assume that the relationship between log (RR) and the exposure level is linear. They apply a more complex and flexible regression model, in which the data from all studies are used directly, leading to a common curve relating the relative risk of lung cancer to exposure.

Comparing the results of the two studies, some discrepancies are observed regarding the risk of cancer, with much greater risk calculated in the meta-analysis of 2009, both for low as well as high exposures. The authors do not analyse the differences, nor do they clarify whether these are due to the introduction of new studies, or to different approach to the nature, linear or not, of the relationship between exposure and cancer risk.

In any case, the authors again warn that the interpretation of this second meta-analysis is conditioned by the heterogeneity existing among the included studies, the wide range of exposure to silica reported by these studies, and the confounding effect of silicosis, which could not be fully evaluated.

The approach of this synthesis is to assess the evidence upon which each of the four analysed studies have based their results and conclusions, despite the different approaches. In order to recover the maximum possible evidence, both primary studies (PSs) belonging to the selected MAs/SRs as well as those included in those of average and low OSTEBA quality have undergone a quality assessment. The result has been the selection of 31 articles considered to be of high quality, analysed in the evidence tables (*Characteristics of high quality primary studies)*.

On the other hand, from the quantitative point of view, the possibility has been considered of performing a new meta-analysis using the PSs that would allow it, provided this lends to new findings for the conclusions already set forth in the selected MAs/SRs

This hypothetical meta-analysis would coincide with the one conducted by Lacasse, 2009, except for four studies included by that study and that based on the criteria established here should not be taken into account. Three of them do not score high on the quality check-list (Westberg, 2003; Bruske-Hohlfeld, 2000 and Steenland, 2001) and the fourth, Ulm, 1999, presents weaknesses that made it be eliminated from reanalysis. To know whether the exclusion of these four studies would alter the results of Lacasse, 2009, they have been analysed and compared.

The study Westberg, 2003 provides results from very low exposures and has very wide confidence intervals. Given that the weight of a study in a meta-analysis is measured by the inverse of the variance, its contribution is very small, and its exclusion is unlikely to alter the results. The studies of Bruske-Hohlfeld, 2000 and Steenland, 2001, demonstrate very similar results to those achieved by the aggregation of data. It is unlikely that their exclusion, based on methodological quality criteria, would vary the quantitative results, however, adding rigour to the findings, given the score obtained on the check-list. The only study that could affect the results, in this case lowering the risk estimate, would be that conducted by Ulm, 1999, which concludes that there is no relationship between exposure to silica and lung cancer, but which has certain

weaknesses, such as the fact that the exposure is the same for cases and controls, and there is no consideration of smoking in the subgroup analysis.

Therefore, in principle, it does not seem necessary to make a new attempt in this direction.

CONCLUSIONS

Systematic reviews of the scientific literature and higher quality meta-analyses published until today unanimously accepted the existence of a relationship between exposure to silica and lung cancer. Nevertheless, there are differences between the studies from both the methodological point of view and from the evidence base on which each stands.

This review adds new evidence provided by Birk, 2003; reinforcing the conclusions that these authors reached, i.e., that a good part of the studies indicate an excess risk among the most exposed, both when discussing cumulative exposures as well as average exposures, demonstrating that there is an increased risk of lung cancer in groups of workers with high exposure to crystalline silica and estimating that it would be found above the current exposure limits. It also coincides with the findings of Lacasse, 2009, the only study categorised as having high OSTEBA methodological quality and high PS quality, with regards to the increased risk of lung cancer associated with cumulative exposure to silica and the fact that the evidence seems to favour the existence of an exposure threshold.

Therefore, with this evidence synthesis, it is concluded that there is a relationship between occupational exposure to silica and the development of lung cancer. Although it is evident that at higher concentrations of silica there is an increased risk of lung cancer, it is not the aim of this working group to establish an exposure threshold at which the risk is greater.

Finally, in view of the data, and taking into account that the estimation of cumulative exposure that takes place in many of the studies contains many uncertainties, we conclude that performing a new meta-analysis with the studies that we have available today would not provide more certainty about the relationship between silica exposure and lung cancer at this time, nor would it provide a better estimate of the relationship between the dose of silica exposure and the risk of developing this cancer.

STATEMENT OF CONFLICTS OF INTEREST

The authors declare that no conflict of interest exists, whether economic or personal, related to the subject matter of this report.

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Smailyte, 2004. Smailyte G, Kurtinaitis J, Andersen A. Mortality and cancer incidence among Lithuanian cement producing workers. Occup Environ Med. 2004; 61(6): 529-34.

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Stone, 2004. Stone RA, Youk AO, Marsh GM, Buchanich JM, Smith TJ. Historical cohort study of U.S. man-made vitreous fiber production workers IX: summary of 1992 mortality follow up and analysis of respiratory system cancer among female workers. J Occup Environ Med. 2004; 46(1): 55-67.

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Winter, 1990. Winter P, Gardner M, Fletcher A, Jones R. A mortality follow-up study of pottery workers: preliminary findings on lung cancer. IARC Sci Publ. 1990; 97: 83-94.

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Cocco P. Silica and lung cancer: state of the art, practical implications and future research. Foreword. Med Lav. 2011 Jul-Aug; 102(4): 307-9.

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Mannetje A, Steenland K, Chekoway H, Kosjela RE, Koponen M, Attfield M et al. Development of quantitative exposure data for a pooled exposure-response analysis of 10 silica cohorts. Am J Ind Med. 2002; 42(2): 73-86.

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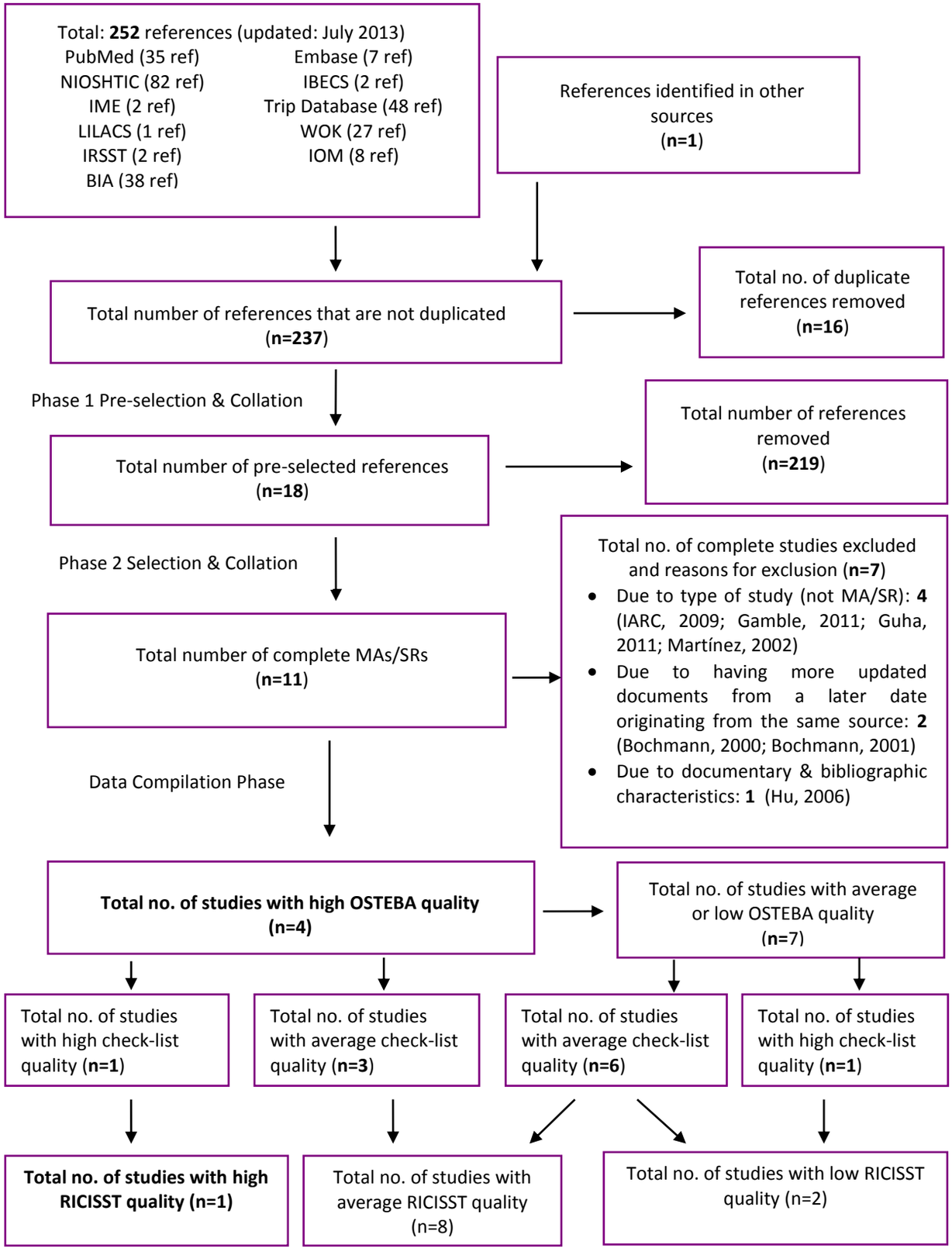
ANNEXES REGARDING RESEARCH STEPS

