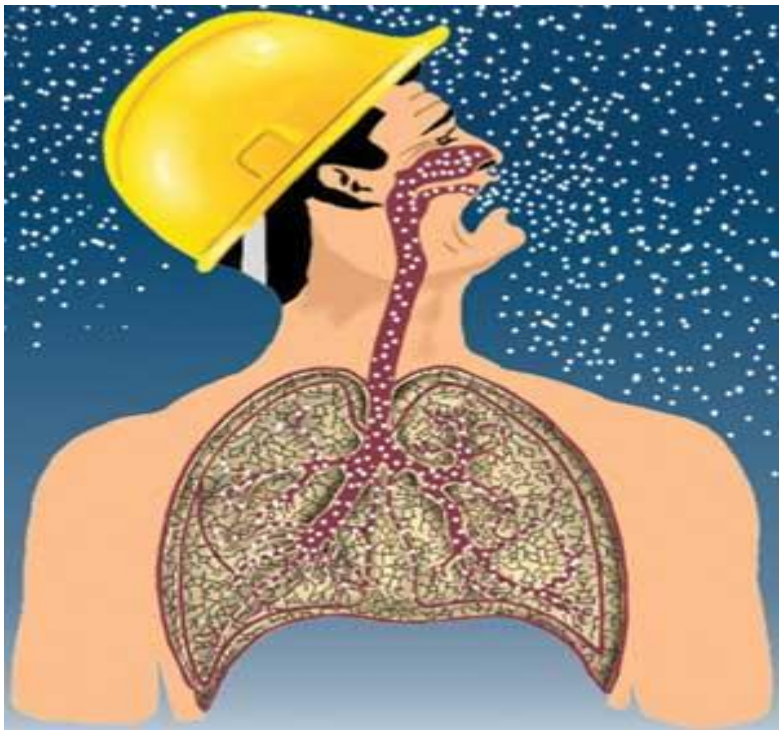
Shape of the exposure response relation for crystalline silica and risk of lung cancer



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ABSTRACT

Crystalline silica exposure mostly occurs in occupational settings such as mining, construction, several industries (e.g. foundries) and agriculture. Occupational exposure to silica dust is known to be related to several non-malignant respiratory health effects. In addition respirable crystalline silica has been classified as malignant by the International Agency for Research on Cancer (IARC) since 1997. However, conflicting data has fueled a debate against this classification for the past decade. In the presented study quantitative data on the exposure response relationship between occupational crystalline silica exposure and risk of lung cancer was evaluated by applying a formal meta regression. Data was collected from studies used in a meta-analysis performed by Lacasse and co-workers in 2009 and more recent studies which reported quantitatively on the relation between crystalline silica and lung cancer. The main aim was to shed light on the actual shape of the exposure response relation for respirable crystalline silica and lung cancer. Both a linear and a natural spline model were fitted to the data. The natural spline model fitted the data better and showed a small, but statistically significant ($p = 0.04$) increase in lung cancer risk resulting from increasing crystalline silica exposure. This increase however was only observed at relatively low levels of cumulative exposure to crystalline silica.

Contents

INTRODUCTION

Silicon dioxide, also known as silica, naturally occurs in crystalline and amorphous forms. Quartz is the most common polymorph form of silica. Crystalline silica, which is mainly used in the production of glass, is processed in a large number of industries and occupational exposure to silica dust is therefore rather common. Occupational exposure to crystalline silica is not restricted to industrial settings as it also occurs during most mining activities, construction and agriculture. Continuous occupational exposure to silica dust is known to have several non-malignant respiratory health effects. Although health effects such as silicosis can be directly contributed to prolonged silica dust exposure, health effects such as lung cancer as a consequence of crystalline silica exposure are still heavily debated .(Erren et al. 2008; Pelucchi et al. 2006)

Silica has been reviewed by the International Agency for Research on Cancer (IARC) on three occasions. Two Monographs published in 1987 and in 1997 and one yet to be published Monograph (Monograph 100C) evaluated the carcinogenicity of crystalline silica exposure in humans. The 1987 IARC monograph concluded that crystalline silica exposure was related to the occurrence of lung cancer in test animals, but not enough evidence was at hand to prove carcinogenicity in humans. The 1997 IARC monograph on silica, which included more recent data, concluded that crystalline silica inhaled from occupational sources is carcinogenic for humans (Pelucchi et al. 2006). The most recent IARC Monograph 100C concluded that the classification of silica as a carcinogen was justified and specified the lungs as the site of action (IARC 2011).

