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An Exposure-Response Threshold for Lung Diseases and Lung Cancer Caused by Crystalline Silica

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Whether crystalline silica (CS) exposure increases risk of lung cancer in humans without silicosis, and, if so, whether the exposure-response relation has a threshold, have been much debated. Epidemiological evidence is ambiguous and conflicting. Experimental data show that high levels of CS cause lung cancer in rats, although not in other species, including mice, guinea pigs, or hamsters; but the relevance of such animal data to humans has been uncertain. This article applies recent insights into the toxicology of lung diseases caused by poorly soluble particles (PSPs), and by CS in particular, to model the exposure-response relation between CS and risk of lung pathologies such as chronic inflammation, silicosis, fibrosis, and lung cancer. An inflammatory mode of action is described, having substantial empirical support, in which exposure increases alveolar macrophages and neutrophils in the alveolar epithelium, leading to increased reactive oxygen species (ROS) and nitrogen species (RNS), pro-inflammatory mediators such as TNF-alpha, and eventual damage to lung tissue and epithelial hyperplasia, resulting in fibrosis and increased lung cancer risk among silicotics. This mode of action involves several positive feedback loops. Exposures that increase the gain factors around such loops can create a disease state with elevated levels of ROS, TNF-alpha, TGF-beta, alveolar macrophages, and neutrophils. This mechanism implies a "tipping point" threshold for the exposure-response relation. Applying this new model to epidemiological data, we conclude that current permissible exposure levels, on the order of 0.1 mg/m^3, are probably below the threshold for triggering lung diseases in humans.

KEY WORDS: Crystalline silica; dose-response model; exposure-response; lung cancer risk; mathematical model; silicosis

1. INTRODUCTION: IS CRYSTALLINE SILICA HAZARDOUS AT CURRENTLY PERMITTED LEVELS?

Crystalline silica (CS) is one of the most studied, yet most controversial, of substances currently classified as known human carcinogens.[1] Like other poorly soluble particles (PSPs), it has been associated with a variety of possible lung diseases. In addition to silicosis, nonspecific responses such as chronic inflammation, fibrosis, lung cancer,[2,3] and, possibly, chronic obstructive pulmonary disease (COPD)[4] have been suggested as possible consequences of high levels of exposure to CS and/or other dusts and respiratory irritants, including cigarette smoke.

Whether CS at currently permitted exposure levels (such as OSHA's PEL-equivalent of 0.1 mg/m^3 of respirable CS, or NIOSH's currently recommended exposure limit of 0.05 mg/m^3 for up to a 10-hour workday) creates an excess risk of lung disease has been much debated, but without clear resolution. For decades, scientists, regulators, and occupational health and safety risk managers have wrestled

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with the following three key questions about human health risks from CS exposures.

(1) Do the causal exposure-response relations between CS exposure and exposure-associated lung diseases have thresholds?
(2) If so, are the exposure levels that cause increased risks of such diseases above or below currently permitted exposure levels?
(3) Are risks of some diseases (such as lung cancer) elevated only at exposures that cause other diseases (e.g., silicosis)?

Expert opinions on all three questions have been sharply divided. Epidemiology, risk assessment, and toxicological research have done much to illuminate the difficulty of answering them decisively,[5,6] but have so far produced few unequivocal answers.

This article examines the causes and exposure-response relations for CS-associated lung diseases, drawing on recent advances in the biology of lung diseases caused by PSPs, which include CS as a special case. For PSPs, chronic inflammation of the lung plays a crucial role in causing lung diseases such as asbestosis, silicosis, fibrosis, COPD, and lung cancer.[2,7–12] We seek to shed new light on the exposure-response relation for CS-associated lung diseases by applying recent insights into this inflammatory mode of action to model the relation between exposure concentrations and durations and the resulting cascade of changes in the lung environment that can hasten the onset and progression of lung diseases.

2. CS EPIDEMIOLOGY IS AMBIGUOUS

A number of epidemiological studies have reported that lung cancer risk is elevated among patients with silicosis, especially among those who smoke.[13–15] Others find no such association,[16–20] and a recent meta-analysis concluded that the association disappears when confounders (such as smoking or occupational coexposures) are correctly adjusted for.[6] Influential investigators have stated that risks of lung cancer appear to them to be elevated even at exposure levels below current standards.[21,22] However, we believe that failure to correctly account for exposure measurement errors invalidates this interpretation of the data, as explained below (see Fig. 1). Risk of COPD and reduced lung function appear to be elevated at estimated occupational exposures above 0.1–0.2 mg/m^3 of silica dust for at least 30–40 years, independent of silicosis,[4] but a recent study of Vermont granite workers found no evidence of increased lung cancer risk due to silica exposure in occupational cohorts, even at the high exposure levels where mortalities due to silicosis and other nonmalignant respiratory illnesses were elevated.[23] The apparent paradox of reduced risk of lung cancer in some workplaces with relatively high levels of silica exposure has also been noted,[24] further complicating any conjectured causal relation between silica exposure and lung cancer. One possible explanation for these differences among studies might be the different (and often highly uncertain) compositions of the dusts in different studies.[25] For example, the toxicity of quartz particles depends on detailed properties of the fracture surfaces, with freshly fractured silica typically being more potent than aged silica in eliciting various cellular responses, including production of reactive oxygen species (ROS) by alveolar macrophages.[26] Differences in dust composition and ages might therefore create heterogeneous exposure-response relations, perhaps triggering different response mechanisms. In this case, biologically effective doses could be very uncertain, even if respired quantities of dust were measured accurately.

Whether or not silicosis increases lung cancer risk, epidemiological studies have not yet revealed whether silicosis is a necessary precondition for increased risk of lung cancer due to CS exposure.[6,27] Yet, the answer is vital for current practical regulatory risk management decisions: "If silicosis were the necessary step leading to lung cancer, enforcing the current silica standards would protect workers against lung cancer risk as well. Alternatively, a direct silica-lung cancer association that has been suggested implies that regulatory standards should be revised accordingly."[24]

Somewhat reassuringly, the increased risk of lung cancer among CS-exposed workers is most apparent "when the cumulative exposure to silica is well beyond that resulting from exposure to the recommended limit concentration for a prolonged period of time,"[28] suggesting that enforcing current standards would protect workers from CS-associated lung cancer risks. However, other researchers have cautioned that, "The hypothesis of a silicosis-mediated pathway [for lung cancer], although more consistent from an epidemiological perspective, and reassuring in terms of the effectiveness of current standards in preventing lung cancer risk among silica exposed workers, does not seem to

explain elevated risks at low silica exposure levels."[29] Thus, the relation between silicosis and lung cancer has remained uncertain, based on various published interpretations of epidemiological evidence. There is no clear evidence that lung cancer risk is elevated in the absence of silicosis, but the question is unsettled. The following statement[27] succinctly captures the present state of the art: "A recent meta-analysis of 30 studies found a pooled relative risk (RR) of lung cancer of 1.32 (95% CI, 1.23–1.41) in subjects exposed to CS. In the same investigation, the pooled RR was 2.37 (95% CI, 1.98–2.84) in silicotics only (based on 16 studies), whereas no increase in risk emerged in non-silicotics (pooled RR = 0.96, 95% CI, 0.81–1.15, based on eight studies). The authors concluded that silica may induce lung cancer indirectly, probably through silicosis." Such evidence, although not conclusive, favors the hypothesis that lung cancer risk is elevated among silicotics, but not among nonsilicotics.

We believe no credible epidemiological evidence actually shows that CS increases lung cancer risk at exposure levels that do not also cause silicosis. Rather, the foregoing observation that the "hypothesis of a silicosis-mediated pathway . . . does not seem to explain elevated risks at low silica exposure levels," as well as published reports of elevated risk of lung cancer at exposures below those that cause silicosis,[21] misinterpret the available epidemiological evidence. They do so by mistakenly interpreting exposure-response relations estimated from epidemiological studies (all of which have missing and highly uncertain and variable (usually, "reconstructed") exposure data) as providing valid evidence of "elevated risks (of lung cancer) at low silica exposure levels." But they do not. At most, such studies provide evidence of elevated lung cancer risks at low estimated levels of silica exposure. These are entirely different propositions, as explained next. When uncertainties in exposures are accounted for in the risk models, there is no evidence that risks are elevated at low levels of silica exposure (specifically, at or below those allowed by current standards). Studies that conclude that relatively low exposures to silica (below currently permitted levels, and below levels that cause silicosis) increase lung cancer risk are undermined—without exception, as far as we know—by important upward biases in their low-exposure risk estimates. These biases result from imperfect control of potential confounders, ignored model specification errors and uncertainties, and unmodeled errors and uncertainties in exposure estimates. Each of these limitations is briefly discussed next.

2.1. Imperfectly Controlled Confounding

Perhaps the most familiar threat to valid inference from epidemiological studies of CS is confounding, especially by cigarette smoking and by occupational co-exposures. For example, a recent study[30] reported that: "In a crude analysis adjusted for smoking only, a significant trend of increasing risk of lung cancer with exposure to silica was found for tin, iron/copper miners, and pottery workers. But after adjustment for relevant occupational confounders (arsenic and polycyclic aromatic hydrocarbons), no relationship between silica and lung cancer can be observed."

The possibility of such confounding has been well recognized and much discussed in the epidemiological literature on CS, but inability to rigorously and fully control for plausible confounders in most past studies continues to limit the validity of the exposure-response relations inferred from these studies.[6] Attempts to adjust for possible confounding by smoking, based on subjective estimates of smoking habits and their effects (and an assumed bias model), have modestly reduced the estimated relation (standardized mortality ratio) for silica exposure and lung cancer (from 1.6 to 1.43).[21] Other assumptions and models might lead to further reductions. Currently proposed methods to account for most of the bias due to confounding by smoking, using differences between COPD and lung cancer rates to estimate bias effects,[31] have not yet been applied to CS, leaving open the question of how much of the apparent relation between CS exposure and lung cancer risk would be eliminated by fully controlling for smoking effects. Similarly, it remains unknown whether fully controlling for occupational co-exposures would fully eliminate the apparent associations between silica exposure and lung cancer risk (in other data sets as well as the one for Chinese miners and pottery workers), since most other studies have not provided the needed co-exposure data.[30]

2.2. Unmodeled Errors and Uncertainties in Exposure Estimates Can Inflate Low-Exposure Risk Estimates and Hide True Thresholds

Perhaps the single most important limitation in CS epidemiology is that true individual exposures

to CS of various types and toxicities are unknown. Therefore, guesses about exposures are used instead, typically based on reconstructions of exposure histories from estimated job exposure matrices, together with simplifying (and inaccurate) assumptions, such as that all silica dust has the same average toxicity or carcinogenic potency value. Exposure-response relations are then fit to the guessed-at exposures and observed responses. Although there is a sophisticated statistical literature on how to use such uncertain predictors in regression models,[32] these appropriate "errors-in-variables," measurement error, and missing data methods have typically not been used in the CS epidemiology literature. Instead, reconstructed exposure estimates are often treated as if they were true (error-free) data, for purposes of fitting statistical models. Then, unwarranted conclusions are drawn that fail to explicitly model and correct for the effects of errors in exposure estimates.[33] This can create large, unpredictable biases in multivariate regression coefficients and other measures of exposure-response association.[34]

If the true exposure-response relation is a threshold function, then failing to explicitly model errors and uncertainties in exposure estimates can smear out the threshold in the estimated exposure-response models, giving a misleading appearance of a smooth, s-shaped exposure-response function, complete with an apparent (but not real) smooth biological gradient (i.e., higher probabilities of response at higher estimated exposure levels) and elevated risks at estimated exposure levels well below the true threshold. Such incorrect modeling will over-estimate excess risks at exposures below the threshold, and underestimate risks at exposures greater than the threshold.

To illustrate how a smoothly increasing estimated exposure-response relation arises from a true threshold relation when there are unmodeled errors in the exposure estimates, consider the following simple hypothetical example. Suppose that true individual exposure rates are uniformly distributed between 0 and 20 mg/m^3-years (for 40-year exposure durations), and that the true exposure-response relation has a threshold at 15 mg/m^3-years, so that the true risk of lung cancer is 0 for exposures of 15 mg/m^3-years or less, and 1 for exposures above 15 mg/m^3-years. Suppose that estimates of individual exposures are unbiased, but with some variance around their means, representing estimation errors. For simplicity, assume that the ratio of the estimated exposure to the true exposure, for each individual, is uniformly distributed between 0 and 2, with a mean value of 1 (i.e., Estimated exposure $= k \times$ True exposure, where k is a random variable, $k \sim U[0, 2]$, with $E(k) = 1$). Table 1 shows true and estimated exposures for 10 individuals, based on this simple model of errors in exposure estimates. Fig. 1 shows the estimated exposure-response relation based on 10,000 individuals.

(For plotting purposes, each estimated exposure is rounded to the nearest integer, from 0 to 40.) The estimated exposure-response relation suggests that risk increases with exposure over the entire range of exposure values, and that it is slightly but significantly elevated even at relatively low exposure levels (e.g., 3 mg/m^3-years), even though we know that, in this example, the true exposure-response relation has no increase in risk at exposure rates below 15 mg/m^3-years. This same conceptual point holds for real data, provided that estimated exposures contain errors. However, for real data, we do not know what the correct exposure-response relation is. The use of estimated individual exposures tends to smear out the true but unknown exposure-response relation (e.g., turning a sharp threshold into a gradually increasing curve, as in Fig. 1, or turning a narrow distribution of individual thresholds into a wider one). Recovering the correct exposure-response relation requires additional analysis to correct for this smearing effect by explicitly modeling the relation between true and estimated exposures.[32,35,36] Estimated exposure-response relations for CS in the epidemiological literature have not made such corrections, and therefore they do not provide useful information about possible true exposure-response thresholds or trustworthy evidence that risks at low exposures are truly elevated.

2.3. Model Specification Errors and Uncertainties Can Obscure Threshold Relationships

Many CS epidemiology studies fit parametric statistical models to estimated exposure-response data, and then interpret the estimated model parameters (e.g., odds ratios or regression coefficients) as providing evidence of a positive effect at all exposure levels. This procedure is not justified if different models hold at different exposure levels, as could be the case if there is an exposure threshold, with no increase in risk below the threshold and some increase above it.

The assumptions built into a statistical model can drive its conclusions, even if these disagree with the data used to fit the model. As an extreme,

Table I. Hypothetical Data for True and Estimated Exposures and Resulting Responses

	True Exposure ~ U[0, 20]	Random Multiplier k ~ U[0, 2], E(k) = 1	Estimated Exposure = $k \times$ True Exposure	Response Threshold	Response
1	0.14	1.4	0.19	15	0
2	6.07	0.7	4.30	15	0
3	18.54	0.0	0.75	15	1
4	7.54	1.6	11.99	15	0
5	19.85	0.6	11.31	15	1
6	17.89	0.4	7.52	15	1
7	9.20	1.6	14.74	15	0
8	7.72	1.0	7.77	15	0
9	5.41	1.2	6.75	15	0
10	15.13	0.1	1.81	15	1

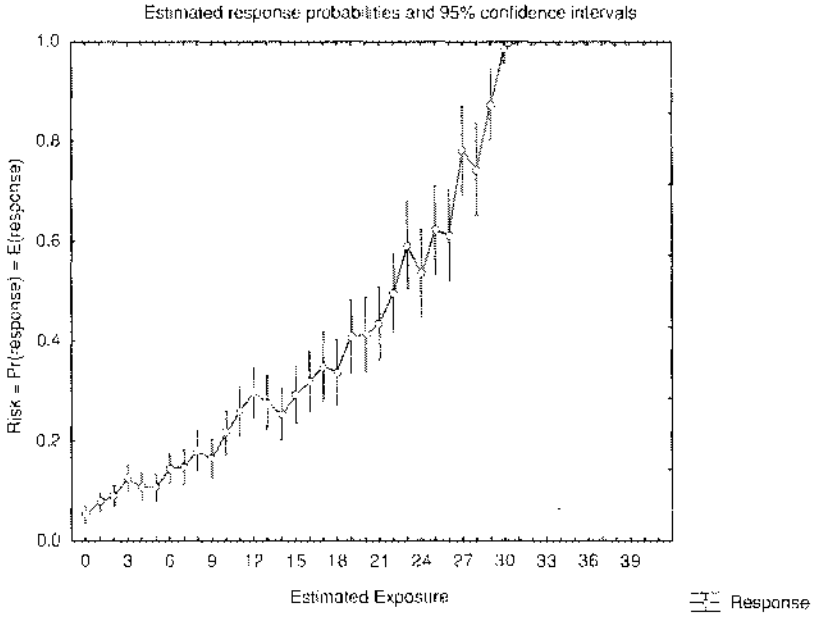

Fig. 1. Estimated exposure-response relation for the simulated data in Table I (using 10,000 individuals instead of 10). The correct relation has a threshold at 15: risk = 0 for exposure $\leq$ 15; risk = 1 for exposure > 15.

hypothetical, example, fitting the regression model Risk = $\beta \times$ Exposure to data that are correctly described by Risk = 1/Exposure would produce a positive estimate for β, which might be misinterpreted as a positive unit risk factor or potency for the effect of exposure on risk, even though the true relation Risk = 1/Exposure shows that risk actually decreases with increasing exposure. This illustrates how a misspecified statistical model can override data, and produce a conclusion that risk is increased at low exposure levels, even if the data imply nothing of the sort.

To avoid such model specification errors and biases, it is useful to fit nonparametric models to exposure-response data. Fig. 2 presents an example: a spline curve fit to estimated exposure-response data in the influential IARC pooled analysis study.[21] The authors interpreted this model as "support[ing] the decision by the IARC to classify inhaled silica in occupational settings as a carcinogen, and suggest[ing] that the current exposure limits in many countries may be inadequate." The y-axis shows estimated RR of lung cancer, with 1 corresponding to no effect.) The authors interpreted Fig. 2 as follows: "Analyses using a spline curve also showed a monotonic increase in risk with increasing exposure." However, a more accurate description is that Fig. 2 shows clear evidence of a threshold, with no increase (and, if anything, a slight decrease) in risk at low exposure levels.

This finding of an apparent threshold can be converted to a reported finding of a "monotonic increase in risk," by fitting a parametric statistical model (such as Risk = $\beta \times$ Exposure, having

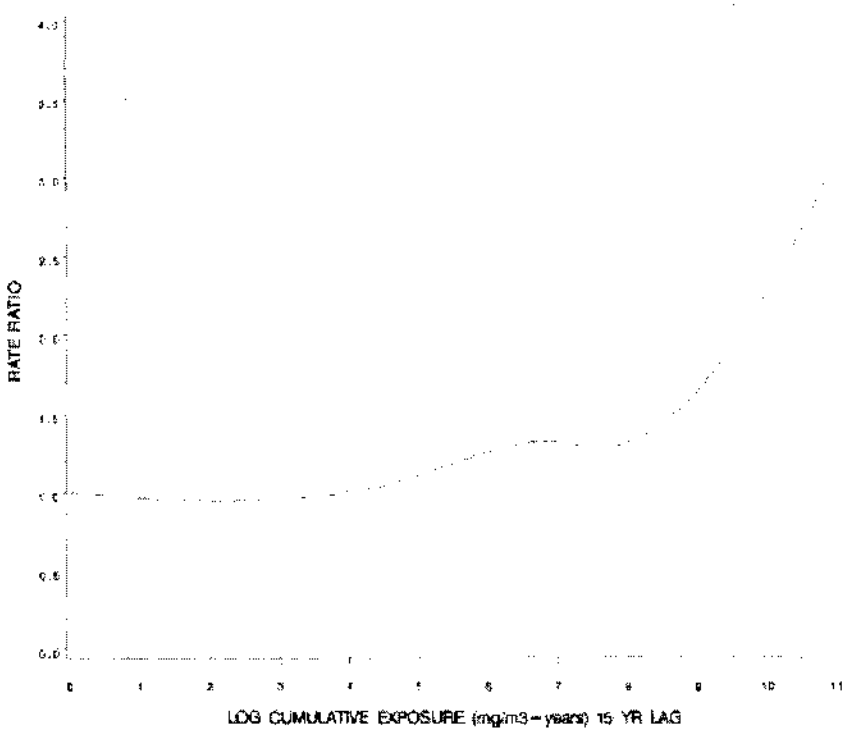

Fig. 2. A spline curve fit to pooled analysis data suggests a threshold.

Source: Figure from Reference 21.

parameter β, in the above example), which guarantees a positive estimate of β (as long as Risk and Exposure values are positive), and hence a monotonic increase in estimated risk even at low exposures, no matter what the data say. (The slope parameter β is necessarily positive when both Risk and Exposure are positive, since the line Risk = $\beta \times$ Exposure necessarily goes through the origin at its lower left, and slopes upward through the positive scatter plot.) The IARC team interpreted the data behind Fig. 2 this way. They fit a similar parametric model (log relative risk = $\beta \times$ Exposure) to data with positive values of Exposure and log relative risk, and therefore (necessarily) concluded that risks were increased at low exposure levels—a finding that they interpreted as supporting classification of CS as a known human carcinogen that might need tighter regulation. Fig. 2 suggests that a less assumption-laden process could have produced a very different conclusion, that is, that the data do not indicate any increase in risk at low exposures.

In summary, epidemiological evidence on CS and lung cancer have often been interpreted as suggesting a causal relation between CS exposure and increased risk of lung cancer,[22] even at relatively low exposure levels that do not cause silicosis. Our review of CS epidemiology indicates that this interpretation is unjustified. CS epidemiological studies and meta-analyses have not corrected for errors in individual exposure estimates, have not applied appropriate methods to estimate and fully control for confounding, and have not accepted and interpreted at face value the results of nonparametric analyses that provide clear, model-free, evidence of an exposure-response threshold. As a result, past epidemiological studies do not provide trustworthy information about the presence or absence of thresholds in exposure-response relations, or about the shape of individual or population exposure-response functions. To obtain more insight, it is necessary to turn to biological information about how and under what conditions CS increases risks of lung diseases.

3. CS MODE OF ACTION

Over the past decade, molecular biologists and toxicologists have dramatically improved understanding of how PSPs in general, and CS in particular, cause lung diseases. The following steps, reviewed in more detail in Cox for COPD,[10] are important in the development of many PSP exposure-related lung diseases.

(1) Sufficient exposure activates alveolar macrophages (AMs) and changes their phenotypes. Intense and prolonged exposure to many PSPs permanently shifts AM populations toward more cytotoxic phenotypes with reduced phagocytic capacity and reduced ability to clear apoptotic cells via efferocytosis.[11] For CS, AMs are activated via the MARCO receptor, which plays a crucial role in CS particle recognition and uptake.[12,37] A shift in AM phenotypes and reduced AM phagocytic capacity has been documented for silica-exposed monkeys,[38] as well as for rodents.[37]

(2) The altered AMs produce increased levels of ROS, reactive nitrogen species (RNS), and pro-inflammatory cytokines, including TNF-α. Exposure to PSPs increases AM production of ROS. Although increases in ROS production may initially be counterbalanced by compensating increases in antioxidants (AOX) (see Ref. 39 for silica and Ref. 40 for a more general overview) sufficient exposure overwhelms and down-regulates AOX in rats, shifting the oxidant-antioxidant balance in the lung toward abnormally high ROS levels and generating oxidative stress.[2] Mechanisms of antioxidant reduction in human bronchiolar epithelial cells (BECs) have started to be elucidated *in vitro*,[41] although more remains to be done (e.g., to clarify the role of the Nrf-2 "master switch" for many antioxidants, and its pathways, such as the Nrf-2-ERK-MAP kinase–heme oxygenase (an antioxidant) pathway).[42,43]

(3) A high-ROS environment, in turn, induces AMs (and, to a lesser extent, other lung cell populations, such as BECs) to secrete more pro-inflammatory mediators—most notably, tumor necrosis factor alpha (TNF-α), as well as IL-1β, TGF-β1, and other pro-inflammatory cytokines.[44] For CS specifically, exposure increases AM production of both ROS and RNS in rats[45] and activates signaling pathways (including NF-kappaB and AP-1) that promote expression of pro-inflammatory mediators, oncogenes, and growth factors important in lung fibrosis and cancer.[76,77] Increased ROS stimulates increased secretion of TNF-α by AMs, as observed *in vivo* in silica-exposed rats[78] and *in vitro* in silica-exposed lung cell lines, in which ROS activates a specific transcription factor (nuclear factor of activated T cells [NFAT]) that increases TNF-α.[79]

In humans, ROS markers such as 8-isoprostane remain elevated, or increase, in patients with silicosis[80] or COPD[10] even long after exposure stops, suggesting that exposure "switches on" a self-sustaining process (e.g., a positive feedback loop) that keeps ROS permanently elevated. The increase in ROS levels and oxidative stress in the lung environment is considered crucial in causing subsequent exposure-associated lung injury and in increasing risk of lung diseases, including fibrosis,[45] silicosis, and lung cancer.[2,12,46–48]

(4) Increased TNF-α and ROS stimulate an influx of neutrophils to the lung. Some specific causal pathways by which TNF-α and ROS attract neutrophils into the lung have been partially elucidated, as follows.

- TNFα up-regulates interleukin 8 (IL-8) expression.[49] IL-8 (also called CXCL8 ligand) is a potent chemoattractant for neutrophils. It recruits additional neutrophils to the lung, via chemotaxis, and activates them (by binding with high affinity to the two chemokine receptors, CXCR1 and R2, on the neutrophil cell surface, stimulating their degranulation).[50] The lungs contain a large reservoir of marginated neutrophils, sequestered within the tiny capillaries of the pulmonary microcirculation and adhering to the capillary lining (endothelium). In response to IL-8, they squeeze across the alveolar–capillary membrane and into the interstitial air spaces. (How quickly this happens depends on the deformability of the neutrophils, which depends on oxidant–antioxidant balance.[51] IL-8 also increases the cellular adhesion of neutrophils (specifically, to fibrinogen and ICAM-1) via the β2-integrin cell surface adhesion molecule, Mac-1, i.e., CD11b/CD18.[52]) Thus, IL-8 increases the local concentration of activated lung neutrophils, both by attracting and by retaining them. This may be diagrammed as: IL-8 $\rightarrow$ *N* (where the arrow indicates that an increase in the quantity on its left (tail) increases the quantity on its right (head).)

- ROS increases the release of IL-8 from cultured macrophages. Specifically, the lipid peroxidation product 8-isoprostane (which is elevated in COPD patients, as well as in the plasma and urine of atherosclerosis patients) increases IL-8 expression in human macrophages *in vitro* (via a pathway that involves both ERK 1/2 and p38 MAPK, but not NF-kappaB).[53]
- ROS also increases IL-8 via the following ROS-EGFR pathway:[10] ROS → TGF-α → EGFR phosphorylation → IL-8, VEGF, *MUC5AC, MUC5B* (where, again, each arrow indicates that an increase in the quantity on the left (tail) increases the quantity on the right (head) of the arrow). This pathway also increases mucus production in airways, via increased expression of the mucin genes *MUC5AC* and *MUC5B*. IL-8 is produced by BECs, dendritic cells, and other lung cell populations, following EGFR activation.
- TNF-α and ROS may also stimulate release of the ligand CXCL2 (i.e., C–X–C motif ligand 2, also called macrophage inflammatory protein 2-alpha [MIP2-α]), as well as of growth-regulated protein beta (Gro-beta) and Gro oncogene-2 by dendritic cells (DCs), monocytes, and macrophages. CXCL2 is chemotactic for neutrophils, enhancing their influx into the airways[54] for murine cells *in vitro*; see Thatcher *et al.*[55] for CXCR2 effects on emphysema in smoke-exposed mice *in vivo*.

In rats exposed to CS, the initial influx of AMs and neutrophils leads to elevated levels of both that persist many months after exposure ceases.[56]

(5) The increased neutrophils and AMs in the lung generate increased ROS levels and oxidative stress, due in part to their respiratory bursts; in part to the release of neutrophil elastase (NE) from neutrophils; and in part to greatly increased numbers of apoptotic cells (primarily neutrophils, but also AMs and epithelial cells). This completes a positive feedback loop: ROS → TNF-α from AMs → IL-8 → neutrophils → ROS. NE also further activates the EGFR pathway (by cleaving pro-TGF-α, which stimulates release of mature TGF-α that binds to and phosphorylates EGFR), and potently stimulates goblet cell degranulation, contributing to mucus hypersecretion into the airways.[57] This creates the following positive feedback loop: TGF-α → EGFR phosphorylation → IL-8→ neutrophils → NE → TGF-α. Activated neutrophils further amplify the EGFR pathway and inflammation by releasing TNF-α, which increases expression of EGFR on airway epithelial cells.[57] Increases in NE can shift an entire protease–antiprotease network toward a new, high-protease state in which the excess proteases digest lung tissue and cause emphysema and COPD, as well as increasing apoptosis of endothelial and epithelial cells.[10]

(6) High ROS and oxidative stress increase apoptosis of AMs, neutrophils, and alveolar epithelial cells, leading to lung tissue damage and destruction. Apoptosis of alveolar epithelial cells, together with damage to the extracellular matrix (ECM) and alveolar wall from increased proteases, can eventually lead to tissue destruction and remodeling of the ECM, including deposition of collagen leading to scarring and fibrosis in human silicosis[58] and COPD.[10] Experiments with silica-exposed knockout mice have confirmed that both IL-1β and inducible nitrogen oxide synthase (iNOS) are involved in apoptosis and inflammation during murine silicosis.[59] Increased ROS leading to increased apoptosis of alveolar cells and neutrophils has been observed in CS-exposed rats.[60,61] Damaged and dying alveolar epithelial cells (especially Type II alveolar cells) cause the lung parenchyma to secrete, activate, and release transforming growth factor beta-1 (TGF-β1), as well as more TNF-α (thus completing still further positive feedback loops: ROS → TNF-α → IL-8 → neutrophils → ROS → apoptotic cells→ TNF-α). Apoptotic cells (and, even more, necrotic cells, which form if apoptotic cells are not promptly and safely removed) also release high levels of ROS into the lung environment. TGF-β1 activates fibrogenic cells and powerfully attracts AMs (which release more TGF-β1) and other inflammatory cells (neutrophils and lymphocytes) into parenchymal tissues.[62] ROS and TGF-β1 stimulate production of new ECM by myofibroblasts, the fibrotic lung's major collagen-producing cell population.[62] High oxidative stress also decreases the ability of

AMs to identify and remove apoptotic cells, further increasing their concentration, and hence the concentration of ROS and TGF-β1 in the lung environment.

(7) In rats, damage to lung tissue and altered apoptosis result in epithelial hyperplasia, clonal expansion of preneoplastic cells that would ordinarily be removed via apoptosis, and increased risk of lung cancer. Oxidative stress from a high-ROS lung environment can both reduce apoptosis among some cells (thereby increasing lung cancer risk, if preneoplastic cells are less likely to be detected and removed via apoptosis) and stimulate proliferation and transformation of cells that contribute to increased lung cancer risk.[2] For CS specifically, exposure causes hyperplasia of epithelial cells and fibroblasts in rats, but CS does not induce similar hyperplasia (or lung cancer) in mice and primates.[7] CS induces hyperplasia of both neuroendocrine lung cells[63] and Type II alveolar cells in rats, although not in mice or hamsters.[64,81] In rats (but, again, not in mice or hamsters, which do not show elevated lung cancer risk in response to CS exposure), TGF-β1 precursor is localized in hyperplastic alveolar type II cells and ECM next to granulomas (and adenomas, if any).[64,65] This suggests a close link between locations of alveolar cell death and attempted repair of ECM (both of which are associated with TGF-β1) and areas of increased hyperplasia/adenomas. Such usefully detailed biomolecular information links the process of silicosis (e.g., TGF-β1-mediated collagen production, ECM remodeling, epithelial–mesenchymal transition,[66] and fibrosis) directly to epithelial cell proliferation and increased lung cancer risk (due to increased hyperplasia/adenoma of damaged lung tissue)—the crucial link that epidemiological data alone could not yet provide.

Studies of silica-induced lung cancer in rats—the only species in which CS exposure is known to cause lung cancer—indicate that CS does not act through classical mutational (e.g., *KRAS* or *EGFR* mutation) pathways for lung cancer, but rather promotes lung carcinogenesis through indirect epigenetic processes associated with increased proliferative stress and hypermethylation of the promoter region of tumor suppressor genes (TSGs), specifically including p16.[9] In humans, aberrant promoter methylation of TSGs is more frequent in serum DNA from silicosis patients with lung cancer than in silicosis patients without lung cancer,[67] suggesting that epigenetic gene silencing of TSGs by this mechanism may be relevant in silicosis-associated lung cancers in humans, as well as in rats. The p16 gene normally participates in checking and regulating cell division (as part of the p16INK4a-Cyclin D1-CDK4-RB cell cycle control axis).[68] Disruption of *p16* gene expression allows damaged cells that would normally be removed via apoptosis to undergo mitotic replication instead, increasing the prevalence of damaged (potentially preneoplastic) cells in lung bronchiolar epithelial tissue. Epigenetic silencing of *p16* by CS-induced hypermethylation of its promoter region thus presumably increases survival and entry of altered (initiated) cells into a clonal expansion phase, thereby promoting expansion of preneoplastic cell populations and increasing the risk of lung tumors.[69]

In summary, CS exposure stimulates production of ROS/RNS, down-regulates counterbalancing antioxidants, and activates immune cells, including AMs (as well as mast cells, and B-lymphocytes).[12] Activated immune cells release more ROS, creating a positive feedback loop.[2],[7] The resulting high-ROS, chronically inflamed lung environment disrupts normal apoptosis and repair of epithelial and endothelial cells, increases epithelial cell proliferation and lung cancer risk, inhibits normal repair of damaged epithelial tissue, and promotes excess secretion of collagen and other proteins in the ECM. In rats, and probably in silicosis patients, these changes promote expansion of preneoplastic clonal patches and increase risk of lung cancer, probably in part by epigenetic silencing of TSGs, such as *p16*. These general features of lung disease processes hold for many PSPs and mineral dusts and fibers, and for CS in particular, as documented in the cited references, although important biochemical details (such as the specific antioxidants generated in response to initial ROS increases) differ for different compounds.[39]

4. EXPOSURE-RESPONSE MODELING

Although the inflammatory mode of action is complex, one of its main features is obvious: the key quantities and the regulatory relations among

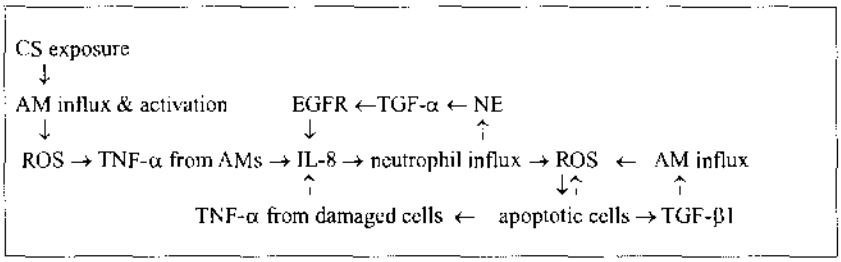

Fig. 3. Examples of positive feedback loops in a silica disease causal network.

them form a network with multiple positive feedback loops. Fig. 3 shows examples. In each loop (i.e., each directed cycle among a set of variables, with arrows entering and leaving each variable in it), an increase in one element stimulates an increase in its successor, so that eventually all variables around the loop increase. (Fig. 3 is not intended to be complete, e.g., it does not show the direct contribution of CS fragments to ROS, the shift in AM phenotypes toward less effective phagocytosis, the production of collagen by fibroblasts, or many other biological effects previously discussed. It simply illustrates some major positive feedback loops involved in CS-associated (and other PSP-associated) lung pathologies.)

