



Silica, Silicosis, and Lung Cancer

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Abstract

Evidence that crystalline silica is associated with an increased rate of lung cancer led the International Agency for Research on Cancer to conclude in 1997 that crystalline silica is a known human carcinogen. In Israel too, crystalline silica is considered as such. The decision raised a debate in the scientific arena, and a few scientists have questioned the basis upon which causality was determined. We review the literature regarding the level of evidence of crystalline silica carcinogenicity.

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In 1997 the International Agency for Research on Cancer declared that crystalline silica is a carcinogen to humans (group 1) [1]. In Israel too, the Interdisciplinary Committee of Carcinogenic, Mutagenic and Teratogenic Substances classified crystalline silica as an established human carcinogen [2], and workers exposed in the workplace to crystalline silica above the acceptable exposure level [3] undergo periodic surveillance checkups. Furthermore, the National Insurance Institute considers lung cancer in a worker exposed to crystalline silica as a “work-related health condition.” Subsequent to the classification of silica as a human carcinogen, critical scientists have tried to demonstrate weaknesses in the evidence that led to the IARC’s decision. We briefly review the literature regarding the level of evidence for carcinogenicity of crystalline silica.

Occupational lung cancer

Lung cancer is the leading cause of cancer death among adults, though its incidence has declined in men and is stabilizing in women [4]. Cigarette smoking is by far the most important risk factor for lung cancer, accounting for about 90% of lung cancer cases in countries where cigarette smoking is common [5]. Yet, the proportion of risks attributable to exposures in the workplace is significant, with occupational lung cancer accounting for 9–15% of all malignant lung tumors [5].

IARC = International Agency for Research on Cancer

Various occupational factors are considered related to the development of lung cancer, including asbestos, silica, metals (cadmium, chromium, nickel, beryllium and arsenic), polycyclic aromatic hydrocarbons, and radon. There are also some processes in which exposure to one particular material is not identifiable but are considered to be associated with an excess of lung cancer cases; these include coke production, coal gasification, and iron and steel founding [6].

Definition of crystalline silica

Silica or silicon dioxide is formed from silicon and oxygen under conditions of increased heat and pressure. It is the most abundant mineral on earth that exists in two forms – crystalline (also called free silica) and amorphous. Amorphous silica has no crystalline structure and relatively non-toxic lung properties [7]. Crystalline silica is based on a tetrahedral structure in which the central atom is silicon and the corners are occupied by oxygen. The structure of the crystal is such that two adjacent tetrahedrons share two oxygen atoms. Free silica has three principal polymorphs: quartz, tridymite and cristobalite, with quartz being by far the most common.

Exposure to silica is a global occupational problem

Quartz is abundant in most rock types, notably granites, sandstones, and in sands and soils. Cristobalite and tridymite are found in volcanic rocks. Because of the wide usage of quartz-containing materials, workers may be exposed to respirable silica in a large variety of industries and occupations and it is estimated that at least 1.7 million U.S. workers are potentially exposed [8].

The occupational exposure to respirable silica is associated with different diseases including reduced lung function, chronic

obstructive pulmonary disease, and the established pneumoconiosis – silicosis, in its various forms.

Review of the scientific evidence

The possibility that crystalline silica is associated with increased risk of cancer was first raised in the 1980s after several epidemiologic studies were published. In 1997, the IARC concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources [1]. Following the decision of the IARC in 1997, a debate ensued regarding the true carcinogenic effect of crystalline silica, i.e., whether there was truly enough evidence to conclude that crystalline silica is carcinogenic to humans. The IARC itself mentioned in the decision the difficulties that accompanied it by stating: "In making the overall evaluation, the Working Group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs" [1].

A second question that was raised was: Is silicosis a necessary precursor for the occurrence of cancer? This question exists because a major study group in the epidemiologic literature constitutes workers with silicosis.

Assessing the relationship between the exposure to silica and lung cancer involves consideration of the causality criteria suggested by Sir Austin Bradford Hill [9], scientific evidence free of confounding and bias, and a correct statistic analysis of available data. Three sources of information were considered by the IARC working group in making its decision: animal bioassays, short-term tests, and epidemiologic studies.

Studies of carcinogenicity in animals

The animal bioassays that demonstrated a carcinogenic effect of silica were those performed on rats, while no evidence of carcinogenicity was found in other species [10]. Skepticism regarding the positive studies emerges from the fact that most of the tests were performed with a single dose, whereas the two studies that included high and low exposure groups did not show a dose-response effect of silica on lung cancer. Secondly, rats are currently considered an inappropriate model for assessing non-fibrous particulate lung carcinogens due to metabolic peculiarities of the species [10].

Although studies on animals are not always necessary to determine causality, as was determined for arsenic [11], they are considered good predictors of human carcinogenicity and contribute, together with studies on genotoxicity, to establishing biological plausibility.