Annex: Flow Diagram



Annex: Search Strategies and Results

Keywords used: *silica, silicon dioxide, lung neoplasm, occupational disease, occcupational exposure*.
Search restrictions: publication date (since 1997) and document type (MA/SR).
Legend of search strategies: / (descriptor), TIAB (title and abstract), * (truncation), PDAT (publication date), AF (all fields), TI (title).

PubMed specific search strategy:

Total References: 35 (last updated 10/07/2013)

Embase specific search strategy:

Total References: 7 (last updated 08/07/2013)

WOK specific search strategy:

Total References: 27 (last updated 14/07/2013)

NIOSHTIC specific search strategy:

Total References: 82 (last updated 10/07/2013)

Trip database specific search strategy:

Total References: 48 (last updated 10/07/2013)

IBECS and LILACS specific search strategy:

1. Silicon dioxide/
2. Pulmonary neoplasms/

Total References: 2 in IBECS, 1 in LILACS (last updated 10/07/2013)

Spanish Medical Index specific search strategy

1. Silica. TI
2. Lung cancer. TI

Total References: 2 (last updated 10/07/2013)

IOM (Institute of Occupational Medicine) specific search strategy

Lung cancer (keywords)

Subject matter: Quartz and silicosis

Total References: 8 (last updated 10/07/2013)

Annex: Pre-selection and Selection Phases

Pre-selection Phase:
Of the 237 references obtained as a result in the last search, only 18 passed the pre-selection phase:

1. Birk T, Burch MT, Mundt KA. Quality based critical review (QBCR) of the epidemiological literature on silica, silicosis, tobacco smoking and lung cancer. Sankt Augustin: Hauptverband der gewerblichen Berufsgenossenschaften; 2003.

2. Bochmann F. Quartz, silicosis and lung cancer: meta-analysis of epidemiological studies. En: 15th Symposium on Epidemiology (EPICOH); Copenhagen 2001.

3. Bochmann F, Nold A, Arndt V. Quartz und Lungenkrebs. Zusammenfassung epidemiologischer Studien. Die BG. 2000; 12: 702-8.

4. Checkoway-H, Franzblau-A. Is silicosis required for silica-associated lung cancer? Am J Ind Med. 2000; 37(3): 252-9.

5. Erren TC, Glende CB, Morfeld P, Piekarski C. Is exposure to silica associated with lung cancer in the absence of silicosis? A meta-analytical approach to an important public health question. Int Arch Occup Environ Health. 2009; 82(8): 997-1004.

6. Erren TC, Morfeld P, Glende CB, Piekarski C, Cocco P. Meta-analyses of published epidemiological studies, 1979-2006, point to open causal questions in silica-silicosis-lung cancer research. Med Lav. 2011; 102(4): 321-35.

7. Finkelstein M. Silica, silicosis, and lung cancer: A risk assessment. Am J Ind Med. 2000; 38(1): 8-18.

8. Gamble JF. Crystalline silica and lung cancer: a critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis. Crit Rev Toxicol. 2011; 41(5): 404–65.

9. Guha N, Straif K, Benbrahim-Tallaa L. The IARC Monographs on the carcinogenicity of crystalline silica. Med Lav. 2011; 102(4): 310-20.

10. Hu JF, Qu H, Wang JZ. Meta analysis for relationship between exposure of free silicon dioxide and lung tumor. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2006; 24(7): 415-7.

11. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (vol 100C): Silica dust, crystalline (quartz or crystobalite). Lyon: IARC; 2009.

12. Kurihara N, Wada O. Silicosis and smoking strongly increase lung cancer risk in silica-exposed workers. Ind Health. 2004 Jul; 42(3): 303-14.

13. Lacasse Y, Martin S, Desmeules M. Silicose, silice et cancer du poumon: méta-analyse de la littérature médicale. Québec: Institut de recherche Robert-Sauvé en santé et en sécurité du travail; 2005.

14. Lacasse Y, Martin S, Gagné D, Lakhal L. Dose-response meta-analysis of silica and lung cancer. Cancer Causes Control. 2009; 20(6): 925-33.

15. Martínez González C, Rego Fernández G. Inhalación de sílice y cáncer de pulmón. Revisión de la evidencia. Arch bronconeumol. 2002; 38(1): 33-6.

16. Pelucchi C, Pira E, Piolatto G, Coggiola M, Carta P, La Vecchia C. Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996-2005. Ann Oncol. 2006; 17(7): 1039-50.

17. Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes and Control. 1997; 8(3): 491-503.

18. Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. Cancer Causes Control. 2001; 12(9): 773-84.

In addition, this reference was retained as a supplementary reading document: Mannetje, 2002 (Mannetje A, Steenland K, Chekoway H, Kosjela RE, Koponen M, Attfield M et al. Development of quantitative exposure data for a pooled exposure-response analysis of 10 silica cohorts. Am J Ind Med. 2002; 42(2): 73-86), as it may be of interest to understanding Steenland, 2001.

Selection phase

Of the 18 references that reached the selection phase, a total of 11 MAs/SRs proceeded.

Below are listed the 7 short references for the studies excluded in the selection phase, grouped by grounds for exclusion:

- For a study design other than an MA/SR. **4** (IARC, 2009; Gamble, 2011; Guha, 2011; Martínez, 2002).
- For more updated documents from a later date originating from the same source (BIA): **2** (Bochmann, 2000; Bochmann, 2001).
- For documentary and bibliographic characteristics: the text provided by the journal was incomplete, and despite the fact that the MA spoke of 27 studies included in its analysis, the bibliography only presented 9 references, for which it was not possible to reference the original studies that provided the primary data: **1** (Hu, 2006).