If specific quantitative formulas linking the rates of changes of different variables were known, then the dynamic response of such a network to changes in its exogenous inputs (such as CS exposure, in Fig. 3) could be simulated. Even without such detailed quantitative information, however, the method of comparative statics analysis[82] can be used to study how equilibrium levels of variables change in response to exposure. The basic idea is to compute how equilibrium points change, even though the details of the adjustment process may be (and, for CS, still are) largely unknown. To do this, we focus on some variable, such as ROS, that appears in one or more loops. Let's call the selected variable X. Now, consider the following artificial adjustment process, which is constructed so that it will lead to the same equilibrium levels of X as the real but unknown adjustment process. (Throughout, we assume, realistically, that all modeled variables are bounded, and that they adjust to their new equilibrium levels (or quasi-equilibrium levels, for slowly changing variables), in response to any change in inputs, relatively quickly—well within the lifetime of the exposed individual. These assumptions hold for the variables in more detailed models of COPD.[10]) The artificial adjustment process is iterative. Each iteration consists of the following two steps.

(i) Hold X fixed at a specified level, denoted by X_t at iteration t. Let all other variables adjust until they are in equilibrium with X_t.
(ii) Next, hold all other variables fixed at their new levels, and let X adjust until it is in equilibrium with them. Denote by X_{t+1} this new value of X.

If the system were understood in enough detail to allow a full, explicit, dynamic simulation model to be constructed, then the mapping from each value of X_t to the corresponding value of X_{t+1} could be evaluated numerically. Even without such complete knowledge, we can denote this mapping by some (unknown) function, f, and consider its qualitative properties. By construction, equilibrium values of X (defined as values such that $X_{t+1} = X_t$) in the dynamic system are also fixed points of the artificial adjustment process represented by f. The model

$$X_{t+1} = f(X_t)$$

corresponds to a curve, which we call a model curve, in a graph that plots X_{t+1} against X_t, as shown in Fig. 4.

Fig. 4 actually shows three different model curves, 1–3, corresponding to successively greater exposure levels and/or sensitivities of exposed individuals. For model curves 1 and 2, there is a unique, globally stable equilibrium value of X, denoted by X^*, where the model curve intersects the equilibrium line (defined by the 45° line $X_{t+1} = X_t$) from above and to the left. This equilibrium is stable because $X_{t+1} > X_t$ to its left and $X_{t+1} < X_t$ to its right. In other words, if X_t differs from X^*, then the levels of other variables that are affected by X_t will not adjust to levels that sustain X_t, but instead will reach levels that, in turn, cause X_t to move closer to X^*. Such a globally stable equilibrium represents the normal, homeostatic equilibrium for the system when no disease is present. Model curve 2 differs from Model curve 1 by showing saturation of X at its right end, that is, a maximum possible level of X. Even a high level of

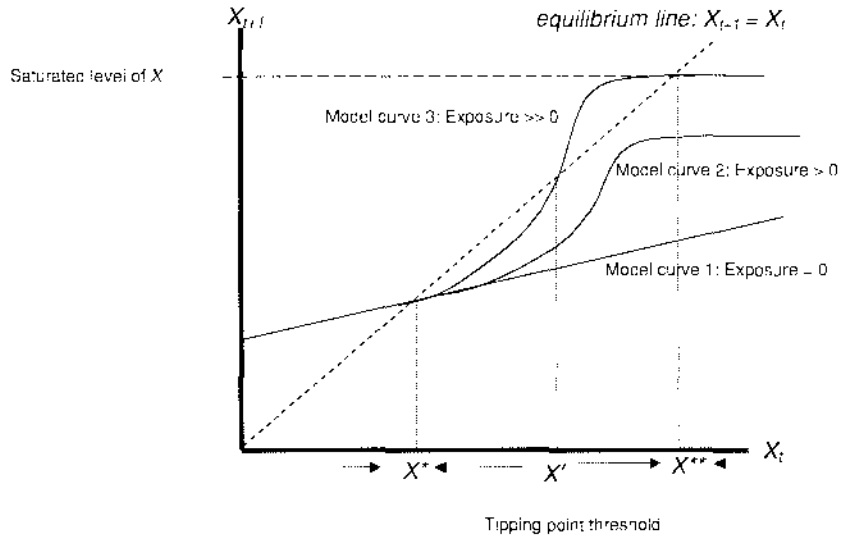

Fig. 4. Exposures high enough to destabilize a feedback-control loop create an alternative equilibrium (potential disease) state (X^{**}) and a threshold (X').

exposure will not lead to an infinite level of X, but will, at most, saturate the response of the feedback loop(s) containing X, sending the affected variables to their maximum levels.

Model curve 3 shows a qualitatively different possibility for an exposed individual for whom the saturated level of X is high enough to intersect the equilibrium line from above and to the left. For such an individual, there are two alternative equilibria: the normal homeostatic equilibrium at X^*, and an alternative, locally stable equilibrium X^{**}, with X at its saturated level. In between them, for any continuous model curve, there must be a threshold or "tipping point," denoted by X' in Fig. 4, such that X will adjust toward X^* from any starting point to the left of X', but will adjust toward X^{**} from any starting level to the right of X'. That is, X' is an unstable equilibrium separating the two basins of attraction for the "healthy equilibrium" X^* and the potential "disease equilibrium" X^{**}. (Topologically, such a threshold must exist whenever two alternative stable equilibria exist, for any continuous model curve; it is unique if the model curve is s-shaped.) As explained in detail for a specific parametric model of COPD (consisting of a system of ordinary differential equations and algebraic equations with estimated parameter values),[10] exposure that increases a model curve enough to produce a saturated equilibrium (such as X^{**} in Fig. 4) does so by destabilizing the positive feedback loop(s) containing X, causing its variables to escalate until saturation is reached.

For a biological interpretation, suppose that X represents ROS, and that the mechanism by which long-term exposure increases the model curve is to shift cell populations (such as AMs) toward phenotypes that produce higher levels of ROS (and/or higher levels of the causal drivers of increased ROS in Fig. 3). Then X^{**} represents a high-ROS equilibrium, in which ROS and all the other variables in Fig. 3 (which participate in positive feedback loops with ROS) have increased levels. If long-term exposures produce a model curve with two alternative equilibria (such as model curve 3), and if short-term exposure transients can then temporarily increase the level of X, then any exposure history that increases X past its tipping-point threshold will trigger a self-sustaining escalation in levels of X (and of all other variables that participate in a positive feedback loop with X, including all variables shown in Fig. 3) until the high-ROS (saturated-equilibrium) state is reached. If defensive and repair resources are insufficient to counter the damage done in this high-ROS state, then tissue destruction and other clinical manifestations of lung disease may result. The threshold model in Fig. 4 predicts that progression to the high-ROS potential disease state will occur, even in the absence of further exposure, once the tipping point has been passed.

The preceding threshold model is motivated by current understanding of the biology of lung responses to PSP exposures in general, and to CS exposures in particular, but it does not require detailed knowledge of the biological mechanisms involved, many of which remain uncertain. For example, with sufficient knowledge and data, each of the links between variables in Fig. 3 could be further

elucidated, perhaps expanding into an entire subnetwork showing molecular-level details of how an increase in the variable at the tail of an arrow propagates through signaling pathways and other mechanisms to cause an increase in the variable at the arrow's head. But such a detailed description would not change the basic topology of the network, nor its properties derived from the fact that multiple positive feedback loops dominate its qualitative behavior. The exposure-response threshold in Fig. 4 does not depend on such details, and hence is robust to uncertainties about them. Although further biological information may eventually allow more detailed simulation and prediction of the time courses of lung disease initiation and progression, it should leave intact the insights that comparative statics analysis, of the type performed in this section, provides today.

4.1. Confirmatory Data: How Well Does the Theory Match Observations?

The analysis of alternative equilibria in Fig. 4 implies the existence of an exposure threshold, below which lung damage is largely reversible (although the homeostatic equilibrium X^* can be shifted rightward if exposure shifts the whole model curve up), and above which escalation of ROS, and of the other variables in Fig. 3, to permanently elevated levels will progress, even without further exposure. It is useful to compare this theoretical prediction to available data, which come largely from a series of studies in rats, undertaken by NIOSH. Porter *et al.*[70] found experimentally that "the time course of rat pulmonary responses to silica inhalation as biphasic, [with] the initial phase characterized by increased but controlled pulmonary inflammation and damage. However, after a threshold lung burden was exceeded, rapid progression of silica-induced pulmonary disease occurred." They reported: "During the first 41 days of silica exposure, we observed elevated but relatively constant levels of inflammation and damage, with no fibrosis. Subsequently, from 41 to 116 days of exposure, rapidly increasing pulmonary inflammation and damage with concomitant development of fibrosis occurred. This suggested that pulmonary defense mechanisms were initially able to compensate and control silica-induced pulmonary inflammation and damage, but after a certain threshold lung burden was exceeded, these control mechanisms no longer were adequate to prevent the progression of silica-induced pulmonary disease." In terms of Fig. 4, these data could be interpreted as indicating that exposure initially moves the model curve upward, thus moving the homeostatic equilibrium rightward (yielding the reported controlled, reversible increases in levels of loop variables). Continued exposure moves the model curve further upward (e.g., because it selects for macrophages that produce higher levels of ROS for the same exposure), eventually creating a tipping point threshold and an irreversible disease state (saturated equilibrium), yielding the reported rapid progression of pulmonary disease.

Such a coincidence between qualitative predictions and experimental observations in rats, while perhaps encouraging, does not prove that our conceptual model is correct. To test the specific biological interpretation (suggested by Fig. 3) that a high-ROS equilibrium accounts for silica-induced lung diseases, it would be necessary to assess the levels of ROS in conjunction with the initiation and progression of silica-induced lung diseases. Fortunately, such experiments have been done. Porter *et al.*[71] examined the mechanism by which injury progresses in rat lungs even after exposure ceases, and found that it is indeed mediated by a continuing increase in the production of ROS (and also RNS). They reported that "even after silica exposure has ended, and despite declining silica lung burden, silica-induced pulmonary nitrogen oxide (NO) and ROS production increases, thus producing a more severe oxidative stress. . . . iNOS and NO-mediated damage are associated anatomically with silica-induced pathological lesions." This is fully consistent with the prediction (from Fig. 4) that, once the tipping point threshold has been passed, the system will be in the basin of attraction for a high-ROS equilibrium, to which it will move (thus increasing the levels of all the loop variables positively linked to ROS) even after silica exposure has ended. A similar tipping-point threshold between two basins of attraction has been reported in an explicit dynamic simulation model of COPD.[10] Thus, this key feature of our theoretical analysis appears to be consistent with some limited available data.

Of course, rats are not people, and the relevance of experimental findings in rats to disease processes in people can be questioned. However, Porter *et al.*[70] note that in human occupational populations, too, "[h]uman epidemiologic studies have found that silicosis may develop or progress even after occupational exposure has ended, suggesting that there is a threshold lung burden above which silica-induced pulmonary disease progresses without further

exposure." Thus, we believe there is empirical support for the inference that CS, like other PSPs that cause lung diseases following chronic inflammation,[2] induces a high-ROS state as a possible alternative equilibrium to the usual, lower-ROS, homeostatic equilibrium—at least in susceptible individuals (defined as those in whom exposure shifts the model curve up enough to create the alternative stable equilibrium state, X^{**}). Exposures that push the dynamic system of interacting variables in the lung (see Fig. 3) into the basin of attraction of this high-ROS state then trigger progression to the high-ROS state, even if no further exposure occurs. Depending on an individual's capacity to repair the multiple types of damage caused by the high-ROS state (see Fig. 3), a variety of lung diseases, from silicosis to lung cancer, can result. We propose this as a unifying conceptual model for understanding the induction and progression of inflammation-mediated lung diseases caused by inhalation of PSPs.

5. DISCUSSION: USING THE MODEL TO ADDRESS POLICY-RELEVANT QUESTIONS

Epidemiological investigations that do not include careful, well-validated modeling of exposure estimation errors may not yet be capable of delivering convincing answers to the policy-relevant questions raised in the introduction: whether exposure-related diseases occur together; whether CS has an exposure-response threshold for causing lung diseases; and, if so, whether currently permissible exposure limits lie above or below the threshold. However, combining available, imperfect epidemiological evidence with recent advances in understanding of lung responses to poorly soluble particulates (PSPs) in general, and CS in particular, as outlined in the previous two sections, allows us to shed new light on each of these practical questions.

5.1. Existence of an Exposure-Response Threshold

There are strong empirical, as well as theoretical, grounds for expecting a threshold in the exposure-response relation. In theory, knowledge that CS acts through positive feedback loops (Fig. 3) suggests the presence of an exposure-response tipping point threshold (such as X' in Fig. 4). Empirically, relatively low exposures have been observed to induce largely self-limiting and reversible effects in rats (consistent with a homeostatic equilibrium, X^*), while high exposures have been observed to trigger a self-sustaining escalation to a permanent high-ROS state (consistent with an alternative equilibrium X^{**}).[70,71] Our review of CS epidemiology in Section 2 suggests that existing epidemiology is fully consistent with the biologically-based understanding of PSP mode of action and the two alternative-equilibria theory in Figs 3 and 4, and with their implied exposure-response threshold for exposure-related increases in lung disease risks (as observed for many PSPs in rats),[8] once a clear distinction is drawn between exposure-response curves for estimated exposures and exposure-response curves for true but unknown exposures. The former may lack a threshold, even if the latter have one (Fig. 1).

5.2. Quantitative Estimation of the Exposure-Response Threshold: $\geq$ 0.4 mg/m^3

A potentially useful quantitative contribution from CS epidemiology is the observation by Rushton[4] that lung function appears to be diminished in some studies at estimated occupational exposure concentrations in excess of 0.1–0.2 mg/m^3 of respirable silica dust for durations of at least 30–40 years, in the presence of other occupational dust exposures. If this finding is confirmed, and if confounding by cigarette smoking and occupational co-exposures is eventually ruled out as an explanation (perhaps by building on recent innovative statistical methods[31]), then 0.1–0.2 mg/m^3 of silica dust for 30–40 years might be accepted as a useful point of departure for estimating the exposure threshold that must be exceeded to create a disease state.

As in other epidemiological studies, there is large uncertainty in this review about true exposures, implying that any real exposure-response threshold is likely to be significantly greater (perhaps by several-fold) than the level at which the estimated exposure-response threshold shows elevated risks (see Fig. 1). To obtain a clear estimated concentration threshold between 0.1 and 0.2 mg/m^3, it is necessary to modify the example in Table I. For example, Fig. 5 shows a simulated exposure-response curve when the true exposure is uniformly distributed between 0 and 1 mg/m^3 and there is a true response threshold at 0.4 mg/m.[3] (With the true probability of response, i.e., exposure-induced illness, being 0 for concentrations below this threshold and 1 above it. In reality, of course, different individuals might have different thresholds, reflecting their own model curves and X' values, but it remains true that

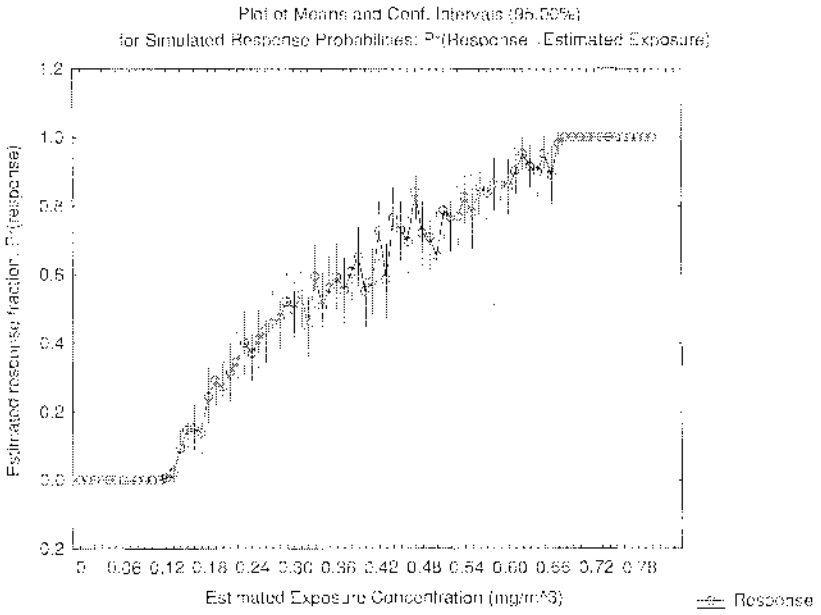

Fig. 5. A true threshold at 0.4 mg/m^3 produces an estimated threshold between 0.1 and 0.2 mg/m^3. ($N = 10{,}000$ samples; $k \sim U[0.3, 1.7]$; true exposure $\sim U[0, 1]$ mg/m^3.)

unmodeled error, even in unbiased exposure estimates, smears out and decreases the apparent threshold level of exposure at which excess population risks start to occur.) In the absence of detailed study of real-world exposure estimation errors, such hypothetical examples suggest that an estimated exposure concentration threshold between 0.1 and 0.2 mg/m^3 might correspond to a true threshold value of about 0.4 mg/m^3 for the concentration threshold that must be exceeded before adverse health effects occur among susceptible workers.

However, this rough estimate of 0.4 mg/m^3 is contingent on as-yet unproved assumptions, including that the adverse health effects in Rushton[4] were caused by CS, rather than by other exposures. We have assumed only a rather modest degree of variability in estimated exposures around the corresponding true values (namely, a uniform distribution around the mean, $k \sim U[0.3, 1.7]$, with no outliers or heavy tails). The true threshold could be substantially higher than 0.4 mg/m^3 if exposure estimates have greater variability than this. (As an extreme example, the true threshold could be as high as 2 mg/m^3 and still give an estimated threshold of 0.1 mg/m^3 if (a) each individual with an estimated exposure of 0.1 has a 5% probability of having been exposed to 2 mg/m^3 and a 95% probability of having been exposed to 0 mg/m^3, for an average exposure of $0.05 \times 2 + 0.95 \times 0 = 0.1$ mg/m^3; and (b) the power of the study is such that at least 5% of individuals in an exposure group must respond in order for an excess risk to be detected.) Thus, to better estimate the true level at which adverse health effects associated with the high-ROS state are induced, it will be essential for future studies to more carefully characterize the error distribution of estimated exposures around true exposure levels, perhaps using more detailed simulations of workplace daily exposure distribution means and variances.

Meanwhile, it appears plausible that currently permitted exposure levels of 0.1 mg/m^3 of respirable CS could be well below (possibly by a factor of 2 to 10, based on the hypothetical examples just described) the levels that might increase risks of adverse health effects. This conclusion becomes more robust if, instead of there being different thresholds for different CS-induced lung diseases, there is one large dichotomy, as illustrated in Fig. 4, between a low-ROS homeostatic equilibrium and a high-ROS disease state equilibrium (which can then produce different ROS-mediated diseases in susceptible individuals, based on different vulnerabilities in their defensive and repair resources for responding to oxidative stress injuries). We now consider further the implications of such a dichotomy.

5.3. Is Increased Risk of Silicosis Necessary for Increased Risk of Lung Cancer?

The study of Rushton[4] examines estimated concentrations for longitudinal effects, so that even long-delayed health effects can eventually be counted.

This is very useful when the alternative-equilibria theory in Fig. 4 is combined with an assumption that the high-ROS equilibrium is necessary (although perhaps not sufficient, if defensive and repair capabilities are sufficiently strong) to cause increased risk of ROS-mediated lung diseases. Together, these assumptions imply that if increased rates of ROS-mediated lung diseases do eventually occur in an exposed occupational population, then exposure must have been sufficient to create the high-ROS state in susceptible individuals—and, therefore, high enough to have increased risks of several different diseases associated with the high-ROS state among individuals susceptible to each type (e.g., due to limited capacity for alveolar epithelial tissue repair, for emphysema; or ECM repair, for fibrosis; or apoptosis of premalignant cells, for lung cancer; and so forth). Conversely, this understanding of the disease process implies that protecting against any of the high-ROS diseases, by keeping exposures below the levels that induce a high-ROS state in an individual or species, will protect against all of them, from silicosis to inflammation-mediated lung cancer. This makes it plausible that exposures that are too low to cause increased risk of silicosis (even among susceptible individuals) will also not cause increased risk of lung cancer, even if silicosis is not a necessary precondition for CS-induced lung cancer: failure to create the high-ROS alternative equilibrium protects against both. According to this logic, increased risk of silicosis (and other indicators of the high-ROS state) in susceptible individuals should be expected as a necessary accompaniment to increased risk of other high-ROS diseases (such as inflammation-mediated lung cancer caused by CS[2,9]), whether or not silicosis causally contributes to CS-induced lung cancer.

6. CONCLUSIONS

Postulating an exposure-response threshold for lung diseases (including lung cancer) associated with exposure to CS and other PSPs is not new. It has long been discussed for CS, with rat data, human data, and mechanistic information being cited in support of thresholds.[8] For example, in 1995, researchers from California's Department of Toxic Substances Control[72] reviewed the then-available evidence on the carcinogenicity of CS, and concluded: "The weight of evidence for both rats and humans indicates that fibrotic and silicotic lesions in the lung result from inhalation exposure to CS and that lung cancer is secondary to those lesions in the lung. Thus CS 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."

Our analysis supports these earlier conclusions. To do harm, exposures to PSPs such as CS must be large enough and last long enough to trigger the chronic inflammatory responses and progression to a high-ROS state that can eventually lead to diseases. *In vitro* evidence in cell cultures, as well as *in vivo* experiments in rats, indicate exposure thresholds for inflammation,[73] oxidative stress, and resulting diseases, including lung cancer.[8] Moreover, normal lung cell populations interact via homeostatic (negative) feedback loops that stabilize and maintain oxidant–antioxidant balance[74,75] and other (e.g., proteinase/anti-proteinase) equilibria.[10] Disease risk is not increased by exposures while homeostasis is maintained. Disrupting normal homeostasis requires activating positive feedback loops (Fig. 3) capable of damaging tissue (respiratory epithelium) and overwhelming normal repair processes. Both rat data[8] and mathematical modeling of inflammation-mediated lung diseases (Fig. 4) indicate that these responses to PSPs have exposure-response thresholds. Of course, these data and models are limited, and much remains to be learned about the details of the biological inputs and feedback loops that they describe, as well as others that may yet be discovered. Thus, we cannot completely exclude the possibility that a threshold does not exist. But our model-based analysis may add to previous weight-of-evidence conclusions by suggesting how exposure-response thresholds naturally arise between alternative basins of attraction in positive feedback loop systems.

For CS and many other PSPs, sufficient exposure triggers AM activation and phenotype change, release of ROS and RNS, attraction of monocytes, AMs, and neutrophils to inflamed areas, damage and destruction of alveolar epithelial tissue and ECM, disruption of normal apoptosis and epithelial tissue repair and ECM repair, sustained epithelial proliferation and hyperplasia, and possible promotion of lung cancer. These disease processes may be modeled as networks of damaging positive feedback loops that are either "switched on" (meaning that the loop is attracted to a new, stable equilibrium with increased values of its variables, such as X^{**} in Fig. 4) or "switched off" (meaning that the loop

remains in the basin of attraction of the healthy equilibrium, X^* in Fig. 4). Excess risk of inflammatory lung diseases and lung cancer arises only at exposure intensities and durations that are large enough to switch on these disease processes. For CS, these trigger levels may be on the order of 0.4 mg/m^3 or more of silica dust, depending on the distribution of exposure estimation errors around true values. Such levels significantly exceed currently permissible levels (e.g., 0.05–0.1 mg/m^3), implying that further reductions in permitted exposure levels—if permitted levels are enforced—should not be expected to produce further reductions in human health risks.

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Respirable Crystalline Silica Exposure–Response Evaluation of Silicosis Morbidity and Lung Cancer Mortality in the German Porcelain Industry Cohort

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Objective: To quantify silicosis and lung cancer risks among porcelain workers occupationally exposed to respirable crystalline silica. **Methods:** We reread historical radiographs to identify silicosis and estimated exposure on the basis of detailed work history and about 8000 industrial hygiene measurements. Cox proportional hazards models estimated risks by cumulative and average exposure. **Results:** Adjusted silicosis hazards ratios were 5.3 (95% confidence interval [CI], 1.6 to 17.3); 7.3 (95% CI, 2.6 to 20.8); and 6.8 (95% CI, 3.0 to 15.3) for cumulative exposures >4 to 5; >5 to 6; and >6 mg/m^3-years, and 3.3 (95% CI, 0.8 to 14.7), 13.6 (95% CI, 4.2 to 44.4) and 23.2 (95% CI, 8.2 to 65.8) for average exposures >0.1 to 0.15; >0.15 to 0.2 and >0.2 mg/m^3, respectively. Exposure was not associated with any cause of death including lung cancer. **Conclusions:** Respirable crystalline silica exposure more than 4 mg/m^3-years (cumulative) or more than 0.15 mg/m^3 (average) were strongly associated with silicosis, but unrelated to lung cancer risks.

The causal association is well established between occupational respirable crystalline silica exposure and silicosis—a specific type of pneumoconiosis. This conclusion is supported by many epidemiological studies of workers historically heavily exposed to respirable crystalline silica in several industries including mining, quarrying, and potteries.[1] In addition to quantity of exposure, risks appear to be greater with freshly fractionated quartz and specific crystalline polymorphs such as crystoballite.[2] Silicosis appears not to occur among workers exposed only to ambient or low concentrations of respirable crystalline silica; however, it remains unknown at which specific concentrations and durations of occupational exposure to respirable crystalline silica risk of silicosis is increased.

Occupational exposure to respirable crystalline silica also has been associated with increased risk of lung cancers,[3] especially among individuals with silicosis.[4] In 1997, the International Agency for Research on Cancer (IARC)[5] found "sufficient evidence" in both humans and in animal studies to classify occupational exposure to respirable crystalline silica in the form of quartz or crystoballite as a known (ie, a Group 1) human carcinogen. This finding was recently reiterated in IARC's Monograph 100, Part C review.[6] However, as noted by IARC, respirable crystalline silica's carcinogenicity is not evident under all industrial exposure circumstances. That lung cancer risk is mostly observed among individuals previously diagnosed with silicosis raises a basic question of whether respirable crystalline silica causes lung cancer in the absence of silicosis[7] or apart from the heavy exposures most strongly associated with silicosis. The scientific debate continues[8–10] and newer research reports and reviews have generated mixed conclusions.[11–19]

Consequently, a key regulatory question remains as to whether silicosis and lung cancer are prevented at current occupational exposure limits (OELs), which vary by country. In Germany, the OEL had been 0.15 mg/m^3 until a change in regulations suspended this OEL in favor of a health-based OEL (to be determined). In the US and the UK, the OEL is 0.10 mg/m^3 and 0.05 mg/m^3 in Denmark, Spain, and Sweden.[20]

The goal of this article is to quantitatively evaluate risks of silicosis morbidity and lung cancer mortality by individually estimated cumulative and average respirable crystalline silica exposures among a cohort of nearly 18,000 German porcelain manufacturing workers previously followed for mortality and evaluated using basic standardized mortality ratio (SMR) analysis.[21] Using German national lung cancer mortality rates as the reference, no excess lung cancer risk was seen: SMR = 0.71 (95% confidence interval [CI], 0.56 to 0.89) based on 74 observed lung cancer deaths among men; and SMR = 0.72 (95% CI, 0.44 to 1.12) based on 20 observed lung cancer deaths among women.[21] For the subcohort from Bavaria—the region where most of the porcelain factories were located—SMRs were closer to unity: SMR = 0.98 (95% CI, 0.75 to 1.27) based on 59 lung cancer deaths among men; and SMR = 0.91 (95% CI, 0.52 to 1.48) based on 16 lung cancer deaths among women. These results provided no evidence of any excess risk of lung cancer among the German porcelain workers. On the other hand, silicosis mortality was significantly elevated (SMR = 11.37; 95% CI, 3.66 to 26.53) but was based on only 5 silicosis deaths, all of which were among men.

These preliminary results, however, were not based on respirable crystalline silica exposures quantified at the individual level. Extensive industrial hygiene exposure data for this cohort have been obtained and used to derive quantitative exposure estimates for each cohort member.[22] Furthermore, evaluation of a large archive of radiographic examinations obtained as part of a medical surveillance program for German porcelain workers including a substantial proportion of this cohort facilitated radiographic determination of silicosis morbidity. Combining the mortality data, the silicosis morbidity data, and the quantitative exposure assessment allows quantitative evaluation of potential relationships between estimates of respirable crystalline silica exposure and silicosis morbidity and lung cancer mortality. This occupational setting, that is, the Post–World War II German porcelain industry, presents an unusual opportunity to evaluate exposure–response relationships for silicosis and lung cancer at exposure levels ranging from near to well above current OELs. In addition, this study allows evaluation of these risks among women, who comprise half of this cohort.

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METHODS

Subjects

The study population and cohort definition have been described previously.[21] Briefly, workers employed by any of more than 100 porcelain-manufacturing plants in the western states of Germany (ie, the former West Germany) and participating in an industry-wide preventive medical screening program for silicosis between January 1, 1985, and December 31, 1987, were eligible. Medical screening results data were maintained electronically or on paper by the Berufsgenossenschaft der keramischen und Glas-Industrie (BGGK), whereas only paper work history records were maintained by the BGGK. On the basis of available records, we defined the eligible cohort as those employees for whom detailed work histories were available ($n = 18{,}000$). Exclusion of individuals employed for a total of less than 6 months in the porcelain industry resulted in a final analytical cohort of 17,644 employees, which we followed for mortality and silicosis morbidity through 2005.

Cause of Death Determination

Vital status and cause of death were determined using information from various sources: the BGGK; health insurance and pension fund records; written enquiries to community registration offices for residential histories and last known residence; and the central population registry for Bavaria. Vital status ultimately was determined for 94% of the cohort, with 1610 (9%) reported to be deceased as of the end of follow-up. Subjects with unknown vital status at the end of the follow-up period were censored, that is, they contributed person time only up to the date last known to be alive.

The underlying cause of death for each decedent was obtained from the official death certificate, which in Germany usually is stored at the community health department in the town or city where the death occurred. However, minimum record retention times differ from state to state in Germany, ranging, for example, from 30 years in Bavaria to only a few years in other states such as Rhineland-Palatinate. Therefore, cause of death determination based on death certificates was slightly more complete for the Bavarian subcohort (95%) compared with the overall cohort (93%). Underlying cause of death was coded by a professional nosologist according to the 10th revision of the *International Classification of Diseases* (ICD-10).

Silicosis Determination

Chest radiograph (x-ray) is the typical method for detecting silicosis. The International Labour Organization (ILO) Classification System for interpreting and classifying radiographs[23,24] is commonly used for epidemiological research. More than 120,000 radiographs since the early 1950s were available on the study population from the preventive medical surveillance program. Medical data have been stored electronically since the mid-1980s, and earlier paper records have also been entered into the electronic database. Most of the follow-up examinations were conducted by the BGGK using mobile radiographic units, and films were read by physicians specially trained in reading these smaller radiographs. Most of original films were available from the BGGK archive, with a mixture of small- to full-sized formats.

The original radiographs had been read over many years by different physician readers, and therefore interreader variability was expected to be large. Known problems resulting from large inter- and intrareader variability include poor sensitivity and specificity of silicosis determination, especially when the signs of silicosis are low-grade.[9] Furthermore, because the original radiographic readings were intended for prevention (ie, early detection of radiographic changes consistent with pneumoconiosis and silicosis specifically) as well as administrative purposes (ie, workers' compensation)—and not for etiological research, per se—we performed a rigorous two-stage standardized rereading exercise.

All radiographic rereadings were performed by specially trained teams of two radiologists certified in the classification of chest radiographs for pneumoconiosis according to ILO 2000, comparable to the B-reader designation in the United States. In addition, readers were required to have experience reading small format radiographs generated by the mobile radiographic units. Rereading was performed blinded to the original BGGK physicians' ratings as well as to the second rereader's interpretation of the same films. Where rereadings disagreed, the two readers were asked to discuss and obtain a consensus reading, invoking a third reader if needed to adjudicate any remaining differences.

The first stage of rereading was based on a representative stratified sample (stratified by gender, birth cohort and silicosis status) of 400 cohort members, resulting in the rereading of more than 1600 individual chest radiographs. Overall, the two independent rereadings were in close agreement, and consensus was easily reached for all films. To classify each cohort member as normal or by degree of silicosis using the ILO categories, each rereader examined all available chest radiographs for each subject using the side-by-side method, consistent with the approach most likely used by the original readers. This approach further reduced variability (partly due to film size and quality) leading to a more stable interpretation against which original BGGK classifications could be compared.