Even though silica is determined to be carcinogenic for humans by the IARC since 1997, the debate on the subject has continued. The IARC also noted that carcinogenicity of crystalline silica was not proven for all settings in which occupational exposure occurs.(IARC 1997) It is also unclear whether there is a direct association between lung cancer and crystalline silica or if lung cancer only occurs when the exposed subjects also suffer from silicosis. This uncertainty further challenges the 1997 IARC classification of silica (Pelucchi et al. 2006).

Since 1997 many studies have focused on the effects of occupational crystalline silica exposure. The most relevant studies on this subject have been reviewed by Pelluchi and co-workers 2005, Erren and co-workers in 2008 and most recently by Lacasse and co-workers in 2009. These reviews pointed out that the available data does show an association between crystalline silica and lung cancer but that evidence on the role of silicosis is not conclusive.

In risk assessment the results of epidemiological studies provide the most relevant evidence for researchers because these study results can easily be applied to real-life situations. In general human epidemiological data is preferable above the use of data from animal studies as the starting point for quantitative risk analysis, because the results of animal studies have to be extrapolated into effects expected in humans, which usually brings with it at certain amount of uncertainty (Goldbohm et al. 2006; Vlaanderen et al. 2008).

For risk estimation and characterization of carcinogenic substances quantitative risk assessment of cancer risks associated with occupational exposure to (potential) carcinogens is very important (Goldbohm et al. 2006; Vlaanderen et al. 2008). However, it is not always possible to measure certain risk for humans in experimental settings however, due to ethical and legislative restrictions (i.e. the dose response of silica dust cannot be measured in a clinical trial because the subjects could possibly get lung cancer). In many cases epidemiological data for potentially hazardous concentrations of

certain substances, can only be derived from observational studies. For quantitative risk assessment of carcinogens human observational studies which focus on the quantitative risk analyses of the substance in question give the most relevant results. Observational studies are however deviate from experimental studies, in the sense that not all variables can be controlled, which can lead to bias in the dose response results (i.e. the estimated association between exposure and health outcome) of these studies. It is therefore important that the quality of these observational studies satisfy certain requirements. Over the past years several frameworks (Goldbohm et al. 2006; Pelucchi et al. 2006; Sanner et al. 2001; Stroup et al. 2000; Vlaanderen et al. 2008; WHO Working Group 2000) have been developed to address the requirements for observational studies to be of sufficient quality for quantitative risk assessment.

A meta-analysis performed by Lacasse and co-workers in 2009, on the relationship between occupational exposure to crystalline silica and lung cancer found evidence that supported the IARC classification for crystalline silica. In this study a meta-analyses was performed on the most relevant studies using the framework described by Stroup et al. in 2000. This method however, like most of the developed frameworks, does not incorporate specific guidelines for the evaluation of observational studies for quantitative risk assessment (Stroup et al. 2000). Since the publication by Lacasse et al. in 2009 a few new studies have been published, which may influence the exposure response relationship for crystalline silica and lung cancer. A framework developed by Vlaanderen et al (Vlaanderen et al. 2008) incorporates guidelines for evaluating and ranking human observational studies and proofed to be the best option for the current study. In this thesis a meta regression-analysis (Vlaanderen et al. 2009) will be performed to evaluate evidence of the association between quantitatively assessed exposure to crystalline silica and occurrence of lung cancer.

The studies selected by Lacasse and new studies that appeared after 1/1/2008 were evaluated following the criteria as outlined by Vlaanderen et al. (2009) and risk estimates for levels of cumulative exposure from selected studies were extracted and consequently used in a meta-regression analysis. The main aim was to shed light on the actual shape of the exposure response relation for crystalline silica and lung cancer.