Short-term tests

These are assays that can provide evidence of genotoxicity without the need for the long period of observation or follow-up required in epidemiologic or animal studies. These studies are subject to several problems of interpretation and are especially difficult for materials that are not suitable for *in vitro* experiments

Genotoxicity of crystalline silica is questionable. Indeed, most *in vitro* and *in vivo* assays that measured the genotoxic effect of crystalline silica were negative or inconclusive, except for the induction of micronuclei formation [8]. Therefore, some researchers deny the biologic plausibility contributed by short-term studies, while others believe that the positivity of some of these tests provides corroboration for the positive findings in animal bioassays in determining the biologic plausibility.

Crystalline silica has been defined as carcinogenic to humans

Epidemiologic studies

A first IARC working group met in 1987 and decided that crystalline silica is a probable carcinogen to humans (group 2A), i.e., the data available at that time suggested a possible causal relationship, but chance, bias and confounding could not be excluded. In fact, only a few of the epidemiologic studies investigated the co-exposure to other occupational carcinogens – such as arsenic, nickel and radon – and the contribution of cigarette smoking [12]. Ten years later, a second IARC working group met; they reviewed more scientific papers and nine cohorts and mortality studies published since the earlier meeting [13–21]. Those nine studies were considered by that working group to be less potentially confounded and led to the decision that crystalline silica from occupational sources is carcinogenic to humans (group 1) [12]. Table 1 shows the IARC classification of carcinogenic agents and mixtures.

Subsequent reviews of the epidemiologic evidence by Hessel et al. [10] and Soutar et al. [22] have called into question the IARC classification of silica as a confirmed human carcinogen,

Table 1. IARC's evaluations of the strength of the evidence for carcinogenicity [7]

Group	Overall evaluation	Comment
Group 1	The agent (mixture) is carcinogenic to humans	The exposure circumstance entails exposures that are carcinogenic to humans
Group 2A	The agent (mixture) is probably carcinogenic to humans	The exposure circumstance entails exposures that are probably carcinogenic to humans
Group 2B	The agent (mixture) is possibly carcinogenic to humans	The exposure circumstance entails exposures that are possibly carcinogenic to humans
Group 3	The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans	The evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals
Group 4	The agent (mixture) is probably not carcinogenic to humans	There is evidence suggesting lack of carcinogenicity in humans and in experimental animals

Table 2. Summary of least confounded epidemiologic studies of crystalline silica and lung cancer

Author, year [ref]	Study design	Population	E-R analysis/trend	Risk (CI)	Control for smoking	Comments
McLaughlin et al., 1992 [13]	Nested case-control	China: pottery workers	Yes/No	OR 1.8–2.1	Yes	Exposure-response trend was not statistically significant
Dong et al., 1995 [16]	Cohort	China: refractory brick workers: silicotics and non-silicotics	Yes/Yes	Silicotics: SRR 2.1 (NR) Non-silicotics: SRR 1.1 (NR)	Yes	Exposure-response trend was found for lung cancer mortality with years since first employment and with severity of silicosis
Guenel et al., 1989 [15]	Cohort	Denmark: stone workers	No	SIR 2.0 (1.5–2.7)	No	Adjusted for regional differences in smoking
Partanen et al., 1994 [28]	Cohort	Finland: silicosis registry	No	SMR 2.9 (2.4–3.5)	Yes	
Cherry et al., 1998 [14]	Nested case-control	UK: pottery workers: silicotics and non-silicotics	Yes/Yes	OR 1.66 (1.14–2.41)	Yes	Association with average silica concentration but not for duration of exposure nor for cumulative exposure.
Merlo et al., 1991 [17]	Retrospective cohort study of mortality	Italy: refractory brick workers	Yes/Yes	SMR 1.5 (1.0–2.1)	Yes	Smoking habits of cohort were compared with the national population
Costello and Graham, 1988 [18]	Cohort mortality study	USA: granite workers	Yes/No	SMR 1.2 (1.0–1.4)	No	
Steenland and Brown, 1995 [20]	Cohort study	USA: goldmine workers	Yes/No	SMR 1.1 (0.9–1.3)	Yes	No exposure-response trend by cumulative exposure; low radon/arsenic exposure
Checkoway et al., 1996 [21]	Cohort mortality study	USA: workers at diatomaceous earth plants	Yes/Yes	SMR 1.4 (1.05–1.8)	Yes	Smoking habits of cohort were compared with smoking prevalence
Amandus et al., 1991 [24]	Cohort mortality study	USA: dust trades workers	No	SMR 2.6 (1.8–3.6)	Yes	No quantitative exposure data

E-R = exposure response, CI = confidence interval, OR = odds ratio, SRR = standardized rate ratio, SIR = standardized incidence ratio, SMR = standardized mortality ratio, NR = not reported.

citing concerns about uncontrolled confounding by smoking, radon and other factors, and some inconsistencies in dose-response trends. Nonetheless, there is now relatively broad acceptance internationally that crystalline silica poses a lung cancer risk, albeit not as potent as seen for asbestos. Table 2 lists the larger epidemiologic studies of silica-exposed workers and individuals with silicosis (silicotics).