The 11 MAs/SRs that were finally decided to be included in the evidence synthesis are:

1. Birk T, Burch MT, Mundt KA. Quality based critical review (QBCR) of the epidemiological literature on silica, silicosis, tobacco smoking and lung cancer. Sankt Augustin: Hauptverband der gewerblichen Berufsgenossenschaften; 2003.
2. Checkoway-H, Franzblau-A. Is silicosis required for silica-associated lung cancer? Am J Ind Med. 2000; 37(3): 252-9.
3. Erren TC, Glende CB, Morfeld P, Piekarski C. Is exposure to silica associated with lung cancer in the absence of silicosis? A meta-analytical approach to an important public health question. Int Arch Occup Environ Health. 2009; 82(8): 997-1004.
4. Erren TC, Morfeld P, Glende CB, Piekarski C, Cocco P. Meta-analyses of published epidemiological studies, 1979-2006, point to open causal questions in silica-silicosis-lung cancer research. Med Lav. 2011; 102(4): 321-35.
5. Finkelstein M. Silica, silicosis, and lung cancer: A risk assessment. Am J Ind Med. 2000; 38(1): 8-18.
6. Kurihara N, Wada O. Silicosis and smoking strongly increase lung cancer risk in silica-exposed workers. Ind Health. 2004 Jul; 42(3): 303-14.
7. Lacasse Y, Martin S, Desmeules M. Silicose, silice et cancer du poumon: méta-analyse de la littérature médicale. Québec: Institut de recherche Robert-Sauvé en santé et en sécurité du travail; 2005.
8. Lacasse Y, Martin S, Gagné D, Lakhal L. Dose-response meta-analysis of silica and lung cancer. Cancer Causes Control. 2009; 20(6): 925-33.

9. Pelucchi C, Pira E, Piolatto G, Coggiola M, Carta P, La Vecchia C. Occupational silica exposure and lung cancer risk: a review of epidemiological studies 1996-2005. Ann Oncol. 2006; 17(7): 1039-50.
10. Steenland K, Stayner L. Silica, asbestos, man-made mineral fibers, and cancer. Cancer Causes and Control. 1997; 8(3): 491-503.
11. Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, et al. Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multicentre study. Cancer Causes Control. 2001; 12(9): 773-84

Annex: Data Compilation and Critical Appraisal Phase

This annex presents, first, the template used for the critical appraisal of systematic reviews and then, OSTEBA evidence tables for the 11 MAs/SRs that passed the selection phase. These tables are the result of the merger of those produced by groups A and B during the months of June and July 2012.

Systematic review
Subject:
Created by:

1. REFERENCE

Bibliographic citation
Abbreviated citation

2. STUDY

Objectives
Search period
Participating entities

3. REVIEWER(S)

Name(s)
Date

4. RESEARCH QUESTION

- Is the study population adequately defined? Yes ☐ No ☐ Do Not Know ☐
- Is/are the study intervention(s) adequately defined? Yes ☐ No ☐ Do Not Know ☐
- Is the comparison intervention adequately defined? Yes ☐ No ☐ Do Not Know ☐
- Are the outcome measures adequately defined? Yes ☐ No ☐ Do Not Know ☐

The review is based on a clearly defined clinical question
Very good ☐ Good ☐ Fair ☐ Poor ☐

5. METHOD

5.1. SELECTION CRITERIA

- Is the type of design of the studies included in the review indicated? Yes ☐ No ☐ Do Not Know ☐
- Was the appropriate type of design chosen? Yes ☐ No ☐ Do Not Know ☐
- Aside from the design of the studies, are other inclusion criteria mentioned? Yes ☐ No ☐ Do Not Know ☐
- Are exclusion criteria mentioned? Yes ☐ No ☐ Do Not Know ☐
- In summary, are the inclusion and exclusion criteria adequate to answer the question? Yes ☐ No ☐ Do Not Know ☐

5.2 LITERATURE SEARCH

- Is the search strategy described in detail? Yes ☐ No ☐ Do Not Know ☐
- Are the search restrictions justified? Yes ☐ No ☐ Do Not Know ☐
- Are the sources from which the information was sought described? Yes ☐ No ☐ Do Not Know ☐
- Are the criteria for the selection of sources identified? Yes ☐ No ☐ Do Not Know ☐
- Do you think that information biases may have been produced? Yes ☐ No ☐ Do Not Know ☐
- Is a reverse lookup performed? Yes ☐ No ☐ Do Not Know ☐
- Is a manual search conducted in key journals? Yes ☐ No ☐ Do Not Know ☐

Overall, is the literature search sufficiently exhaustive and rigorous? Yes ☐ No ☐ Do Not Know ☐

5.3. QUALITY OF STUDIES

- Is the method employed for evaluating the quality of the studies described? Yes ☐ No ☐ Do Not Know ☐

Overall, are the qualities of the studies evaluated appropriately? Yes ☐ No ☐ Do Not Know ☐

5.4. DATA EXTRACTION

- Is there some form used for data extraction? Yes ☐ No ☐ Do Not Know ☐
- Is information regarding the intervention and the results extracted clearly for all the subjects and relevant groups? Yes ☐ No ☐ Do Not Know ☐
- Is the number of reviewers mentioned? Yes ☐ No ☐ Do Not Know ☐

Overall, is the data extraction carried out rigorously? Yes ☐ No ☐ Do Not Know ☐

The methodology used for the selection and evaluation of the individual studies is well-described and is suitable:

Very good ☐ Good ☐ Fair ☐ Poor ☐

6. RESULTS

6.1. RESULTS OF THE SEARCH AND SELECTION PROCESS

- Is the number of studies and patients/participants included in the evaluated systematic review indicated? Yes ☐ No ☐ Do Not Know ☐
- Are the qualities of studies included in the review evaluated? In the event that the quality of the studies is evaluated, record the relevant results Yes ☐ No ☐ Do Not Know ☐
- Are the data from studies included in the review well-described? Yes ☐ No ☐ Do Not Know ☐

6.2. EVIDENCE SYNTHESIS

- In the systematic review evaluated, is possible publication bias considered? Yes ☐ No ☐ Do Not Know ☐

- Is possible heterogeneity between studies combined in the Systematic Review or Meta-Analysis taken into account? Yes ☐ No ☐ Do Not Know ☐

6.3. CLINICAL RESULTS OF THE SYSTEMATIC REVIEW EVALUATED

- Is the accuracy of the clinical results analysed in the review indicated? Yes ☐ No ☐ Do Not Know ☐
- Is the magnitude of the effect of the clinical results analysed in the review well-described? Record the results. Yes ☐ No ☐ Do Not Know ☐

Are the results of the evaluated systematic review correctly synthesised and described?