Consistent differences were identified between the original BGGK classification and the consensus results, with considerably more films having been classified as "positive" (ie, 1/1 or greater) by the original BG readers than by the study rereaders. On the contrary, no films read by the original readers as clearly negative (ie, 0/0 or 0/1) were classified as positive (ie, 1/1 or greater) by the consensus rereading, indicating a very low false negative rate. Therefore, we were reasonably confident that original readings of 0/0 or 0/1 were unlikely to represent true positive results (on the basis of our rereading criteria). Because a majority of films fell into this category, we were able to avoid rereading these films for which the yield of true positive (1/1 or higher) readings likely would have been very low.

For the second phase of rereading two of us (E.B.G. and K.S.)—both experienced radiographic readers—independently reread all available x-ray films for all 606 cohort members whose most recent radiograph was originally classified by the BGGK as 1/0 or above, using the same methods as in the first phase. For some radiographs, an original BGGK assessment was unavailable, and for some individuals radiographs were unavailable possibly because they have been lost, misfiled, or were in use by the BGGK at the time of our request, leaving 552 (91% of the original sample) for rereadings. In addition, a random sample of radiographs from the first phase was included to verify that the new readers would replicate the results of the first consensus reading (ie, especially no false negative results). Ultimately, more than 4700 radiographs were reread by both rereaders. For this study, we defined silicosis as radiographic evidence of small rounded opacities with a profusion score equal to or greater than 1/1 (according to ILO, 2000) on the basis of the consensus rereading.

Exposure Assessment

Details of the historical exposure assessment have been reported elsewhere.[22] In short, more than 8000 combined static (stationary area) and personal total, respirable and silica dust industrial hygiene measurements were available for about 100 discrete production area or job task code combinations beginning in 1954 and covering all years through the end of follow-up. Original sampling and analysis protocols were available for these measurements. Because gravimetric measurements were not available before 1959, we performed laboratory and field exercises to derive conversion factors for particle count measurement results to mass values, and for gravimetric results using obsolete devices to values comparable with post-1975 gravimetric techniques.[22]

Exposure data were summarized into similar exposure groups or SEGs for production areas such as preparation, forming, drying, firing preparation, firing and finishing, and by calendar year to form a job exposure matrix (JEM). The cells of the JEM were populated by smoothing longitudinal industrial hygiene measurement data for each SEG using LOESS regression (SAS v9.1, SAS Institute, Cary, NC). Estimates for the earliest years with no exposure data (ie, 1938 to 1953) were derived by extrapolating the values backward from the summary exposure measurement data from 1954 through the 1960s.

A detailed employment history record was reconstructed for all cohort members on the basis of official employment records and in part on questionnaire information collected by medical personnel during the industry-wide medical screening program. By linking the work histories with the JEM, we calculated cumulative respirable crystalline silica exposure, average exposure, and 10-year lagged cumulative exposure for each cohort member. Lagging of cumulative exposure was time-dependent and was achieved by disregarding the previous 10-years exposure as of each time increment of follow-up. The employment records also provided necessary information on sex, smoking status as of the date of the medical screening examination, date of birth, date of hire and separation, and documentation of silica exposure outside of the porcelain industry (eg, in a previous job). Potential prior silica exposure was coded as probable, possible, unlikely or unknown by an expert (K.G.) in occupational exposures and familiar with the historical BGGK records.

Statistical Methods

We used Cox proportional hazards models to evaluate the time-dependent relationships between cumulative and average exposure estimates and silicosis morbidity and lung cancer mortality, allowing control for other time-dependent variables such as duration of employment.[25] Because follow-up time differs for mortality and silicosis morbidity, separate estimates of person-time were generated. The date of the first radiograph meeting the silicosis definition (ie, consensus reading of 1/1 or higher on the ILO scale) was recorded as the date of diagnosis. Person-time for each cohort member was accumulated until the later of the date of the last available radiograph or the date of silicosis diagnosis. We used age at end of follow-up as the time scale variable in all Cox models, and additional variables considered included sex, smoking status, age at hire, and duration of employment. Covariates producing 10% or more change in the estimate compared to the bivariate model were retained.[26] Analyses were generated both including and excluding cohort members with evidence of prior occupational silica exposure, with and without lagging exposures 10 years and limited to those hired since 1960.

Exposure cutpoints were arbitrarily selected in 0.5 mg/m^3-years increments up to 1.5 mg/m^3-years, and cumulative exposures above 1.5 mg/m^3-years were divided using 3.0 mg/m^3-years as an additional cutpoint.[22] These values provided adequately large numbers in each group to allow further stratification within categories. More than 40% of the cohort failed to exceed a cumulative exposure of 0.5 mg/m^3-years, and just more than a third of the cohort members accumulated exposures greater than 1 mg/m^3-years. Roughly, 2000 cohort members fell into each of the highest three exposure groups, with similar numbers of men and women, except in the highest category where there were considerably more men. However, for both silicosis morbidity and lung cancer mortality, the largest number of cases fell into the highest exposure category, and there was no indication of increased risk across the lower exposure categories. We therefore combined the lowest four original categories as the new referent category and subdivided the highest category into the following categories: $\leq$3.0; >3.0 to 4.0; >4.0 to 5.0; >5.0 to 6.0; and >6.0 mg/m^3-years. Average annual exposure (cumulative divided by duration of employment on a time-dependent basis) was categorized into the following groups: $\leq$0.05; >0.05 to 0.10; >0.10 to 0.15; >0.15 to 0.20; and >0.20 mg/m^3. Because an ancillary goal of this analysis was to evaluate the possibility of a threshold effect for silicosis and lung cancer, cumulative exposure was also modeled as a continuous variable using polynomial models of the second, third, and forth degrees. A formal threshold analysis using more sophisticated techniques is beyond the scope of this article.

RESULTS

More than 40% of the cohort accumulated less than 0.5 mg/m^3-years, and nearly 70% of the cohort had average exposures (over all working years) less than 0.05 mg/m^3 respirable crystalline silica. On the contrary, over a third of the cohort (approximately, 4700 cohort members) accumulated more than 1.5 mg/m^3-years, and nearly 10% of the cohort (approximately, 1600 cohort members) had average exposures (over all working years) of more than 0.15 mg/m^3 respirable crystalline silica. Similarly, half of those ever working in the materials preparation area accumulated over 3 mg/m^3-years, whereas only 12% of those never working in this area accumulated exposure this high.

A total of 1595 deaths (9.2% of the cohort) occurred, 535 (33% of decedents) due to cancers and 94 (17% of all cancers) due to lung cancer. Only 5 deaths were attributed to silicosis, and only 2 of the 10 decedents we determined to have silicosis were identified by death certificate to have died of this disease. A total of 40 cases of silicosis were identified on the basis of radiographic evidence. None of the individuals identified as having silicosis subsequently died of lung cancer, precluding analyses to detect elevated lung cancer risk among silicotics.

Descriptive statistics for the cohort, overall and by lung cancer mortality and silicosis morbidity status, are presented in Table 1. Men represented 79% and 85% of lung cancer deaths and silicosis cases, respectively, compared with 47% of the overall cohort. Risks of both diseases were also higher among those hired before 1960, employed longest and among smokers (much stronger for lung cancer). Lung cancer mortality and silicosis morbidity also were associated with higher categories of cumulative and average exposure, as well as annual exposure ever 0.15 mg/m^3 or more, especially for those with silicosis (85% compared with 25.5% of the remainder of the cohort).

Respirable Crystalline Silica Exposure, Lung Cancer, and Other Mortality

Lung cancer mortality among men (n = 74) was not associated with cumulative exposure in adjusted Cox proportional hazards analyses using either the lower or higher cumulative exposure classification scheme (Table 2). Nearly half of the lung cancer deaths occurred among those with more than 3 mg/m^3-years and one quarter among those with more than 6 mg/m^3-years cumulative exposures; yet, hazard ratios (HRs) for both these categories were essentially unity. Statistical analyses modeling silica exposure as a continuous term (with and without second to fourth order terms) showed no relationship with lung cancer risk (results not shown). Increasing levels of average exposure were not consistently associated with increasing risks of lung cancer, although some of the HRs were inconsistently elevated (Table 2). Excluding individuals with probable prior silica exposure had no clear impact on results (not shown). Risks were clearly high, however, among men known to be smokers at the time of their medical surveillance examination and those with unknown smoking status compared with known never smokers (Table 2).

Among women (n = 20), only six lung cancer deaths occurred among those with the highest cumulative exposure category from the original classification (ie, >3 mg/m^3-years), and only one in the lowest category (ie, $\leq$ 0.5 mg/m^3-years), resulting in elevated but highly unstable HRs (CIs spanning from 0.2 to 63). However, no pattern with exposure category was seen (Table 2). Excluding individuals with probable prior exposure to silica did not meaningfully change results (not shown). Hazard ratios were only weakly, and not statistically significantly, elevated for smoking, suggesting that the

TABLE 1. Characteristics of Cohort Members With Silicosis, Lung Cancer, and With Neither of These Outcomes

	Silicosis ($n = 40$)		Lung Cancer ($n = 94$)		Neither ($n = 17,479$)	
	n	%	n	%	n	%
Sex						
Female	6	15.0	20	21.3	9,296	53.2
Male	34	85.0	74	78.7	8,183	46.8
Decade of hire						
<1950	8	20.0	10	10.6	714	4.1
1950–1959	16	40.0	40	42.6	2,799	16.0
1960–1969	8	20.0	14	14.9	2,570	14.7
1970–1979	6	15.0	19	20.2	4,900	28.0
≥1980	2	5.0	11	11.7	6,496	37.2
Years employed						
≤10	1	2.5	13	13.8	4,595	26.3
>10–20	4	10.0	17	18.1	4,728	27.0
>20–30	11	27.5	26	27.7	4,121	23.6
>30	24	60.0	38	40.4	4,035	23.1
Smoking status						
Ever	20	50.0	54	57.4	6,560	37.5
Never	10	25.0	6	6.4	5,432	31.1
Unknown	10	25.0	34	36.2	5,487	31.4
Prior silica exposure						
Probable	9	22.5	12	12.8	654	3.7
Possible	5	12.5	24	25.5	1,440	8.2
Unlikely	24	60.0	50	53.2	14,313	81.9
Unknown	2	5.0	8	8.5	1,072	6.1

observed results for women may be unreliable because of uncontrolled confounding by smoking but mainly because of very small numbers. As with men, average exposure was not clearly associated with lung cancer risk among women.

Mortality due to all cancers combined, pancreatic cancer, liver cancer, kidney cancer, cardiovascular disease, digestive diseases, diabetes, renal disease,* and ill-defined conditions were not statistically significantly associated with cumulative silica exposure at any level, stratified by sex and adjusting for age, smoking history, and duration of employment (see Table 1 and Supplemental Digital Content Table A at http://links.lww.com/JOM/A47, Table B at http://links.lww.com/JOM/A48, and Table C at http://links.lww.com/JOM/A49). Smoking was statistically significantly associated with many of these causes of death, as was years of employment, with lower HRs seen among those employed longest.

Respirable Crystalline Silica Exposure and Silicosis

For this study, silicosis status was determined on the basis of rereading of radiographs by two independent readers according to a standard rereading protocol. Exact agreement between radiograph rereaders was reached for approximately 90% of all initial film rereadings. Most disagreements were within one ILO scoring category with similar proportions higher and lower, suggesting only expected random error. After consensus reading, 92.7% of all radiographs were classified below 1/1, and ultimately 89.3% of cohort members were classified as not having silicosis. Compared to the original BGGK classifications, the consensus rereading agreed exactly for 58% of all radiographs, but disagreement was systematically different: for 3% of radiographs, rereaders assigned a higher score, but for 39% the rereading generated a lower score. Among radiographs with BGGK and rereader consensus disagreement, 57% differed by one scoring category and for 43% the discrepancy was two or more categories. A total of 61 cohort members were therefore classified as having radiographic evidence of silicosis on the basis of a reading of 1/1 or higher. We excluded 21 silicotics from the analysis regarding silicosis morbidity, because their diagnosis date fell before ($n = 20$) or after ($n = 1$) the study follow-up period; however, their person-time during the study follow-up period (and cause of death, if deceased) were retained for the mortality analyses. Only 6 of the 40 silicosis cases were identified among women; however, four of these cases fell into the two highest cumulative exposure categories (ie, >5 mg/m^3-years). Therefore, all analyses combined men and women and statistically controlled for sex.

Silicosis risk was strongly associated with both average and cumulative exposure (Table 3). Adjusted HRs for groups with average exposures greater than 0.15 tended to be large (ranging from about 13 to 23) and statistically significant and exclusion of

TABLE 2. Lung Cancer Hazards Ratios (HRs) and 95% Confidence Intervals (95% CI) by Categories of Cumulative Exposure (mg/m^3-years), Average Exposure (mg/m^3), Duration of Employment (years), and Smoking, Stratified by Sex and Controlling for Age and Smoking*

		HR (95% CI)		
	n†	Male	n†	Female
Cumulative exposure				
≤0.5	19	Reference	1	Reference
>0.5–1.0	5	0.3 (0.1–0.9)	7	7.8 (1.0–63.2)
>1.0–1.5	5	0.4 (0.1–1.1)	3	4.2 (0.4–40.4)
>1.5–3.0	16	0.6 (0.3–1.2)	3	2.2 (0.2–21.8)
>3.0	29	0.5 (0.3–1.0)	6	3.2 (0.4–27.6)
≤3	45	Reference	14	Reference
>3–4	5	1.0 (0.4–2.4)	3	1.9 (0.5–6.6)
>4–5	3	0.7 (0.2–2.3)	1	0.7 (0.1–5.4)
>5–6	5	1.1 (0.5–2.9)	1	0.8 (0.1–6.1)
>6	16	0.8 (0.5–1.5)	1	0.4 (0.1–3.4)
Average exposure‡				
≤0.05	25	Reference	10	Reference
>0.05–0.1	20	2.1 (1.1–4.0)	3	0.5 (0.1–1.9)
>0.1–0.15	6	1.3 (0.5–3.3)	5	1.8 (0.5–6.3)
>0.15–0.2	12	2.4 (1.1–5.2)	2	1.1 (0.2–6.0)
>0.2	11	1.5 (0.7–3.3)	0	—
Years employed				
≤10	12	Reference	1	Reference
>10–20	11	0.3 (0.1–0.8)	6	1.9 (0.2–15.6)
>20–30	18	0.4 (0.2–0.9)	8	1.8 (0.2–14.5)
>30	33	0.3 (0.1–0.6)	5	0.8 (0.1–6.7)
Smoking				
Never	2	Reference	4	Reference
Ever	49	17.0 (4.1–69.8)	5	3.4 (0.9–12.7)
Unknown	23	4.8 (1.1–20.4)	11	2.1 (0.7–6.6)

*Results for Smoking adjusted for age only
†Number of observed deaths
‡Additionally adjusted for duration of employment

*The only exception was one very high HR (31.0; 95% CI, 2.5 to 387) for renal disease, based on four deaths among men in one of the lowest cumulative exposure categories (>1.0 to 1.5 compared with those with <0.05 mg/m^3-years)

TABLE 3. Silicosis Hazards Ratios (HRs) and 95% Confidence Intervals (95% CI) by Categories of Cumulative Exposure (mg/m^3-years), Average Exposure (mg/m^3), Duration of Employment (yrs), and Smoking, Controlling for Age, Sex, and Smoking*

		HR (95% CI)				
		Full Cohort	Exposure Lagged 10 yrs		Limited to Those Hired Since 1960	
Cumulative exposure	*n*†		*n*		*n*	
≤0.5	4	Reference	5	Reference	4	Reference
>0.5–1.0	1	0.3 (<0.1–2.6)	2	0.7 (0.1–3.7)	1	0.3 (<0.1–2.6)
>1.0–1.5	2	0.7 (0.1–3.8)	1	0.4 (0.1–3.7)	2	0.8 (0.1–4.4)
>1.5–3.0	2	0.4 (0.1–2.2)	2	0.5 (0.1–2.4)	1	0.5 (0.1–4.8)
>3.0	31	3.1 (1.1–9.3)	30	3.7 (1.4–9.9)	8	4.2 (1.2–15.1)
<3	9	Reference	10	Reference	8	Reference
>3–4	1	0.9 (0.1–7.5)	3	2.9 (0.8–10.6)	1	2.2 (0.3–18.0)
>4–5	4	5.3 (1.6–17.3)	4	4.9 (1.5–15.7)	2	8.2 (1.7–39.0)
>5–6	6	7.3 (2.6–20.8)	4	5.2 (1.6–16.9)	0	–
>6	20	6.8 (3.0–15.3)	19	6.7 (3.0–14.9)	5	11.8 (3.6–38.5)
Average exposure‡						
≤0.05	5	Reference				
>0.05–0.1	2	1.1 (0.2–5.6)				
>0.1–0.15	3	3.3 (0.8–14.7)				
>0.15–0.2	9	13.6 (4.2–44.4)				
> 0.2	21	23.2 (8.2–65.8)				
Years employed						
≤10	2	Reference			2	Reference
>10–20	6	0.7 (0.1–3.4)			6	0.8 (0.2–4.1)
>20–30	12	0.9 (0.2–4.1)			7	0.6 (0.1–3.0)
>30	20	0.6 (0.1–2.6)			1	0.1 (<0.1–1.5)
Smoking						
Never	10	Reference			2	Reference
Ever	20	1.7 (0.8–3.7)			10	3.5 (0.8–16.5)
Unknown	10	0.6 (0.2–1.4)			4	1.8 (0.3–9.8)

*Results for Smoking adjusted for age only. Additional results for cumulative exposure lagged 10 years and for cumulative exposure and duration of employment restricted to those hired since 1960.
†Number of observed deaths
‡Additionally adjusted for duration of employment

individuals with probable prior occupational exposure to silica only moderately reduced HRs.

Increased risk of silicosis was observed only among the group with cumulative exposure above 3.0 mg/m^3-years on the basis of the initial cutpoints (Table 3). Combining all categories below 3.0 mg/m^3-years as the referent, adjusted HRs tended to be consistently elevated for all exposure categories above 4 mg/m^3-years. Similar results were obtained when analyses were restricted to cohort members hired only after 1960; however, this reduced the number of exposed cases to eight and eight in the referent group. Lagging exposure by 10 years for the whole cohort produced larger but less precise relative risk estimates; however, all HRs were statistically significant for all categories above 4.0 mg/m^3-years. Exploratory models using cumulative exposure as a continuous variable and sequentially incorporating polynomial terms of the second, third, and fourth order (not shown) generated considerable differences in the Akaike's information criterion, or AIC score (605.9; 595.0; 592.4 and 578.1, respectively), suggesting that the relationship between cumulative respirable silica exposure and silica is not linear (all of the models with higher-order terms generated lower AIC scores, indicating a better fit than the model with only a first-order exposure term). Formal threshold analyses may be warranted; however, available numbers of silicosis cases may limit their precision.

DISCUSSION

This study is the largest to date that evaluates cancer and silicosis risks among porcelain workers, and one of only a few with substantial industrial hygiene data on which quantitative exposure–response analyses may be based. Other studies have considered respirable crystalline silica exposures in the ceramics industry, but none focus on the porcelain sector. We focused on the porcelain sector because (1) exposures to respirable crystalline silica were common and relatively well-documented; (2) the health surveillance program, including periodic chest radiographs, was nearly comprehensive; and (3) technological developments and work processes are highly comparable across plants over time.[22]

The majority of results using age, sex, and smoking-adjusted Cox proportional hazards models demonstrated no association between any major category of cause of death and cumulative respirable crystalline silica exposure levels. These results are consistent with previous findings of no important excesses of these causes of death based on SMR analyses.[21] One exception noted earlier was renal disease mortality among men, based on four observed deaths and only two deaths in the referent category. While probably due to chance (there were no other statistically significant results among the nearly 100 stratum-specific HRs calculated), other investigators have reported associations between respirable crystalline silica exposure and renal disease morbidity and mortality.[27,33]

Consistent with the previously reported SMR results,[21] lung cancer mortality results by cumulative and average respirable crystalline silica exposure provided no support for an association with lung cancer risk at exposure levels prevalent in the German porcelain industry during the study period. The only exception was a statistically significantly elevated HR for the subgroups with average exposure of less than 0.05 to 0.1 and less than 0.15 to 0.2; however, there was no apparent trend with increasing exposure. Whether this finding reflects some actual risk, residual confounding or random measurement error is not clear. With a study size of approximately 18,000 and 132 expected lung cancer deaths (from the SMR analyses), the statistical power was more than 99% to detect (at the $\alpha = 0.05$ level) a relative risk for lung cancer of at least 1.5, and 80% power to detect a relative risk as small as 1.2. In addition, we were able to adjust for smoking on about 70% of the cohort, for which there was evidence of confounding by smoking. Among those with known smoking status, approximately two-thirds were smokers. The significantly increased lung cancer risk among those with unknown smoking status indicates that some proportion of these workers were smokers. Finally, the strong and statistically significant association seen between respirable crystalline silica exposure and silicosis underscores that the lack of a positive finding for lung cancer cannot be explained by an invalid exposure assessment.

None of the individuals identified as having silicosis subsequently died of lung cancer (with approximately 1.7 expected on the basis of the overall rate in this cohort), precluding any statistical analyses of lung cancer risk among silicotics. However, most (75%) cohort members with silicosis were still alive as of the end of follow-up. Conversely, the number of lung cancer decedents expected to have silicosis (on the basis of the overall rate in this cohort) is less than one. Because of the modest number of silicotics in this study, the fact that 75% of those with silicosis were still alive at the end of follow-up, and the relative rarity of lung cancer (17% of all deaths in this cohort), no conclusion can be made regarding lung cancer risk among silicotics. Some,[34–38] but not all,[7] studies have advanced the hypothesis that lung cancer risk may be increased only in association with silicosis.

The study that is the most similar to ours is that published by Cherry et al[39] on the British potteries, which included porcelain workers among ceramics workers. Lung cancer (SMR = 1.91; 95% CI, 1.48 to 2.42) was significantly elevated compared with national rates (England and Wales) but not when regional reference rates were used (SMR = 1.28; 95% CI, 0.99 to 1.62). A JEM was developed for 12 job groups by 10-year period beginning in 1930.[40] Exposure estimates were based on 390 area air samples (1950s-1960s) evaluated as particle counts, and 1000 personal air samples evaluated as gravimetric silica mass (late 1960s and later). Smoking information was extracted from medical records from the employment period. Average concentration of respirable crystalline silica (0.1 mg/m^3) was significantly associated with lung cancer risk after adjustment for smoking (OR = 1.67; 95% CI, 1.13 to 2.47) but not with cumulative exposure (OR = 1.01; 95% CI, 0.85 to 1.19).[39]

Silicosis in the British potteries study was defined as radiographic evidence of small rounded opacities compatible with an ILO (1980) score equal to or greater than 1/0 (vs 1/1 in our study). Radiographs were obtained approximately every 4 years, but apparently assessed by only one reader. No rereading of radiographs was performed. Sixty-four cases were statistically evaluated using a nested case-control approach, and a dose–response relationship for cumulative (OR = 1.38 per 1 mg/m^3-year; 95% CI, 1.24 to 1.53) and average silica exposure (OR = 2.69 per 0.1 mg/m^3; 95% CI, 1.96 to 3.70) were reported. Exposure estimates were not time-dependent, but reflected values at the end of follow-up. Because of these and other differences between the British potteries study and the German porcelain workers study, direct comparison of specific findings may not be valid.

In a pooled analysis of 10 cohorts with 66,000 workers (two-thirds from mining populations and two-thirds from the Chinese study) exposed to respirable crystalline silica, a significant positive exposure–response for lung cancer was reported on the basis of more than 1000 lung cancer cases.[14] Lung cancer rate ratios (RR) were moderately increased in cumulative exposure categories above 2 mg/m^3-years (RRs of 1.3, 1.5, and 1.6 for 2.0 to 5.4, 5.4 to 12.8, and more than 12.8 mg/m^3-years, respectively). Smoking and silicosis status information was not available. The overall SMR of 1.2 (95% CI, 1.1 to 1.3) and the increased RRs in the categorical analysis led the authors conclude that respirable crystalline silica is likely a rather weak carcinogen.[14]

A meta-analysis of 10 studies examining silica exposure and lung cancer risks reported a dose–response relationship.[17] Considerable heterogeneity across studies was noted, with two studies presenting sharp increases in lung cancer risk at comparatively low cumulative exposure levels (ie, <2 mg/m^3-years),[18,41] in contrast to the remaining eight studies, some of which demonstrated no increase in risk with higher cumulative exposures.[13,42–44] Furthermore, only 2 of the 10 studies[43,44] appear to have intentionally excluded individuals with silicosis. Other methodological criticisms of this meta-analysis have been raised.[45] Erren et al[19] evaluated lung cancer risk among nonsilicotics and discussed methodological limitations of both epidemiological and toxicological approaches. Nevertheless, this meta-analysis identified three studies that controlled for smoking, estimating a meta-relative risk of 1.0 (95% CI, 0.8 to 1.3); however, for eight remaining studies, the meta-relative risk was slighted but statistically significantly elevated (RR = 1.2; 95% CI, 1.1 to 1.4) with significant heterogeneity noted.[19]

In contrast with the lack of support for an association between respirable crystalline silica exposure and lung cancer risk, our study demonstrated clearly and statistically significantly increased risk of radiographic evidence of silicosis (ILO 1/1 or higher) in the highest categories of both average (generally above 0.15 mg/m^3) and cumulative (generally >4.0 mg/m^3-years) exposure, controlling for age, sex, smoking, and duration of employment. Although no formal threshold analyses were performed, this study generated considerable support for a threshold.

Although smoking is believed not to contribute to silicosis risk, our study generated a nonstatistically significant sex-adjusted HR of 1.7, for smoking. On the contrary, those with unknown smoking status—believed to include some proportion of smokers on the basis of the lung cancer results—generated an HR less than unity. Therefore, the elevated HR likely reflects overestimation of silicosis risk among smokers. Duration of employment was inversely associated with silicosis risk. This might have been expected, given the cross-sectional definition of the cohort, that is, included were those actively employed and participating in the medical surveillance program during 1985 to 1987, regardless of when they were first employed in the porcelain industry. Those first employed in the 1940s and 1950s had to remain employed (or returned to employment) and survived until 1985 to be included. Thus, there is evidence of a survivor bias, but this is potentially addressed by controlling for duration of employment. Analyses limited to cohort members first employed since 1960 resulted in the loss of 60% ($n = 24$) silicosis cases. Further follow-up of the 14,026 employees hired since 1960 will be important, as there may not have been sufficient follow-up time to observe all cases of diseases with long latencies including lung cancers and silicosis.

Study Strengths and Weaknesses

Apart from this study's large size and inclusion of nearly equal proportions of men and women, one of its main strengths was the extent and quality of the available exposure data, allowing quantitative exposure–response evaluation of cause-specific mortality and silicosis morbidity. Workers' exposures were estimated on the basis

of a JEM created from approximately 8000 personal and area industrial hygiene measurements.[22] To include older data obtained using obsolete measurement devices, we conducted special exercises using historic equipment side by side with modern industrial hygiene devices. Series of measurements were made in both controlled dust tunnel and actual porcelain material preparation settings and were compared to derive conversion factors for data originally based on the historical measures. Because no exposure measurement data were available before the mid-1950s, we considered backward extrapolations on the basis of actual data trends apparent through the 1960s and of flat backward extrapolations from the earliest years for which data were available. Because there was a relatively small quantity of person-time accrued over these early decades, the potential impact of any misclassification is expected to have been modest. Nevertheless, estimated exposures for these early years were similar regardless of extrapolation approach. Therefore, for these analyses, we used those estimates extrapolated from actual data trends observed during the late 1950s and through the 1960s, a period over which significant advances in dust control and worker safety were implemented, including ventilation systems and replacement of wood floors with less porous and easier-to-clean materials.

Despite having access to information on prior employment on much of the study cohort, misclassification of respirable crystalline silica exposure before employment in the porcelain industry may have occurred. Although excluding those with known prior exposure resulted in some minor differences, it did not change the fact that several silicosis cases occurred among cohort members estimated to have the lowest exposures. Available work history records for these subjects indicate that prior employment was in jobs tracked by the BG, and most were classified into the "unlikely" outside exposure group. If these subjects actually had meaningful prior exposure, they would have inappropriately been included in the referent group. Similarly some false positive interpretations of radiographs likely occurred, even among those with low exposure. On the contrary, a total lack of (or too few) silicosis cases in the referent group would have prevented or limited the statistical analyses.

Although results of analyses lagging cumulative exposure by 10 years are reported, it is not clear whether this is entirely valid, as cases of silicosis can occur after only a few years of high-intensity exposure.[46] Furthermore, it is not known whether crystalline silica exposures sustained after the silica-related fibrotic process begins accelerates the disease process and probability of radiographic changes consistent with silicosis. Therefore, we believe that lagging may introduce additional exposure misclassification and that results should be interpreted with caution.

Another strength of this study derives from the comprehensive records systems we were able to access at the BGGK, including remarkably detailed work history information and the large collection of historical radiographs. This not only allowed independent verification of silicosis status according to a standard protocol but also confirmation of no signs of silicosis on most cohort members. By rereading all radiographs that originally were scored as abnormal (ie, ILO-equivalent scores of 1/0 or higher) with modern standard criteria and blind to occupational history and exposure status, we enhanced the quality and consistency of the silicosis determination. Rereading of all available films for each employee with radiographic evidence of silicosis allowed assignment of a date associated with the first radiograph interpreted as category 1/1 or higher, which in turn allowed more precise estimation of follow-up time for each employee.

Because of exhaustive retrieval of vital status information from multiple sources, no significant loss to follow-up occurred in this study. Nevertheless, among the 5% of decedents for which we were unable to ascertain cause of death, there could be specific causes of death that, if known, would have changed our results. For the causes of death of primary interest, however, this is unlikely, as dust-exposed porcelain workers were under active surveillance for these respiratory diseases. Furthermore, participation in the surveillance program—including periodic radiographic evaluation—preserved the employees' eligibility for compensation should they contract a work-related disease, at least until retirement.

Additional evaluation of the 94 lung cancer cases using additional exposure metrics—or using a nested case-control approach—is unlikely to be informative because of the clear lack of any detectable excess of lung cancer deaths and lack of association between respirable crystalline silica exposure and lung cancer. However, additional evaluation of the silicosis cases by various additional exposure attributes (or combinations thereof) is warranted. For example, a formal exposure–response threshold modeling may elucidate where the threshold of effect likely falls.[47,48] Additional follow-up of this cohort may be valuable, as only 9.2% of the cohort was deceased as of end of follow-up. Additional follow-up would also be helpful for silicosis evaluation, as the median age at silicosis determination was only 56. The quantitative exposure assessment covering the past 75 years is unlikely to be further improved, unless additional historical exposure data are discovered or more innovative methods for using them are derived. Modern exposures are uniformly low and will make a relatively minor additional contribution to the estimated exposures.

In conclusion, this study evaluated quantitative respirable crystalline silica exposure in the German porcelain industry and silicosis morbidity and mortality due to several selected causes of death including lung cancer. Our preliminary finding of no increased risk of lung cancer based on our SMR analyses was corroborated by exposure–response analyses demonstrating no consistent associations. Increased risk of silicosis morbidity was clear, with evidence of possible thresholds at or above roughly 4 mg/m^3-years cumulative and at or above roughly 0.15 average respirable crystalline silica exposure. More formal threshold analyses might elucidate where such thresholds might lie on the exposure distribution scales; however, accurate determination may require a larger number of silicosis cases.

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Mortality in the German Porcelain Industry 1985–2005: First Results of an Epidemiological Cohort Study

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Objectives: *To evaluate mortality due to lung cancer, silicosis, renal cancer, renal disease and other causes among German porcelain production workers potentially exposed to crystalline silica.* ***Methods:*** *Seventeen thousand six hundred forty-four medical surveillance participants (1985–1987) were followed through 2005 for mortality. Cause-specific Standardized Mortality Ratios (SMR) and 95% confidence intervals were estimated.* ***Results:*** *Women (SMR = 0.85; 95% CI = 0.78 to 0.93), but not men, demonstrated a healthy worker effect. Lung and renal cancers, and renal disease (non-malignant renal disease) were not associated with employment or exposure surrogates. Mortality was increased from silicosis (SMR = 7.20; 95% CI = 2.32 to 16.8) liver (SMR = 1.99; 95% CI = 1.29 to 2.93) and pancreatic (SMR = 1.71; 95% CI = 1.18 to 2.41) cancers among men, and diabetes among women (SMR = 1.74; 95% CI = 1.07 to 2.65). A sub-cohort of Bavarian workers generated similar but generally higher SMRs.* ***Conclusions:*** *Silicosis mortality was increased in this, among the largest studies to date. However, associations previously observed between crystalline silica exposure and renal or lung cancers or non-malignant renal disease were not supported.* (J Occup Environ Med. *2009;51: 373–385*)

Chronic inhalation of dust containing sufficient concentrations of free crystalline silica has been linked for decades with disabling lung diseases such as silicosis and silico tuberculosis. Studies also have suggested that crystalline silica may increase risk of lung cancer as well as some other diseases. Exposure to crystalline silica has long been recognized as a significant health hazard for workers engaged in mining, quarrying, stone cutting and crushing operations, sandblasting, foundry works, construction, ceramics manufacturing and other occupations where significant dust exposures have occurred. Risks to workers appear to vary according to quantity and type of crystalline silica polymorph, with greater risks associated with freshly fractionated quartz and with specific crystalline structures such as crystoballite.[1]

In 1997, the International Agency for Research on Cancer (IARC) found "sufficient evidence" in both humans and in animal studies to classify occupational exposure to crystalline silica in the form of quartz or crystoballite as carcinogenic in humans.[2] However, carcinogenicity in humans was not evident under all industrial exposure circumstances. Risk appeared to be stronger among individuals previously diagnosed with silicosis, raising a basic question of whether lung cancer risk was also elevated among individuals without silicosis, including those less heavily exposed. The scientific debate continues well after

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the 1997 IARC evaluation,[3–5] and newer research reports and reviews have generated additional, divergent evidence and conclusions.[6–11]

In addition to the relationship between crystalline silica exposure, silicosis and lung cancer risk, several recent studies have suggested relationships between crystalline silica exposure and non-malignant renal disease (NMRD) and kidney cancer.[6,12–18] To date the total number of cases studied has been relatively small, precluding firm conclusions regarding their association with crystalline silica exposure.

