

Evaluation of crystalline silica as a threshold carcinogen

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Klein AK, Christopher JP. Evaluation of crystalline silica as a threshold carcinogen. *Scand J Work Environ Health* 1995;21 suppl 2:95—8.

The Office of Scientific Affairs within the California Department of Toxic Substances Control has reviewed the evidence on the carcinogenicity of crystalline silica. The authors consider the current evidence to be convincing to classify crystalline silica as a human carcinogen by the inhalation route. The weight of evidence for both rats and humans indicates that fibrotic and silicotic lesions in the lung result from inhalation exposure to crystalline silica and that lung cancer is secondary to those lesions in the lung. Thus crystalline silica should be considered to have a threshold for causing cancer. The critical exposure criterion is that exposure level which does not produce a fibrogenic or silicotic response; thus it is necessary to determine the no observed adverse effect level (NOAEL) for fibrogenesis. The authors recommend that the United States Environmental Protection Agency review all appropriate studies to develop a reference concentration that can be used for regulatory purposes.

Key terms fibrosis, human carcinogen, inhalation, lung cancer, reference concentration, silicosis, threshold.

Crystalline silica has been found in ash produced when certain biogenic materials are burned to generate electricity. These materials include rice hulls, wood, straw, and sewage sludge. The California Department of Toxic Substances Control has been struggling with the following two questions: (i) should ash containing respirable crystalline silica be classified as hazardous waste, and (ii) what is a safe level of exposure for respirable crystalline silica? In order to answer both questions, regulatory agencies must identify the primary human health hazard that is posed by exposure to silica, delineate the probable mechanism by which silica causes the health effect, and, finally, provide a toxicity criterion value that can be compared with potential ambient exposures to determine the risk from these exposures and to establish safe emission levels. Neither United States or California regulatory agencies have developed accepted ambient criterion values for respirable crystalline silica. The only possible values available are those that are specific for occupational exposure: threshold limit values (TLV) published by the American Conference of Governmental Industrial Hygienists, permissible exposure limits (PEL) from the Occupational Safety and Health Administration, and recommended exposure limits (REL) listed by the United States National Institute for Occupational Safety and Health (1). These values are meant to be used in the workplace and are not casually applied to nonoccupational settings (2). The Office of Scientific Affairs within the California Department of Toxic Substances Control reviewed the literature on the adverse health effects of crystalline silica — silicosis and respiratory cancer — and determined that the weight of evidence suggests the following: (i) silica should be classified as a known human carcinogen and (ii) the safe level of silica should be based on a threshold model in which fibrotic

lung disease is a necessary precondition for the appearance of cancer (3—5).

Classification of respirable crystalline silica as a known human carcinogen

In 1987, the International Agency for Research on Cancer (IARC) published its evaluation of the carcinogenic risk of silica. It concluded that the evidence was sufficient to show that crystalline silica causes cancer in experimental animals, but the evidence was limited regarding the carcinogenicity of silica for humans (6). In 1990, IARC published the results of several epidemiologic studies on the relationship between lung cancer and silica (7). In addition, there have been numerous other studies reported in the literature. The workers evaluated by IARC in both volumes and elsewhere can be divided into the following three groups: (i) workers exposed occupationally to silica and a variety of other agents that can cause lung cancer, (ii) workers probably exposed only to silica in their work environment, and (iii) workers with silicosis. In most of the studies described in the 1987 IARC report, little or no data were provided on smoking or relative exposure levels. However, as a group they show an increase in silicosis and lung cancer among silica-exposed workers (6). We focus on studies in groups ii and iii, since they provide information relevant to the question of the carcinogenicity of silica. Eleven of the twelve selected studies of workers (8—19) indicate that exposure to silica dust results in a modestly increased risk of lung cancer, with a statistical significance of < 0.05 in five studies (11, 12, 15, 18, 19). The observed:expected ratios ranged from 1.2 to 2.9 for lung cancer. Simultaneous exposure to other carcinogenic agents cannot be ruled out in any of these studies. However, ceramic, granite, and

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stone workers are exposed primarily to silica, and nine of these studies focused on workers in these industries. Eight of the nine studies showed an increased risk of lung cancer, the single exception being the study by Costello & Graham (8).