METHODS

Study identification and selection

Studies were initially identified by performing a literature search in Web of Knowledge for publications published between 1/1/2008 and 8/16/2011 with the key words "silica" and "lung cancer". For inclusion in the meta regression-analysis studies had to be original human observational studies which reported a quantitative exposure-response analysis for occupational exposure to crystalline silica and lung cancer. The initial search identified 108 publications from which 7 studies were selected for further evaluation and potential inclusion in the meta regression-analysis. 10 studies were selected for further evaluation following a meta analyses done by Lacasse et al. The 17 initially selected studies were further evaluated and ranked using the frame work developed by Vlaanderen et al in 2008.

This framework consists of 3 tiers. The first tier included 6 criteria in the form of questions which focused on the quality and type of the study design, the way data was gathered and analyzed and the way confounders, if any, were handled. Studies that did not satisfy all criteria were not suitable for the meta-regression analysis and were excluded (Vlaanderen et al. 2008). Following the first tier evaluation 4 studies were excluded from the meta-regression analysis. One study (Birk et al. 2010) was excluded because it only reported the exposure estimates for crystalline silica in the German porcelain industry and not specifically on the relationship of crystalline silica exposure to the occurrence of lung cancer. Two other studies did not report the exposure in specific units, but reported it as years exposed (Checkoway et al. 2011) and in undefined units (Vida et al. 2010). The last study was excluded because it did not report specifically on lung cancer. From the 12 remaining studies data was extracted and consequently used in a meta regression-analysis.

Data extraction and preparation

The remaining studies fell into 3 categories, namely Cohort, Case-Control and Nested Case-Control studies. From these studies risk ratios (from cohort studies) and odds ratios (from case-control and nested case-control studies) for the cumulative exposure to crystalline silica (mg/m^3 year) were extracted. Further each study was designated with a study identifier and the confidence interval for the risk estimates, the number of cases and controls for each exposure category (from case-control and nested case-control studies) or the size of the study population for the exposure category (cohort studies) and data to identify the study (author, year of publication, location etc.) were extracted from the studies. The reported risks estimates were all interpreted as relative risks for use in the meta-regression analysis.(Vlaanderen et al. 2009).

To prepare the data for use in a meta-regression analysis it was important to assign a specific exposure estimate to each of the reported risk estimates. For most of the selected studies only the boundaries of the exposure categories were reported. The specific exposure estimates were assigned by calculating the mean of the exposure categories. The means were calculated using a method described in Vlaanderen et al. 2009. In this method the cumulative exposure for each study is presumed to have a log-normal distribution. By using data that provided information on the distribution of the exposure, such as the number of person years per exposure category or the number of people exposed per exposure category, the probability density function could be fitted to the data using the maximum likelihood estimation. The maximum reported cumulative exposure was used in these estimations as the upper limit to avoid unreasonably high estimates.(Vlaanderen et al. 2009)

As a result of the method described above, 3 studies (Checkoway et al. 1997; Mundt et al. 2011; Steenland and Sanderson 2001) had to be excluded from the meta-regression analyses, because they did not provide enough information on the distribution to determine specific exposure estimates for the reported risk estimate categories. The exposure estimates were not determined with the above described method for all remaining studies. Two studies (Bergdahl et al. 2010; Westberg and Bellander 2003) reported the mean exposure levels of the exposure. The average exposure levels where estimated with R, version 2.13.1 (R Core Development Group, Vienna, Austria).

In the meta-regression analysis models were fitted to the data using a macro for SAS written by L Portengen (Vlaanderen et al. 2009). Using SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA) to perform statistical analyses, both linear and natural spline models were fitted to the data to investigate the relationship between crystalline silica exposure and lung cancer. The fitted exposure-response models were subsequently used to predict risk estimates at different exposure levels to better compare the results to other studies. Figure 1 shows a scatter plot of the risk data extracted from the 9 studies used in the meta-regression analysis including the confidence intervals.