In this paper, we report on the mortality experience of nearly 18,000 German porcelain workers potentially exposed to crystalline silica and participating in a medical surveillance program in the mid-1980's that included periodic x-ray evaluations as well as nearly complete documentation of employment history.

The German Porcelain Industry

From the 18th century until around 1920, large porcelain factories were constructed in Bohemia, Thuringia, Upper Franconia and Upper Palatinate with a basic technology that did not change substantially over the years. In 1929 in Germany, the 2nd Ordinance on Occupational Diseases made "Severe Silicosis" in combination with jobs in specific industry sectors, a compensable occupational disease.[19] Among qualifying industries was porcelain manufacturing, where silicosis was known as "porcelain workers' disease." By 1938 the Berufsgenossenschaft der keramischen-und Glas-Industrie (BGGK)—the official institution for worker accident insurance/compensation and prevention in the ceramics and glass industry—implemented systematic preventive medical checkups for early detection of silicosis among dust-exposed employees of its member companies, which since that time has been mandatory for all member companies. The results of preventive medical checkups have been stored electronically since the mid-1980s, when participation in the preventive medical program by blue-collar workers had reached approximately 85%.

In addition, since 1951 but more frequently beginning in the 1960's, the BGGK conducted numerous dust measurements among their member companies. Since 1972 and until 2006, the occupational exposure limit (OEL) in Germany had been 0.15 mg/m^3 Time Weighted Average as respirable silica. In 2006, however, many established OELs in Germany were suspended—including the limit for crystalline silica—if they were not based on health data as required by the 2005 German Ordinance on Hazardous Substances.

The cohort of German porcelain industry production employees, which has never been evaluated epidemiologically, presents a rare opportunity to evaluate health effects of occupational exposures to crystalline silica generally (but with clear exceptions) around or below the OEL and in contrast with much higher levels associated with porcelain production in the first half of the 1900's. Furthermore, half of the available study population are women, allowing for many causes of death including lung cancers evaluation of silica-related mortality risks among women.

This paper, the first of several investigations underway on this cohort, presents the overall study approach as well as the results of a basic standardized mortality ratio (SMR) analysis. For this report, we focus on diseases of recent interest including lung cancer, silicosis, renal disease, and kidney cancer. Because silicosis often is not fatal, a separate evaluation of silicosis risk will be presented in a subsequent paper, based on the x-ray film evaluations of the cohort over time, and incorporating a quantitative exposure assessment based on the extensive IH data available. However, silicosis mortality results are considered in this report.

Methods

Study Population

The source population for this study consisted of employees from more than 100 plants of the German porcelain and fine ceramics (hereafter referred to as "porcelain") industry. Most of the porcelain manufacturing plants are located in two regions of the German State of Bavaria—Upper Palatinate and Upper Franconia—mainly due to the proximity to large kaolin deposits in these areas. Kaolin, along with quartz and feldspar, are the main ingredients of porcelain products. Other porcelain plants that are included in this study are scattered throughout the Western States of Germany. Because the BGGK conducted examinations as well as exposure measurements in the plants in the Eastern States of Germany only after reunification in 1990, the study population is restricted to employees of plants located in the Western States (former West Germany).

The study population was initially defined as all employees who participated in the preventive medical surveillance program for early identification of silicotic signs between January 1, 1985 and December 31, 1987, according to the German regulation "Berufsgenossenschaftlicher Grundsatz G 1.1 'Quarzhaltiger Staub.'" This time window was chosen for two reasons. First, the BGGK maintains an electronic database on all preventive medical checkups since 1985, including demographic information and the results of radiological examinations according to International Labor Organization (ILO) criteria (1980). Second, the German Ordinance for Hazardous Substances required employers to conduct preventive medical examinations of employees exposed to quartz (ie, crystalline silica) dust. Under these rules, if a threshold level for a workplace hazardous substance has been exceeded in a workplace subject to this ordinance, employees are only allowed to work in such

workplaces if they undergo special periodic preventive medical examinations. For crystalline silica, medical examinations are required every 3 years. Therefore the 3-year time window of 1985 to 1987 was selected to facilitate identifying nearly all exposed porcelain workers at this time.

Not included in the electronic database of the BGGK, however, is information regarding the employees' work history (except the specific plant where the employee worked at the time of the medical examination), smoking habit, medical examination results (apart from the radiological results) and home address. Much of this information is recorded in the paper records maintained by the BGGK. Based on the electronic database, we identified 20,039 employees of the German porcelain industry, of which 48% were males and 52% were females.

In retrieving the paper records for the cohort, it was determined that records were not available for all members of the study population. Due to storage space limitations, the general policy of the BGGK was to destroy paper records of persons older than 75 years, provided they had no signs of silicosis (defined as ILO 1980 1/0 or greater) as of their last examination. However, this rule had not been consistently applied. When the cohort was created early in 2005, paper records were located for 408 (32%) of the 1295 members of the study population who were older than 75 years at that time. Among those with records were 88 persons with some sign of silicosis based on the BGGK x-ray film evaluations. Additionally, folders for a few companies which closed many years ago were destroyed, and some missing files are believed to have been destroyed accidentally. Therefore, we redefined the eligible cohort as those employees for whom work histories were available from paper records (N = 18,000). Further exclusion of individuals employed for less than 6 months (cumulative) in the porcelain industry resulted in a final analytical cohort of 17,644 employees. This population was followed through December 31, 2005 for mortality (and for silicosis morbidity based on periodic x-ray films, to be published separately). Because the majority of porcelain plants are located in the German State of Bavaria, we defined a sub-cohort of Bavarian porcelain workers comprised of 15,045 employees (85.3% of the Full Cohort). Figure 1 summarizes the numbers in each cohort grouping, as well as the Full Cohort and the Bavarian Subcohort by sex, vital status, and person-years of follow-up.

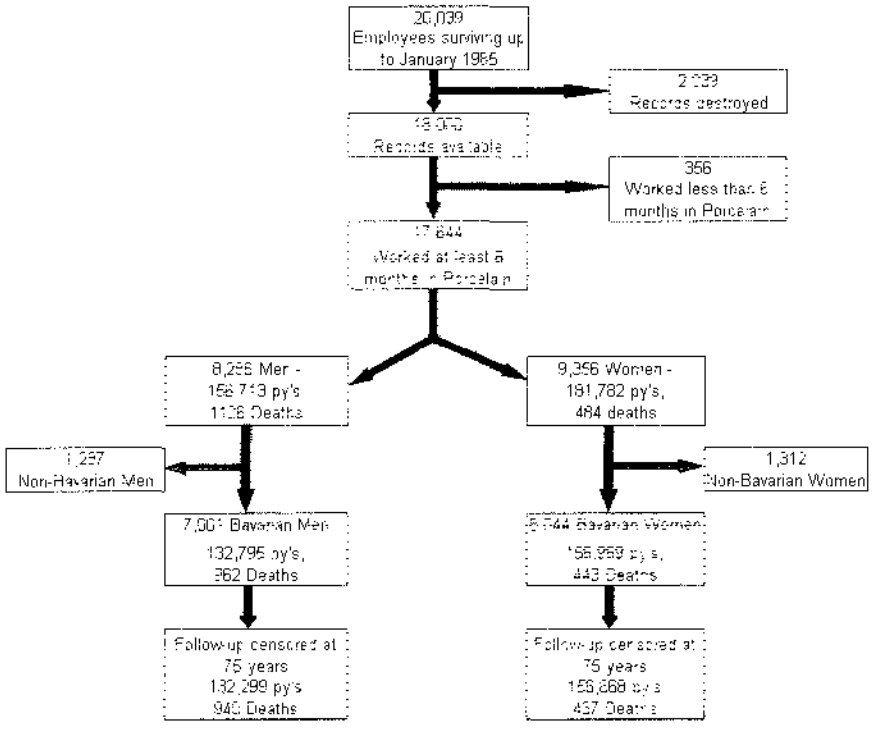

Fig. 1. Study population, Full Cohort and Bavarian Subcohort.

Vital Status Ascertainment and Determination of Cause of Death

Several available data sources were consulted to determine the vital status for each cohort member, including the BGGK internal information as well as company health insurance and pension fund data. However, most of the vital status information was determined through direct written enquiries to the community registration offices for the location in which each employee was last known to reside, or by searching a central registration database for Bavaria. Vital status of the cohort ultimately was determined for 94%, with 1610 (9%) of the cohort members reported to be deceased. For the Bavarian Subcohort, follow-up was truncated at age 75, as many records on cohort members over age 75 and with no signs of silicosis had been destroyed. Approximately 50% of employees from the original study population who were 75 years of age or older at the end of the follow-up period had no paper record available and therefore are not part of the analytical cohort. We investigated the possible influence on the risk estimates due to restricting follow-up to the age of 75 years. The result of this subanalysis showed that very few cohort members contributed person-years at risk in the ages older than 75 (0.3% of all person-years) leading to only a very small increase in the SMRs for this population. We subsequently used this cohort with follow-up truncated at age 75 for all further analyses of the Bavarian Subcohort.

Subjects with unknown vital status at the end of the follow-up period contributed person time up to the date last know to be alive. Although quantitative exposure estimates are being developed, some basic surrogates for higher exposure were derived, such as decade of hire and hire before or after the end of 1960, given that earlier years in this industry were dustier; and ever having worked in the preparation area, as this is the area with greatest potential exposure historically to respirable crystalline silica. Follow up time for individual subjects was divided into single calendar years and 5-year age categories to correspond with the available mortality referent rates.

The underlying cause of death was sought on each decedent from the official death certificate, which in Germany usually is stored at the community health department in the town or city where the death occurred. However, minimum record retention times differ from state to state in Germany, ranging, for example, from 30 years in Bavaria to only a few years in other States such as Rhineland-Palatinate. Therefore, cause of death determination based on death certificates was more complete for the Bavarian Subcohort (95%) compared with the Full Cohort (93%). For those cohort members who died in Bavaria between 2000 and 2005—approximately one third of all decedents—the official cause of death code was directly provided by the Statistical Office of Bavaria, according to the tenth revision of the International Classification of Diseases (ICD-10).[23] All other death certificates were coded by a professional nosologist from an official German State Statistical Office, also according to the ICD-10.

Employment History

A detailed employment history was reconstructed for all cohort members, using available files at the BGGK. Files included records of employment before starting work in a porcelain plant, including dates, name, location, and type of plant as well as the specific job. Year of hire, department and/or job in the porcelain plant, and the respective start date of the job were recorded in the forms documenting the initial and all follow-up medical surveillance examinations. Therefore, all potential changes of job or department over time could be reconstructed. Using these data and historical industrial hygiene measurements, we are currently developing quantitative Job-Exposure Matrices for use in dose-response analysis. For this report, however, detailed work history data were used to derive indicators of exposure differences like duration of employment, decade of hire (to evaluate potential for survival bias among cohort members hired before the start of follow up) and ever having worked in the preparation department. This department is the area believed to have the highest consistent crystalline silica exposure potential, and which, until recent years, consistently had average monitored exposures exceeding the former German OEL of 0.15 mg/m^3 as a Time Weighted Average of respirable crystalline silica.

Statistical Analyses

Cause-specific mortality patterns were examined by calculating SMRs for all cause and selected groupings of cause of death, comparing observed number of deaths in the cohort with expected numbers based on two sets of reference rates. For the Full Cohort, rates for the former Western Germany population (1985–1997) and the total German population (1998–2005) were derived based on mortality and population numbers made available by the Statistical Office of Germany. A second set of reference rates was derived based on the Bavarian population (numbers of deaths and population counts were provided by the Statistical Office of Bavaria). Higher all cause, all cancer, and CVD mortality rates in Upper Palatinate and Upper Franconia, the two sub regions in which a majority of Bavarian Subcohort members worked, compared with other Bavarian regions are reported in official Bavarian health status reports.[24] Because of the greater variability in rates for these sub-regions (especially for rarer causes of death), however, we decided to present SMR results based on the Bavarian referent only. Rates for both reference groups were calculated by gender, 5-year age group (from 15 to 84 and 85+) and calendar year, although analyses of the Bavarian Subcohort were limited to the cohort experience up to age 75.

For the Full Cohort, SMRs and 95% confidence intervals (95% CIs) were calculated for all causes combined and approximately 40 different cause-of-death categories (Appendix). A subset of causes of death (principally those reflecting the key study research questions) was examined for the Bavarian Subcohort. All analyses were conducted using SAS v9.1 (SAS Institute Inc, Cary, NC). We calculated exact CI's using Byar's approximation.[22] Because of considerable differences in the risk and distribution of causes of death, and because of the large number of women included in this cohort, SMR analyses are stratified by gender.

For the Bavarian Subcohort, SMRs stratified by date of hire before/after 1960 were estimated to evaluate the potential impact survival bias might have on the cohort results. Because follow-up of the cohort started on January 1, 1985 at the earliest, those starting employment many years prior to this had to survive until the start of follow-up, and the patterns of mortality among this subset may be different from those hired closer to the start of follow up and not subject to (or at least as strongly to) potential survival bias. We also stratified Bavarian Subcohort results by ever/never having worked in the preparation area—a surrogate for the highest likely exposures to crystalline silica. No further stratification by work area or estimated exposure to crystalline silica was performed at this stage, as a

detailed quantitative exposure assessment is underway.

The possible influence of the record retention policy of the BGGK on the risk estimates was evaluated two ways: by excluding those cohort members aged 75 years or more on January 1, 2005 and with signs of silicosis; and by excluding all cohort members older than 75 years as of this date.

Results

The full cohort of 17,644 workers employed in porcelain production for at least 6 months generated 338,495 person-years of observation at risk, 156,713 person-years among men and 181,782 person-years among women. Figure 1 shows the numbers of individuals, person-years observed and numbers of death for the Full Cohort and the Bavarian Sub-Cohort, by sex. Bavarian men comprised approximately 84% (by count and person-time up to age 75) and Bavarian women approximately 86% (by count and person-time up to age 75) of the Full Cohort. Truncating follow-up at age 75 for all in the Bavarian Sub-Cohort resulted in the loss of only 22 deaths (and 496 person-years) among men and 6 deaths (and 301 person-years) among women, so only the truncated Bavarian Sub-Cohort results are presented.

The average age at start of follow up for men was about 35 and about 34 for women (Table 1). At the end of follow-up, 14,935 (85%) were known to be alive, 1610 (9%) were determined to be deceased, and vital status remained unknown for 1099 (6%) (Table 2). Among the 1126 male decedents (13.6% of men), all cancers accounted for 32.1% of all deaths, all circulatory system diseases 32.9%, all respiratory diseases 5.2% and other causes of death 29.8%. Among the 484 female decedents (5.2% of women), all cancers accounted for 39.3% of all deaths, all circulatory system diseases 25.8%, all respiratory diseases 3.7% and other causes of death 31.2%. Follow-up status as well as numbers of deaths in each of these broad categories, by full or Bavarian sub-cohort are presented in Table 2. Duration of employment was similar for both the full and Bavarian groups (Table 1).

Table 3 presents SMR estimates for the full cohort, by sex, for 39 categories of cause of death, using the German population as the referent. The SMR estimate for all causes among men was not statistically different from unity. However, we observed a significantly decreased SMR for women (0.85, 95% CI = 0.78 to 0.93), compatible with a Healthy Worker Effect. Significantly elevated SMRs for liver and pancreatic cancer, and for silicosis, (1.99, 95% CI = 1.29 to 2.93; 1.71, 95% CI = 1.18 to 2.41; 7.20, 95% CI = 2.32 to 16.8) were estimated for men. Only the SMR for diabetes was significantly elevated among women (1.74, 95% CI = 1.07 to 2.65). We observed no statistically significant

TABLE 1
Duration of Employment, Age at Start of Follow-up and Date of Hire, Full Cohort and Bavarian Subcohort, by Sex*

	Full Cohort		Bavarian Subcohort	
	Men (n = 8,288)	Women (n = 9,356)	Men (n = 7,001)	Women (n = 8,044)
Duration employment, yrs				
Mean	22.5	20.6	22.4	20.9
Minimum	0.5	0.5	0.5	0.5
Maximum	57.6	49.9	57.6	49.9
Age at start of follow-up†				
Mean	35.2	34.0	34.8	34.3
Minimum	15.3	14.6	15.3	14.6
Maximum	63.7	61.7	62.6	61.7
Date of hire				
Median	9/1/1975	8/2/1978	7/1/1978	4/30/1976
Latest	1/1/1991	4/17/1996	1/1/1991	4/17/1996
Earliest	7/1/1938	1/1/1943	7/1/1938	1/1/1943

*Excludes subjects with <6 mo employment in porcelain.
†n = 2 women missing DOB.

TABLE 2
Vital Status and Distribution of Deaths (ICD-10 Codes) From All Cancers, All CVD and All Respiratory Diseases, Full Cohort and Bavarian Subcohort, by Sex

Full Cohort	Men 8,288	Women 9,356
Vital status n (%)		
Alive	6707 (80.9)	8228 (87.9)
Deceased	1126 (13.6)	484 (5.2)
Unknown	455 (5.5)	644 (6.9)
All cancers (C00-C97)	361 (4.4)	190 (2.0)
All circulatory system (I00-I99)	371 (4.5)	125 (1.3)
All respiratory (J00-J98)	58 (0.7)	18 (0.2)
Other	336 (4.1)	151 (1.6)
Bavarian Subcohort	**Men 7,001**	**Women 8,044**
Vital status n (%)		
Alive	5698 (81.4)	7114 (88.4)
Deceased	962 (13.7)	443 (5.5)
Unknown	341 (4.9)	487 (6.1)
All cancers (C00-C97)	315 (4.5)	169 (2.1)
All circulatory system (I00-I99)	329 (4.7)	120 (1.5)
All respiratory (J00-J98)	48 (0.7)	18 (0.2)
Other	270 (3.9)	136 (1.7)

TABLE 3
SMR and 95% CIs for 39 Categories of Cause of Death for the Full Cohort, by Sex

		Men 156,713 Person-Yr				Women 181,782 Person-Yr			
Cause of Death	ICD-10	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	A00–Y98	1126	1091.91	1.03	0.97–1.09	484	569.94	0.85	0.78–0.93
Infective and parasitic diseases	A00–B99	13	17.32	0.75	0.40–1.29	6	7.94	0.76	0.28–1.64
Malignant neoplasms	C00–C97	361	352.71	1.02	0.92–1.13	190	246.65	0.77	0.66–0.89
Buccal cavity and pharynx	C00–C14	21	18.62	1.13	0.70–1.72	7	3.48	2.01	0.81–4.15
Oesophagus	C15	20	14.31	1.40	0.85–2.16	1	2.55	0.39	0.01–2.18
Stomach	C16	23	21.25	1.08	0.69–1.62	6	11.85	0.51	0.18–1.10
Large intestine	C18	28	26.03	1.08	0.71–1.55	13	18.74	0.69	0.37–1.19
Liver and gallbladder	C22–C24	26	12.56	1.99	1.29–2.93	10	6.31	1.59	0.76–2.92
Pancreatic cancer	C25	33	19.25	1.71	1.18–2.41	9	12.41	0.72	0.33–1.38
Larynx	C32	4	6.29	0.64	0.17–1.63	1	0.62	1.61	0.02–8.96
Lung	C34	74	104.07	0.71	0.56–0.89	20	27.60	0.72	0.44–1.12
Other respiratory and intrathoracic organs	C37–C38, C45	1	3.51	0.28	0.00–1.58	0	1.08	—	
Breast	C50	1	0.56	1.79	0.02–9.96	48	61.73	0.78	0.55–0.99
Female genitourinary	C53–C55, C58	—	—	—		8	10.31	0.78	0.33–1.53
Ovary, other uterine adnexa and other female	C51–52, C56–C57	—	—	—		17	13.35	1.27	0.74–2.04
Prostate	C61	13	19.14	0.68	0.36–1.16	—	—	—	
Bladder	C67–C68	10	8.19	1.22	0.58–2.25	2	2.38	0.84	0.09–3.04
Kidney	C64–C66	11	16.84	0.65	0.32–1.16	5	7.48	0.67	0.22–1.56
Brain & nervous system	C47, C70–C72	14	11.39	1.23	0.67–2.06	5	8.66	0.58	0.19–1.35
Miscellaneous malignant	C76–C80, C97	24	18.88	1.27	0.81–1.89	9	11.66	0.77	0.35–1.46
Hodgkin's disease	C81	1	1.33	0.75	0.01–4.18	2	0.89	2.25	0.25–8.11
Non-Hodgkin's lymphoma	C82–C85	9	8.49	1.06	0.48–2.01	5	5.81	0.86	0.28–2.00
Multiple myeloma	C88–C90	2	4.80	0.42	0.05–1.51	2	3.58	0.56	0.06–2.02
Leukaemia	C91–C95	7	10.42	0.67	0.27–1.38	7	7.31	0.96	0.38–1.97
Neoplasms in situ and unspecified	D00–D09, D37–D48	7	6.15	1.14	0.46–2.35	4	3.84	1.04	0.28–2.66
Diabetes	E10–E14	20	19.43	1.03	0.63–1.59	21	12.09	1.74	1.07–2.65
Blood and blood-forming organs	D50–D89	0	1.83	—		2	1.41	1.42	0.16–5.12
Mental disorders	F00–F99	15	26.55	0.57	0.32–0.93	5	8.12	0.62	0.20–1.44
Nervous system and sensory organs	G00–G99, H00–H95	15	18.00	0.83	0.46–1.36	6	12.80	0.47	0.17–1.02
Diseases of the circulatory system	I00–I99	371	371.13	1.00	0.90–1.11	125	151.48	0.83	0.69–0.98
Diseases of the respiratory system	J00–J98	58	54.26	1.07	0.81–1.38	18	22.66	0.79	0.47–1.26
COPD	J40–J44	25	27.64	0.90	0.58–1.34	10	9.33	1.07	0.51–1.97
Silicosis	J62	5	0.69	7.20	2.32–16.8	0	0.01	—	
Diseases of the digestive system	K00–K93	73	78.41	0.93	0.73–1.17	39	37.53	1.04	0.74–1.42
Cirrhosis	K70, K73–K74, K76.0	44	54.22	0.81	0.59–1.09	24	29.27	0.82	0.52–1.22
Diseases of the genitourinary system	N00–N39	11	9.35	1.18	0.59–2.11	4	6.01	0.67	0.18–1.71
Renal disease	N00–N08, N10–N12, N14–N19, N26–N29	10	7.56	1.32	0.63–2.43	4	4.69	0.85	0.23–2.18
Ill-defined conditions	R00–R99	13	35.91	0.36	0.19–0.62	8	15.33	0.52	0.22–1.02
External causes	V01–Y98	81	92.81	0.87	0.69–1.08	18	35.30	0.51	0.30–0.81

TABLE 4
SMR and 95% CIs for Selected Categories of Cause of Death for the Bavarian Subcohort, by Sex

		Men 132,299 Person-yr				Women 156,668 Person-yr			
Cause of Death	ICD-10	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	A00–Y98	940	801.24	1.17	1.10–1.25	437	457.39	0.96	0.87–1.05
Malignant neoplasms	C00–C97	301	262.25	1.15	1.02–1.29	162	208.52	0.78	0.66–0.91
Lung	C34	59	99.92	0.59	0.45–0.76	16	17.55	0.91	0.52–1.48
Kidney	C64–C66	9	18.60	0.48	0.22–0.92	5	9.57	0.52	0.17–1.22
Diseases of the circulatory system	I00–I99	315	266.83	1.17	1.05–1.31	119	115.57	1.03	0.85–1.23
Diseases of the respiratory system	J00–J98	47	37.57	1.25	0.92–1.66	18	17.27	1.04	0.62–1.65
COPD	J40–J44	18	17.14	1.05	0.62–1.66	10	6.17	1.62	0.78–2.98
Silicosis	J62	5	0.44	11.37	3.66–26.53	0	0.01	—	
Renal disease	N00–N08, N10–N12 N14–N19, N26–N29	9	5.45	1.65	0.75–3.14	3	3.09	0.97	0.20–2.84

increased risk of mortality due to lung cancer, renal cancer, or NMRD (identified a priori as causes of interest); however, the point estimate for renal disease among men was elevated (1.32, 95% CI = 0.63 to 2.43).

Using the Bavarian sub-cohort and the Bavarian population as referent resulted in increases for the SMRs calculated for broad categories of cause of death as well as specific causes of interest (Table 4), suggesting that Bavarian mortality rates are generally lower than comparable German rates. The SMR estimate for lung cancer increased from 0.71 to 0.98 (95% CI = 0.75 to 1.27) for men, and from 0.72 to 0.91 (95% CI = 0.52 to 1.48) for women. SMRs for circulatory system diseases increased from 1.00 to 1.17 (95% CI = 1.05 to 1.31) for men, and from 0.83 to 1.03 (95% CI = 0.85 to 1.23) for women. The estimate for renal disease among men remained elevated, but not significantly so (1.65, 95% CI = 0.75 to 3.14).

Analyses were repeated, first excluding the 88 cohort members with signs of silicosis and those older than 75 years at beginning of the study in 2005, and second by restricting the cohort to those younger than 75 years. No remarkable changes in any of the risk estimates were seen (results not shown) except for silicosis, for which the number of silicosis death was reduced from 5 to 3. This led to reduced SMRs for silicosis mortality as follows: Full cohort: SMR 4.67 (95% CI = 0.94 to 13.66) and SMR 6.41 (95% CI = 1.29 to 18.74) for each alternative analysis, respectively; Bavarian sub-cohort: SMR 6.95 (95% CI = 1.40 to 20.32) and SMR 7.95 (95% CI = 1.60 to 23.23), respectively.

When comparing Bavarian men hired through 1960 to those hired after 1960, the excess risk of death due to cancer and respiratory disease appeared to be confined to those hired in the earlier period (Table 5). SMRs for both time periods were 1.24 (95% CI = 1.06 to 1.44) and 1.02 (95% CI = 0.85 to 1.23) for

TABLE 5
SMR and 95% CIs for Selected Categories of Cause of Death for the Bavarian Subcohort, by Sex and by Period of Hire (Pre-/Post-1960)

	Men								Women							
	Hired Through 1960				Hired Post-1960				Hired Through 1960				Hired Post-1960			
Cause of Death	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	466	474.99	1.17	1.07–1.28	454	386.25	1.18	1.07–1.28	210	214.51	0.98	0.85–1.12	227	242.68	0.93	0.82–1.06
Malignant neoplasms	187	150.62	1.24	1.06–1.44	126	116.84	1.08	0.89–1.23	62	68.12	0.91	0.70–1.15	70	110.40	0.63	0.50–0.80
Lung	35	34.88	1.00	0.7–1.40	24	25.06	0.96	0.61–1.43	8	7.93	1.01	0.43–1.99	8	9.81	0.82	0.36–1.64
Kidney	3	10.93	0.27	0.05–0.80	6	7.67	0.78	0.28–1.70	3	5.23	0.57	0.12–1.68	2	4.55	0.46	0.05–1.66
Diseases of the circulatory system	175	156.09	1.12	0.96–1.30	140	112.74	1.24	1.04–1.47	53	61.99	0.86	0.64–1.12	66	53.68	1.23	0.95–1.56
Diseases of the respiratory system	37	22.51	1.36	0.94–1.96	16	15.06	1.06	0.61–1.73	8	8.69	0.92	0.40–1.84	10	8.58	1.17	0.56–2.14
COPD	10	12.39	0.92	0.44–1.69	8	6.25	1.28	0.55–2.52	4	3.34	1.20	0.32–3.07	6	2.83	2.12	0.78–4.62
Silicosis	5	0.30	16.66	5.42–39.34	0	0.12	—		0	0.01	..		0	0.01	—	
Renal disease	4	3.15	1.27	0.34–3.25	5	2.30	2.17	0.7–5.07	1	1.67	0.60	0.01–3.34	2	1.42	1.41	0.16–5.09

TABLE 6
SMR and 95% CIs for Selected Categories of Cause of Death for the Male Bavarian Subcohort, by Work in Materials Preparation (Ever/Never)

	Ever in Preparation				Never in Preparation			
Cause of Death	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	103	76.28	1.35	1.10–1.64	937	724.96	1.15	1.08–1.24
Malignant neoplasms	33	25.39	1.30	0.89–1.83	268	236.86	1.13	1.00–1.27
Lung	5	5.87	0.85	0.27–1.99	54	54.05	1.00	0.75–1.30
Kidney	1	1.82	0.55	0.01–3.06	8	16.78	0.48	0.21–0.94
Diseases of the circulatory system	37	26.38	1.40	0.99–1.93	278	242.45	1.15	1.02–1.29
Diseases of the respiratory system	3	3.71	0.81	0.16–2.37	44	33.86	1.30	0.94–1.74
COPD	0	1.72	—		18	15.42	1.17	0.69–1.84
Silicosis	3	0.04	67.19	13.5–196	2	0.40	5.06	0.57–18.27
Renal disease	1	0.53	1.90	0.02–10.57	8	4.92	1.63	0.70–3.20

all-cancers, and 1.38 (95% CI = 0.94 to 1.96) and 1.06 (95% CI = 0.61 to 1.73) for respiratory diseases, respectively. Among Bavarian women, the point estimate for COPD appeared to be considerably higher among those hired in the later periods: 1.20 (95% CI = 0.32 to 3.07) versus 2.12 (95% CI = 0.78 to 4.62), although the wide confidence intervals indicate these estimates were not very precise. SMR estimates for lung cancer were similar for those hired through 1960 versus those hired after 1960 and close to unity, for both men and women. All five silicosis deaths (plus additional three which were coded as contributing cause of death) were among men in the Bavarian sub-cohort hired before the end of 1960, resulting in a very high and statistically significant but unstable SMR.

Although no excess of lung cancer deaths was identified, we stratified results by ever having worked in the materials preparation department—the work area known to have the highest potential crystalline silica exposures over time—to determine whether elevated risks might be obscured by combining these workers with those in other work areas. No deaths for any of these selected causes were observed among women ever having worked in preparation, who generated only about 6% of the person-years among women. Table 6 demonstrates that among men, the SMR for lung cancer is not elevated in the subgroup ever having worked in the preparation area. However, SMRs for all causes combined, all cancers and all circulatory system diseases were higher (not significantly) for the preparation workers than for those never working in this area. Interestingly, three of the five silicosis deaths occurred among men in this subgroup, two of whom were part of the 88 individuals whose records were retained beyond age 75 due to x-ray film evidence of silicosis.

Discussion

This paper presents the first results of a large epidemiological study of workers in the modern (ie, post-WWII) German porcelain industry. Included were a large majority of employees from nearly all manufacturing facilities in Western Germany operating during 1985–1987, the time window in which the study cohort was defined due to the availability of electronic information and the triennial individual occupational medical examinations. The study population was identified by mandatory (those with potential for some level of exposure) and voluntary (those with potential for only low level of exposure) participation in the BGGK preventive medical surveillance program, and therefore is not representative of workers with only very low levels of crystalline silica (white-collar workers, decoration workers). However, we have determined that approximately 85% of all blue-collar employees of the porcelain manufacturing facilities at this time participated in this program. Therefore, the study population is likely to be highly representative of all porcelain production workers in Germany.

There are several noteworthy advantages provided by this study cohort. First, this study group represents one of the largest cohorts of porcelain (including ceramics or pottery) workers or any other type of silica exposed workers, with over 8200 men and over 9300 women. Other epidemiological cohorts have tended to include smaller numbers of men only. For example, the recent studies of British and Chinese pottery cohorts included 5115[23] and 4547[24] men, respectively. Earlier cohort studies have included 2055 white men employed in three ceramic plumbing fixture factories in the US[25]; 2480 men employed in the ceramics industry in Italy[26]; and 1794 male ceramic workers in the Netherlands.[27] In fact, other than from China, we are unaware of any cohort study including substantial numbers of women employed in the porcelain industry.

Second, because the cohort was defined based on participation in the BGGK preventive medical surveillance program, all cohort members have a "baseline" x-ray film examination made before starting work in the porcelain industry and most cohort members have many follow-up x-ray film evaluations through the end of the individual follow-up. Although not taken into account in this preliminary SMR analysis, the x-ray films can demonstrate the presence or absence of lung cancers and signs of silicosis at start of follow-up for each cohort member, as well as the date of the first x-ray film demonstrating signs of silicosis or lung cancer. Participation in the program also assures documentation of each

cohort member's work history—including job held prior to entering the porcelain workforce—and, for over two thirds of the cohort, information on smoking status. All of these data resources will be considered in subsequent evaluations of the cohort.

Third, this cohort's exposure to crystalline silica overall—in contrast to individuals employed in the first half of the 1900's—is possibly more relevant to modern industrial conditions and related questions regarding health effects at more modest levels of exposure. Specifically, the 1929 Ordinance on Occupational Diseases led to substantial efforts to reduce employees' exposure to quartz dust for the first time (eg, by governmental or BGGK regulations, medical surveillance and dust prevention programs). By 1952, the 5th Ordinance on Occupational Diseases determined that all silicosis cases may be compensated by the BGs. This resulted in a dramatic rise in the number of compensated cases, and fuelled considerable efforts by the porcelain companies and the authorities to reduce exposures by replacement of rough wooden floors, improving dust controls, introduction of ventilation equipment, training employers and employees regarding health risks, monitoring of exposures, and comprehensive and systematic medical surveillance by the BGGK. Between 1955 and 1965 additional substantial technological changes took place, for example, replacement of intermittent (loaded and unloaded) kilns with gas-fired tunnel kilns.[28]

Although exposures to crystalline silica would have been reduced over time, parts of the present cohort still had the potential for considerable exposure. Depending on specific work area and time period, respirable crystalline silica levels obtained since the 1960's ranged from below detection level to several times the most recent German OEL of 0.15 mg/m^3 (as noted above this has been suspended), with most measured concentrations between the detection limit and the OEL.