Relationship between silicosis and lung cancer

Group iii studies (ie, lung cancer among workers with silicosis) show that the association becomes much stronger in silicotic persons, the observed:expected ratios ranging from 1.7 to 6.9 in 10 studies (3–5, 20–26). In three of the four studies comparing silicotic and nonsilicotic persons (3–5, 20), lung cancer risk was increased twofold for the silicotics, whereas the number of observed lung cancer cases among the nonsilicotics was virtually unchanged from that expected (observed:expected 1.3, 0.9, 1.0) (3–5). In two studies of Italian ceramic workers and German slate workers, there was little or no known exposure to other lung carcinogens in the workplace (4, 5). In one study of Italian silica brick workers, the mortality from respiratory cancer was nearly the same for silicotic and nonsilicotic persons (observed:expected 1.7 and 2.1, respectively) (20).

In addition to the presented studies at least eight other epidemiologic studies have been published recently on the relationship between work in dusty trades, silicosis, and lung cancer. Meijers et al (27) did not find any relationship between work in Dutch dusty trades and lung cancer. Hessel et al (28) and Carta et al (29) did not find any relationship between lung cancer and the presence or severity of silicosis in South African and Sardinian miners. However, four studies found a strong association between silicosis and the incidence of or mortality from lung cancer. Forastiere et al (30) and Chia et al (31) showed an excess risk of lung cancer among silicotic patients which could not be accounted for by smoking. Sherson et al (32) found a positive correlation between silicosis in long-term employees of foundries (more than 20 years) and lung cancer incidence. Infante-Rivard et al (33) reported that the risk of death from lung cancer was more than three times higher than expected for silicotic workers. In a recent extensive review of the epidemiologic data that includes an examination of the relationship between silicosis and lung cancer, Goldsmith (34) concluded that chronic silicosis predisposes to an increased lung cancer risk.

These observations from humans are consistent with results seen when rats, mice, or hamsters are exposed to crystalline silica. Saffiotti et al (35) reported that, in rats, lung tumors are seen only when there is also a fibrotic response. Histologically, epithelial hyperplasia was nearly always associated with areas of fibrosis. Mice develop fibrosis but no persistent epithelial hyperplasia and no tumors. Hamsters exposed to crystalline silica in the respiratory tract do not mount a fibrotic response and do not get lung tumors. Saffiotti and his co-workers (35) postulated that these responses in rodent species may be representative of different susceptibilities in subsets of the human population.

Discussion

There are two conclusions that can be drawn from these data. First, the studies presented and published by IARC and elsewhere provide compelling and sufficient evidence for the carcinogenicity of respirable crystalline silica in humans. Second, increased lung cancer risk is concentrated among the exposed workers who develop silicosis (36). The question is whether it is plausible that the sequence of events culminating in silicosis occurs independently

from the direct action of crystalline silica on cellular DNA (deoxyribonucleic acid). This direct action could result in the initiation of the carcinogenic process. Silica has been shown to cause the formation of micronuclei in cells and the transformation of tissue-cultured cells (6). However, crystalline silica does not appear to be mutagenic in bacterial systems and does not induce sister chromatid exchanges, chromosome aberrations, or aneuploidy (6). Daniel et al (this volume) have shown that silica can interact directly with DNA by hydrogen bonding in vitro. Another question that must be addressed when the possibility of silica acting directly on DNA is considered is "Do lung epithelial cells have the capability to phagocytize particles so that silica can gain access to the DNA of the cell type that eventually becomes cancerous?" In an in vitro experiment, Daniel et al (this issue) observed silica particles in the nuclei of cultured lung epithelial cells from rats after the application of crystalline silica. In summary, there is some evidence that crystalline silica has the ability to enter the cell nucleus and interact directly with DNA under in vitro conditions but, as yet, there is no evidence that these events occur in vivo and little evidence that silica is mutagenic.