• Exposure-response studies

The most convincing report of a carcinogenic effect is contained in the paper by Steenland and co-workers [23], which was a pooled exposure-response analysis that included ten exposure cohorts of silica-exposed workers. The authors developed comparable quantitative exposure estimates by occupation and time for the ten cohorts, hence permitting a uniform approach to data analysis despite the differences in analytic methods in the

various cohorts. The results demonstrate a clear relationship ($P = 0.0001$) between cumulative exposure to silica in different industries and lung cancer mortality [23]. Notably, there were excesses seen both in underground miners where radon or diesel fumes may occur and in other industries where there is minimal exposure or exposure to these agents only, thus indicating an absence of confounding.

• Descriptive studies

Descriptive epidemiologic studies exhibit a lower degree of certainty, since they do not point clearly to the exposure factor or factors that might have caused the excess of disease. In other words, competing potential causes, other than the one studied, have to be eliminated.

Soutar et al. [22] reviewed descriptive studies of ten silica-exposed populations that, except for one, were free of selection bias. Seven of the remaining nine showed elevated risks for lung cancer (standardized mortality rates between 1.13 and about 3) in some selected subgroups.

• Studies of silicosis case registers

Two case register studies of silicosis [24–28] demonstrated the least-biased (well-documented silicosis and low probability of confounding) relationship between silicosis and excess lung cancer and therefore were considered by IARC's working group [1]. Though studies on silicotics give

indirect information about silica exposure and thus a way to study the association between this exposure and lung cancer, it is difficult to draw conclusions from studies of silicosis case registers. Moreover, the question emerges whether the excess of lung cancer is limited only to those with silicosis. We address this dilemma later in our review.

Studies of silicosis case registers can present significant selection and information bias: the subject might be included in registers not because they have the disease, but because they smoke and have smoking-related symptoms or chest radiographic changes, or they could even have other diseases that mimic silicosis [22]. Since these individuals are at increased risk to develop lung cancer, enrolling them in the study could end in an increased cancer rate. Furthermore, the diagnosis of lung cancer is more likely in registered silicotics who receive close medical care than in non-registered silicotics.

Hence, the increased risk of lung cancer in subjects with silicosis might be an effect of the fibrosis rather than a direct effect of silica exposure. The possibility that silicosis is a necessary condition for elevated risk of lung cancer in silica-exposed workers has important implications. Clarification of this issue would influence the determination of exposure standards, the designation of medical monitoring programs, and the outcomes in medico-legal circumstances. Checkoway and Franzblau [29] published a review of published cohort studies that examined lung cancer risk in relation to both silica exposure and silicosis. The authors found that "the association between silica and lung cancer is generally, but not uniformly, stronger among silicotics than nonsilicotics." In their review they underline the fact that the reviewed studies were limited by biased diagnosis of silicosis, inadequate exposure assessment, and the fact that there was a strong correlation between silica exposure and silicosis, thus impeding the description of the individual contributions to lung cancer risk. They affirm that more epidemiologic evidence is needed for determining whether the elimination of new cases of silicosis would make the excess of lung cancer from silica exposure disappear.

Conclusion

In this article we presented the evidence of a causal relationship between crystalline silica and lung cancer. Crystalline silica is considered carcinogenic to humans, and was declared as such in 1997 by the IARC and soon after by the Israel Interdisciplinary Committee of Carcinogenic, Mutagenic and Teratogenic

carcinogenicity of a substance or other health hazard should aim for the highest degree of evidence available, when the available information is not sufficient to determine the probability that the studied substance would cause the disease, its potential harm should be considered in various exposure circumstances. On balance, we believe that the determination that crystalline silica is carcinogenic to humans is evidence based.

With regard to the question whether exposure to silica is associated with increased risk of lung cancer only if silicosis is present, in our judgment this concept has not yet been established. Thus, the presence of silicosis in a silica-exposed worker is not an obligatory finding for an increased risk of lung cancer.

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Policy makers must take steps to prevent this life-threatening disease among workers exposed to silica

Substances. Nevertheless, evidence of the association is not fully consistent, and the effects are not especially strong as compared to asbestos or cigarette smoking, for example. Asbestos, in fact, is a well-established human carcinogen. Major epidemiologic evidence that demonstrated a lung cancer effect was published as early as 1955 in England and 1964 in the United States, showing tenfold and sevenfold increases in lung cancer risk in exposed workers respectively [5]. Less strong is the epidemiologic evidence for crystalline silica carcinogenesis. A meta-analysis performed by Steenland and Stayner [30] demonstrated a relative risk of 1.3 from silica exposure studies, and 2.3 from studies among silicotics. In a later study, conducting a pooled exposure-response analysis, Steenland and team [23] found a trend of odds ratios (1.0-1.6) with cumulative exposure to silica.

In the present article we reviewed the differences of opinion as to whether scientific evidence is adequate to conclude that a substance has carcinogenic potential. Although evaluating the

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