Where silica exposures are both likely and substantial for at least some work areas and time periods represented by this cohort, there is relatively low potential for exposures to other known or suspected lung carcinogens in the porcelain industry. Crystoballite, a specific structural form of crystalline silica, historically occurred in the firing area. Until 1950 only intermittent kilns (round kilns) were used for firing of the porcelain and fireclay boxes were repeatedly re-used as firing auxiliaries for the biscuit firing. Quartz was partially transformed to crystoballite within these firing auxiliaries and may have generated crystoballite dusts. Measurements in other work areas during the early 1960s did not detect crystoballite. Workplace air measurements recorded in the MEGA database, a comprehensive chemical workplace exposure database maintained by the Institute for Occupational Safety and Health of the German Statutory Accidence Insurance in St. Augustin suggest no or only low levels of several other lung carcinogens. However, historical asbestos exposure cannot be excluded in the area of the kilns where asbestos-containing insulation was used in and around the kilns, on the tunnel kiln cars or associated with other asbestos containing materials and equipment. Therefore, for the silica-related diseases of interest (especially lung cancer and silicosis) the porcelain industry offers an environment in which historical risks associated with crystalline silica, typically in the form of quartz dusts, may be evaluated.

Although the cohort is still rather young, mortality is approaching 10% overall (greater for men in the Bavarian Sub-Cohort), and already more than 90 lung cancer deaths have been observed during the follow-up period. Because of the relatively young cohort and short follow-up, the observed numbers are too low to produce highly stable SMR estimates for many specific causes of death. Kidney cancers and renal diseases had 16 and 14 deaths among the full cohort, respectively, numbers too small to precisely estimate SMRs for relatively small excesses. Small observed numbers were especially clear for silicosis mortality, for which only 5 deaths were observed. However, as part of the evaluation of this cohort, over 500 cohort members have x ray films that originally were read by the BGGK physicians according to the ILO as 1/0 or higher, ie, with possible signs of silicosis. All x-ray films are currently being re-read by two expert B-readers to verify the original film readings, and the results will be used in conjunction with the exposure assessment to quantitatively evaluate risks of silicosis morbidity associated with the levels of crystalline silica occurring in the porcelain industry since WWII, and risks of lung cancer associated with silicosis.

Based on the current SMR results, the overall mortality patterns observed in the study cohort were similar to both the German national and the Bavarian referent populations, with some exceptions. The slightly higher SMRs obtained when the regional Bavarian reference rates were used suggest that the porcelain workers, although predominately from Bavaria, experience mortality rates for broad categories of cause of death that lie between Bavarian rates and the German national rates (as defined in the Methods section), which might, however, be caused by regional rate variability leading to variability in SMR results unrelated to occupational exposures.

Nevertheless, although the purpose of this study was to evaluate mortality patterns for specific causes of death previously associated with crystalline silica exposure (lung cancer, silicosis, kidney cancer, and renal disease), we calculated SMRs for many additional categories of cause of death. Although the SMRs for most of these causes of death were not different from unity, some deviations from expected were seen.

Among men, statistically significant excesses were seen for liver/gallbladder cancers as well as for pancreatic cancer, and this did not materially change in supplemental analyses using Bavarian reference rates (not shown). Risk factors for liver cancer include chronic Hepatitis B or C infection, liver flukes, aflatoxin exposure and alcohol consumption, but apparently not crystalline silica.[29] Of these, it is possible that the porcelain workers consume higher levels of alcohol, although men did not have an excess risk of cirrhosis of the liver (generally associated with alcohol consumption) compared with German men overall. Liver/gallbladder cancer SMRs for women were slightly but not statistically significantly increased, but this was based on only 10 observed cases.

Risk factors for pancreatic cancer include smoking, diabetes, diet, obesity, and pancreatitis, K-ras gene mutation, and possibly occupational chemical exposures.[29] However, Ojajärvi et al[30] reported a non-significant meta-relative risk of 1.4 for silica dust in a 2000 review, and two other papers were located in which pancreatic cancer appeared to be associated with dusts containing crystalline silica: a study of Finnish asphalt workers, who would be exposed to numerous compounds in addition to mineral dusts[31]; and a population-based occupational case-control study of pancreatic cancers in Finland, which generated an odds ratio of 2.0 (95% CI = 1.2 to 3.5) for exposure to inorganic dusts containing crystalline silica.[32] Analyses based on the Bavarian sub-cohort and using Bavarian reference rates were similar (not shown), suggesting less variability by region. In future analyses the possible role of tobacco smoking may be evaluated; however, the male porcelain workers mortality patterns (especially for lung cancer and other smoking-related cancers) do not suggest that this group has a disproportionately high smoking prevalence. In contrast, the SMR for pancreatic cancer among women was not elevated.

Among women but not men, the SMR for diabetes mellitus was significantly elevated using German reference rates, and was slightly higher using Bavarian reference rates. No occupational exposures (including crystalline silica) have been consistently associated with diabetes. However, mortality from complications of diabetes might reflect low utilization of diagnostic and preventive medical services, as well as poor case management.

Lung Cancer

A primary focus of our study was evaluation of lung cancer mortality in this cohort of porcelain workers exposed to moderate levels of crystalline silica. However, based on 94 observed cases (and over 130 expected, based on German rates) there is no indication of an excess lung cancer risk among the German porcelain workers. Based on the Bavarian sub cohort, the SMRs were closer to unity, but still provided no evidence for an excess rate of lung cancer among porcelain workers. Non-malignant respiratory disease results also were unremarkable.

Research since IARC's 1997 evaluation has not resolved the debate surrounding lung cancer risk in the absence of silicosis and/or at low to moderate levels of exposure. A recent, large multi-country, community based case-control study[10] reported increased risk of lung cancer associated with occupational exposure to crystalline silica (OR 1.37, 95% CI = 1.14 to 1.65), and estimates were increased for both men (OR 1.32, 95% CI = 1.10 to 1.59), and for women (2.07, 95% CI = 0.91 to 4.74), although the number of women with lung cancer was small. Risk was elevated for the two upper tertiles of cumulative exposure: OR 1.47 (95% CI = 1.04 to 2.06) for 35 to 200 mg/m^3-hrs, and OR 2.08 (95% CI = 1.49 to 2.90) for >200 mg/m^3 hrs, suggesting a dose response. However, this study was not able to identify whether there is a threshold for lung cancer risk. Unknown silicosis status for this cohort precludes any conclusions about lung cancer risk in the absence of silicosis.

Pelucchi et al[1] have published an extensive review of the occupational epidemiological literature published since the IARC evaluation. Most of the reviewed studies evaluated cohorts with known silicosis, or undefined silicosis status. The authors concluded that the evidence supports an association with lung cancer among known silicotics and reported pooled RRs from cohort studies of 1.34 (95% CI = 1.25 to 1.45) overall, and 1.69 (95% CI = 1.32 to 2.16) in cohort studies of silicotics only. Only two reviewed studies assessed lung cancer risk in the absence of silicosis. A cohort study by Checkoway et al[33] reported an overall SMR of 1.19 (95% CI = 0.87 to 1.57) among non-silicotics, based on 48 cases, and an SMR of 1.57 (95% CI = 0.43 to 4.03) among silicotics, based on only 4 cases. Exposure response analysis, however, showed elevated risk for non silicotics for the highest tertile of cumulative exposure (≥5 mg/m^3-yrs, SMR 2.40, 95% CI = 1.24 to 4.20). The second, a case-control study[34] on a cohort of non-silicotic, stone, quarry, and ceramic workers (247 cases, 795 controls) failed to show an association between lung cancer and occupational exposure to crystalline silica. Several exposure measures were analyzed, including peak, time-weighted average, and cumulative exposure, yielding non significant ORs ranging from 0.85 to 1.02. Pelucchi et al[11] concluded that any association between lung cancer and exposure to crystalline silica, in the absence of silicosis, remains unclear.

An additional case-control study on Chinese mine and factory workers,[35] published after the Pelucchi review, reported increased risk of lung cancer among pottery workers exposed to silica (OR 3.4, 95% CI = 1.45 to 8.66 for the highest quintile

of exposure, 10.1 to 72.4 mg/m^3 yr), which disappeared after adjustment for relevant occupational confounders (OR 0.9, 95% CI = 0.19 to 4.32).

Our results do not indicate an increased risk of lung cancer among porcelain workers in Germany, though complete silicosis status was not available. Future plans include analyses incorporating detailed exposure assessment and linkage of workers to x-ray films and medical records indicating first signs of silicosis, as well as the point at which silicosis is diagnosed (as ILO 1/1). This future work should help clarify the carcinogenic role of crystalline silica.

NMRD and Kidney Cancer

The SMRs for renal disease were slightly but not significantly elevated among men, but not for women, based on either the full cohort or the Bavarian sub-cohort. These results, however, are limited by small numbers of observed deaths ($n = 14$ and $n = 12$, respectively) in this category. For 24 additional deceased, renal disease was mentioned as contributing cause of death on the death certificate. However, there is no direct way to evaluate this using the SMR approach. It is possible that analyses using internal comparison groups could evaluate whether these cases were among employees more likely exposed at higher levels of crystalline silica than the rest of the cohort.

Several studies of occupational cohorts exposed to crystalline silica have reported excess risks of morbidity and mortality due to NMRD,[12–18] whereas some have not.[36,37] In a recent report, Steenland[12] suggests that kidney disease may present a higher risk than mortality from silicosis or lung cancer, and may be more important for regulatory purposes. He summarizes results from earlier investigations[38] reporting an SIR of 1.97 (95% CI = 1.25 to 2.96) for end stage renal disease (ESRD), based on 23 cases identified through the US ESRD registry, as well as a positive exposure-response trend for ESRD (based on 18 cases). Similarly, he reports a strong exposure response (based on 50 cases) for mortality using data from a 2002 study of three cohorts of industrial sand workers, granite workers, and diatomaceous earth workers.[12,16] Another recent report[13] also describes excess mortality from renal disease (SMR 2.80, $P < 0.001$) based on 18 cases in an updated study of 2670 employees of the sand industry. In this study, renal disease mortality was not related to cumulative exposure, though the authors cite small numbers as limiting statistical power.

Kidney cancer SMRs were low for both men and women regardless of which analytical cohort was examined. Again results were limited by small numbers observed, with a total of 16 in the full cohort and 14 in the Bavarian sub-cohort, which resulted in substantial deficits for each gender-cohort grouping (Tables 4 and 5). Renal cancer has much less frequently been associated in the published literature with crystalline silica exposure. Only two recent studies have reported elevated risk estimates. Attfield and Costello[6] reported a small, not significant excess of mortality (SMR 1.37) in granite workers. McDonald et al[13] reported an SMR of 2.02 ($P = 0.03$) based on 10 cases, though they characterize the finding as "unforeseen."

Summary and Conclusions

This cohort study represents one of the largest available to date, particularly noteworthy in that large numbers of men and women potentially exposed to various levels of crystalline silica over several decades have been followed as part of a preventive medical surveillance program offered throughout the glass and ceramics industry. Primary research questions included whether the cohort provides evidence supporting increased risks of lung cancer, silicosis, renal disease, and kidney cancer among porcelain workers potentially exposed to crystalline silica at concentrations from below to well above the former German OEL (ie, 0.15 mg/m^3).

Unexpected findings include a small excess of pancreatic cancer among men but not women, and elevated liver and gallbladder cancer risks among men with some suggestion of an increase among women as well. Kidney cancer was not increased in this cohort, and renal disease was only slightly (and not statistically significantly) elevated among men; however, small numbers limited the precision of these estimates.

Based on the first SMR results presented in this paper, it appears that some increased risk of silicosis mortality is seen (but based on very small numbers), especially among porcelain workers first employed before the end of 1960 and among those having worked in the materials preparation area where the highest crystalline silica exposures in the industry consistently have been documented. Despite this direct but preliminary evidence of substantial crystalline silica exposure potential, the mortality experience of this cohort, to date, suggests no excess risk of lung cancer.

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APPENDIX

List of ICD-9 Codes (1985–1997) Used in the SMR Analysis, ICD-10 Equivalents (1998–2005), and Distribution of Deaths

COD	International Classification of Diseases From Revision		Observed Deaths	
	9th (1985–1997)	10th (1998–2005)	Men	Women
All causes	001–999	A00–T98	1,126	484
Infective & parasitic diseases	001–139	A00–B99	13	6
Malignant neoplasms	140–208	C00–C97	361	190
Buccal cavity & pharynx	140–149	C00–C14	21	7
Oesophagus	150	C15	20	1
Stomach	151	C16	23	6
Large intestine	153	C18	28	13
Rectum	154	C19–C21	23	11
Liver & gall bladder	155–156	C22–C24	25	10
Pancreas	157	C25	33	9
Peritoneum & unspecified digestive organs	158–159	C26, C48	3	1
Nasal cavities & sinus	160	C30–C31	2	0
Larynx	161	C32	4	1
Lung	162	C34	74	20
Other respiratory & intrathoracic organs	163–165	C37–C38, C45	1	0
Breast	174–175	C50	1	46
Female genitourinary	179–182	C53-C55, C58	0	8
Ovary, other uterine adnexa & other female	183–184	C51–C52, C56–C57	0	17
Prostate	185	C61	13	0
Bladder	188*	C67–C68	10	2
Kidney & suprarenals	189*	C64–C66	11	5
Brain & nervous system	191–192	C47, C70–C72	14	5
Miscellaneous malignant	195–199	C76–C80, C97	24	9
Neoplasms of lymphatic and hematopoietic tissue	200–208	C81–C95	19	16
Hodgkin's disease	201	C81	1	2
Non-Hodgkin's lymphoma	200, 202	C82–C83, C84–C85	9	5
Multiple myeloma	203	C88–C90	2	2
Leukaemia	204–208	C91–C95	7	7
Neoplasms in situ & unspecified nature	230–239	D00–D09, D37–D48	7	4
Diabetes mellitus	250	E10–E14	20	21
Blood & blood-forming organs	280–289	D50–D89	0	2
Mental disorders	290–319	F00–F99	15	5
Nervous system & sense organs	320–389	G00–G99, H00–H95	15	6
Diseases of the circulatory system	390–459	I00–I99	371	125
Hypertensive heart disease	401–405	I10–I15	11	5
Ischaemic heart disease	410–414	I20–I25	198	44
Other diseases of the heart	420–429	I30–I52	85	23
Cerebrovascular disease	430–438	I60–I69	46	39
Diseases of the respiratory System	460–519	J00–J98	58	18
Pneumonia	480–486	J12–J18	11	0
Chronic obstructive pulmonary diseases	490–492, 496	J40–J44	25	10
Asthma	493, 477	J45–J46	12	4
Silicosis	502	J62	5	0
Other diseases of the respiratory system	510–519	J80–J99	5	4
Diseases of the digestive system	520–579	K00–K93	73	39
Cirrhosis & other chronic liver disease	571	K70; K73–K74; K76.0	44	24
Diseases of the genitourinary system	580–629	N00–N99	11	4
Renal†	580–589†	N00–N08; N10–N12; N14–N19; N26–N29	10	4
Ill-defined conditions	780–799	R00–R99	13	8
External causes	E800–E999	V01–Y98	81	18

*ICD-9 codes for kidney cancer currently include some codes that belong to bladder cancer category (ICD-9189.3, 189.4, 189.8, 189.9). Therefore, kidney cancer rates are overestimated and bladder cancer rates are underestimated for yr before 1998.

†ICD-10 codes for renal diseases generally include more codes, many of which are directly comparable to ICD-9 codes, than the ICD-9 codes included in the rate set (for example, infections of kidney are included in the ICD-10 codes but not the ICD-9 codes) leading to an overestimation of rates based on ICD-10 codes. In one case, rates for a comparable ICD-10 code (N25) were not included in the category, although the ICD-9 code was included (ICD-9 588) leading to an underestimation of rates based on ICD-10 rates. The direction of the change in the effect cannot be predicted.

Mortality in Vermont granite workers and its association with silica exposure

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ABSTRACT

Objectives To assess mortality in Vermont granite workers and examine relationships between silica exposure and mortality from lung cancer, kidney cancer, non-malignant kidney disease, silicosis and other non-malignant respiratory disease.

Methods Workers employed between 1947 and 1996 were identified. Exposures were estimated using a job–exposure matrix. Mortality was assessed through 2004 and standardised mortality ratios (SMRs) were computed. Associations between mortality and exposure to silica were assessed by nested case–control analyses using conditional logistic regression.

Results 7052 workers had sufficient data for statistical analysis. SMRs were significantly elevated for lung cancer (SMR 1.37, 95% CI 1.23 to 1.52), silicosis (SMR 59.13, 95% CI 44.55 to 76.97), tuberculosis (SMR 21.74, 95% CI 18.37 to 25.56) and other non-malignant respiratory disease (SMR 1.74, 95% CI 1.50 to 2.02) but not for kidney cancer or non-malignant kidney disease. In nested case–control analyses, significant associations with cumulative exposure to respirable free silica were observed for silicosis (OR 1.13, 95% CI 1.05 to 1.21 for each 1 mg/m^3-year increase in cumulative exposure) and other non-malignant respiratory disease (OR 1.10, 95% CI 1.03 to 1.16) but not for lung cancer (OR 0.99, 95% CI 0.94 to 1.03), kidney cancer (OR 0.96, 95% CI 0.84 to 1.09) or non-malignant kidney disease (OR 0.95, 95% CI 0.84 to 1.08).

Conclusions Exposure to crystalline silica in Vermont granite workers was associated with increased mortality from silicosis and other non-malignant respiratory disease, but there was no evidence that increased lung cancer mortality in this cohort was due to exposure. Mortality from malignant and non-malignant kidney disease was not significantly increased or associated with exposure.

What this paper adds

- Although crystalline silica was classified as a known human carcinogen by the International Agency for Research on Cancer (IARC) in 1997, epidemiological evidence for this is inconsistent.
- The Vermont granite industry has played an important role in US regulation of exposures to silica because of its long history of exposure and health monitoring and a general absence of occupational co-contaminants.
- The current study is the most comprehensive mortality assessment of Vermont granite workers conducted to date.
- Mortality from lung cancer was higher than previously observed in this industry, but there was no evidence of a relationship with silica exposure.
- The results of this study do not provide support for proposed changes to the US exposure limit for silica on the basis of lung cancer risk.

The Vermont granite industry has been closely scrutinised since the 1920s, when a high prevalence of respiratory morbidity and mortality among workers was first documented.[1] This led the Vermont Department of Health Division of Industrial Hygiene (DIH) to conduct a series of environmental surveys to assess exposure levels, adopt a standard to keep dust exposure levels below 10 million particles per cubic foot (mppcf) and begin a medical surveillance program.[2] As a consequence, the Vermont granite workers have played an important role in the development of US standards for occupational exposure to crystalline silica.

The US Occupational Safety and Health Administration (OSHA) and the US Mine Safety Health Administration currently have an occupational exposure limit (OEL) for respirable silica of essentially 0.1 mg/m^3. However, the National Institute for Occupational Safety and Health (NIOSH) has promoted a recommended exposure limit of 0.05 mg/m^3 and the American Conference of Governmental Industrial Hygienists has a current threshold limit of 0.025 mg/m^3, based primarily on concerns about lung cancer risk.[3 4] In light of this, OSHA has given notice of its intention to revise its OEL for silica in the near future.

Previous mortality studies of the Vermont granite industry have not provided consistent evidence of a relationship between silica exposure and lung cancer. Davis *et al* carried out a proportionate mortality analysis of 969 deaths occurring between 1952 and 1978 and found an excess of deaths from silicosis and tuberculosis, but no proportionate excess from lung cancer.[5] Costello and Graham studied 5414 men employed in the granite industry from 1950 to 1982 and found that, in addition to mortality from silicosis and tuberculosis, overall lung cancer mortality was significantly increased compared to the rates for white males in the USA (standardised mortality ratio (SMR) 1.19).[6 7] They also found that men hired after the implementation of dust controls in 1940 had lung cancer mortality rates similar to those for men with comparable tenure and latency who were hired before that time. Because exposures are known to have been much higher prior to 1940, they concluded that the

increased lung cancer mortality was not due to silica exposure. Data from that study were subsequently analysed by Attfield and Costello, using exposure estimates derived by Davis *et al* to examine the exposure–response relationship for lung cancer.[7 8] Their results indicated an increase in the SMR for lung cancer with increasing cumulative exposure to silica.

These previous studies had potential limitations arising from their use of records from the DHI medical surveillance program to identify cohort members and determine work histories. There was the potential for selection bias because the DHI program was voluntary and the employment information in the DHI records was often incomplete. The availability of additional sources of employment data provided us with an opportunity to conduct a new mortality study with a more inclusive cohort and more accurate work histories. We independently assessed mortality and used raw data and unpublished reports from all previous environmental surveys to estimate exposure levels.

METHODS

Cohort assembly

The target population was all men who had worked in the Vermont granite industry at any time between 1 January 1947, when all workers were enrolled in a group insurance program, and 31 December 1998. In addition to insurance records, we used the following resources to identify workers: data abstracted from DHI records,[6] pension records, data from a study of workers employed from 1979 to 1987,[9 10] and data from a study of retired workers.[11] Data from all sources were linked and compared to eliminate duplications and resolve discrepancies in identifying information.

Mortality ascertainment

We determined vital status through 2004 by searching the US National Death Index (NDI), US Social Security Administration vital status records and Vermont State Records Office. Additional information sources included a commercially available Social Security death index, obituary and genealogy websites, and websites for locating individuals who are currently alive. We requested death certificates from relevant state record offices to evaluate questionable NDI matches and to obtain cause of death information for deceased individuals without a valid NDI match. Workers whose vital status remained unknown and workers who were known to have died in Canada were included in a search of Quebec vital records. We used coded cause of death information from the NDI when available and an experienced nosologist coded cause of death information from death certificates. All causes were coded to the 9th Revision of the International Classification of Diseases (ICD-9). Underlying cause of death was determined by either the nosologist or the NDI's automated algorithm, based on the ICD-9 selection and modification rules.

Exposure assessment

We used three primary sources of data to determine employment in the Vermont granite industry: work history information obtained from DHI surveillance program participants, self-reported work histories from a pulmonary function study conducted during 1979–1987,[10] and pension records for individuals who worked during or after 1967 and left work prior to 1999. The source that provided the earliest evidence of employment in the industry was used to determine a subject's initial year of work, which defined their date of entry into the cohort. To compile detailed work histories for subjects included in the exposure–response analyses described below, we carefully reviewed data from all sources while blinded to the subject's vital status and cause of death. To resolve discrepancies between data sources, we used additional employment information in obituaries, autopsy reports and death certificates whenever available.

We used 5204 exposure measurements made in the Vermont granite industry between 1924 and 2004 to construct a job exposure matrix (JEM). Details of the methodology are described in a separate paper (Verma *et al*, *J Occup Environ Hyg*, submitted 2010). Briefly, jobs were classified into 22 categories reflecting their exposure potential and the concentration of respirable free silica for each category was estimated for three time periods: before 1940, 1940–1949 and 1950–2004 (table 1). Estimates for the middle time period, when dust controls were being implemented, are averages of the earlier and later time periods. Impinger counts (mppcf) were converted to gravimetric respirable free silica (mg/m^3) using 10 mppcf ≈0.1 mg/m^3, based on earlier studies and NIOSH recommendations.[12 13] A worker's exposure level for each year of employment was determined by classifying his job into one of the 22 categories and assigning the silica concentration for that category and year as specified in the JEM. We then computed summary exposure metrics by accumulating yearly exposure over the relevant time period for each case and control.

Statistical analysis

We used a modified life table approach as implemented by OCMAT statistical software[14] to compute SMRs, adjusted for 5 year age and calendar year groupings. Confidence intervals and significance tests were based on the Poisson distribution and an SMR was considered to be statistically different from 1.00 if the p value was <0.05. Both US and Vermont white males were used as reference populations.

Table 1 Estimated exposure concentrations of respirable free silica by time period

Job class	Location	<1940		1940–1949*	≥1950	
		N	mg/m^3	mg/m^3	N	mg/m^3
Bit grinder†	Quarry	1	0.17			
Blacksmith†	Quarry	4	0.33			
Boxer	Shed	14	0.08	0.05	133	0.04
Carver	Shed	19	0.37	0.27	146	0.07
Channel bar	Quarry	3	0.15	0.08		0.01‡
Crane	Shed	9	0.16	0.11	32	0.05
Cutter	Shed	33†	0.38	0.23	1568	0.07
Draftsman	Shed	12	0.01	0.01		0.01
Driller	Quarry	120	1.07	0.54	7	0.01
Foreman	Shed		0.12	0.06	9	0.05
Grinder	Shed	31	0.19	0.13	5	0.07
Jackhammer	Quarry	10	1.05	0.56	7	0.06
Laborer	Shed		0.24	0.17	6	0.10
Lumper	Shed	5	0.30	0.18	138	0.06
Maintenance	Shed	12	0.24	0.16	28	0.07
Quarry (general)	Quarry	22	0.13	0.07		0.01‡
Office worker	Shed	29	0.04	0.04		0.04
Polisher	Shed	35	0.12	0.10	570	0.07
Sandblaster	Shed	43	0.24	0.16	337	0.07
Sawyer	Shed	13	0.13	0.10	634	0.06
Shed (general)	Shed	153	0.12	0.09	481	0.05
Surfacer	Shed	150	0.28	0.18	101	0.08

*Estimates are averages of those for the earlier and later periods because few measurements were available from 1940 to 1949.
†Job not performed after 1939.
‡Trend applied using jackhammer and driller data.

We assessed exposure–response relationships by performing nested case–control analyses. For each disease of interest, cases were grouped into risk sets based on year of birth and year of death. Three controls for each risk set were randomly selected from among all cohort members who were born in the same year and survived through the case's year of death. We used conditional logistic regression to model the relationships between mortality and net exposure duration, cumulative exposure and average exposure. Net exposure duration was computed as the number of years employed in the granite industry (excluding gaps in employment), while cumulative exposure was computed by summing average annual exposures for the relevant years. All analyses were performed both by accumulating exposures up to the year of death for the case or cases in a particular risk set, as well by excluding exposures occurring within 10 years before the time of death of the case to reflect a lag between exposure and mortality. We analysed cumulative exposure as both a continuous and a categorical variable, with category cut points based on the quintiles of the combined distribution for cases and controls. Multivariate models were used to examine the effect of exposure after adjustment for the number of years since the start and end of exposure. All models were fitted by maximum likelihood using EGRET statistical software.[15]

The research methods used in this study were approved by the University of Vermont Committees on Human Research.

RESULTS

Description of the cohort

Of 7661 men identified as eligible for the study, 609 were excluded because of missing birth date or date of hire. Missing data occurred most often for men who were hired after the last survey of the industry in 1937 and who were still working in 1999, when pension records for current employees became unavailable. The 7052 workers remaining in the cohort contributed 269 258 person-years of follow-up for computation of SMRs. The birth year, year of first employment and vital status of these workers are given in table 2. More than half (54.5%) were deceased by 31 December 2004, but the date of death was unknown for 14. All 74 workers with unknown vital status were born before 1920, so presumably many of these men had also died before the end of 2004. The 74 men with unknown vital status and 14 deceased men with unknown date of death were included in computation of SMRs, but follow-up on these workers was censored at the time their employment ended, when they were last known to be alive. They were eligible for selection as a control in the case–control analyses if the censoring date was not before the year of death of the case.

Table 2 Characteristics of the final cohort

	N	%
Date of birth		
<1900	781	11.1
1900–1909	933	13.2
1910–1919	1003	14.2
1920–1929	1177	16.7
1930–1939	1083	15.5
1940–1949	997	14.1
≥1950	1286	18.1
Date began employment		
<1930	1170	16.6
1930–1939	544	7.7
1940–1949	1137	16.1
1950–1959	1350	19.1
1960–1969	1456	20.6
≥1970	1396	19.8
Vital status through 31 December 2004		
Alive	3183	44.4
Deceased	3845	54.5
Unknown	74	1.0
Total	7052	

Standardised mortality ratios

Information about cause of death was unavailable for 207 (5.4%) of the 3851 deceased workers with known date of death. Overall mortality, including unknown cause, was significantly elevated in the cohort compared to US white males (SMR 1.08, 95% CI 1.05 to 1.12). This is attributable to significantly increased mortality from tuberculosis, malignant neoplasms and non-malignant respiratory disease (table 3). Mortality from all heart disease and from all external causes was significantly lower in the cohort than in the reference population. The increased mortality from malignant neoplasms reflects the significantly elevated SMR for cancers of the bronchus, trachea or lung (SMR 1.37). No other cancers were significantly elevated.

Silicosis mortality was very high in the cohort (SMR 59.13) and contributed to the significantly increased mortality from non-malignant respiratory disease. However, mortality from other respiratory diseases, which excludes silicosis, influenza, pneumonia, bronchitis, emphysema and asthma, was also significantly increased (SMR 1.74). Of the 174 deaths in this category, chronic airway obstruction was listed as the cause for 122 (70%).

Most deaths from tuberculosis and silicosis occurred in men who began work before 1940, prior to the implementation of dust controls in the industry. No deaths from tuberculosis occurred in men who began work in 1950 or later. Only six of the 86 men who died of silicosis began work after 1940. Three of these began work after 1949 and worked for less than 10 years in the Vermont granite industry. However, one was known to have previously worked for 40 years as a stone cutter in Canada. Information about previous employment was unavailable for the other two, but they began working in the Vermont granite industry at 43 and 52 years of age, so may also have been exposed to silica elsewhere. All deaths from silicosis occurred in workers born before 1925.

For most diseases we obtained similar results when white Vermont males were used as the reference population. As expected for a rare disease in a small population, the SMR for silicosis (SMR 15.35, 95% CI 11.95 to 20.66) was lower than the estimate based on US mortality rates because silicosis deaths in the cohort elevated the Vermont mortality rate.

Exposure–response analyses

To examine exposure–response relationships, we performed nested case–control analyses for silicosis, other non-malignant respiratory disease, lung cancer, kidney cancer and non-malignant kidney disease. We did not examine tuberculosis because reductions in silica exposure levels coincided with the introduction of effective treatment for the disease, making it impossible to estimate their independent effects on mortality. The results presented for kidney cancer include a 10 year lag, while those for non-malignant diseases do not. For lung cancer the results from both analyses are presented. For all diseases the results based on the two computations of exposure were very similar. We also performed the analyses both with and without adjustment for the number of years since first and/or last employment. These adjustments had little effect on the results, so the unadjusted results are presented.

Table 3 Causes of death through 2004: SMRs and CIs based on US white male rates

Cause of death (ICD-9 codes)	Observed	Expected	SMR	95% Confidence limits	
				Lower	Upper
Tuberculosis	147	6.8	21.75‡	18.37	25.58
All malignant neoplasms	888	795.4	1.13‡	1.05	1.20
Buccal cavity and pharynx	20	19.8	1.01	0.62	1.55
Digestive organs and peritoneum	215	209.9	1.04	0.91	1.19
Larynx	10	10.1	0.99	0.48	1.82
Bronchus, trachea, lung	358	281.6	1.27‡	1.23	1.52
Cancer of prostate	61	68.5	0.89	0.68	1.14
Kidney	28	19.8	1.41*	0.94	2.04
Bladder and other urinary organs	34	23.8	1.43	0.99	2.00
All lymphatic, haematopoietic tissue	73	78.8	0.93	0.73	1.16
All other malignant neoplasms	93	105.1	0.88	0.71	1.08
Cerebrovascular disease	217	213.0	1.02	0.89	1.16
All heart disease	1219	1372.4	0.89‡	0.84	0.94
Non-malignant respiratory disease	377	272.5	1.38‡	1.25	1.53
Influenza and pneumonia	71	88.1	0.81	0.63	1.02
Bronchitis, emphysema, asthma	77	81.6	0.94	0.75	1.18
Silicosis	55	0.9	58.13‡	44.55	76.67
Other non-malignant respiratory disease	174	100.0	1.74‡	1.50	2.02
Diabetes mellitus	67	61.2	1.09	0.85	1.39
Cirrhosis of liver	63	77.3	0.82	0.63	1.04
Nephritis and nephrosis	34	34.4	0.99	0.68	1.38
All external causes of death	264	306.7	0.87*	0.77	0.98
All other causes of death	326	410.7	0.79‡	0.71	0.89

ICD-9, 9th Revision of the International Classification of Diseases; SMR, standardised mortality ratio.
*Significant at the 5% level.
‡Significant at the 1% level.

When analysed as continuous variables, cumulative exposure, exposure duration and average exposure concentration were not significantly related to lung cancer mortality, regardless of whether or not exposures included a 10-year lag (table 4). Lags of 15 and 20 years were also examined and led to reductions in the ORs. To examine whether deaths from silicosis and tuberculosis might have biased the results by eliminating men with high exposures who died before they had an opportunity to develop lung cancer, we performed separate analyses for men born before 1920 (289 cases) and during or after 1920 (169 cases). All tuberculosis deaths and all but three silicosis deaths occurred in men born before 1920. A third of the deaths from other non-malignant respiratory diseases occurred in men born since 1920, but these are of less concern as a competing cause of death because their average age at death was 74.0 years, compared to 67.3 years for the lung cancer cases. There were no statistically significant associations between exposure and lung cancer mortality in either subcohort (table 4).