Very good ☐ Good ☐ Fair ☐ Poor ☐

7. CONCLUSIONS

- Do the conclusions provide answers to the study objectives? Yes ☐ No ☐ Do Not Know ☐
- Are the conclusions presented based on the results obtained? Yes ☐ No ☐ Do Not Know ☐

The conclusions are justified and useful: Very good ☐ Good ☐ Fair ☐ Poor ☐

8. CONFLICTS OF INTEREST

- Is the funding source mentioned? Yes ☐ No ☐ Do Not Know ☐
- Do the authors declare the existence or absence of any conflict of interest? Yes ☐ No ☐ Do Not Know ☐

The results and conclusions are free of influences arising from conflicts of interest:

Very good ☐ Good ☐ Fair ☐ Poor ☐

9. EXTERNAL VALIDITY

The results of the review are generalisable to the population and context of interest:

Very good ☐ Good ☐ Fair ☐ Poor ☐

10. QUALITY OF THE EVIDENCE

This is a summary of what has been answered so far:

RESEARCH QUESTION: The review is based on a clearly defined clinical question.
Very good ☐ Good ☐ Fair ☐ Poor ☐
METHOD: The methodology used for the selection and evaluation of the individual studies is well-described and is suitable.
Very good ☐ Good ☐ Fair ☐ Poor ☐
RESULTS: Are the results of the evaluated systematic review correctly synthesised and described?
Very good ☐ Good ☐ Fair ☐ Poor ☐
CONCLUSIONS: The conclusions are justified and useful:
Very good ☐ Good ☐ Fair ☐ Poor ☐
CONFLICTS OF INTEREST: The results and conclusions are free of influences arising from conflicts of interest:
Very good ☐ Good ☐ Fair ☐ Poor ☐
EXTERNAL VALIDITY: The results of the review are generalisable to the population and context of interest.
Very good ☐ Good ☐ Fair ☐ Poor ☐

Taking into account your answers in the 6 areas shown on this screen, rate the quality of the evidence provided by the study you have analysed. As a guide, consider the following suggestions:

	Good method	Average method	Poor method
Rest of criteria Good	High Quality	Average Quality	Low Quality
Rest of criteria Average	Average Quality	Average Quality	Low Quality
Rest of criteria Poor	Low Quality	Low Quality	Low Quality

QUALITY OF THE EVIDENCE

Record your comments on the critical appraisal

SR/MA of high OSTEBA quality

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Birk, 2003	**Objectives:** The goal of this study is to conduct a quality-based critical review (QBCR) of the existing epidemiological literature on silica, silicosis, smoking and lung cancer, focusing on and reviewing in depth a subset of the available literature that meets several quality criteria. **Search period:** 01/1995-12/2002	**Population:** Workers grouped in the following industrial activities: pottery/ceramics, refractory brick, foundry/steel, silicon carbide, mining, industrial sand and diatomaceous earth. Three additional studies are not encompassed by any of these groups of activity. 35 cohorts originating from 78 selected documents are defined.	**Intervention:** Exposure to silica.	**Comparison:** Not applicable.	**Number of studies and patients:** 78 articles included, representing 35 cohorts. The number of participants for each study is indicated in the tables. **Effect size:** The risk of lung cancer is only presented from studies rated as relevant due to adequate quality.	**Conclusions:** According to the authors, in general, the high quality studies analysed show a greater risk of lung cancer in groups with greater exposure to silica, taking into account the potential influence of smoking and the presence of silicosis. However, due to the lack of reliable data on exposure to crystalline silica in the studies analysed, it is not possible to establish an exposure limit value.	**Comments:** The authors perform an exhaustive assessment of the quality of primary articles. The risk of lung cancer is only presented from studies rated as relevant due to adequate quality. For this reason, the conclusions do not exactly fit to that sought. This study provides a good, detailed description of confounding factors and selective survival bias. Given that the exposures in the studies considered are based on different data, both in quality and in quantity and often, using different methods (including assumptions for situations of unknown exposure), the authors consider that comparisons between estimated exposure values are likely to be invalid. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest.	**OSTEBA Quality:** High

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Kurihara, 2004	**Objectives:** Investigate whether crystalline silica and silicosis increase the risk of lung cancer, through the summary of epidemiological reports by meta-analysis. **Search period:** 01/1966 - 10/2001	**Population:** Working population with and without silicosis.	**Intervention:** Exposure to silica.	**Comparison:** Not applicable.	**Number of studies and patients:** A total of 30 studies. Specifically, to study the risk of lung cancer among subjects without silicosis exposed to silica, 6 cohort studies and 2 case-control studies were selected. The number of participants in each study is detailed. **Effect size:** The combined RR of developing lung cancer was: 0.96 (95% CI: 0.81-1.15) for non-silicotic subjects with exposure to silica; 1.32 (95% CI: 1.23-1.41) for silica exposure and 2.37 (95% CI: 1.98-2.84) for silicosis.	**Conclusions:** According to the authors, the study reveals that silicosis is a risk factor for lung cancer. A small risk of lung cancer in subjects exposed to silica (including silicotic subjects) is also observed. This suggests that crystalline silica indirectly induces lung cancer in humans. Further analysis shows that smoking greatly increases the risk of lung cancer among silicotic subjects.	**Comments:** There is some doubt raised as to the quality of the individual studies. Some studies regarding silica and lung cancer do not exclude silicotic patients, so the overall RR could be lower than 1.32. It raises an interesting discussion about whether the carcinogenic effect is due to exposure to silica or due to silica-induced silicosis. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	**OSTEBA Quality:** High

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Lacasse, 2005	**Objectives:** This study examined the association between silicosis and lung cancer in a systematic review (and meta-analysis) of the epidemiological literature, with special reference to the methodological quality of observational studies. **Search period:** 01/1966 - 05/2004	**Population:** Working population.	**Intervention:** Exposure to different concentrations of silica (quantified exposure, mg/m^3 *year).	**Comparison:** Not applicable.	**Number of studies and patients:** 32 studies included in the part regarding silicosis-lung cancer. In the part on silica exposure-lung cancer: 8 studies included (4 of them consider a latency period of 13-15 years in the association of measures of calculation). The number of participants in each study is also detailed (Table 8) **Effect size:** For exposure-cancer: For each unit of silica exposure (in mg/m^3 * year), the risk of lung cancer is: RR=1.08; 95% CI: 1.02-1.15; and for a dose-response analysis with a latency period of 15 years the RR = 1.15; 95% CI 1.10-1.20. Exposure levels are high.	**Conclusions:** There is a weak dose-response relationship between silica exposure and the risk of lung cancer. The authors conclude that the data published to date suggest that occupational exposure to silica represents a low risk factor for developing lung cancer at exposure levels exceeding exposure limits permitted according to North American standards. The interpretation of these results is limited due to the heterogeneity of the results of the studies analysed in the MA. These conclusions, other than some nuances, agree with those of the IARC.	**Comments:** Comprehensive study. This MA explains several important aspects of the studies considered, including their heterogeneity, their conflicting results, the lack of adjustment for smoking in certain instances. It performs two analyses of the silica exposure-lung cancer relationship: without latency and with 15 years of latency. The interpretation of these results is limited due to the heterogeneity of the studies. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	**OSTEBA Quality:** High

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Lacasse, 2009	**Objectives:** To examine the association between occupational exposure to silica and lung cancer from a systematic review (and meta-analysis) of the epidemiological literature, with special reference to the methodological quality of observational studies. **Search period:** 01/1966 - 12/2007	**Population:** Working population.	**Intervention:** Exposure to different concentrations of silica (quantified exposure, mg/m^3 * year).	**Comparison:** Not applicable.	**Number of studies and patients:** 10 studies. The number of participants in each study is also detailed. **Effect size:** There is an exposure-response relationship between exposure to silica and lung cancer upon exceeding the level of 1.84 mg/m^3 * year. If two levels of exposure are considered, for example, x_1= 1.0 mg/m^3*year and x_2= 6 mg/m^3*year, the RRs are 1.22 (1.01-1.47) and 1.84 (1.48-2.28), respectively. The meta-analysis of 6 studies with cumulative exposures to silica with a latency of 10-20 years provides similar results.	**Conclusions:** The results of the study indicate that there is a relationship between exposure to silica and lung cancer development above a threshold level of 1.84 mg/m^3*year. However, the interpretation is limited by the wide range of exposures to respirable silica in the original studies, the heterogeneity between studies, and the confounding effect of silicosis, which cannot be fully assessed.	**Comments:** Only two studies excluded subjects with silicosis. Since silicosis is a risk factor for lung cancer, this may overestimate the association between silica exposure and lung cancer. The magnitude of this error is unknown, since the proportion of silicotic subjects among those exposed to silica is unknown. The results are not presented clearly. The RR CI confidence levels are not specified. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	**OSTEBA Quality:** High

