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Future research needs in the silica, silicosis and cancer field

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Biological evidence of the relationships among silica exposure, silicosis, and the risk of cancer is evolving. When the First International Symposium on Silica, Silicosis and Cancer convened in 1984, suspicions based on studies with laboratory rats were raised that the inhalation of silica dust may produce pulmonary tumors. In addition there was limited information from epidemiologic studies on silica-exposed workers and compensation claimants with silicosis who appeared to have elevated risks for pulmonary and gastric malignancies. The findings were generally supportive of a hypothesis articulated in the mid-1930s by a British pathologist that either silica was carcinogenic or silicosis acted as a cancer precursor (1).

In the last decade the hypothesis was re-examined by the scientific community, including four major agency reviews of the silica and cancer issue by the International Agency for Research on Cancer (2), the Science Advisory Panel of California's Proposition 65 (3), the Australian National Occupational Health and Safety Commission (4), and the Occupational Disease Standards Panel of Ontario, Canada (5). In addition there have been numerous published literature reviews (6—10) on this topic. This supplement of the *Scandinavian Journal of Work, Environment & Health* contributes to the body of knowledge by assembling key papers from the Second International Symposium on Silica, Silicosis, and Cancer convened in October 1993 in San Francisco, California.

Purpose

The purpose of this paper is to summarize the current state of knowledge and to suggest areas needing further research. It is clear by the scope of the papers presented at the Second Symposium that many new insights have been gained during the last 10 years of investigation and some new disciplines have begun to focus on this area of investigation. Specifically, the results by investigators such as Stopford & Stopford and Dosemeci et al in this issue expand our insights into the exposure assessment and industrial hygiene aspects of silica emissions. The work in this field has stimulated the interests of the physicochemistry community represented by Fubini et al, Guthrie & Heaney, and Shoemaker et al. They have raised perceptive questions about differential toxicity for silica particles according to surface area and surface chemistry, the freshness of particulate cleavage, and the roles played by other surface metals. Rabovsky reminds us that the biological activity of amorphous silica, including biogenic silica fibers, remains to be determined. These areas seem ripe for new collaborations between the disciplines of mineralogy, environmental hygiene, and silica toxicology. The importance of the accurate measurement of silica exposure and cumulative lung burdens remains a priority for both epidemiology and for hazard surveillance studies. Although there is extensive literature linking silica dust measurements to the risk of chronic silicosis, only during the past three to five years have adequate industrial hygiene data become available for dose-response studies of occupational silica exposure and cancer (11—13).

In the field of tumor biology, data from two rat studies in the past seven years confirmed the initial findings that inhaled silica can produce pulmonary cancers (14, 15). (See Muhle et al, this issue, for additional findings.) Saffiotti and his colleagues described the histogenesis of rat lung reactions to instilled quartz leading to lung tumors — mostly adenocarcinomas — adjacent to silicotic granulomas, with an emphasis on progressive hyperplasia of alveolar type II epithelial cells (16). There remains the question of why rats are responsive to the fibrotic and oncologic potential of silica, while other rodents appear to be either resistant or nonresponsive (17). The work of Williams et al and Daniel & Saffiotti in this issue have added to the biochemical understanding of the likely role silica plays in carcinogenesis. In particular, the ability of silica to bind with DNA (deoxyribonucleic acid) in vitro and its mechanistic links through transforming growth factor β1 suggest

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new avenues for additional investigation. In addition, while freshly cleaved silica has been known previously to be more toxic and to produce greater levels of reactive oxygen than aged dust, Shoemaker and his colleagues have provided new vital evidence of these phenomena.

New epidemiology studies of populations exposed to silica continue to bring evidence to this field. Although practitioners in occupational medicine have known for decades the role of silica in causing silicosis and methods to prevent this disease, information (this issue) on residual silicosis rates in Ontario, Canada, and China and among ceramic workers in Italy helps define the level of risk for exposed workers. New findings such as those by Rosenman et al, Dong and his co-workers, Merlo and his colleagues in this issue, Finkelstein (31), and Goldsmith and his co-workers (18) add to the mounting literature showing that silicotics have significantly higher risks for lung cancer. These findings must be considered in context. Silicotics are less healthy than the general population, including increased cancer risks, but why are the cancer risks now emerging and what are the pathological and biochemical mechanisms to explain the current findings?

Despite numerous studies of diverse occupational cohorts, the question of association between quartz exposure and lung cancer continues to fuel scientific debate and new research investigations [such as the immunologic role of silica in carcinogenicity (19)]. Studies asking similar questions in different populations and using a variety of methods have arrived at contradictory conclusions. It is difficult to quantify silica exposures accurately, particularly when cohorts are assembled for historical prospective investigation. Furthermore, exposures to other toxic agents such as radon, smoking, and other known carcinogens make this task more difficult. Misclassification of exposure and patterns for selecting study subjects may act to bias the risk measures. Despite these common limitations, some studies (11, 12, 20—24) presented in the Second Symposium or published elsewhere suggest an increased lung cancer risk even in the absence of radiological silicosis. Other research (13) suggests no association. When complete, the preliminary research presented by McDonald et al and de Klerk and his colleagues in this issue will expand data in this evolving field.

Another discipline being applied in this area is quantitative risk assessment (25), which seeks to extrapolate the potential cancer and noncancer risks of silica relative to occupational and ambient environments. Although some authors suggest that there is no need to conduct risk determinations (26), this supplement of the *Scandinavian Journal of Work, Environment & Health* has included five new perspectives on the issue by Collins & Marty, Goldsmith et al, Klein & Christopher, Rice & Stayner, and Zhong & Li. The methodology for occupational risk assessment is in the process of being modified (27), and new documents relative to this question are being planned by agencies in Australia and the United States. Thus there is likely to be more, rather than less, quantitative risk assessment focusing on silica in the future.

What next?

Ultimately, a determination must be made on the best available evidence as to the probable health effects of exposure to quartz at various exposure levels. In this instance, the evidence supporting concern about cancer risk among workers with silicosis is generally consistent, temporally appropriate, consistent with laboratory models, and it also has overall coherence (9). In some investigations, but not all, exposure-response or dose-response relationships have been reported (11, 12).

There is no debate about the need to eliminate exposure conditions which inevitably lead to silicosis (32). The extent to which additional measures are justified to control exposures producing silicosis depends on the interpretation of often contradictory literature. Perhaps current laboratory investigations directed towards improving our understanding of the toxicity of crystalline silica dusts combined with longer follow-up of occupational cohorts will provide the scientific basis for such action. In the meantime, the public health dictum of prudent action in the face of uncertainty should guide preventive efforts. Specifically, preventive efforts should be intensified to control silica emissions in sand blasting, mine drilling, and other types of work in which high silica dust levels occur (28, 29). The need for more precise investigation should not be used to avoid the imperative of health protection. Standard setting and the adoption of health protective measures are an iterative process: the best available information should inform the best course of action. Experience gained in the implementation of new approaches should be evaluated through ongoing hazard and health surveillance, as well as through continued research. As more information emerges, recommendations for and the application of improved dust control practices must evolve. And in no instance should the egregious exposure conditions [described by Weisenfeld et al in 1993 at the Second Symposium (30)] continue unabated, because these conditions will inevitably lead to silicosis and perhaps to lung cancer. Thus the application of current knowledge will go far to eliminate the possibility of future disease.

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