In contrast, cumulative exposure was significantly related to both silicosis and other non-malignant respiratory disease. The

Table 4 Associations between lung cancer risk and exposure measured as continuous variables

	No lag				10-Year lag			
	Coefficient	OR*	95% CI	p Value	Coefficient	OR	95% CI	p Value
All workers (956 cases, 841 controls)								
Cumulative exposure: 1 mg/m^3-year	−0.0100	0.99	0.95 to 1.03	0.641	0.0120	0.99	0.94 to 1.03	0.588
Log transformed cumulative exposure: ln(mg/m^3 years)	0.0518	1.05	0.97 to 1.14	0.208	0.0319	1.03	0.95 to 1.11	0.388
Net duration of employment: 10 years	0.0123	1.01	0.93 to 1.10	0.771	0.0203	1.02	0.93 to 1.12	0.671
Average exposure: 0.10 mg/m^3	0.0207	0.98	0.83 to 1.16	0.803	0.0092	0.99	0.85 to 1.15	0.907
Workers born before 1920 (289 cases, 497 controls)								
Cumulative exposure: 1 mg/m^3-year	−0.0175	0.98	0.94 to 1.03	0.450	−0.0182	0.98	0.94 to 1.03	0.444
Log transformed cumulative exposure: ln(mg/m^3-years)	0.0407	1.04	0.93 to 1.16	0.466	0.0246	1.03	0.94 to 1.12	0.597
Net duration of employment: 10 years	−0.0648	0.94	0.84 to 1.05	0.266	0.0082	0.94	0.83 to 1.05	0.337
Average exposure: 0.10 mg/m^3	0.0159	0.98	0.82 to 1.18	0.860	0.0062	1.01	0.85 to 1.19	0.939
Workers born in or after 1920 (167 cases, 444 controls)								
Cumulative exposure: 1 mg/m^3 year	0.0420	1.04	0.93 to 1.17	0.464	0.0838	1.09	0.91 to 1.30	0.362
Log transformed cumulative exposure: ln(mg/m^3 years)	0.0846	1.07	0.95 to 1.20	0.285	0.0433	1.04	0.93 to 1.17	0.456
Net duration of employment: 10 years	0.0962	1.10	0.98 to 1.24	0.114	0.1260	1.13	0.98 to 1.30	0.082
Average exposure: 0.10 mg/m^3	−0.0585	0.95	0.58 to 1.54	0.827	0.7720	0.80	0.44 to 1.45	0.465

*OR per specified units of increase in exposure.

ORs indicate that for each 1 mg/m^3 year increase in cumulative exposure, the risk of silicosis mortality increased by 18% (OR 1.18, 95% CI 1.05 to 1.21) and the risk of mortality from other non-malignant respiratory disease increased by 10% (OR 1.10, 95% CI 1.03 to 1.16). Cumulative exposure was not significantly related to mortality from kidney cancer (OR 0.96, 95% CI 0.84 to 1.09) or non-malignant kidney disease (OR 0.95, 95% CI 0.84 to 1.06).

Silicosis mortality was also significantly associated with the net duration of exposure, analysed as a continuous variable (OR 1.36 per 10 years of work, 95% CI 1.06 to 1.76). No significant associations were observed between exposure duration and other non-malignant respiratory disease (OR 1.02, 95% CI 0.90 to 1.15), kidney cancer (OR 0.80, 95% CI 0.58 to 1.11) or non-malignant kidney disease (OR 0.91, 95% CI 0.69 to 1.20). Average exposure concentration was significantly related to both silicosis (OR 1.60 per 0.10 mg/m^3, 95% CI 1.18 to 1.98) and other non-malignant respiratory disease (OR 1.35, 95% CI 1.09 to 1.68). However, many men worked both before and after the large reduction in exposure levels due to dust controls, so average exposure does not reflect their actual work environment.

To explore potential non-linear exposure–response relationships, we used a logarithmic transformation of cumulative exposure and also fitted polynomial regression models and spline functions. The logarithmic transformation yielded an even stronger relationship with silicosis, but was not significantly related to mortality from the other diseases. Likelihood ratio tests indicated that the quadratic models significantly improved fit to the data for both silicosis (p=0.003) and other non-malignant respiratory disease (p=0.019). Neither higher order polynomials nor spline functions provided further improvements in fit. These analyses indicated that the linear models underestimated risk of silicosis mortality at high cumulative exposures and overestimated risk of non-malignant respiratory disease at all but very high cumulative exposures. We did not observe significant non-linear relationships with cumulative exposure for any of the other diseases. Exposure–response relationships were also examined using categories based on quintiles of cumulative exposure and a statistically significant trend was observed only for silicosis (table 5).

DISCUSSION

This study found a strong relationship between exposure to silica and mortality from silicosis. All silicosis deaths occurred in men born before 1925, consistent with earlier studies indicating that silicosis mortality was confined to workers with documented or probable exposure before the introduction of dust controls in 1938–1940.[6 7] We also found that mortality from non-malignant respiratory disease, other than silicosis, bronchitis, emphysema and asthma, was associated with high cumulative exposures. Our study does not provide exposure–response information about non-fatal silicosis, but a radiographic study in 1963 indicated a low prevalence of the disease.[9] Of 972 workers, 28 (3%) had films showing abnormalities that were consistent with pneumoconiosis, all with low grades of profusion, and only seven of these had the finding typically seen in uncomplicated silicosis.

Table 5 Associations between categories of cumulative exposure and mortality from selected disease

Quintiles of cumulative exposure	Cases	Controls	OR	95% CI	p Value	Trend test p value
Silicosis (55 cases)						
≤1.04 mg/m^3 years	4	40	1.00			<0.001
1.05–3.64 mg/m^3 years	5	38	2.02	0.48 to 8.39	0.338	
3.65–6.71 mg/m^3 years	13	30	8.62	1.66 to 39.95	0.008	
6.72–10.71 mg/m^3 years	17	27	12.36	2.67 to 57.2	0.001	
>10.71 mg/m^3 years	16	27	10.65	2.30 to 48.4	0.002	
Other non-malignant respiratory disease (172 cases)						
≤0.36 mg/m^3 years	36	82	1.00	—	—	0.318
0.37–1.18 mg/m^3 years	28	87	0.67	0.37 to 1.18	0.170	
1.19–2.57 mg/m^3 years	31	84	0.76	0.43 to 1.33	0.331	
2.58–5.41 mg/m^3 years	25	88	0.68	0.37 to 1.26	0.271	
>5.41 mg/m^3 years	47	78	1.39	0.76 to 2.54	0.278	
Lung cancer (356 cases)						
≤0.26 mg/m^3 years	84	241	1.00			0.316
0.26–0.82 mg/m^3 years	58	178	0.87	0.60 to 1.28	0.481	
0.82–2.09 mg/m^3 years	91	206	1.28	0.90 to 1.83	0.170	
2.09–4.10 mg/m^3 years	74	167	1.29	0.87 to 1.88	0.202	
>4.10 mg/m^3 years	51	151	0.96	0.63 to 1.54	0.860	
Kidney cancer (28 cases)						
≤0.49 mg/m^3 years	9	14	1.00	—	—	0.987
0.50–1.42 mg/m^3 years	3	19	0.22	0.05 to 1.07	0.061	
1.43–2.54 mg/m^3 years	2	20	0.13	0.18 to 1.52	0.217	
2.55–4.47 mg/m^3 years	7	16	1.05	0.37 to 2.69	0.925	
>4.47 mg/m^3 years	7	15	0.90	0.20 to 3.97	0.886	
Non-malignant kidney disease (32 cases)						
≤0.68 mg/m^3 years	7	18	1.00			0.913
0.69–1.66 mg/m^3 years	5	20	0.61	0.17 to 2.17	0.446	
1.67–3.19 mg/m^3 years	7	16	1.04	0.32 to 3.34	0.945	
3.20–5.01 mg/m^3 years	7	18	1.08	0.26 to 4.52	0.904	
>5.01 mg/m^3 years	6	18	0.78	0.19 to 3.06	0.724	

We found no statistically significant increase in mortality from either malignant or non-malignant kidney disease and no evidence of an association between silica exposure and these diseases. These result differ somewhat from those of McDonald *et al* who found significantly elevated SMRs for both kidney cancer and nephritis/nephrosis, but did not find significant associations with silica exposure.[16] Another study of industrial sand workers did find a significant association between kidney disease and silica exposure,[17] while in a recent study of the German porcelain industry there was no increase in mortality from malignant or non-malignant kidney disease.[18] Although the numbers of deaths from kidney cancer (28) and nephritis/nephrosis (34) in our study were quite small, they were substantially larger than in any of these other studies.

Lung cancer mortality was significantly elevated in the study cohort (SMR 1.37), but there was no evidence of an association with silica exposure. In the previous mortality study of the Vermont granite workers, a lower SMR for lung cancer (1.18) was observed and some results indicated a relationship with silica exposure, while others did not.[7 8] A number of key differences preclude direct comparison of results from the current and previous study. Most notably, our study had approximately 1700 more workers, 10 additional years of follow-up and more complete mortality ascertainment. In addition, although both studies used employment information collected as part of the DIH surveillance program, we re-examined this data and augmented it with information from other sources. This revealed that the DIH information was incomplete for many workers.

Our lung cancer results are of particular interest because of continuing debate about the risk associated with silica exposure. Although the International Agency for Research on Cancer (IARC) concluded in 1997 that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans", they recognised that not all of the 10 least confounded studies cited in their review demonstrated excess cancer risks.[19] The weakness and inconsistencies in the evidence on which IARC relied were pointed out by Hessel *et al*, who also noted inconsistencies in exposure–response relationships.[20] In a 2006 review, Peretz *et al* concluded that the determination that silica is carcinogenic was evidence based.[21] However, their table of the 10 least confounded epidemiological studies showed no consistent statistically significant trends in lung cancer risk with cumulative crystalline silica exposure.

More recent epidemiological studies continue to yield inconsistent results. A large study of German porcelain workers showed increased silicosis mortality, but an association between crystalline silica exposure and renal or lung cancers was not found.[18] In contrast, a study of a Dutch population with potential exposure to silica in a wide range of occupations showed a statistically significant association between lung cancer risk and duration of exposure.[22] There was also an increased risk of lung cancer in workers with over 3 mg/m^3-years of silica exposure compared to those unexposed that was statistically significant in the group of subjects included in analyses to adjust for probable co-exposure to asbestos.

A key question for many years has been whether those with silicosis are at increased risk of lung cancer. A recent study of workers with silicosis in Hong Kong found that after adjustment for smoking there was no consistent exposure–response relationship between silica dust or severity of silicosis and lung cancer mortality.[23] Erren *et al* conducted a meta-analysis to determine whether exposure to silica was associated with lung cancer risks in individuals without silicosis and concluded that there were insufficient data to answer this question.[24] As our study does not include chest radiographs, it cannot directly address this issue. The strong relationship that we observed between estimated silica exposure and mortality from silicosis implies an association with non fatal silicosis as well. Thus, if silicosis contributed to lung cancer risk in the Vermont cohort, we would have expected lung cancer mortality to also increase with exposure, but there was no evidence of this. The low prevalence of silicosis in a 1988 radiographic study of Vermont granite workers has not been accompanied by a decline in lung cancer mortality, but interpretation of this is complicated by temporal changes in smoking prevalence.

We were unable to obtain information on smoking for most workers in the cohort because of data confidentiality protections, but it is likely that the elevated SMR for lung cancer is due, at least in part, to differences between the smoking habits of the cohort and those of the reference population. Smoking prevalence was 50% among the 1457 cohort members who were interviewed between 1979 and 1985 for a pulmonary function study.[10] In contrast, the estimated smoking prevalence for white males in the USA in 1980 was 37%,[25] giving a relative prevalence in the cohort of 1.35%. This difference is consistent with the differences seen among various occupational groups in the USA.[25] Smoking prevalence reliably predicts future lung cancer mortality,[27] so if the relative prevalence of smoking among the workers remained at about 1.35% over time, the expected number of lung cancer deaths in the cohort after adjusting the reference rates for smoking would be 353, yielding a SMR of 1.02 (95% CI 0.92 to 1.14).

Another limitation of this study is the potential for errors in the exposure estimates due to inaccuracies in both the job histories and the JEM. Use of multiple sources of employment data likely reduced but did not eliminate errors in work histories, and construction of the JEM involved a number of assumptions and extrapolations. Estimation of exposure levels for quarry jobs prior to dust controls was particularly difficult because of the wide variation between measurements made near specific operations and those of general quarry air. Short-term samples obtained during drilling, jackhammering and blowing out channels indicated extremely high particle counts, but these do not reflect time-weighted daily exposures because men only spent a portion of the workday doing these jobs. It is also possible that the per cent of respirable free silica in the dust generated from these activities differed from that for other jobs. We were also concerned that our pre-1940 estimate of 0.15 mg/m^3 for channel bar operators, which was based on measurements made during the 1930s at two quarries using wet processes for this activity, was much lower than the estimate of 1.07 mg/m^3 used previously for both channel bar operators and drillers.[9]

To examine the impact of potential errors in the exposure estimates for quarry jobs, we conducted sensitivity analyses using four different modifications to the pre-1940 estimates: (1) 1.07 mg/m^3 for channel bar operators and drillers, 1.05 mg/m^3 for jackhammer operators; (2) 0.53 mg/m^3 for channel bar operators and drillers, 0.52 mg/m^3 for jackhammer operators; (3) 0.15 mg/m^3 for channel bar operators, 0.53 mg/m^3 for drillers, 0.52 mg/m^3 for jackhammer operators; and (4) 0.15 mg/m^3 for all three jobs. Corresponding changes were made to the extrapolated 1940–1949 estimates. The relationship between silicosis and cumulative exposure remained statistically significant under all four modifications, with ORs ranging from 1.06 to 1.17 per unit increase in cumulative exposure. Assigning 1.07 mg/m^3 to channel bar operators gave the poorest fit to the data, while

assigning 0.15 mg/m[3] to drillers, jackhammer operators and channel bar operators provided the best fit. The modifications had little effect on the lung cancer results, with ORs ranging from 0.98 to 1.01 per unit increase in cumulative exposure, and there were no significant exposure—response relationships.

It should be emphasised that despite the uncertainties in the exposure estimates, which are an inherent part of most epidemiological studies, we found an unequivocal, quantitative relationship between respirable free silica and mortality from silicosis. This provides evidence of the validity of the exposure estimates, making it unlikely that the absence of a relationship between silica exposure and lung cancer or kidney diseases is due to error in the exposure estimates.

Although our study was more inclusive than previous mortality studies of Vermont granite workers, 609 (8%) eligible men were excluded from the cohort because of missing data and an additional 99 were excluded from the case—control analyses because of insufficient work history information. However, most of those excluded were younger workers with short, recent exposures and hence they would not have been selected for the exposure—response analyses. Only 170 of the excluded workers were born in or before 1947, the latest birth year in the lung cancer case—control analysis, and just 11 would have been selected as controls. It is therefore unlikely that their inclusion would have substantially altered the results. There were eight lung cancer cases among all the excluded workers, six of whom were born between 1886 and 1910 and had left work before 1957, when pension records began. Available information indicated lengthy employment in the granite industry for one of these workers, but short employment for the others. One of the other two excluded cases was born in 1929 and stopped working in the granite industry at age 26, while the other was born in 1966 and began working in 1986, so both would have low cumulative exposure. The implications of excluding these eight cases are unclear, but we would not expect a substantial impact given the apparent variability in their exposures and the large number of cases in the analysis.

Despite its limitations, our study has many strengths. It is the largest and most complete cohort of Vermont granite workers studied to date. The study also had a lengthy follow-up (on average 38 years) and exhaustive investigation ensured that mortality ascertainment was as complete as possible. Our study encompassed 100 years of employment in the Vermont granite industry, and the changes in work conditions occurring over this time ensured ample variation in exposure, which facilitates detection of exposure—response relationships. Finally, we used multiple sources of information to estimate exposure levels for specific jobs and reconstruct work histories.

CONCLUSIONS

This study found that silica exposure was related to mortality from silicosis and other non-malignant respiratory disease. There was no evidence of an association between silica exposure and lung cancer mortality, indicating that the increased mortality from this disease among cohort members is most likely attributable to cigarette smoking or other exposures unrelated to employment in the Vermont granite industry. The study also found no evidence of an increased risk of mortality from malignant or non-malignant kidney disease associated with employment in this industry.

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REVIEW ARTICLE

Crystalline silica and Lung cancer: A critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis

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Abstract

IARC (2009; Metals, Particles and Fibres. IARC Monographs on the Evaluaton of Carcinogenic Risks to Humans. Volume 100C. Lyon, France: IARC) concluded that crystalline silica in occupational settings is a lung carcinogen. This conclusion is based primarily on studies with exposure-response (E-R) analyses and a pooled analysis of 10 major studies with about 1000 lung cancer cases. The purpose of this review is to critically assess this cancer classification based on E-R analyses in 18 studies from eight countries with about 2000 lung cancer cases and the same database used by IARC (2009). The most appropriate exposure-response analysis is selected from latest study with least effect from bias, confounding, and presented graphically to assist individual assessment of the weight of evidence. Strength of association is consistently weak in the majority of studies. At the highest exposure level the mean relative risk (RR) is 1.5; four studies have strong associations (RRs > 2), three have moderate strong associations (RRs 1.5–2.0), six have weak-negligible associations (RRs 1–1.5), and five have no associations (RRs ≤ 1.0). Biological gradients were an inconsistent finding. Three studies had clear positive E-R trends; 3 had suggestive trends; and 12 had no E-R trends, 9 of which were flat or negative. There was a negative ER slope using RRs at the highest exposure of each study. Consistent findings of weak associations and lack of E-R trends does not support a causal association. Weight of evidence from occupational epidemiology does not support a causal association of lung cancer and silica exposure, which is contrary to the IARC conclusion using essentially the same data.

Keywords: Bias, confounding, crystalline silica, epidemiology, exposure-response (E-R), lung cancer, quartz; review, weight of evidence

Contents

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Abbreviations

CI	95% confidence interval
COLD	chronic obstructive lung disease
DE	diatomaceous earth
E-R	exposure-response
GM	geometric mean
HWE	healthy worker effect
IARC	International Agency for Research in Cancer
IHD	ischemic heart disease
MSHA	Mining Safety and Health Administration
NMRD	nonmalignant respiratory disease
OR	odds ratio
PAHs	polyaromatic hydrocarbons
RR	relative risk
SD	standard deviation
SE	standard error
SMR	standardized mortality ratio
SRR	standardized relative risk
TB	tuberculosis
UG	underground
UR	unit risk
WLM	working level months
YOB	year of birth

1.0. Introduction

In 1986 the International Agency for Research in Cancer (IARC) concluded there was "limited" evidence that crystalline silica caused cancer in humans (IARC, 1987). In 1996 IARC concluded there was "sufficient" evidence for the carcinogenicity of quartz and cristobalite in humans, although "carcinogenicity was not found in all industrial circumstances" (IARC, 1997). This conclusion was

controversial in that the vote was very close and several reviews of the same literature were produced by this classification (Cassidy et al., 2007; Checkoway et al., 2000; Erren et al., 2007, 2008; Hessel et al., 2000; Kurihara et al., 2004; McDonald, 2000; Pelucchi et al., 2006; Peretz et al., 2006; Soutar et al., 2000; Stayner, 2007; Steenland et al., 1996, 1997; Wong, 2002). Few of the published studies included estimates of quantitative exposure-response (E-R) trends, which is the strongest evidence of causality (Mannetje et al., 2002). Therefore an attempt was made to quantify existing exposure data from cohorts used by IARC (IARC, 1997) to help "clarify the continuing controversy regarding whether silica causes lung cancer" (Mannetje et al., 2002). Out of 10 silica-exposed cohorts included in that analysis, follow-up was extended or E-R added in 4 beyond the published date in the original study (Steenland; Mannetje et al., 2001).

Silica is a crystalline polymorph (such as silica, cristobalite). Silica and quartz are considered synonymous and if the text refers to amorphous silica it will be so stated.

In March 2009 another IARC Working Group convened in Lyon to update previous monographs on silica. IARC (2009) focused on E-R studies because they provide "stronger evidence of causation," because there are enough to "provide a reasonably reliable assessment of causation," and because they facilitate "accurate assessment of exposure-response in the presence of confounder variables." This updated Monograph will be published as Volume 100C (IARC, 2009), concluding there is sufficient evidence that quartz is carcinogenic.

The evidence cited by IARC as supporting this conclusion for humans included the following points. Evidence was from five main industrial settings: ceramics, diatomaceous earth, ore mining, quarries, and industrial sand. Most studies with quantitative exposures were said to show clear associations. Studies without E-R analyses generally lent support to a carcinogenic conclusion. Studies from other industrial segments generally lent support but there were some problems from confounding (arsenic, radon, polyaromatic hydrocarbons [PAHs]). Effects of quartz were unclear in three cohorts of Chinese workers: (a) tin miners because arsenic and quartz were colinear and effects could not be separated; (b) adjustment for PAHs in pottery workers "removed a significant silica exposure effect"; and (c) silica effect disappeared after adjustments for radon among iron/copper miners.

IARC (2009) concluded strongest evidence came from the pooled analysis (Steenland; Mannetje et al., 2001) showing clear E-R trends from 10 studies and from meta-analyses that "strongly confirmed an overall effect" of quartz.

The purpose is to review individual studies of silica-exposed workers with quantitative estimates of exposure, including studies considered by IARC (IARC, 2009) and the pooled analysis (Steenland; Mannetje et al., 2001). All known studies with quantitative exposure estimates and E-R analyses are summarized with a focus on potential roles of confounding/bias and visual presentation of E-R results to assist independent confirmation of results. The weight of evidence will be compared to the conclusions of IARC and the pooled analysis and will be used to evaluate causality between silica exposure and lung cancer.

Guidelines for establishing causality are similar to those of IARC (WHO, 2006). First, it is necessary to consider the quality of the study and whether bias, confounding, and chance have been taken into account. "Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect" (WHO, 2006).

When appropriate study results are identified, a judgment regarding causality can be made regarding the weight of the evidence. Several guidelines for causality are drawn from Hill (Hill, 1965), including consistent findings of strong associations (or high risks at high exposure levels). Increased risk with increased exposure (exposure-response trends) is considered a strong indicator of causality. This includes a decline in risk after reduction in exposure as in an intervention study.

The format of this paper is to determine the most appropriate study results. These results comprise the epidemiological evidence for evaluating causality. The results will be compared with IARC, which concluded there was sufficient evidence for carcinogenicity based on essentially the same studies.

2.0. Results of analyses of epidemiological studies and pooled analysis study

Studies are assigned to one of the five industrial groups identified by IARC. These are reduced to four groups by combining diatomaceous earth (DE) and potteries where quartz is heated in both industries. However this combination is not meant to suggest there is a significant exposure to cristobalite in potteries.

- Ore mining: There are a total of six gold miner cohorts from three countries: the USA (Steenland et al., 1995a), South Africa (Hessel et al., 1986, 1990; Hnizdo et al., 1997; Reid et al., 1996), and Australia (de Klerk et al., 1998). Three studies are included in the pooled analysis: USA, Australia, and Hnizdo et al. from South Africa. Qualitative exposure of Australian gold miners was quantified for the pooled analysis. There are three Chinese cohorts mining tin, iron/copper (Fe/Cu), and tungsten (McLaughlin et al., 1992). Except for Fe/Cu, these cohorts were updated and exposure estimates improved (Chen et al., 2007) and should replace the original analysis. Tin and tungsten were included in the pooled analysis. There is one Sardinian cohort of miners with silicosis (Carta et al., 2001).

- Diatomaceous earth (DE) and pottery cohorts: There is one DE cohort in California (Checkoway et al., 1997). There are two pottery studies from China and the UK (Cherry et al., 1996; McLaughlin et al., 1992). The UK study was only a preliminary report used by IARC (1998) and is replaced by a more detailed report (Cherry et al., 1997, 1998). The Chinese pottery study was updated and improved (Chen et al., 2007). One German study includes both pottery workers and stone workers and was published after IARC (1997) (Ulm et al., 1999). A 2011 cohort was of the German Porcelain industry assessing silicosis and lung cancer (Mundt et al, 2011). DE and China pottery cohorts were included in the pooled analysis.
- Quarries and stone cutters: The cohort of Vermont granite workers (Costello et al., 1988) was updated with an intervention analysis (Graham et al., 2004) and an E-R analysis (Attfield et al., 2004). An earlier unpublished E-R version was included in the pooled analysis. The Vermont granite shed cohort was recently updated again and included both the intervention and E-R designs found in the previous two studies (Vacek et al., 2010). German stone and quarry worker (and pottery worker) (Ulm et al., 1999) studies were unavailable for IARC (1997). The original Finnish granite worker study (Koskela et al., 1994) had no E-R analysis, but exposure was quantified and included in the pooled analysis (Steenland; Mannetje et al., 2001).
- Industrial sand: There are three new cohorts published since IARC (1997). Two are from the USA (McDonald et al., 2005; Steenland and Sanderson, 2001) and one from the UK (Brown et al., 2005a).

These studies are now discussed by industry segment.

2.1.Ore mining

IARC (2009) considered several cohorts of miners: US gold miners (Steenland et al., 1995b) with no "obvious evidence of exposure-response"; Australian gold miners (de Klerk et al., 1998) with semiquantitative estimates of quartz exposure and E-R trends by exposure score-years; South African gold miners (Hnizdo et al., 1997) with an elevated lung cancer risk in the highest exposure category after adjusting for smoking; Chinese tin miners (Chen et al., 2002, 2006, 2007; McLaughlin et al., 1992) where there was significant and collinear exposure to arsenic; Chinese iron/copper with potential confounding from PAHs and radon; tungsten miners showing no occupational confounding and no E-R association (Chen et al., 2007); and Sardinian lead and zinc miners with little evidence of an E-R trend with quartz (Carta et al., 2001).

Based on IARC (2009) analysis, there are perhaps four cohorts with no E-R trends (US gold, iron/copper, tungsten, lead/zinc), two with uncertain trends (Australian and South African gold miners), and a Chinese tin miner cohort so confounded with arsenic that an effect of quartz cannot be determined.

2.1.1.Gold mining

2.1.1.1. US gold miners (Steenland et al., 1995a) (Figure 1) This cohort of South Dakota miners is one of the least confounded E-R studies in both the 1996 and 2009 IARC monographs on silica. Quartz exposures were high, particularly before 1950s when dust control measures were installed. Silicosis and silico-tuberculosis showed clear positive E-R trends, indicating dust exposures were reasonably accurate. Arsenic and radon levels were well below Occupational Safety and Health Administration (OSHA) standards in the mid-1970s when measurements were available. In 1960, the prevalence of smoking was higher among gold miners than the national population, and relative risk (RR) due to smoking alone was estimated as 1.07. Applying smoking adjustments to the standardized mortality ratio (SMR) data, the overall lung cancer SMR would be reduced from 1.13 to 1.06 and RRs in the E-R analysis reduced to 1.09, 0.97, 0.97, 0.91, and 1.22 in exposure quartiles. A nested case-control study of 115 cases showed a negative, nonsignificant E-R trend with less dust-days cumulative exposure among cases than controls, 28,389 versus 31,060, respectively (Steenland et al., 1995a).

Six additional years of follow-up was conducted for the pooled analysis (Steenland; Mannetje et al., 2001) with straight-forward conversion from mppcf (million particles per cubic foot)-years to mg/m^3-years. The E-R trend was a nonsignificant positive slope with a unit risk (UR) of 1.006 (0.76–1.34) per mg/m^3-years. These updated results are largely unchanged from the 1995 study and continue to show no association of lung cancer and silica exposure.

Results from this cohort were said to have the lowest E-R in the pooled analysis. This was true for average exposure, but the lowest UR was the Chinese pottery cohort, with URs = 1.006 versus 1.004 per unit mg/m^3-years.

This is clearly a negative study and is not supportive of a silica lung cancer hypothesis.

2.1.1.2. Australian gold miners (de Klerk et al., 1998) (Figure 1) A cohort of 2297 Kalgoorlie gold miners was established from respiratory surveys conducted 1961, 1974, and 1975. Follow-up was 1962 to 1994, with over 50% mortality. Miners were matched to all Western Australia deaths 1969 to 1993 by year of death (YOD), year of birth (YOB), and alive at time of case death. Exposure was semiquantitative, based on an expert panel making subjective ranking from 1 to 10 for dust levels in every job.

SMRs were 1.23 (1.17–1.30) for all causes, 11.2 (8.4–14.8) for pneumoconiosis, and 1.49 (1.26–1.76) for lung cancer. E-R was analyzed by conditional logistical regression adjusting for smoking, bronchitis, and work in nickel mines. Smoking was a strong risk, with RRs increasing monotonically with increasing cigarettes/day: 19 (2.6–144) for <15/day, 23 (3.2–167) for 15–24/day, and 33 (4.4–241) for ≥25 cigarettes/day. Only one lung cancer case was a nonsmoker. Quartz was not significantly associated with lung cancer by exposure variables: URs were

Gold miners in US (Steenland and Brown, 1995) and Australia (de Klerk and Musk, 1989)
E-R of lung cancer, silicosis and pneumoconiosis with cumulative silica exposure (mg/m3 yr
and cumulative exposure-score year adjusted for smoking, silicosis & bronchitis (de Klerk)
plus pooled analyses (Steenland et al, 2001) for lung cancer and silicosis (Mannetje, 2002)

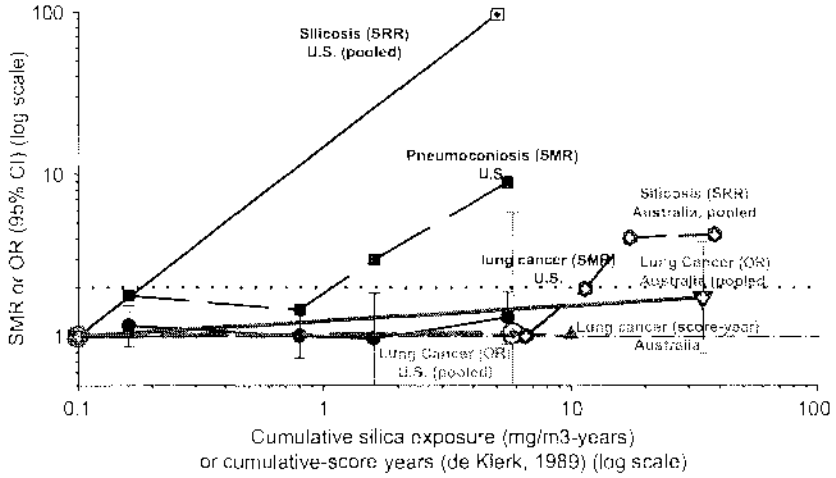

Figure 1. US and Australian Gold miners, including pooled analysis.

1.04 (0.93–1.16) and 1.02 (0.96–1.08) for average intensity of surface exposure and UG exposure respectively. Logs of surface and UG tenure showed URs of 1.02 (0.94–1.09) and 1.06 (0.97–1.15), respectively. For total cumulative exposure (exposure score-years) UR = 1.003 (0.999–1.005), but was significantly elevated to 1.31 (1.01–1.70) for log (exposure-year score). If adjustments for compensated silicosis were added to the models results were similar but none were statistically significant.

IH (industrial hygiene) data had been collected since 1925 and were converted by de Klerk to respirable mass quantities for E-R analysis in the pooled analysis (Steenland; Mannetje et al., 2001). Eighty-four miners without complete work history were deleted and exposures were estimated in mg/m^3 respirable silica, revised from the qualitative exposure score-years used originally. Silicosis showed a highly significant association with cumulative exposure ($p < .001$) in the pooled analysis (Mannetje et al., 2002). The estimated lung cancer unit risk (UR) was 1.016 (0.76–1.34) per mg/m^3-years exposure and 15-year lag in the pooled analysis (Figure 1). Radon exposure was considered negligible.

Comments on de Klerk et al. (1998)

IARC (2009) notes the lack of E-R for all exposure variables except log (exposure score-years), and then only when silicotics were included.

Incidence of silicosis was significantly associated with tenure of UG and surface employment with RRs of 1.96 (1.65–2.34) and 1.58 (1.31–1.91) respectively, but was a deficit when working both above and underground, 0.61 (0.52–0.72). Intensity of UG exposures was also significant, but the RR was lower at 1.24 (1.18–1.31). Tenure was not a reliable surrogate of silicosis risk for miners who worked both on the surface and UG (de Klerk et al., 1998).

The authors concluded that exposure was related to compensated silicosis, which increased risk of subsequent lung cancer. This suggests that silicosis is an intermediary, and therefore the usual statistical methods of adjusting for confounders do not provide interpretable results. Among nonsilicotics there was no evidence that quartz exposure caused lung cancer. This is consistent with the lack of any E-R trend among quartz-exposed German workers without silicosis (Ulm et al., 1999).

There was a strong association of silicosis and quantitative cumulative exposure in the pooled analysis, suggestive that exposure estimates are probably reliable for the lung cancer analyses.

The IARC Working Group (IARC, 2009) commented that "presence or absence of silicosis is not a critical issue for evaluating lung cancer carcinogenicity in relation to silica exposure." This plus the significant association of log cumulative exposure with lung cancer after adjustment for bronchitis and smoking, but not silicosis, indicates the preferred analysis of IARC. Six exposure variables were assessed, with consistently low and nonsignificant risks (RR ≤ 1.06). The consistent finding of no associations between exposure and lung cancer risk is suggestive that these results do not support a causal association.

Nearly a third (27%) of miners received compensation for silicosis, and the 10-fold excess in silicosis mortality are suggestive that quartz exposures were high. This plus the significant E-R associations of quartz exposures with silicosis mortality, but not lung cancer, is consistent with a conclusion that quartz is not a significant predictor of lung cancer.

Some selection bias is possible as only 89% of workers' vital status could be determined. Whether this biases risk at all or in what direction is not known.

Study conclusions are related to whether cumulative exposure or log cumulative exposure is the more appropriate measure of exposure.

Based on cumulative exposure the study of Australia gold miners does not support a silica–lung cancer hypothesis.

2.1.1.3. South African gold miners (Hessel et al., 1986, 1990; Hnizdo et al., 1997; Reid et al., 1996) (Figures 2–4) (Table A-1) There are four cohorts of South African gold miners. Two were case-control studies utilizing necropsy records (Hessel et al., 1986, 1990). Two mortality studies extended the follow-up of previous studies (Hnizdo et al., 1997; Reid et al., 1996).

The 1996 IARC Working Group discussed the 1990 Hessel necropsy study (Hessel et al., 1990) but not the 1986 Hessel study (Hessel et al., 1986), and discussed the mortality studies (Hnizdo et al., 1991; Reid et al., 1996). None played a major role in reaching a conclusion, perhaps because of concern about possible radon exposure. IARC (2009) cited one mortality study (Hnizdo et al., 1997), and mentioned the lack of association with uranium production and the authors' suggestion that silica exposure could be a surrogate for radon exposure.