SR/MA of average and low OSTEBA quality

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Checkoway, 2000	**Objectives:** To review relevant epidemiological literature bearing on the question "Is silicosis required for elevated lung cancer risk? To Indicate how uncertainties in medical techniques for detecting silicosis, accompanied by severe limitations of epidemiological study design, have impeded attaining a conclusive answer. **Search period:** 01/1985 - 12/1999	**Population:** Working population.	**Intervention:** Exposure to silica.	**Comparison:** Some of the studies compare silicotic subjects to non-silicotic subjects.	**Number of studies and patients:** 17 studies. 10 of the studies study the relationship between silica and lung cancer separately for silicotic subjects and non-silicotic subjects. The other 7 studies provided data on the association between lung cancer and exposure to silica and silicosis, but do not provide results for silicotic subjects and non-silicotic subjects. The number of participants for each study is indicated in the tables. **Effect size:** Not applicable.	**Conclusions:** The study concludes that there remains uncertainty about the question posed. According to the authors, by not having conclusive epidemiological findings, silicosis and lung cancer should be treated as different aspects, whose cause-effect relationship is not necessarily associated.	**Comments:** Summary of the quality of evidence: only the section on the conflict of interest has been rated as correct. The remaining blocks (question, methodology, results, conclusions and external validity) are rated as average.	**OSTEBA Quality:** Average

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Erren, 2009	**Objectives:** This report investigates epidemiologically whether exposure to silica is associated with lung cancer risks in individuals without silicosis. **Search period:** 01/1966 - 01/2007	**Population:** Working population without silicosis.	**Intervention:** Exposure to silica.	**Comparison:** Not applicable.	**Number of studies and patients:** The number of studies is 11. The number of workers is not specified in each of them. **Effect size:** In non-silicotic individuals exposed to silica: smoking-adjusted data (3 studies) RR = 1.0 (95% CI: 0.8-1.3); data without adjusting for smoking (8 studies) RR = 1.2 (95% CI: 1.1-1.4).	**Conclusions:** The primary conclusion of the study is that even after using sophisticated statistical tools on seemingly relevant epidemiological studies conducted to date, the authors were unable to answer the question: Is exposure to silica associated with lung cancer in the absence of silicosis? According to the authors, silica exposure, both to high and low concentrations at levels producing silicosis, should be studied in order to identify the exposure-response relationship, adjusted for confounding factors, including silicosis.	**Comments:** Search limited to references in English. Only 3 of the 11 studies in non-silicotic subjects were adjusted for smoking. It does not present the method used to assess the quality of the studies. Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest. Paragraphs on methodology and conflict of interest are rated as fair.	**OSTEBA Quality:** Average

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Erren, 2011	**Objectives:** The objective was to examine in depth whether current data allows to answer the pressing question "does silica cause lung cancer in the absence of silicosis?" **Search period:** 1979 - 12/2006 (Although the period is not clearly defined)	**Population:** Working population with and without silicosis.	**Intervention:** Exposure to silica.	**Comparison:** Not applicable.	**Effect size:** 38 studies were included. The number of patients is not detailed. **Number of studies and patients:** for silicotic subjects: RR = 2.1 (95% CI: 2.0-2.3). From Erren 2009 in non-silicotic individuals exposed to silica: Data adjusted for smoking (3 studies): RR = 1.0; (95% CI = 0.8-1.3). Data unadjusted for smoking (8 studies): Fixed effects RR = 1.2; (95% CI = 1.1-1.3). Random effects RR = 1.2; (95% CI = 1.0-1.4).	**Conclusions:** This study shows evidence of a strong association between silicosis and lung cancer, however, leaves unanswered the causal relationship between silica, silicosis and lung cancer development. The nature of the association remains unclear. The authors suggest that future research consider the full range of the exposure-response relationship between silica exposure, the development of silicosis and lung cancer. They also suggest that the data be analysed in terms of processes, considering intermediate confounding factors.	**Comments:** Search limited to references in English. It incorporates improvements to the previous study Erren 2009, such as more detailed information on the methodology. It focuses a lot on the heterogeneity of the studies. Aspects of the search are not detailed (strategy, sources...). Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest. Paragraphs on methodology and conflict of interest are rated as fair.	**OSTEBA Quality:** Average

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Pelucchi, 2006	**Objectives:** As about 50 studies have been published since 1996 on the relation between occupational silica exposure and lung cancer, we conducted a systematic review to provide summarising data of investigations in the last decade. **Search period:** 1996-07/2005 (Note: 1996 excludes those previously reviewed by the IARC Monograph)	**Population:** Working population.	**Intervention:** Occupational exposure to silica.	**Comparison:** Defined state of silicosis, defined state of no silicosis or indefinite state of silicosis.	**Number of studies and patients:** 7 cohort studies and 1 case-control study with silicosis; 20 cohort studies with undefined states of silicosis and 13 case-control studies with an undefined state of silicosis; 1 non-silicotic cohort study and 1 non-silicotic case-control study; 2 PMR studies. In the tables the samples from each study are detailed. **Effect size:** Adjusted results (fixed effects): Cohort studies: RR: 1.19 (95% CI: 1.16-1.21) Case-control studies RR: 0.99 (95% CI: 0.98-1.00) PMR mortality studies: 1.17 (95% CI: 1.15-1.19).	**Conclusions:** According to the authors, in this reanalysis, a consistent association between lung cancer and silicosis is observed; in the case of the absence of silicosis, data are limited (only 1 study), and for an undefined state of silicosis, the association is difficult to explain. This leaves open the debate on the dose-risk relationship and the pathogenic mechanisms by which the disease develops, and supports the conclusion that the carcinogenic role of silica in the absence of silicosis is still unclear.	**Comments:** This investigation presents an interesting discussion of the limitations of the reviewed articles, but does not select the studies used in the meta-analysis as a function of their quality. Does not discuss publication bias. The moderate increase in the risk of cancer in workers without silicosis and the limitations of many of the included studies, do not allow the determination of whether silica itself increases the risk of lung cancer in the absence of silicosis. Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest. Paragraphs on methodology and conflict of interest are rated as fair.	**OSTEBA Quality:** Average

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Steenland, 2001	**Objectives:** To conduct a pooled exposure-response analysis of 10 silica exposed cohorts to investigate lung cancer. **Search period:** Not indicated	**Population:** Working population.	**Intervention:** Different levels of silica exposure in the industry (mining and non-mining).	**Comparison:** Not applicable.	**Number of studies and patients:** 10 cohorts included. 65,980 workers in total. 15,171 deaths. 1,072 deaths due to lung cancer. **Effect size:** The estimated excess risk of lung cancer (at 75 years) for a worker exposed from age 20 to 65, to a respirable crystalline silica concentration of 0.1 mg/m^3 (The limit set in several countries) is 1.1-1.7%.	**Conclusions:** According to the authors, the results support the decision of the IARC to classify inhaled silica in workplaces as carcinogenic and suggest that the exposure limits in several countries (0.1 mg/m^3) may be inadequate. These data represent the first quantitative analysis of exposure-response and risk assessment of silica using data from multiple studies.	**Comments:** It would be desirable to have a more detailed explanation of the methodology or study procedure. The heterogeneity between studies is high. No important confounding factors are controlled: tobacco, other carcinogens such as radon... Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest. The paragraph on methodology was rated as fair.	**OSTEBA Quality:** Average