To examine the effect of individual studies on the meta-regression a jackknifing analysis was preformed. This analysis is performed by excluding studies one by one and visually examining the resulting regression curve and comparing it to the regression curve which includes all the studies.

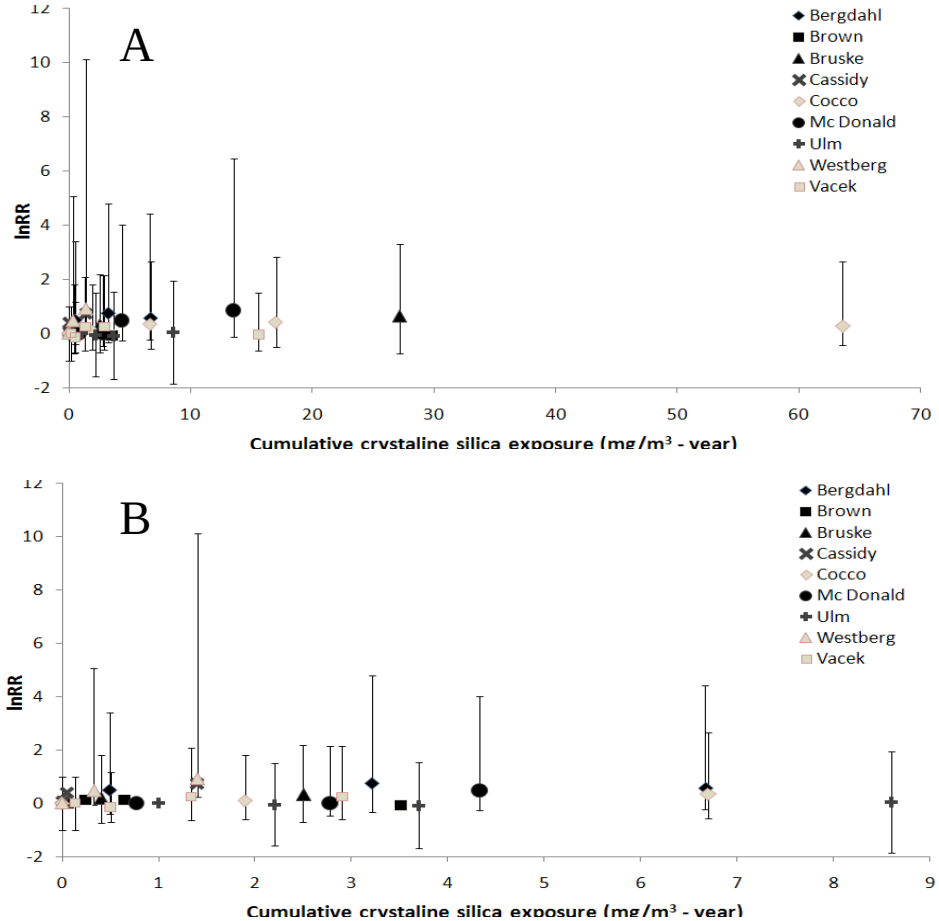

Figure 1. Scatter plot of the risk estimates with confidence intervals used in the meta-regression analysis against the corresponding exposure estimates up to 70 mg/m^3 – year *(A),* and up to 9 mg/m^3 – year *(B).*

Table 1. Characteristics of the studies included in the meta regression-analysis of silica and lung cancer