Reid et al. (Reid et al., 1996) is a case-control study nested in a cohort mortality study that extended the follow-up of Wyndham et al. through 1990 (Wyndham et al., 1986).

IARC (1996) noted a possible overlap in the mortality cohorts (Hnizdo et al., 1991; Reid et al., 1996) but it remains unclear how much overlap there is. There clearly is overlap in time of death. It is useful to consider the source, eligibility, and time of mortality in study subjects (Figure 2).

In South Africa, cardiorespiratory organs of miners are supposed to be sent for postmortem examinations that are estimated to occur on about 86% of about 3000 necropsies/year among several hundred thousand gold miners employed in South Africa (Hessel et al., 1990; Hnizdo et al., 1997). The Hessel et al. studies (Hessel et al., 1986, 1990) are comprised of miners in the necropsy file or in the pension fund dying during the years 1974 to 1986. The Hnizdo et al. (Hnizdo et al., 1997, 1991) cohort was a sample of 2260 gold miners from all over South Africa originally selected to study morbid respiratory disorders (Wiles et al., 1975). Mortality follow-up was 1968–1986 (Hnizdo et al., 1997); 88% of cases had necropsies. The other cohort consisted of 4925 miners working in East, Central, and West Rand regions of the Transvaal near Johannesburg on January 1, 1970; mortality follow-up was 1970–1990 (Reid et al., 1996; Wyndham et al., 1986). One study is confined to miners in the Transvaal region (Reid et al., 1996) and the other three are based on records collected on all miners in South Africa (Hessel et al., 1986, 1990) or a sample of these workers (Hnizdo et al., 1997) (Figure 2).

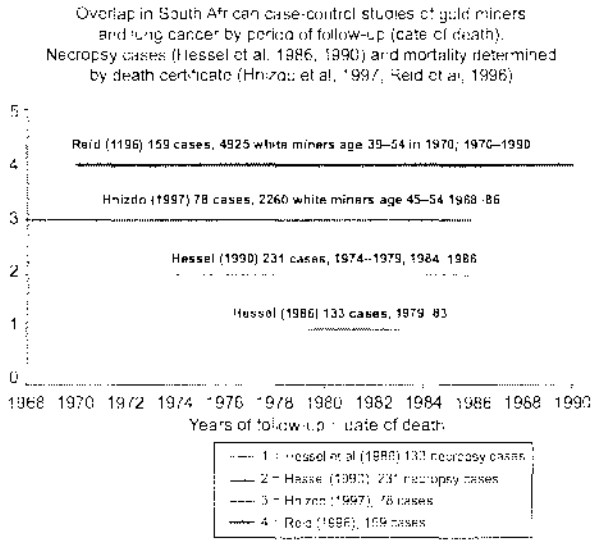

Figure 2. Overlap in South African gold miner studies.

Radon has been considered a possible confounding exposure in these miners. Mines are quite deep, and low level concentrations of radon are common; average working levels ranged from 0.1 to 3 in different mines (Hnizdo et al., 1991). The 2008 TLV for radon is 4 working level months (4 WLM/year).

It seems appropriate that all of these studies should be evaluated and considered on their individual merits and limitations.

Comments on Hnizdo et al. (1997) (Figure 3)

This is a study with 78 lung cancer cases and 318 matched controls from a sample of 2209 gold miners and ex-miners undergoing a medical examination with Medical Bureau for Occupational Diseases (MBOD) during the 4-year period 1968–1971. Other eligibility criteria included minimum 10 years UG (underground) and residents in South Africa at least 20 years. Ex-miners comprised 30% of the cohort, and had a higher prevalence of bronchitis and lower mean MMF (maximum mid-expiratory flow) at most of the dust levels than current miners. Smoking prevalences among miners and ex-miners were similar overall, with 65% smokers, 23% ex-smokers, and 12% nonsmokers.

Ex-miners were not more fit than miners, but were not thought to be a selected group with chest problems who had left the mines on this account. This opinion was based on the impression that "there was not a disproportionate number of complaints about chronic chest

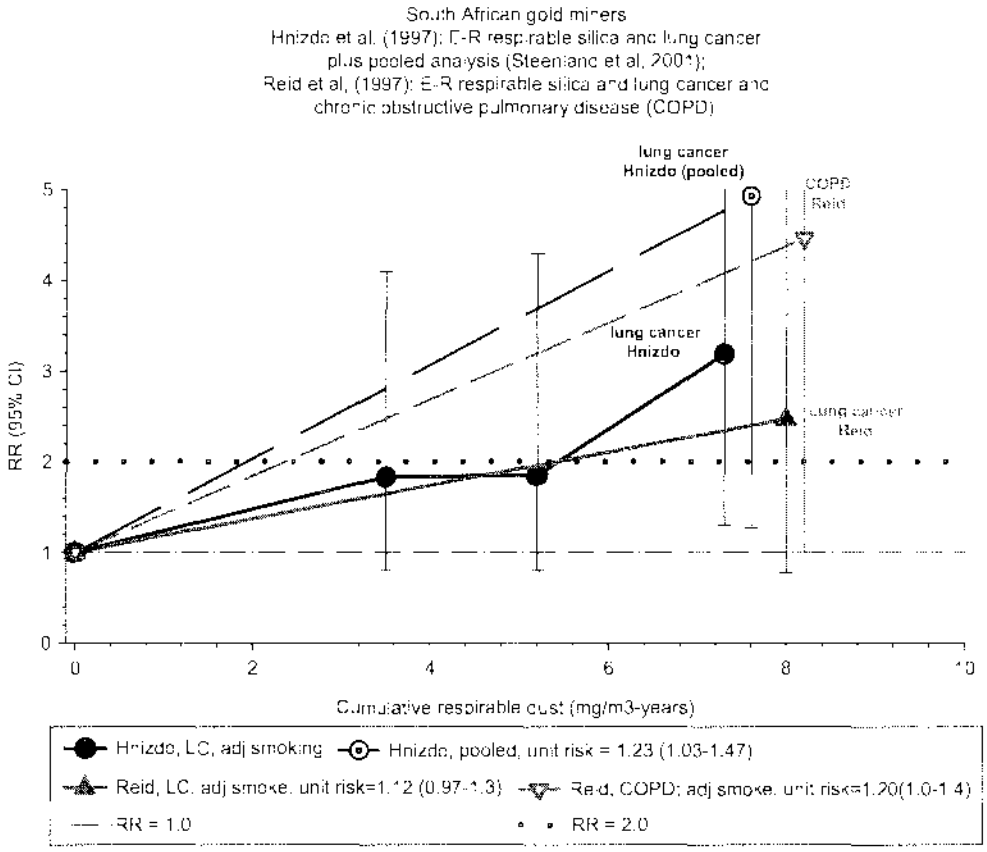

Figure 3. South African gold miners (Hnizdo et al., 1997; Reid and Sluis-Cremer, 1996) and the Hnizdo et al. pooled analysis.

disease among ex-miners as compared with working miners" (Wiles et al., 1975). Follow-up of the original cohort was to 1989.

The most significant predictor of lung cancer was tobacco smoking. Cumulative dust exposure and years UG, both lagged 20 years, were the most significant predictors of occupational exposures. There was a clear E-R trend, with a 3-fold significantly increased odds ratio (OR) in the high cumulative dust exposure group with, 20-year exposure lag and adjustments for smoking and uranium mining (Hnizdo et al., 1997).

The authors suggested results are not definitive in terms of a causal association. One reason was these results differ from other South African studies of gold miners. Other possible interpretations were (a) those developing silicosis are at increased risk of lung cancer (RR for silicotics was 2.45 [1.2–2.5]); (b) high quartz exposure is independently important in lung cancer and silicosis is coincidental; (c) high quartz exposures may be a surrogate for radon exposure.

Only minor work was needed to include this study in the pooled analysis (Steenland; Mannetje et al., 2001). UR for cumulative exposure was 1.23 (1.03–1.47). Radon levels were considered low; however, over a 24-year working life, average RR might be increased 1.2–1.3 fold. It was not considered a confounding factor. Excluding this study in the pooled analysis reduced the unit risk from 1.064 to 1.062. This study had the highest E-R trend, and is the only South African study included in the pooled analysis.

The E-R trend in the pooled analysis has a steeper slope than in the original analysis (Figure 3). The differences are that the original analysis was categorical, with a 20-year lag and adjustments for smoking and uranium mining. The pooled analysis had a 15-year lag and no adjustments for possible confounders.

Comments on Hnizdo et al. (1997)

If hypothesis (c) is correct, then there was confounding from radon. The 1996 IARC Working Group noted that radon is a potential confounding factor in South African gold mines.

The hypothesis that ex-miners were less healthy than miners and subject to selection bias has not been tested; i.e., mortality of ex-miners versus miners was not assessed. But lung cancer cases differed from the rest of the cohort (which were the controls) with lower lung function (forced vital capacity [FVC], forced expiratory volume at one second [FEV_1], forced expiratory flow between 25% and 75% vital capacity [FEF_{25-75}]), higher prevalence of rhonchi (35% vs. 22%) and bronchitis (51% vs. 35%), and more sputum >2 ml (53% vs. 41%) (Hnizdo et al., 1991).

When silicosis and smoking were included in the model evaluating E-R with cumulative dust exposure, only silicosis and smoking remained significant. Silicotic and nonsilicotic cases had similar pack-years (36 vs.

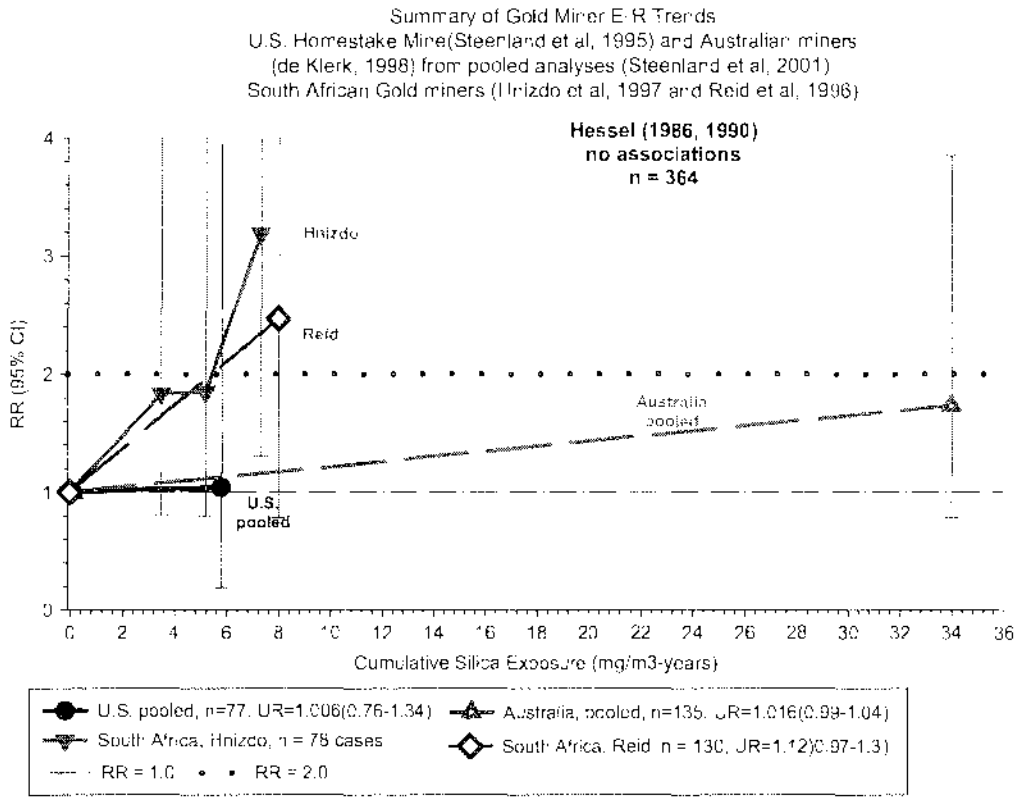

Figure 4. Summary of most appropriate E-R of gold miner cohorts.

38), about 15 pack-years more than controls. RR was increased 49-fold for silicotic cases with 30+ pack-years, but 12-fold for nonsilicotic cases with 30+ pack-years. Smoking was not a significant predictor of silicosis, but was a strong risk factor for lung cancer when silicosis was present. The authors suggest that silicosis "may be more important than exposure to dust," that dust exposure is not a lung cancer risk factor among nonsilicotic cases, and there is a "strong multiplicative" synergistic effect of silicosis and smoking.

The authors' observation that these results are inconsistent with other gold miner studies is another reason for examining other South African studies (Hessel et al., 1986, 1990; Hnizdo et al., 1991; Reid et al., 1996). It is also not clear why the regression from the pooled analysis produced an OR of 4.9 compared to a somewhat reduced RR of 3.2 in the highest exposure category (Figure 3).

Cohort and nested case-control (Reid et al., 1996) (Figure 3)

This is a cohort mortality study of 4925 white South African gold miners in the Transvaal around Johannesburg aged 39–54 who got their annual medical examination from the Medical Bureau of Occupational Diseases in 1969 and were alive in 1970. The men in this cohort were born in 1916–1931; follow-up was to 1990. A majority (59%) had died by 1990. SMRs were elevated for total deaths (1.30, 1.24–1.35), tuberculosis (TB) (3.06, 1.92–4.64), chronic obstructive pulmonary disease (COPD) (1.89, 1.62–2.19), ischemic heart disease (IHD) (1.24, 1.15–1.34), liver cirrhosis (1.55, 1.13–2.08), and lung cancer (1.40, 1.18–1.65) with 143 deaths.

A nested case-control study analyzed smoking adjusted E-R trends by cumulative exposure lagged 5 years for lung cancer, COPD (chronic obstructive pulmonary disease), and IHD (ischemic heart disease) among miners who spent 85%+ of time as gold miners and 15% of shifts underground. Cumulative dust exposure was not significantly associated with risk of lung cancer, although there was a nonsignificant (p=.13) positive slope with a unit risk=1.12 (0.97–1.3) (Figure 3).

Comments on Reid et al. (1996)

Possible reasons for the excessive death rates for several diseases were mentioned. The most persuasive to the authors was the adoption of an unhealthy lifestyle, in particular excessive smoking and drinking. Smoking is the best-known contributor to IHD, COPD, and lung cancer. The cohort was comprised of 83% ever smokers and most averaged about a pack/day. Drinking rates were not known, but the excess of cirrhosis of the liver is suggestive of a high rate.

A healthy worker effect in the SMR study was "patently not the case" given the 30% excess of total deaths of miners compared to the national referent population.

Time spent working UG was considered a surrogate for radon exposure. The lack of association led to the authors concluding radon was either "not a concern in

these mines or that the effect was so small compared with cigarette smoking that it was not demonstrable."

Estimating dust exposures is done by thermal precipitation of respirable mass treated with acid. This method is different from other studies. Whether it is more or less than straight gravimetric analysis by mppcf or cyclone was not mentioned. The typical gold miner worked UG 27 years, with a cumulative exposure of 3.7 mg/m^3-years.

It would be helpful if more data were presented on smoking of cases and controls and methods. UR for cumulative exposure was 1.08 (0.94–1.2), but oddly increased to 1.12 (0.97–1.3) "after entering smoking to model." This increase indicates lung cancer cases smoked less than controls, which seems implausible because only four cases (3%) were nonsmokers. It is a limitation of this study that smoking prevalence was not indicated. In the Hnizdo et al. study, 12% of the cohort were nonsmokers. The size and direction of the large increased risk are required to determine whether controls smoked more than cases, in which case the increase in smoking-adjusted risk would be plausible. Based on the evidence the adjustments for smoking appear implausible, as essentially all controls would have to be smokers and even then it would not be expected to produce this large an increased risk.

Reid et al. indicated that "Dust was not shown to increase the risk of lung cancer." There is not a significant association either with (p=.13) or without (p=.27) adjustment for smoking. Visual comparisons (Figures 3, 4) with Hnizdo et al. (1997) suggest similar E-R response trends. This similarity is denied by both set of authors and the Hnizdo et al. data are described as "inconsistent" with the rest of the South African data. The "inconsistency" exists in the significant elevated risk in the highest exposure cavity only. The biggest inconsistency is in the pooled E-R trend that suggests stronger associations than the original analysis (Figure 3). The major difference may be the potentially confounding effect of smoking, which was adjusted for in Hnizdo et al. but not in the pooled analysis.

Gold miners selected from necropsy and pension files (Hessel et al., 1986, 1990) These are case-control studies of white South African gold miners selected from the necropsy records of the Medical Bureau for Occupational Diseases (MBOD) (Hessel et al., 1990) or deaths reported to the Provident (pension) fund where autopsy results were a major factor in diagnosis of silicosis (Hessel et al., 1986). The combined studies included eligible lung cancer cases from the beginning collection (1975) up to 1986. In both studies miners working <1000 shifts (~4 years) were excluded. Controls without primary lung cancer were selected at random from the same group of deaths as cases.

Hessel et al. (Hessel et al., 1986) had 133 matched triplets of 1 case/3 controls. Cigarettes/day, cumulative dust exposure, average dust intensity, total dusty shifts, and high dust shifts were similar and not statistically significant (p>.20). These data indicate "no association between lung cancer and silica dust exposure." The abstract reported a negative E-R trend for lung cancer by quartiles of dust exposure with ORs = 2.43, 1.72, 1.35, and 0.62 (p>.05)

Hessel et al. (Hessel et al., 1990) extended the initial necropsy case-control study in the years not covered by that study with an added 231 lung cancer cases. Results are similar as cases and controls in this study had comparable exposures measured as cumulative dust, average intensity, total dusty shifts, and total UG shifts. These characteristics are also similar between studies and the conclusion is the same; no association between lung cancer and exposure to silica dust.

Comments on Hessel et al. (1986, 1990)

Neither of these studies reported associations of cumulative dust exposure with either silicosis or lung cancer.

The 1996 IARC Working Group noted that elimination of cases and controls with low exposure may have biased results so it would be difficult to find an exposure effect. They also noted that "workers in South African gold mines were exposed to radon."

Elimination producing low exposure refers to exclusion of study subjects working <1000 shifts (~4 years) for both the studies by Hessel et al. This is similar to not including study subjects that have short working times. A more common exclusion criterion is <1-year tenure, but longer periods are occasionally used as well. The South African mortality studies have more restrictive criterion for eligibility; 10 (Hnizdo et al., 1997) or 15 (Reid et al., 1996) years UG. There was a clear E-R trend despite the more restrictive requirement of 10 versus ~4 years.

Hessel et al. (Hessel et al., 1990) addressed the bias question by asking whether exclusion of <1000 shifts might produce limited variability in exposure. Their answer was no, given that standard deviations and ranges indicated a fairly wide spread of exposures. Mean cumulative exposure (SD) of cases and controls was 35,377 (18,937) and 35,369 (19,088) and a range of 3093–101,907 exposure units.

Hessel et al. also pondered the question of whether there is a threshold for risk of lung cancer from silica exposure and if dust concentrations in the last 20–30 years have been so low that an E-R trend can't be found. Data consistent with that problem is one case of pneumoconiosis as a cause of death and 10 cases with TB. Sluis-Cremer (Sluis-Cremer, 1986) noted a steep drop in exposure levels of about 50 mg/m^3 up to 1905 and about 2 mg/m^3 in 1923. With the use of water to reduce dust levels, better ventilation and control of blasting, exposure and prevalence of silicosis decreased significantly in the 1930s. In late 1930s konimeter samples results showed levels of 0.2–0.5 mg/m^3. Gravimetric sampling and X-ray diffraction showed an average of about 0.7 mg/m^3 total dust and 0.2 mg/m^3 quartz, but with wide scatter.

Hnizdo et al. (Hnizdo et al., 1997, 1991) suggested that overmatching for smoking and exposure occurred, thereby removing a possible E-R trend. These assertions

are based on (a) use of dead controls at same age as cases and matching on smoking and death; (b) cases with >15-year tenure are more likely to have a necropsy than cases with <15-year tenure, thus causing overmatching on exposure; and (c) controls were matched on smoking (and therefore death as well) so both cases and controls likely died prematurely, thereby overmatching for both dust exposure and silicosis. These biases were considered to have limited ability to detect an E-R trend for a weak association, if there is an association.

Cases and controls died on average at the same age (about 65 years), but cases smoked more cigarettes/day than controls. Hessel et al. (Hessel et al., 1990) noted that gold miners significantly disabled in life may be underrepresented because they are more likely to be compensated and therefore get no remuneration by having a necropsy. But since cases were selected on the basis of necropsy lung cancer and not smoking, this was thought to not affect results. Results in this study are similar to the previous study where subjects were selected from pension fund records that reduce problems associated with underrepresentation of fully compensated cases.

These studies provide limited descriptions of methods and results regarding the silica–lung cancer hypothesis. They focused on the relationship between silicosis and lung cancer. The relationship between quartz exposure and lung cancer is given minimal attention and is based on the close similarity of cumulative exposure, average exposure, and shifts worked between cases and controls. It would have been helpful to analyze E-R trends directly by exposure categories or regression. For example, E-R for silicosis and dust levels by quartiles dust exposure was analyzed. It is not clear whether dust exposure was intensity or cumulative as units of exposure are not provided. When values are provided, they are too high to be mg/m^3.

Overall comments on South African gold miners

IARC monographs on silica have essentially ignored the South African studies of gold miners. There is a wealth of information because of monitoring of health status and exposures since the beginning of the 20th century (Sluis-Cremer, 1986). Radon levels appear to be relatively low, and probably are not a significant confounder. If radon were a confounder, one might expect lung cancer cases to have higher exposures than controls (Hessel et al., 1986, 1990) or risk of lung cancer to increase with increasing levels of quartz exposure levels, assuming radon is correlated with dust levels (Hnizdo et al., 1997; Reid et al., 1996). The results from the two South African studies with E-R trends are consistent with potential radon confounding. These positive E-R trends are inconsistent with most other studies of quartz- or cristobalite-exposed workers and provide some plausibility to the authors' (Hnizdo et al., 1997) alternative hypothesis that radon might be a surrogate for quartz exposure and a possible primary causal agent.

Strength of association is moderate and moderate E-R trends are counterbalanced by the two case-control studies that showed higher average exposure of controls than cases indicating no associations (Hessel et al., 1986, 1990). Confounding and bias do not appear to be major factors, with the possible exception of bias from overmatching (Hessel et al., 1986;, 1990), possible selection bias from ex-miners and confounding from radon exposure (Hnizdo et al., 1997).

2.1.1.4. Overall conclusions from gold miner studies (Figure 4) Six studies from three countries represent E-R studies of gold miners. Radon is a potential confounding exposure in gold mines, but levels were thought to be low in America and Australia (de Klerk et al., 1998; Steenland et al., 1995a), and not a confounder in at least two of the South African studies (Hessel et al., 1986, 1990). Radon was a possible confounder in the other South African studies (Hnizdo et al., 1997; Reid et al., 1996).

Among South African cohorts the probability of some overlap in study subjects seems high, but the degree of overlap is relatively small. The fact that at least two of the authors (Hessel, Hnizdo) have not voiced concerns, to my knowledge, about this issue may be suggestive of little overlap. Overmatching was suggested as biasing results. There was no sensitivity analysis to assess overmatching, and the use of a different source of study subjects that produced similar results is a plausible argument that overmatching was not a major factor in producing no associations (Hessel et al., 1990). Whether inclusion of ex-miners was a source of bias was not assessed (Hnizdo et al., 1997). The remaining study (Reid et al., 1996) is larger than Hnizdo et al., and seems to be less subject to possible bias and confounding than the other three South African studies, except the adjustment for smoking appear to have spuriously increased the risk ratio.

Four of the six studies clearly do not provide support for a silica–lung cancer hypothesis because of the lack of E-R trends (de Klerk et al., 1998; Hessel et al., 1986, 1990; Steenland et al., 1995b). One of the six clearly shows an E-R trend based on a 3-fold increased risk at the highest exposure (Hnizdo et al., 1997). A 3-fold increased RR in lung cancer risk in quartz-exposed miners is uncommonly high in silica-exposed workers. The reason for the outlying positive result may be related to confounding from radon. However, the E-R trends of Hnizdo et al. appear similar to Reid et al., and exposures above 7 mg/m^3-years show greater than 2-fold increased risks. It is not clear why the Reid et al. study is not statistically significant, since it has a larger number of cases. Perhaps the distribution of exposure is different with fewer high exposed workers in Reid (Figure 4).

Consideration of Hill's guidelines suggests the current weight of evidence is against causality because of consistent findings of weak associations, consistent lack of E-R trends (4/6 studies), and a relatively large database of 723 lung cancer cases, 6.4 times more cases than considered by IARC (1996). These data from gold miner cohorts are

consistent with the 1996 IARC Working Group observation that not all studies demonstrate an excess of lung cancer. The additional data since 1996 also suggest no excess lung cancer risk among gold miners. These additional data comprise cohorts from the USA and Australia with flat E-R trends and no associations, and the pooled analysis of Hnizdo et al. (1997) where the trend becomes steeper without any change in the dataset. The IARC (2009) conclusion that "most studies with quantitative exposures report clear associations between silica exposure and lung cancer risk" is somewhat inconsistent with data from gold mining cohorts where 4/6 studies suggest no associations.

The weight of evidence from studies of gold miners does not support the silica-lung cancer hypothesis.

2.1.2.Chinese ore mining (tin, iron/copper, tungsten) (Chen et al., 2007; McLaughlin et al., 1992) and Sardinian silicotic miners (Carta et al., 2001)

The 1996 IARC Working Group did not include the Chinese studies of mining cohorts among their least-confounded studies (McLaughlin et al., 1992). The most important analysis available from the Chinese mining studies was the nested case-control studies of tungsten miners because of large size and lack of occupational confounders. Follow-up was extended for these cohorts (except Fe/Cu) with improved analyses adjusting for important confounding factors within the models to get an improved evaluation of the role of quartz (Chen et al., 2007).

The updated 2007 version (Chen et al., 2007) includes several improvements from the original study (McLaughlin et al., 1992), which are summarized here, and are equally applicable to the discussions of Chinese pottery workers.

The purpose of the update was to separate effects of silica exposure from other occupational risk factors (e.g., arsenic, radon, PAHs) by extending follow-up (1989 to 1994) and using improved individual exposure data. The analysis was also improved via control of residual confounding using conditional logistic regression models giving silica effects adjusted for smoking and relevant occupational confounders (e.g., arsenic, PAH, radon). The overall analysis included all 511 cases and 1879 controls, compared to 316 cases and 1352 controls in the first study (McLaughlin et al., 1992).

All monitoring data collected since the 1950s were used for a job exposure matrix (JEM) of average total dust exposure (>60% of all jobs) or monitoring data for similar jobs at different times. Cumulative exposure was Σ (job exposure × time exposed) using exact average values instead of crude exposure categories. A conversion factor was developed and used to convert total dust to respirable silica. An independent JEM was developed for arsenic, radon, and PAHs. Analyses were based on 15-year lags. Results unadjusted for occupational confounders can be

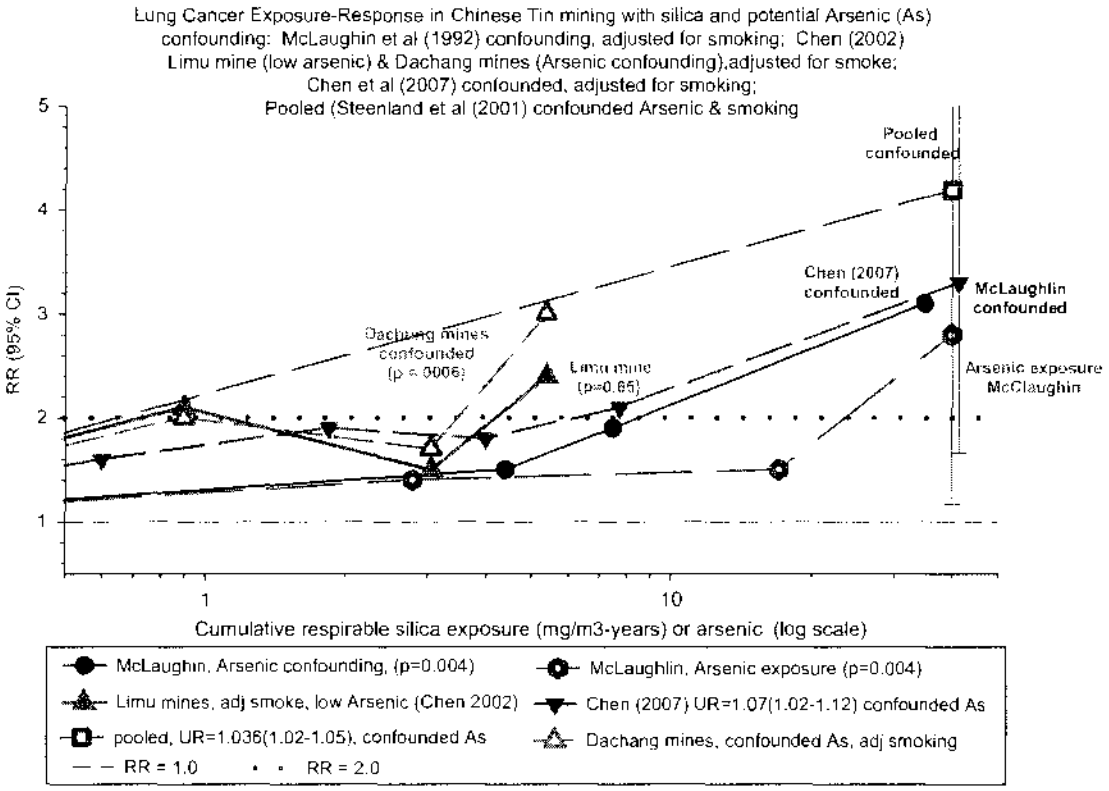

Figure 5. All Chinese tin mining cohorts.

compared to previous E-R trends for pottery, tungsten, and tin miners (McLaughlin et al., 1992).

Conversion factors were based in part on side-by-side sampling of total dust and respirable dust using Chinese traditional methods and current National Institute for Occupational Safety and Health (NIOSH) methods. The purpose was to convert Chinese dust measurements to respirable silica measurements so Chinese estimates are comparable to other results in the literature. The conversion factor (CF) is the ratio of respirable crystalline silica concentration (CS) from a cyclone to total dust (CTD) from Chinese airborne dust samples, or CF=CS/CTD. The conversion factors were estimated to be 0.014 for iron/copper, 0.036 for pottery, 0.043 for tin mines, and 0.086 for tungsten. Crystalline silica dust content was estimated as 12.5% in iron/copper mine dust, 37.4% in pottery dust, 29.5% in tin mine dust, and 50.4% in tungsten mine dust (Zhuang et al., 2001).

2.1.2.1. Chinese tin mining (Chen et al., 2002, 2007; McLaughlin et al., 1992) (Figure 5) A cohort study of 7855 tin miners (1972–1989) from four mines in Guangxi Provence was conducted (Chen et al., 1992). From this cohort, three nested case-control lung cancer studies were developed (Chen et al., 1992, 2007; McLaughlin et al., 1992).

McLaughlin et al. was the first study of this cohort and consisted of 87 cases and 371 controls employed in 1972–1974, with follow-up to 1990. There were strong, smoking-adjusted E-R trends to respirable silica ($p=.004$) and arsenic ($p=.004$), with ORs of 2.69 and 2.8 in the highest-exposure groups. Arsenic and PAHs were highly correlated ($r=.80$) with silica exposure, preventing adjustment for these confounding exposures. Results from this study are highly confounded by arsenic, and the individual effects of silica could not be ascertained. This study should be excluded from consideration (Figure 5).

Four more years with follow-up to 1995 produced 130 lung cancer cases matched to 627 controls (about 5:1) on age and mine (Chen et al., 2002). Silica and arsenic exposures were based on (total dust × % quartz content) from samples collected since the 1950s. Confounding exposures after 1988 were from individual samples for arsenic, PAHs, radon, and cadmium. The three mines from Dachang had high content of silica (35%), arsenic (6%), and PAHs (373 μg/m³), but low radon (0.02 WLM). The Limu tin mine also had high silica exposure (35%) but low arsenic (0.46%), PAHs (7.6%), and radon (0.01 WLM). E-R trend from the Limu tin mine appears relevant because of high silica and low arsenic. Results from the two groups of mines are summarized:

a. E-R for silicosis was similar in the two groups of tin mines so total dust estimates appear reliable.
b. E-R between lung cancer and cumulative dust exposure was found in Dachang tin mines ($p=.006$), but not in the Limu mine ($p=0.65$), which has low (nonconfounding) arsenic contamination. McLaughlin et al. showed E-R trends for both respirable silica and arsenic (Figure 5).
c. Carcinogenic PAHs were not detected and radon exposures were low.
d. Smoking increased risk of lung cancer with high rates of smoking (89% in cases, 83% in controls).
e. Arsenic was associated with increased risk with positive E-R trends at Dachang where exposure was high, but not Limu where exposure was low.
f. Lung cancer risk was associated with increased silicosis in Dachang but not Limu.

The authors (Chen et al., 2002) suggest these results "provide little support for the hypothesis that respirable crystalline silica induces lung cancer. Ore dust... acts as a carrier, the exposure to arsenic and tobacco smoking play a more important part in carcinogenesis of lung cancer in tin miners." The high correlations of arsenic to dust and silica exposures prevented adjustment for confounding from arsenic, so E-R analysis from these data produces spurious associations with silica confounded by arsenic where exposures are high. The small number of cases (29) in the Limu mine cohort limits the ability to reach definitive conclusions from this cohort.

The 2007 analysis had 144 cases and 575 controls matched on decade of birth and workplace (Chen et al., 2007). Average respirable silica exposure was 2.6 mg/m³-years (range 0–35 mg/m³-years); arsenic was 92.3 μg/m³-years (range 0–3542 mg/m³-years). There was a clear E-R trend without adjustments for occupational risk factors similar to that in the original. Chen et al. (2007) did not analyze lung cancer E-R because adjustment for arsenic "cannot produce reliable results ...due to the strong correlation (colinearity) between the cumulative exposure to respirable silica and arsenic."