The epidemiologic evidence examined in this paper and the animal studies summarized by Saffiotti et al (35) and Saffiotti & Stinson (37) suggest that fibrogenic and carcinogenic processes do not occur independently, but that silicosis is a necessary precondition for carcinogenesis. If so, there are several postulated mechanisms (38, 39) as Williams & Saffiotti (this volume) have observed. First, fibrosis causes structural disorganization of the microstructure of the lungs. This disorganization leads to the production of various cytokines causing growth disturbances with subsequent chronic dysplasia, increased proliferation of epithelial cells adjacent to fibrotic areas, and serendipitous survival of mutated cells in that epithelial population. Second, with increased fibrosis, the lung is less able to clear other bioactive agents with consequent increased opportunity for interaction between these agents and susceptible cells (40). Third, pulmonary macrophages, damaged by engulfing inhaled silica particles, produce cytokines and possibly set off autoimmune reactions which could accelerate not only fibrotic changes in the lung but also the proliferation of mutated cells (38).

Concluding remarks

On the basis of this review we believe that there is sufficient evidence to classify crystalline silica as a human carcinogen. Therefore, wastes containing crystalline silica should be considered hazardous and assessed for potential carcinogenic risk. We agree with the recommendation made by the California Environmental Protection Agency, Office of Health Hazard Assessment, that the long-term effects of inhaling crystalline silica should be tested by the US National Toxicology Program. The testing protocol should address the following questions: (i) do lung cancers appear only in rodents with fibrosis, (ii) are pulmonary tumors located in the same area as the silicotic nodules, (iii) does fibrosis occur before neoplasia or at lower doses, (iv) does the severity of fibrosis correlate with the incidence of tumors, (v) does silica cause tumors in tissues other than lung, and (vi) what is the exposure level that does not produce a fibrogenic or silicotic response?

Our opinion is that the linearized multistage model should not be used to estimate carcinogenic risks due to ambient silica exposure or to develop toxicity criterion values. This linearized model was developed from studies of mutagenic radiation effects and

assumes a nonthreshold mechanism for carcinogenicity. Crystalline silica does not appear to be mutagenic (6). Instead, fibrogenesis, the *sine qua non* of the carcinogenic response to silica in humans, seems to exhibit a threshold.

We recommend that the US Environmental Protection Agency establish a reference concentration for crystalline silica based on a no observed adverse effect level (NOAEL) for fibrogenesis. Rice & Stayner (this issue) calculated NOAEL values ranging from 7 to 30 $\mu\text{g} \cdot \text{m}^{-3}$ from human epidemiologic studies on silica exposure and silicosis. Applying an uncertainty factor of 10 to these values to protect sensitive human subpopulations (40) provides possible toxicity criterion values or safe levels of 0.7 to 3.0 $\mu\text{g} \cdot \text{m}^{-3}$. These levels assume that the development of silicosis is the critical threshold event. They are higher than those based on cancer slope factors calculated using the linearized multistage model. Using the multistage model to derive safe levels depends on the assumption that the development of lung cancer is independent of the development of silicosis and that any exposure to crystalline silica poses some risk. The safe level of silica in air corresponding to a one-in-a-million risk is 0.02 $\mu\text{g} \cdot \text{m}^{-3}$ calculated using a cancer slope factor of $4.5 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ and 0.04 $\mu\text{g} \cdot \text{m}^{-3}$ using a cancer slope factor of $2.3 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ (Collins & Marty, this issue). The evidence supports the NOAEL approach because it best reflects the probable mechanism by which silica causes cancer in humans. Although using this approach may result in slightly higher safe levels, we believe these levels would adequately protect human health.

Disclaimer

The views expressed herein by the authors do not necessarily represent the official policies of the California Department of Toxic Substances Control or of any other state or federal agency.

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