Author	Year	Study Design	Risk Estimate	Country/Region	Reference Category	Exposure level (mg/m^3-years) Lowest	Upper	Study outcome	Study population size
Bergdahl	2010	Cohort	RR	Zweden, Kiruna	Unexposed cohort members	0	>5	lung cancer	Cohort of 227000 person years and 112 cases
Brown	2005	Cohort	SMR	UK	Workers exposed to <0.13 mg/m^3 - years	<0.13	>1	death	Cohort of 2272 with 82 cases
Bruske	2000	Case-Control	OR	Germany		0 - 1	> 5	lung cancer	cases and 513 controls 321
Cassidy	2007	Case-Control	OR	Europe	people not exposed 20 years before interview	<0.05	>0.2	lung cancer	311 controls and 435 cases
Cocco	2001	Case control	OR	China	Unexposed cohort members	1.0 - 3.7	>27	lung cancer	1356 controls and 316 cases
Mc Donald	2005	Case control	OR	North-America	Workers exposed to <0.77 mg/m^3 - years	<0.77	>13.51	lung cancer	188 controls and 105 cases
Ulm	1999	Case control	OR	Germany	Unexposed cohort members	<1.56	>4.68	lung cancer	795 controls and 247 cases
Westberg	2003	Nested Case Control	OR	Sweden	Unexposed cohort members	0	>1	lung cancer	233 controls and 31 cases
Vacek	2010	Case Control	OR	USA, Vermont	Workers exposed to <0.26 mg/m^3 - years	<0.26	>4.1	death	1297 controls and 356 cases

RESULTS

The 9 studies which were eventually selected for the meta-regression analysis (see table 1), yielded a total of 27 observations. The cumulative crystalline silica exposure estimates determined from the reported exposure categories reached from 0 to 63.3 mg/m^3-year of which 93% was lower than 20 mg/m^3-year. The highest exposure estimates were reported by study preformed in Chinese mines and pottery industry (Cocco et al. 2001). These high cumulative exposures did not show a significantly higher effect than the lower cumulative exposure groups. The selected studies were all preformed in an occupational setting, and the results lay close together even though the study populations worked in different industries.

In the analyses a natural spline and a linear model were fitted to the data. The natural spline model proved to fit slightly better than the linear model (deviance: 18,1 vs 19.7). The natural spline model also showed that crystalline silica exposure significantly increases the risk for lung cancer ($p = 0.04$) were the linear regression model shows no significant relationship between exposure and effect. Due to the lack of data in the higher exposure levels both models show wide confidence intervals at these exposure levels. The linear model shows a gradual increase in effect as the exposure increases, whereas the natural spline model shows a sharper increase in effect at low exposure levels and a negligible increased effect for higher exposure levels.

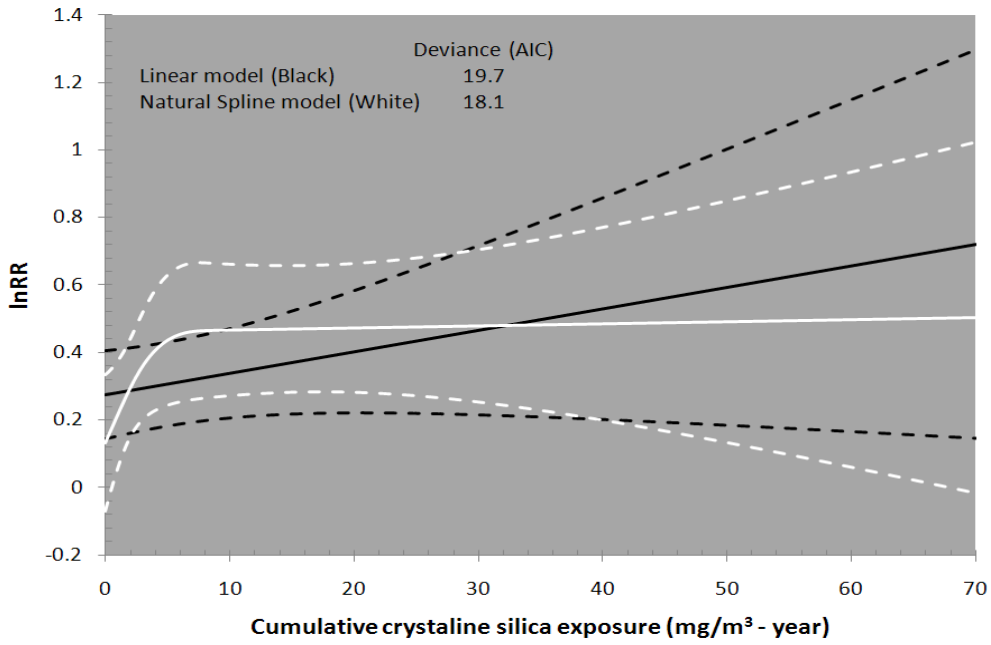

Figure 2. Plots of the linear (black line) and natural spline (white line) regression model using the 9 selected studies. The dashed lines represent the 95% confidence intervals.