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Finkelstein, 2000	**Objectives:** To review the information pertinent to the quantification of the risk of developing silicosis or lung cancer following exposure to crystalline silica. **Search period:** Not specifically indicated	**Population:** Working population.	**Intervention:** Exposure to different concentrations of silica. Note: The study consists of two parts: 1) silica exposure and risk of silicosis and, 2) silica exposure and risk of lung cancer. The second is of interest for this evidence synthesis.	**Comparison:** Not applicable.	**Number of studies and patients:** 3 studies on silica exposure and risk of lung cancer. It does not specify the number of cases and controls in one study. **Effect size:** The risk of lung cancer due to cumulative exposure to silica (latency period of 15-20 years) increases by 16% per mg/m^3 * year.	**Conclusions:** According to the authors, the risk of lung cancer with an exposure time at the current OSHA value of 0.1 mg/m^3 is likely to increase by 30% or more. They claim that the shape of the curve for silica exposure-lung cancer is unknown, but is assumed to have a linear pattern. However, if silicosis plays a causal role in the pathway, the ratio should not be linear, as occurs with silicosis.	**Comments:** Only entails three primary studies. This study describes many of the difficulties of the problem in question, and quantifies the curve for the development of the disease in terms of years of exposure. This study is methodologically difficult to assess, because although it attempts to separate, it does not make completely independent the issue at hand (silica exposure-lung cancer) from silicosis. Summary of the quality of evidence: question clearly defined, however, the paragraphs regarding the results, conclusions and external validity were rated as fair. The low quality of the evidence from the study is determined by the score obtained from the method block, which was rated poor. The paragraphs encompassed in this block, as well as the literature search, the inclusion and exclusion criteria, assessment of study quality and data extraction do not meet the criteria of rigour and completeness marked. In addition, the section on conflict of interest received the lowest rating.	**OSTEBA Quality:** Low

REFERENCE	STUDY	POPULATION	INTERVENTION	COMPARISON	RESULTS	CONCLUSIONS	COMMENTS	QUALITY OF THE EVIDENCE
Abbreviated citation: Steenland, 1997	**Objectives:** To review the evidence of carcinogenicity (lung cancer and mesothaelioma) for three common occupational exposures: silica, asbestos, and man-made mineral fibres (MMMF). **Search period:** Not indicated. Articles from 01/1966 - 12/1965	**Population:** Working population.	**Intervention:** Exposure to different concentrations of silica.	**Comparison:** Not applicable.	**Number of studies and patients:** 16 studies included on lung cancer among workers exposed to silica. The number of participants in each study included is detailed **Effect size:** The combined RR of lung cancer among workers exposed to silica is 1.3 (95% CI: 1.2-1.4).	**Conclusions:** According to the authors, despite some inconsistencies, the weight of the evidence supports the thesis that silica is carcinogenic to the lung. Those with the highest exposures (silicotic subjects) are those presenting a higher risk; cohorts of exposed workers generally have a slightly increased risk.	**Comments:** Insufficient information is presented to be able to evaluate the methodology used in the study. Nor are there any comments on how the literature search was performed. Summary of the quality of evidence: question clearly defined, however, the paragraphs regarding the results, conclusions and external validity were rated as fair. The low quality of the evidence from the study is determined by the score obtained from the method block, which was rated poor. In addition, the section on conflict of interest also received this rating.	**OSTEBA Quality:** Low

Annex: Primary Study quality evaluation phase

The check-list used for the evaluation of primary studies included in Silica MAs/SRs is presented below.

Reviewer:_____

Date of this evaluation:_____

Bibliographical citation of the study: _____

1. Type of study

☐ Meta-analysis	☐ Clinical trial	☐ Case control
☐ Systematic review	☐ Prospective cohort	☐ Descriptive
☐ Narrative review	☐ Retrospective cohort	☐ Others

2. Population/Sample

Population (No.):	Exposed in the final sample (No.):
Final sample (No.):	Not exposed in the final sample (No.):
Are the criteria for inclusion and exclusion of participants in the sample defined? Yes ☐ No ☐	

3. Is the silica exposure defined clearly and precisely? Yes ☐ No ☐

State whether it uses estimates, or whether measurements, sampling systems, doses, exposure times (years worked), etc. exist

_____

_____

4. Does it pertain only to silica exposure or to a mixture of substances?

   Silica ☐ Mixture ☐

5. Is exposure measured the same way for all participants in the study?

   Yes ☐ No ☐

6. Observation period

Cohort formation: Start: End:	Follow-up period: Start: End:

7. Was the follow-up period sufficiently long and complete? Yes ☐ No ☐
8. Are potential confounding factors mentioned (smoking, age, sex, silicosis,...)?Yes ☐ No ☐
9. Has their effect attempted to be minimised (stratification, regression...)? Yes ☐ No ☐

How:_____

_____

10. Is lung cancer the only disease under study? Yes ☐ No ☐ (If the answer is "No", indicate the other diseases described)

    _____

11. Has the possible existence of lung cancer been studied across the entire sample?

    Yes ☐ No ☐

12. Are the diagnostic criteria used to identify lung cancer detailed?

    Yes ☐ No ☐

13. Is disease measured the same way for all participants in the study?

    Yes ☐ No ☐

14. Detail the diagnostic tests used: _____

15. Are the statistical tests used specified? Yes ☐ No ☐

16. Effect size is indicated by:

Point estimate (OR, RR,…) ☐ Confidence Intervals ☐ P Values ☐ Not indicated ☐

Indicate the results: _____

FINAL CHECK-LIST SCORE:_____

Instructions for obtaining the final check-list score.

To obtain the final score of the check-list, it is necessary to add the scores, using the procedure described below. The maximum score that can be obtained in each check-list is 10 points. Scoring procedure:

- One point will be added for "yes" answers to the following questions: 2, 3, 4, 5, 7, 11, 12, 13.
- One point will be added if the condition that both of the answers to questions 8 and 9 are "yes" is met.
- One point will be added if the condition that both of the answers to questions 15 and 16 are "yes" is met.

Table: Brief references of high quality EP and the MAs/SRs in which they appear

High quality PS (check-list score ≥ 7)	MA/SR including it	Subgroup conducting evaluation*
Amandus, 1991	Erren 2009, Erren 2011 and Checkoway 2000	AdV and CD
Attfield, 2004	Lacasse 2005	1 and 2
Brown, 2005	Lacasse 2009 and Pelucchi 2006	1 and 2
Calvert, 2003	Pelucchi 2006	AdV and CD
Cassidy, 2007	Lacasse 2009	1 and 2
Cocco, 2001	Lacasse 2005, Lacasse 2009 and Pelucchi 2006	1 and 2
Costello, 1995	Kurihara 2004	1 and 2
Checkoway, 1993	Steenland 1997	AdV and CD
Checkoway, 1997	Birk 2003, Lacasse 2005, Lacasse 2009, Pelucchi 2006, Finkelstein 2000 and Steenland 2001	1 and 2
Checkoway, 1999	Birk 2003, Kurihara 2004, Erren 2009, Erren 2011, Pelucchi 2006 and Checkoway 2000	1 and 2
Chen, 2002	Pelucchi 2006	AdV and CD
Chen, 2007	Lacasse 2009	1 and 2
Cherry, 1998	Birk 2003, Kurihara 2004 and Pelucchi 2006	1 and 2
Hessel, 1990	Checkoway 2000	AdV and CD
Hnizdo, 1991	Finkelstein 2000, Steenland 1997 and Steenland 2001	AdV and CD
Hnizdo, 1997	Birk 2003, Pelucchi 2006 and Finkelstein 2000	1 and 2
Hughes, 2001	Birk 2003 and Lacasse 2005	3 and 4
Koskela, 1994	Steenland 1997 and Steenland 2001	AdV and CD
Lagorio, 1990	Erren 2009 and Erren 2011	AdV and CD
McDonald, 2001	Kurihara 2004	3 and 4
McDonald, 2005	Lacasse 2009 and Pelucchi 2006	3 and 4
McLaughlin, 1992	Kurihara 2004 and Steenland 1997	3 and 4
Moulin, 2000	Pelucchi 2006	AdV and CD
Pukkala, 2005	Lacasse 2009 and Pelucchi 2006	3 and 4
Puntoni, 1988	Erren 2009, Erren 2011 and Checkoway 2000,	AdV and CD
Rafnsson, 1997	Kurihara 2004 and Pelucchi 2006	3 and 4
Rodriguez, 2000	Pelucchi 2006	AdV and CD
Siemiatycki, 1990	Steenland 1997	AdV and CD
Steenland, 1995	Kurihara 2004, Steenland 1997 and Steenland 2001	3 and 4
Ulm, 1999	Kurihara 2004, Lacasse 2005, Lacasse 2009 and Pelucchi 2006	3 and 4
Winter, 1990	Steenland 1997	AdV and CD

Average and low quality PS (check-list score < 7)	MA/SR including it	Subgroup conducting evaluation*
Amandus, 1992	Kurihara 2004	1 and 2
Armstrong, 1979	Erren 2009 and y Erren 2011	AdV and CD
Bruske-Hohlfeld, 2000	Pelucchi 2006, Kurihara 2004, Lacasse 2005 and Lacasse 2009	1 and 2
Cocco, 1994	Steenland 1997 and Kurihara 2004	1 and 2
Coggiola, 2003	Pelucchi 2006	AdV and CD
Costello, 1988	Steenland 1997, Steenland 2001 and Kurihara 2004	1 and 2
Checkoway, 1996	Pelucchi 2006	AdV and CD
Chen, 1992	Steenland 2001	AdV and CD
Chiazze, 1997	Pelucchi 2006	AdV and CD
Davis, 1983	Steenland 1997	AdV and CD
De Klerk, 1998	Pelucchi 1998, Steenland 2001 and Kurihara 2004	1 and 2
De Stefani, 1996	Pelucchi 2006 and Kurihara 2004	1 and 2
Dong, 1995	Erren 2009, Erren 2011, Checkoway 2000, Steenland 1995 and Kurihara 2004	1 and 2
Fillmore, 1999	Pelucchi 2006	AdV and CD
Finkelstein, 1995	Erren 2009, Erren 2011, Checkoway 2000 and Kurihara 2004	1 and 2
Finkelstein, 2005	Pelucchi 2006	AdV and CD
Forastiere, 1986	Checkoway 2000 and Kurihara 2004	1 and 2
Guenel, 1989	Steenland 1997 and Kurihara 2004	1 and 2
Graham, 2004	Pelucchi 2006	AdV and CD
Kauppinen, 2003	Pelucchi 2006	AdV and CD
Martin, 2000	Pelucchi 2006 and Kurihara 2004	3 and 4
Mastrangelo, 1988	Erren 2009, Erren 2011, Checkoway 2000 and Kurihara 2004	3 and 4
Mehnert, 1990	Erren 2009, Erren 2011, Checkoway 2000, Steenland 2001 and Kurihara 2004	3 and 4
Meijers, 1996	Erren 2009, Erren 2011, Checkoway 2000 and Kurihara 2004	3 and 4
Menvielle, 2003	Pelucchi 2006	AdV and CD
Merlo, 1991	Steenland 1997 and Kurihara 2004	3 and 4
Merlo, 2004	Pelucchi 2006	AdV and CD
Moshammer, 2004	Pelucchi 2006	AdV and CD
Neuberger, 1986	Steenland 1997	AdV and CD
Ogawa, 2003	Pelucchi 2006	AdV and CD
Salg, 2005	Pelucchi 2006	AdV and CD
Smailyte, 2004	Pelucchi 2006	AdV and CD
Sherson, 1991	Erren 2009, Erren 2011 and Kurihara 2004	3 and 4

Steenland, 1986	Steenland 1997	AdV and CD
Steenland, 2001	Steenland 2001, Birk 2003, Kurihara 2004, Lacasse 2005 and Lacasse 2009	3 and 4
Steenland, 2001	Birk 2003	3 and 4
Steenland, 2004	Pelucchi 2006	AdV and CD
Stern, 2001	Kurihara 2004	3 and 4
Stone, 2004	Pelucchi 2006	
Szadkowska-Stanczyk , 2001	Pelucchi 2006 and Kurihara 2004	3 and 4
Tsuda, 2002	Pelucchi 2006	AdV and CD
Watkins, 2002	Pelucchi 2006	AdV and CD
Westberg , 2003	Pelucchi 2006, Lacasse 2005 and Lacasse 2009	3 and 4

*Subgroups who conducted evaluations:
Subgroup 1: MI and CP
Subgroup 2: NL and JR
Subgroup 3: LA and CC
Subgroup 4: AdG and PH

Annex: Critical evaluation of the quality of MA/SR studies phase

REFERENCE (Abbreviated citation)	CONCLUSIONS	COMMENTS	OSTEBA QUALITY:	CHECK-LIST QUALITY	RICISST QUALITY
Lacasse, 2009	The results of the study indicate that there is a relationship between exposure to silica and lung cancer development above a threshold level of 1.84 mg/m^3*year. However, the interpretation is limited by the wide range of exposures to respirable silica in the original studies, the heterogeneity between studies, and the confounding effect of silicosis, which cannot be fully assessed.	Only two studies excluded subjects with silicosis. Since silicosis is a risk factor for lung cancer, this may overestimate the association between silica exposure and lung cancer. The magnitude of this error is unknown, since the proportion of silicotic subjects among those exposed to silica is unknown. The results are not presented clearly. The RR CI confidence levels are not specified. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	High	High (7.0)	**High**
Lacasse, 2005	There is a weak dose-response relationship between silica exposure and the risk of lung cancer. The authors conclude that the data published to date suggest that occupational exposure to silica represents a low risk factor for developing lung cancer at exposure levels exceeding the exposure limit permitted according to North American standards. The interpretation of these results is limited due to the heterogeneity of the results of the studies analysed in the MA. These conclusions, other than some nuances, agree with those of the IARC.	Comprehensive study. This MA explains several important aspects of the studies considered, including their heterogeneity, their conflicting results, the lack of adjustment for smoking in certain instances. It performs two analyses of the silica exposure-lung cancer relationship: without latency and with 15 years of latency. The interpretation of these results is limited due to the heterogeneity of the studies. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	High	Average (6.6)	**Average**
Birk, 2003	According to the authors, in general, the high quality studies analysed show a greater risk of lung cancer in groups with greater exposure to silica, taking into account the potential influence of smoking and the presence of silicosis. However, due to the lack of	The authors perform an exhaustive assessment of the quality of primary articles. The risk of lung cancer is only presented from studies rated as relevant due to adequate quality. For this reason, the	High	Average (6.6)	**Average**