The effects of each study was tested with a jackknife test. In this test the studies were excluded from the model one by one to test the effect it had on the model. This test showed that the effect of most studies is limited. The intercepts of all the models are close together for both the linear (2.3 – 3.0) and the natural spline (1.2 – 2.1) models. The exclusion of two studies (Cocco et al. 2001; Vacek et al. 2011) allowed for a more pronounced exposure effect prediction by the regression model (i.e. the model plot shows a steeper slope). Further the exclusion of the study performed by Brüske et al (Brüske-Hohlfeld et al. 2000) considerably lowered the predicted slope of the exposure-response

curve. The natural spline models show that the effects caused by exclusion of the above mentioned studies is predominantly observed at the higher exposure levels.

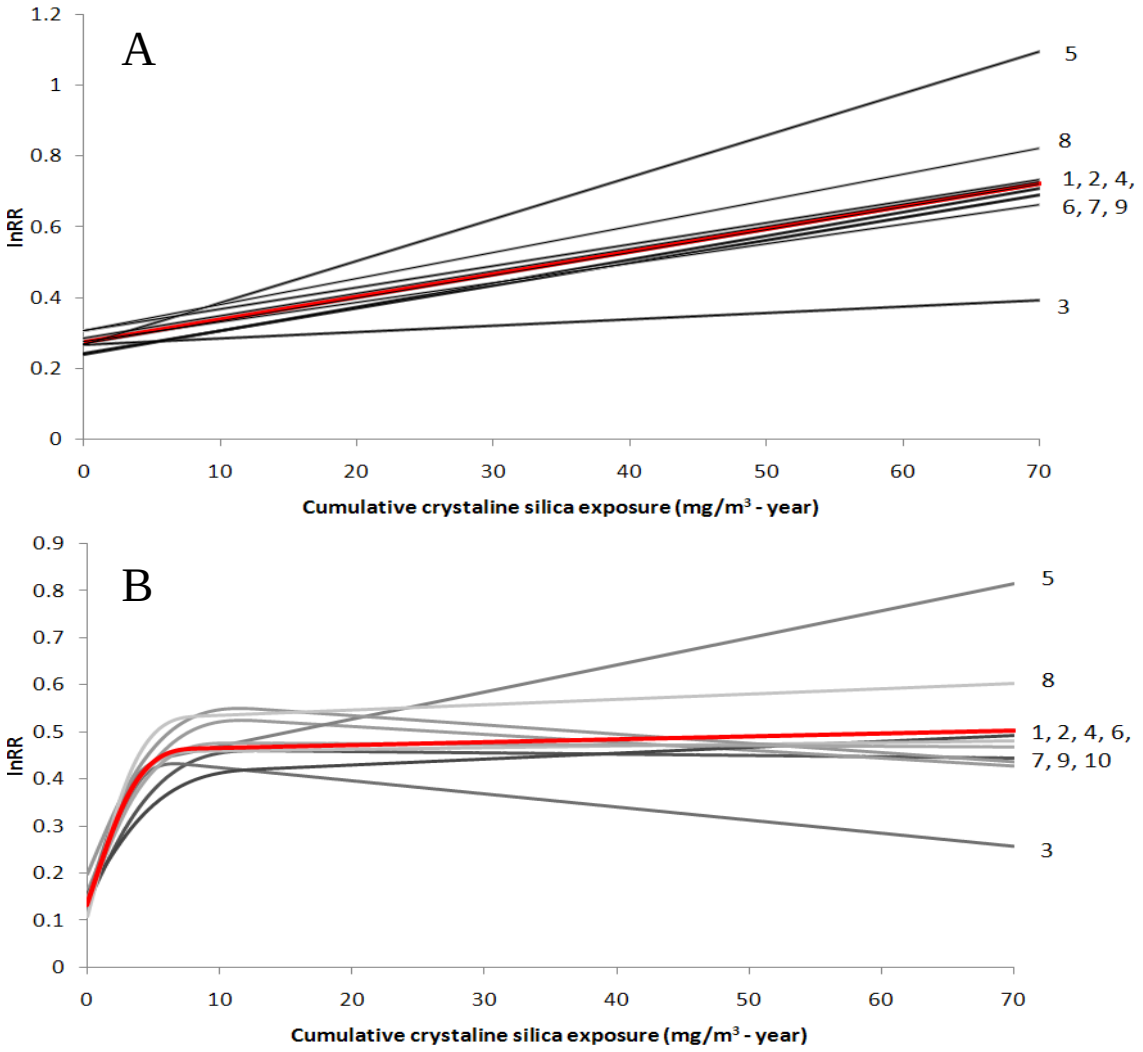

Figure 3. Effects of individual studies on the linear (A) and natural spline (B) regression model. The graph represents the model using all studies (10, red line) compared to the model with one study excluded. The plots identified by the excluded study are: Bergdahl *(1)*,Brown *(2)*, Bruske *(3)*, Cassidy *(4)*, Cocco *(5)*, Mc Donald *(6)*, Ulm *(7)*, Vacek *(8)*, Westberg *(9).*

DISCUSSION

The selected studies reported different types of risk estimates (RRs, ORs and SMRs). OR and SMR are however good approximations when dealing with rare responses like cancer and could therefore be pooled with RR in this meta-regression analysis.

The results show that the relationship between occupational crystalline silica exposure and the occurrence of lung cancer in workers is best explained by a supralinear exposure response curve (natural spline model) using the data derived from the selected studies. This exposure response curve indicates that increasing silica exposure increases the risk for lung cancer only a low level of cumulative exposure. At higher exposure levels the risk does not longer increase. This however could be due to bias because of lack of exposure response data at the higher levels of cumulative exposure to crystalline silica. This decrease in data for relatively high exposure levels is a commonly seen in occupational cohort mortality studies and is caused by bias such as the healthy worker survivor effect, a misclassification or errors in measurements of the estimated exposure levels and the lack of cases at high exposure levels (Stayner et al. 2003).