REFERENCE (Abbreviated citation)	CONCLUSIONS	COMMENTS	OSTEBA QUALITY:	CHECK-LIST QUALITY	RICISST QUALITY
	reliable data on exposure to crystalline silica in the studies analysed, it is not possible to establish an exposure limit value.	conclusions do not exactly fit to that sought. This study provides a good, detailed description of confounding factors and selective survival bias. Given that the exposures in the studies considered are based on different data, both in quality and in quantity and often, using different methods (including assumptions for situations of unknown exposure), the authors consider that comparisons between estimated exposure values are likely to be invalid. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest.			
Kurihara, 2004	According to the authors, the study reveals that silicosis is a risk factor for lung cancer. A small risk of lung cancer in subjects exposed to silica (including silicotic subjects) is also observed. This suggests that crystalline silica indirectly induces lung cancer in humans. Further analysis shows that smoking greatly increases the risk of lung cancer among silicotic subjects.	There is some doubt raised as to the quality of the individual studies. Some studies regarding silica and lung cancer do not exclude silicotic patients, so the overall RR could be lower than 1.32. It raises an interesting discussion about whether the carcinogenic effect is due to exposure to silica or due to silica-induced silicosis. Summary of the quality of evidence: question clearly defined, well-described and appropriate methodology, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest.	High	Average (5.9)	**Average**
Erren, 2009	The primary conclusion of the study is that even after using sophisticated statistical tools on seemingly relevant epidemiological studies conducted to date, the authors were unable to answer the question: Is exposure to silica associated with lung cancer in the absence of silicosis? According to the authors, silica exposure, both to high and low concentrations at levels producing silicosis, should be studied in order to identify the exposure-response relationship, adjusted for	Search limited to references in English. Only 3 of the 11 studies in non-silicotic subjects were adjusted for smoking. It does not present the method used to assess the quality of the studies. Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions	Average	Average (6.1)	**Average**

REFERENCE (Abbreviated citation)	CONCLUSIONS	COMMENTS	OSTEBA QUALITY:	CHECK-LIST QUALITY	RICISST QUALITY
	confounding factors, including silicosis.	justified and useful and with results that are generalisable to the population and context of interest. Paragraphs on methodology and conflict of interest are rated as fair.			
Erren, 2011	This study shows evidence of a strong association between silicosis and lung cancer, however, leaves unanswered the causal relationship between silica, silicosis and lung cancer development. The nature of the association remains unclear. The authors suggest that future research consider the full range of the exposure-response relationship between silica exposure, the development of silicosis and lung cancer. They also suggest that the data be analysed in terms of processes, considering intermediate confounding factors.	Search limited to references in English. It incorporates improvements to the previous study Erren 2009, such as more detailed information on the methodology. It focuses a lot on the heterogeneity of the studies. Aspects of the search are not detailed (strategy, sources...). Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest. Paragraphs on methodology and conflict of interest are rated as fair.	Average	Average (6.1)	**Average**
Checkoway, 2000	The study concludes that there remains uncertainty about the question posed. According to the authors, by not having conclusive epidemiological findings, silicosis and lung cancer should be treated as different aspects, whose cause-effect relationship is not necessarily associated.	Summary of the quality of evidence: only the section on the conflict of interest has been rated as correct. The remaining blocks (question, methodology, results, conclusions and external validity) are rated as average.	Average	Average (6.1)	**Average**
Pelucchi, 2006	The authors conclude that in this reanalysis, a consistent association between lung cancer and silicosis is observed; in the case of the absence of silicosis, data are limited (only 1 study), and for an undefined state of silicosis, the association is difficult to explain. This leaves open the debate on the dose-risk relationship and the pathogenic mechanisms by which the disease develops, and supports the conclusion that the carcinogenic role of silica in the absence of silicosis is still unclear.	This investigation presents an interesting discussion of the limitations of the reviewed articles, but does not select the studies used in the meta-analysis as a function of their quality. Does not discuss publication bias. The moderate increase in the risk of cancer in workers without silicosis and the limitations of many of the included studies, do not allow the determination of whether silica itself increases the risk of lung cancer in the absence of silicosis. Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest.	Average	Average (6.0)	**Average**

REFERENCE (Abbreviated citation)	CONCLUSIONS	COMMENTS	OSTEBA QUALITY:	CHECK-LIST QUALITY	RICISST QUALITY
		Paragraphs on methodology and conflict of interest are rated as fair.			
Steenland, 2001	According to the authors, the results support the decision of the IARC to classify inhaled silica in workplaces as carcinogenic and suggest that the exposure limits in several countries (0.1 mg/m^3) may be inadequate. These data represent the first quantitative analysis of exposure-response and risk assessment of silica using data from multiple studies.	It would be desirable to have a more detailed explanation of the methodology or study procedure. The heterogeneity between studies is high. No important confounding factors are controlled: tobacco, other carcinogens such as radon... Summary of the quality of evidence: question clearly defined, results correctly synthesised and described, conclusions justified and useful and with results that are generalisable to the population and context of interest, while also being free from influences arising from conflicts of interest. The paragraph on methodology was rated as fair.	Average	Average (6.0)	**Average**
Finkelstein, 2000	According to the authors, the risk of lung cancer with an exposure time at the current OSHA value of 0.1 mg/m3 is likely to increase by 30% or more. The shape of the curve for silica exposure-lung cancer is unknown, but is assumed to have a linear pattern. However, if silicosis plays a causal role in the pathway, the ratio should not be linear, as occurs with silicosis.	Only entails three primary studies. This study describes many of the difficulties of the problem in question, and quantifies the curve for the development of the disease in terms of years of exposure. This study is methodologically difficult to assess, because although it attempts to separate, it does not make completely independent the issue at hand (silica exposure-lung cancer) from silicosis. The low quality of the evidence from the study is determined by the score obtained from the method block, which was rated poor. The paragraphs encompassed in this block, as well as the literature search, the inclusion and exclusion criteria, assessment of study quality and data extraction do not meet the criteria of rigour and completeness marked. In addition, the section on conflict of interest received the lowest rating.	Low	High (7.3)	**Low**
Steenland, 1997	According to the authors, despite some inconsistencies, the weight of the evidence supports the thesis that silica is carcinogenic to the lung. Those with the highest exposures (silicotic subjects) are those presenting a higher risk; cohorts of exposed workers generally have a slightly increased risk.	Insufficient information is presented to be able to evaluate the methodology used in the study. Nor are there any comments on how the literature search was performed. Summary of the quality of evidence: question clearly defined,	Low	Average (6.5)	**Low**

REFERENCE (Abbreviated citation)	CONCLUSIONS	COMMENTS	OSTEBA QUALITY:	CHECK-LIST QUALITY	RICISST QUALITY
		however, the paragraphs regarding the results, conclusions and external validity were rated as fair. The low quality of the evidence from the study is determined by the score obtained from the method block, which was rated poor. In addition, the section on conflict of interest also received this rating.			

Annex: Characteristics of High Quality Primary Studies

Available in Spanish in:
http://www.oect.es/Observatorio/5%20Estudios%20tecnicos/Monografias/Estudios%20de%20evidencia%20cientifica%20en%20salud%20laboral/Síntesis%20sílice%20cristalina.pdf

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