The results of the natural spline model, which show a significant exposure-response relationship between silica exposure and lung cancer, support the IARC classification on Silica (IARC 2011). The association is relatively weak and due to the lack of data the natural spline model does not show a significantly better fit to the data than the linear regression model (deviance respectively 18.1 and 19.7). The linear model however does not support the IARC classification of silica because even though it shows the same effect this is not statistically significant. Adding more data to the meta-hyh8regression, especially exposure - response data for high exposure levels, will lead to better fit for the models, which may show a better correlation for the linear regression model.

The debate on the carcinogenity of respirable crystalline silica, which was sparked by the IARC's decision in 1997(IARC 1997), is not settled by the results of the current study. Even though the results support the IARC's classification on crystalline silica, the relatively weak association is not convincing prove to end the ongoing debate. Most studies which research the exposure response curve for crystalline silica and lung cancer show weak or inconclusive results (Erren et al. 2008; Gamble 2011). As with other studies on the subject the limitations of the current study are caused by the lack of quantitative and reliable exposure-response data on the subject, which is especially the case for high exposure level. For more conclusive results this subject requires a broader and more extensive research, with the focus on accurate exposure measurements for higher exposure levels.

CONCLUSION

The meta-regression analysis shows an increased risk of lung cancer due to occupational exposure to crystalline silica, when using a natural spline regression model. The exposure effect relationship based on a linear model shows a similar effect but it does not reach statistical significance. Even though the results are not very strong they do not contradict the IARC's classification of silica, but do imply the necessity for reliable quantitative research on the exposure- response curve for crystalline silica and lung cancer.

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