Results of Chinese tin miners are uninformative regarding the silica-lung cancer hypothesis because of confounding from arsenic. A possible exception are results from the Limu mine, which does not support the hypothesis (Chen et al., 2002).

IARC (1996) and IARC (2009) concluded that quartz and arsenic exposures were too correlated to evaluate the possible causal role of quartz in increasing risk of lung cancer. The analyses of tin mines should therefore be excluded, with the possible exception of the Limu tin mine, which shows no E-R association of silica and lung cancer, but is limited by small number of cases (29). Despite the nonmonotonic E-R trend and instability, the Limu results are classified as equivocal largely because of the high OR in the high-exposure category.

Results from all four Chinese tin miner cohorts were included in the pooled analysis with a unit risk of 1.036 (1.02–1.45) per unit mg/m³-years. E-R for silica could not be reliably estimated in the tin mines because of high correlation with arsenic. With an unadjusted OR of 3.1 in the high-exposure group, it is plausible that inclusion of tin miners in the pooled analysis significantly biases the

E-R trend upward (Figure 5). Arsenic was recognized as a potential confounder but since "potentially confounding exposures were not available in other cohorts, preventing a uniform treatment in the pooled analysis, and as quantitative job-specific exposure over time had not been developed for them, we did not attempt to adjust for these other exposures in our pooled analysis" (Steenland; Mannetje et al., 2001). The entire tin cohort should be excluded from all analyses estimating the effect of silica on lung cancer.

2.1.2.2. Chinese iron/copper (Fe/Cu) mining (Chen et al., 2007; McLaughlin et al., 1992) (Figure 6) The Fe/Cu group of miners was not updated from McLaughlin et al. Cumulative respirable silica was lowest among the Chinese Fe/Cu mines, with a median of 0.2 (0–6.8) mg/m^3-years. Radon, PAHs, and arsenic exposures were negligible, except for a few mines that had very high concentrations of radon at 311 WLM and PAHs at 2000 μg/m^3-years.

There were 74 cases and 346 controls in the McLaughlin et al. study and no associations with cumulative exposure to respirable silica, PAHs, or radon. Arsenic exposure was low, with the highest odds ratios in the low-exposure category (<5.5 μg/m^3-years). Despite the low silica exposure, 20% of cases and 11% of controls were silicotics, and OR for lung cancer was 3.1 for silicotics versus nonsilicotics. IARC (1996) ignored this study.

Chen et al. (2007) had 75 cases and 277 controls with no additional follow-up but a different analysis and exposure findings than McLaughlin et al. In the E-R without adjustment for occupational risk factors (PAH, radon), there was a nonsignificant E-R trend. Adjustment for PAH and radon produced no significant findings for respirable silica (UR = 1.1 [0.82–1.42]), although there was an increased nonsignificant risk (OR = 1.4) in the 4th quintile (~4 mg/m^3-years) of respirable silica exposure (Figure 6). There was no E-R trend for PAH (UR = 1.0 [0.86–1.12]) but a suggestive trend for radon (yes vs. no) of 1.5 (0.49–4.66). Although these data were not updated from McLaughlin et al. (1992), there were "minor changes," likely due to the use of different exposure categories and 15-year lag.

IARC (2009) noted that silica exposures were "very low," and that the unadjusted trend with silica exposure "disappeared after adjustment for radon." Exposures were not too low to produce silicosis and 3.1-fold increased rate of lung cancer compared to nonsilicotics (McLaughlin et al., 1992). Several other mining cohorts (US and South African gold miners) have similar low quartz exposures. The Fe/Cu cohort was not included in the pooled analysis.

The nested case-control study of Chinese Fe/Cu miners does not support the silica-lung cancer hypothesis.

2.1.2.3. Chinese tungsten mining (Chen et al., 2007; McLaughlin et al., 1992) (Figure 7) There were 93 cases and 401 controls among the tungsten-mining group, and a significant negative trend with respirable silica. Arsenic, PAHs, and radon were not confounders in the first analysis (McLaughlin et al., 1992), as there were negative E-R trends with lung cancer.

In the follow-up (Chen et al., 2007), the number of cases and controls were increased to 172 and 568, respectively. Median cumulative respirable silica exposure was 8.56 (0–232) mg/m^3-years (Mannetje et al., 2002), but the

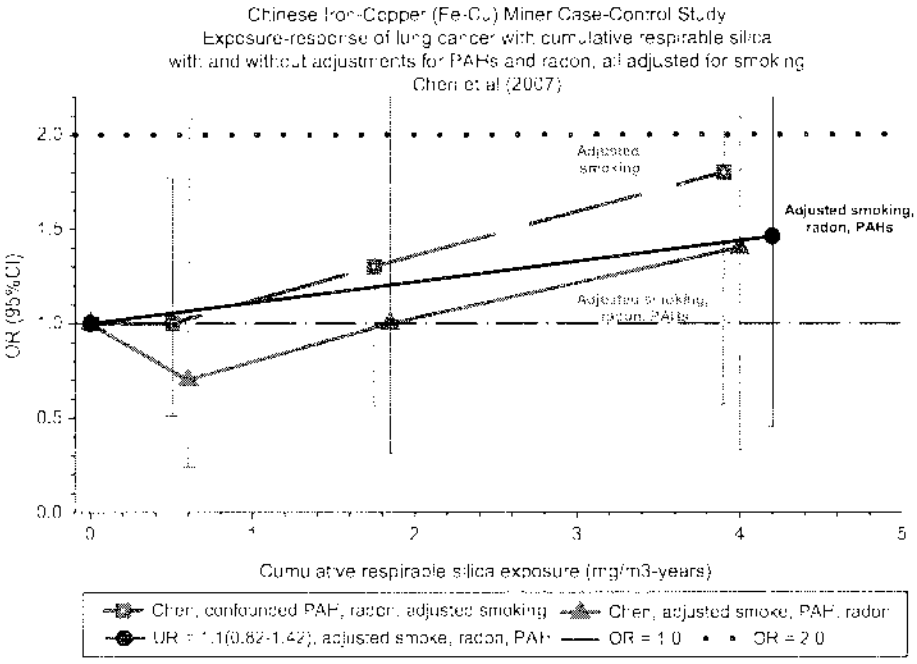

Figure 6. Chinese iron/copper cohorts.

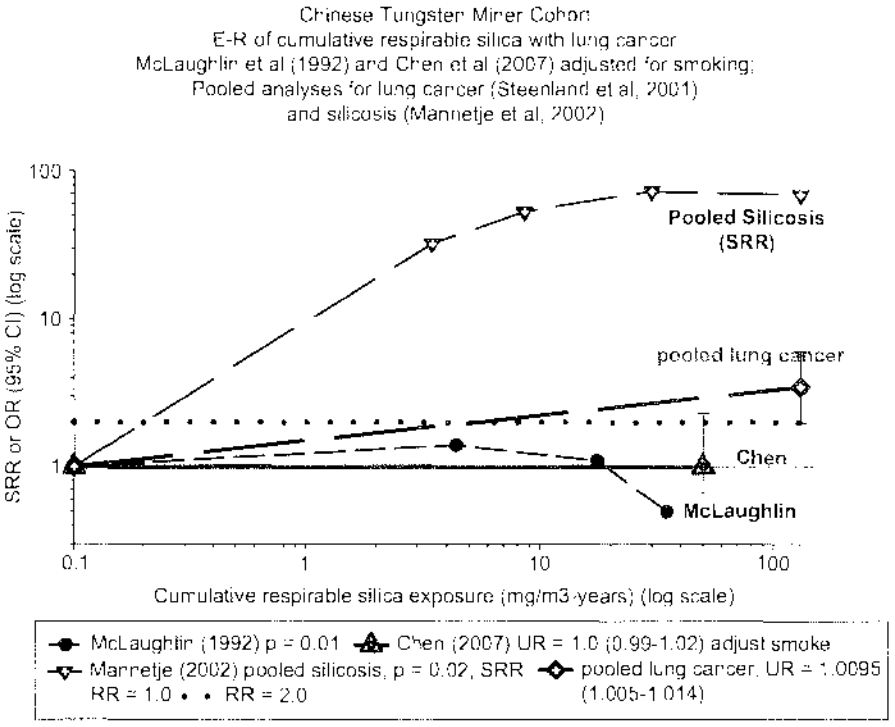

Figure 7. Chinese tungsten miner cohort.

maximum was 72.4 according to Chen et al. (2007). These exposures to respirable silica are among the highest in all studies. Median exposures to PAH, radon, and arsenic were 24 (0–144) μg/m^3-years, 7.3 (0–95) WLM, and 6.1 (0–80) μg/m^3-year, respectively, and considered negligible with no necessity for adjustments for confounding. There was no E-R trend, with a UR = 1.0 (0.99–1.02) after adjustment for smoking (Chen et al., 2007) (Figure 7).

This study is among the least-confounded studies, has high quartz exposures, and is one of the larger studies with 172 cases of lung cancer. The prevalence of silicosis was 22% and 26% among cases and controls, with a lung cancer RR of 0.8 for cases with silicosis (McLaughlin et al., 1992). Both analyses showed negative or flat E-R trends between silica and lung cancer after adjusting for confounding from smoking, and there was no significant confounding from occupational exposures (Chen et al., 2007; McLaughlin et al., 1992). Chen et al. reported a UR = 1.0 (0.99–1.02).

The pooled analysis included this cohort of Chinese tungsten miners used by Chen et al. (2007) with revised work histories and extended follow-up from 1989 to 1994 (Steenland; Mannetje et al., 2001). The analysis appears to be similar to the published revised and updated study (Chen et al., 2007), with the exception that the pooled analysis did not adjust for smoking (Steenland; Mannetje et al., 2001). The unit risk in the pooled analysis is small but significantly positive at 1.0095 (1.005–1.013). The small positive trend from the pooled analysis is inconsistent with the depressed lung cancer SMRs and the updated analysis of these miners (Chen et al., 2007) (Figure 7).

The updated analysis (Chen et al., 2007) is the best test of the silica–lung cancer hypothesis among miners because of adjustments for smoking, longer follow-up with more cases, and more reliable exposure estimates. This negative study with a flat E-R curve does not provide support for a causal association between silica exposure and lung cancer.

2.1.2.4. Sardinia miners with silicosis (Carta et al., 2001) (Figure 8) Carta et al. conducted a cohort mortality study and nested case-control study to evaluate the association between silica exposure, silicosis, and lung cancer. Individual data on potential confounders included smoking history, work history, lifetime exposure to respirable silica and radon, International Labour Organization (ILO) classifications of silicosis, and lung function. The cohort study comprised 724 miners with radiographic evidence of silicosis diagnosed in 1964–1970 and follow-up to 1998. The case-control study comprised 34 lung cancer cases and 4 controls per case matched on year of birth and survival. Miners worked in UG lead and zinc mines with 2–29% respirable silica, metal mines with low airborne silica content (median 3%), metal mines with high silica content (median 13%), lignite coal with 2–10% silica, and granite quarries with 5–25% airborne silica.

Overall mortality was high with 579 observed deaths and an SMR of 1.35 (1.24–1.46). Other SMRs were 1.37 (0.98–1.91) for 34 cases of lung cancer, 22 (17.4–27.8) for 33 cases of TB, and 6.03 (5.4–6.1) for 278 cases of non-malignant chronic respiratory disease (NMRD). NMRD

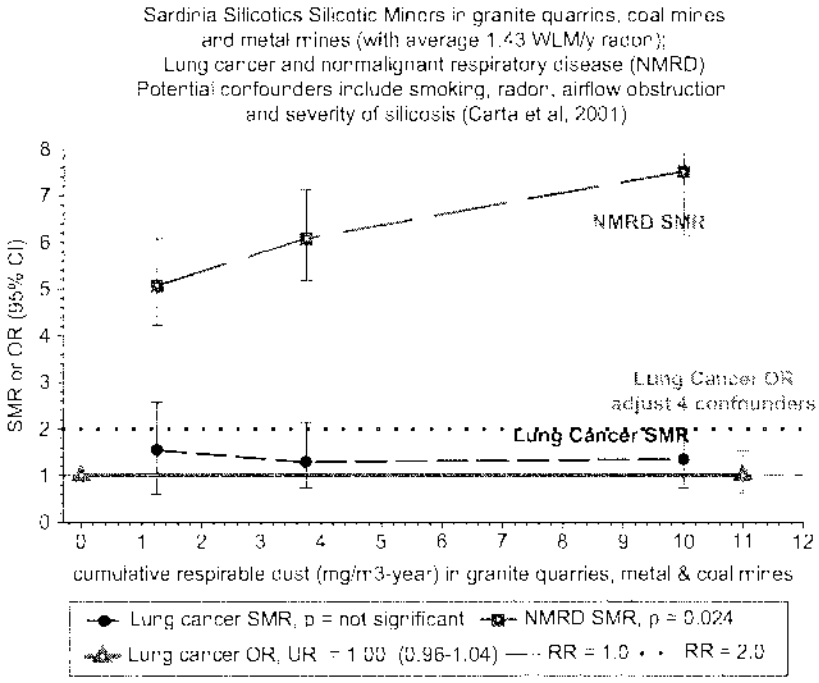

Figure 8. Sardinia silicotics in granite quarries, metal mines, and lignite.

SMRs increased 7-fold at the category 3/2+ silicosis ($p = .008$) and >10 at 5 mg/m^3-years ($p = .024$).

Lung cancer mortality was not associated with cumulative respirable silica exposure, but there was a significant E-R with NMRD (Figure 8). NMRD is mainly silicosis and chronic obstructive lung disease (COLD) and the association "proves the consistency of the environmental dust measurements and estimates and the validity of the exposure index." Lung cancer mortality showed a significant upward trend associated with radon estimated by grouping industries based on radon exposure independent of respirable silica.

The relationships between lung cancer and potential risk factors were evaluated by multivariate regressions using as the controls the 655 cohort members with spirometry. There were no associations of lung cancer (RRs no different than unity) with silica exposure or silicosis severity. There were significant associations with smoking ($p = .02$), airway obstruction ($p = .0001$), and radon exposure ($p = .01$).

The results from the nested lung cancer case-control study using stepwise logistic regression to adjust for confounding variables confirmed results from the cohort analysis as did analysis by continuous variables. This analysis shows a flat slope of the E-R trend after adjustments for smoking, airway obstruction, and radon (Figure 8).

The authors conclude these findings "mostly do not show a significant association between...cumulative exposure to crystalline silica and lung cancer mortality, after controlling for smoking and other covariates. "The most significant predictors of lung cancer mortality were smoking, airflow obstruction, and high exposure to radon.

Confounding variable	RR (95% CI)	Unit
Smoking	1.60 (1.07–2.37)	10 cigarettes/day
Obstruction (FEV/VC)	2.67 (1.63–4.36)	20% <predicted
Radon exposure	1.45 (1.10–1.90)	100 WLM
Cumulative respirable quartz	1.001 (0.86–1.18)	mg/m^3-year
Severity of silicosis	1.0	1/0–1/2
	1.03 (0.66–1.61)	2/1–2/2
	1.05 (0.43–2.57)	3/2+

Comments on Carta et al. (2001)

This study was not included in the pooled analysis. IARC (2009) noted that this study was small with a limited range of exposure because of restriction to silicotics. The smallness is suggestive of reduced power to observe significant associations, but the small size did not prevent significant effects on NMRD, radon, and airflow obstruction. Note that the lung cancer E-R trends are flat, so that even if statistically significant they would not be suggestive of an association. The lack of trends were consistent in both cohort and case-control analyses, so the small size and lack of statistical significance does not change the biological significance of these findings.

The data do not indicate the range of exposure is limited. In fact, there is evidence of high cumulative exposure, despite no obvious association between silica exposure and lung cancer and silicosis and lung cancer (Figure 8). For example, average exposures for silicosis categories 1, 2, and 3- were 3.7, 4.1, and 4.3 mg/m^3-years, respectively, with high ends of the range at 12, 14, and 15 mg/m^3-years. A related limitation arising from restriction to silicotics is the lack of low-exposed or

nonexposed miners. This deficit could make the referent "low-exposed" group at higher than expected risk and reduce the ability to measure an E-R trend. The design would be improved by inclusion of nonsilicotic cases, but the authors indicated that was not feasible.

The authors comment that selection or diagnostic bias seems unlikely in this study of silicotics, which is not always true (Hessel et al., 2000). The cohort contains nearly all incident cases of silicosis in Sardinia, where the diagnosis was tested by blinded rereading of X-rays without knowledge of lung function, smoking, and exposure. The authors' conclusion of no bias would be improved if X-rays were known to include normal individuals, with a proportion of the X-rays being recycled for rereading and checking of reader consistency, and use of at least three different readers.

The authors comment that if they had excluded miners with NMRD as controls, ORs would have been biased upward. As a result the negative results in the face of this positive bias "further support our conclusions."

There is a negative E-R trend in lung cancer SMRs that is not subject to bias, as expected deaths were based on Sardinian regional rates. And despite the positive bias from radon exposure that is not accounted for in this external comparison, the negative trend does provide further support for the authors' conclusion of no silica–lung cancer association. Radon, airway obstruction, and smoking also may explain the 25–55% elevation in SMRs for lung cancer.

This study does not support a carcinogenic effect of silica exposure.

2.1.2.5. Summary of Chinese and Sardinia mining studies (Figure 9) Arsenic and silica are so highly correlated in the study of tin miners that results evaluating individual effects are unreliable, uninformative, and infeasible. Results should not be included in the weight of evidence regarding a causal association of silica and lung cancer. An exception is the Limu tin mine where arsenic was not a confounder, as exposure was low. There was no significant positive E-R in this mine, although ORs at low- and high-exposure groups was >2-fold. This analysis does not support a silica–lung cancer hypothesis.

When ORs are adjusted for radon in the Fe/Cu study, there is no convincing E-R trend, with all ORs at or below 1.0, except a nonsignificant OR of 1.41 at the highest exposure category (2.6–5.4 mg/m^3-years). The IARC working group noted that exposures were very low (<5.4 mg/m^3-years), but exposures were high enough to produce silicosis prevalences of 20% and 11% among cases and controls. Nearly half of silica-exposed cohorts (40%) have low exposures of less than 10 mg/m^3-years. There was a slight E-R trend that disappeared when PAHs and radon were adjusted for. These results detract from a silica–lung cancer hypothesis.

Parenthetically, it is interesting that the IARC working group criticized the Chen et al. (2007) analysis of Chinese potters because it reduced the positive trend of McLaughlin et al. to no trend. The Chen et al. (2007) analysis did the opposite for Fe/Cu miners, changing the negative trend of McLaughlin et al. to a slight positive trend in the highest exposure category (Figure 6).

The only observed confounder in the tungsten miners study is smoking. After adjustment for smoking there is a flat E-R trend (Figure 7). This study is powerful evidence against a silica–lung cancer hypothesis.

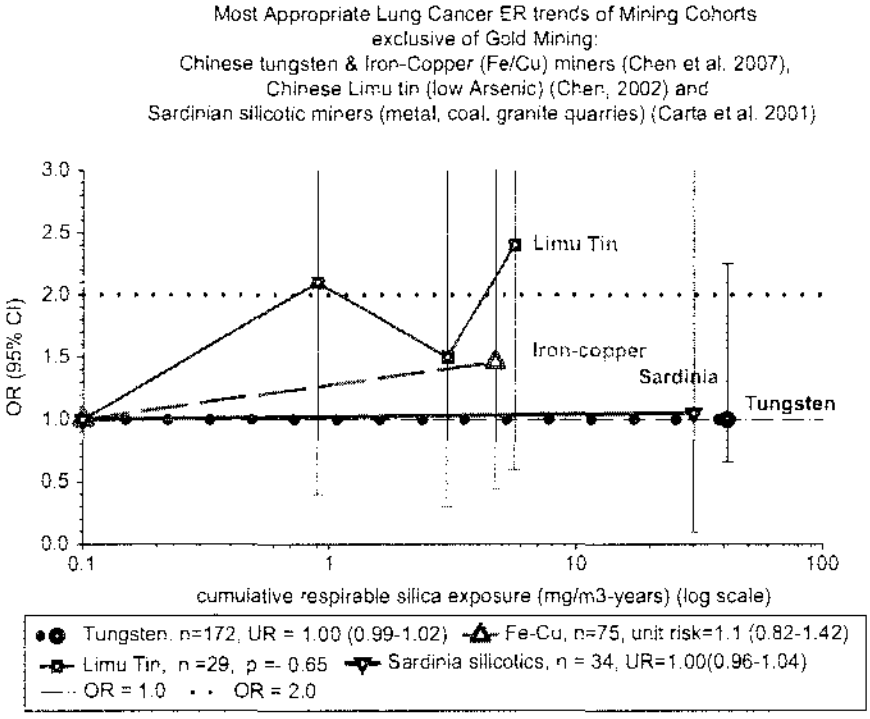

Figure 9. Summary of non-gold mining cohorts (tungsten, Fe/Cu, Limu tin, Sardinia).

The lack of association with lung cancer among the highest exposed Sardinia miners with confirmed radiological silicosis is strong evidence against the silica–lung cancer hypothesis despite the small numbers.

Figure 9 summarizes the most appropriate E-R analyses among the non gold miner cohorts. This industrial group does not provide support for the silica–lung cancer hypothesis, as strengths of association are consistently small and nonsignificant and there is a consistent lack of E-R trends.

2.1.3. Summary of all mining studies (Figure 10)

Ten mining studies are appropriate for contributing to the weight of evidence regarding lung cancer risk from respirable silica exposure.

A limitation in some of the mining studies is confounding occupational exposures to radon or arsenic. Radon was a potential confounder in the South African gold miner studies, but does not appear to be a strong confounder. In Hnizdo et al. (1997), radon exposure was estimated to increase risk 20–30%, but even if it had been adjusted for, there would still be an E-R trend. IARC does not use the South African gold miner cohort for reaching a conclusion and IARC (2009) noted that lung cancer was not associated with uranium but silica might be a surrogate for radon exposure. The Hnizdo et al. study was one of the studies included among the 10 cohorts in the pooled analysis. All South African gold miner cohorts were included in this report.

In the Chinese iron/copper cohort, radon produced a RR = 1.2 that was adjusted for in the analysis.

Arsenic was a confounder in three of the Chinese tin mines. The correlation was so high that silica effects could not be differentiated from arsenic effects, so these studies are excluded when considering weight of evidence. The exception is the Limu tin mine that had low arsenic levels. It is included in the weight of evidence and provides limited information, as there are only 29 lung cancer cases.

There are six gold miner cohorts. Two large South African gold miner studies by Hessel et al. have been largely ignored in IARC deliberations. These two studies with a total of 364 lung cancer cases showed no associations between silica exposure and lung cancer based on equal mean cumulative exposure of cases and controls but no formal E-R analysis.

The Hnizdo et al. and Reid et al. South African studies of gold miners were characterized as having contradictory results, one positive study and the other a negative study. However, visual inspection of the E-R trends suggests similar slopes. The Hnizdo et al. study is statistically significant but Reid et al. is not despite having more lung cancer cases ($n = 159$) in the latter compared to 77 cases in the former ($p > .05$).

Results from the Australian cohort of gold miners are based on the pooled analysis and indicate a nonsignificant E-R trend compared to a flat trend using exposure score-years and adjusted for smoking and bronchitis. The pooled analysis provides the only available quantitative E-R results. The results are considered largely negative with an UR = 1.016 (0.99–1.04) but an OR = 1.73 (0.78–3.9) at a high of 34 mg/m^3-years.

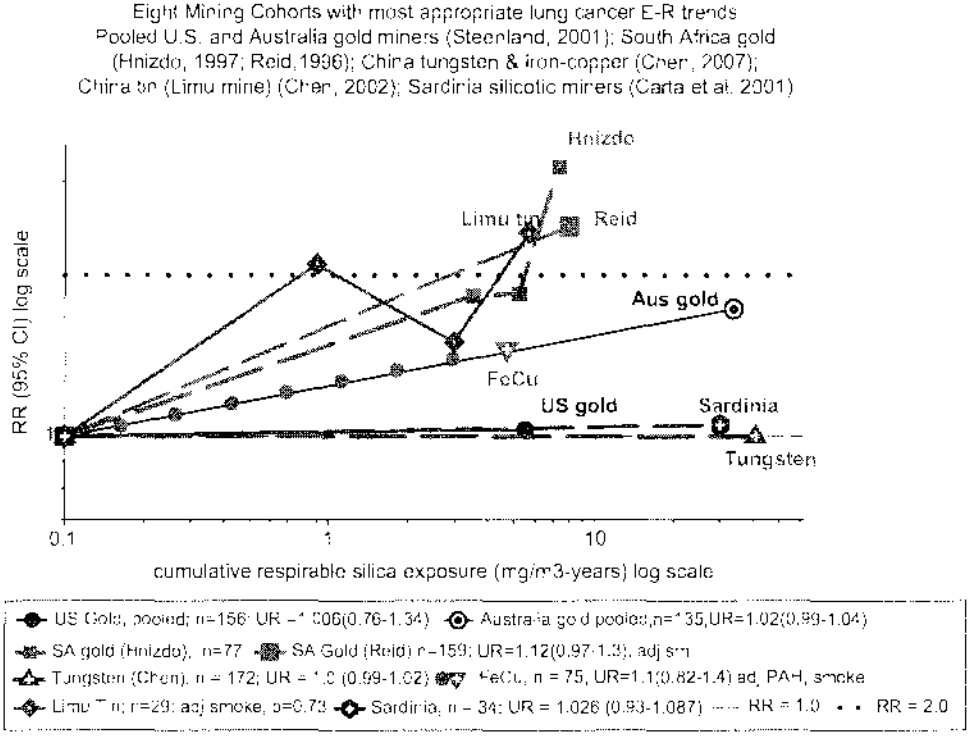

Figure 10. Summary of all eight mining cohorts with E-R analysis.

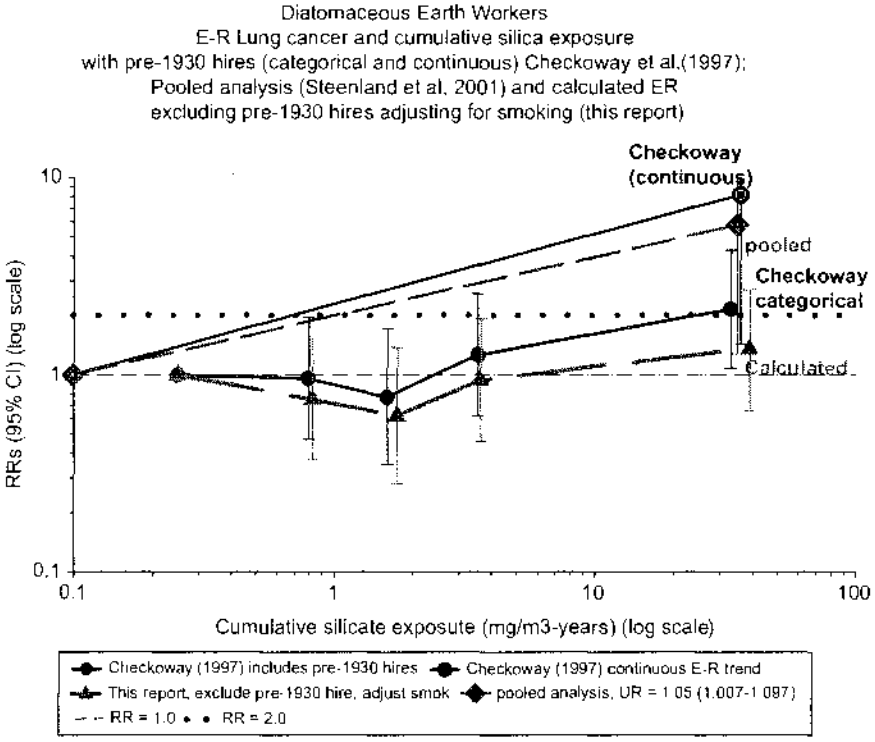

Figure 11. Diatomaceous earth E-R with and without adjustments plus pooled analysis.

The US gold miner cohort showed no trend in the SMR analysis and a negative trend in the case-control analysis. Further follow-up in the pooled analysis showed similar risks with an OR = 1.03 at highest exposure of ~6 mg/m^3-years. This is a clear and definitive negative study that does not support the silica–lung cancer hypothesis.

The Chinese iron/copper mine cohort has been criticized for low exposures, but they appear to be in same range as the US gold miner cohort, which is reduced from the McLaughlin et al.'s high estimates of >20 mg/m^3-years. This is an example where adjustments for confounding exposure to smoking, PAHs, and radon substantively reduces the E-R trend, with a nonsignificant 1.4-fold increased risk in the high-exposure group only. Limitations include the small size, lack of additional follow-up, lack of improvements in estimates of silica exposure, confounding exposures from smoking, PAHs, and radon. The contradictory results from McLaughlin et al. show much higher silica exposure despite the same exposure database, no apparent confounding from PAH and radon, and lower ORs (Figure 7). The unusual lack of consistency in results despite the similarity in the two cohorts is discomforting.

The Chinese tungsten cohort has (a) the highest silica exposure of any cohort, with a maximum of 232 mg/m^3-years according to the pooled analysis (Mannetje et al., 2002); (b) the largest number of cases (n = 172) in mine cohorts with E-R analysis; (c) no known occupational confounding exposure; and (d) shows no association with lung cancer with a unit risk of 1.0 (0.55–1.66) after adjustment for smoking (Chen et al., 2007). These characteristics made it difficult to understand why IARC (1997) did *not* include it among those studies providing "least confounded examinations" of the silica–lung cancer hypothesis. This is clearly a definitive negative study that makes it difficult to understand increased risk at much lower exposures. The pooled analysis showed a significant weak E-R association, perhaps due to confounding from smoking. Adjustments for smoking, improved exposure estimates, and longer follow-up with more cases, are important differences, making the Chen et al. results more appropriate than those of Steenland et al.

The Chinese cohort of tin miners was excluded by IARC (1997) and IARC (2009), but included in the pooled analysis. The inability to control for arsenic confounding was recognized by IARC (1997, 2009), and was made even more explicit in the improved updated version of this study (Chen et al., 2007) where the effects of arsenic and silica could not be separated. For this reason, this cohort should be excluded from any consideration of the silica–lung cancer hypothesis. The only exception is the Limu tin mine where arsenic appears to be at low enough concentrations to not be a confounder. With only 29 cases, the E-R trend is unstable and not statistically significant.

There is a fairly consistent pattern of no association in the mining studies, with the exception of the South African gold miner cohorts (Hnizdo et al. and Reid et al.) where there are strong association with 3.5-fold and 2.5-fold increased risks at low exposures (<10 mg/m^3-years). Three studies showed no associations at these same low

exposures. Three showed no associations despite high exposures 3–5 times higher (≥30 mg/m³-years) than in the South African gold mines (Figure 10).

Strength of association is weak or nonexistent, with ORs < 1.5 at highest exposures in all but three studies, and only one of these is statistically significant. This guidepost does not provide evidence supporting a causal association among miners.

Biological gradients are weak or nonexistent except for the two South African gold miner cohorts and perhaps the Limu tin mine cohort. The three cohorts with the highest exposures show no increased lung cancer risk at those exposures.

Overall seven studies show no association (perhaps one of these is equivocal) and three studies are suggestive of an association. The three largest and least confounded studies show no increasing E-R trend and no associations with silica exposures. The weight of evidence from mining studies is considered insufficient to declare silica exposure as carcinogenic.

2.2. Diatomaceous earth (DE) and potteries

2.2.1. Diatomaceous earth (Checkoway et al., 1997)

The updated cohort of 2342 DE workers from one plant in California (Checkoway et al., 1997) is the basis for assessing effects of cristobalite, a polymorph of crystalline silica. For 75% of the cohort, mean cumulative exposure was about 2.5 mg/m³-years or less, and the 4th quartile average was between 2.5 and the maximum of 63 mg/m³-years (Mannetje et al., 2002). IARC (2009) noted significant excess risk in the highest exposure categories for both 0 lag (2.11, 1.07–4.11) and 15-year lag (2.15, 1.08–4.28). Trends were of "borderline significance"; the unlagged UR was 1.06 (1.01–1.11).

A risk assessment of this same cohort (Rice et al., 2001) reported a significant UR of 1.07 with a 10-year lag and internal adjustments for time since first observed, calendar time, age, and ethnicity.

No revisions were made in the pooled analysis, so the criticisms regarding confounding from smoking and exposure misclassification caused by including pre-1930 hires remain. The unit risk was 1.05 (1.01–3.02) with 15-year lag. The E-R trend is similar to the original analysis using continuous analysis, and both are inconsistent with the categorical analysis (Figure 11).

This study should be considered unreliable for assessing causality in the pooled analysis unless adjustments are made for bias and confounding. When made, the results detract from the silica–lung cancer hypothesis. This study detracts from the importance of the pooled analysis because confounding and bias were not accounted for, and the trend appears inconsistent with the original data (Figure 11).

Comments on DE

An exchange of letters to the editor (Checkoway et al., 1998; Gibbs, 1998; Merliss, 1998) presents information important for evaluating the exposure-response relationships of this study.

The first concern is confounding and exposure misclassification from asbestos. Asbestos was definitely used before 1930 in this plant. Exposure levels were extrapolated from 1930 levels when no asbestos was used. So some production workers could be misclassified as nonexposed when in fact they might have been exposed to high levels of asbestos (Gibbs, 1998). Checkoway et al. acknowledged that asbestos exposure was "uncertain" for the eight lung cancer cases in the pre-1930 hires. Exclusion of these workers reduced the RR from 2.15 to 1.74 and the number of cases from 20 to 12 in the highest exposure category (15-year lag). But the assertion was made that asbestos confounding did not occur before 1930 because the RR was nearly the same (1.73) after adjusting for asbestos. Pleural abnormalities (surrogate for asbestos exposure) were similar for pre-1930 and 1930–1939 hires and no lung cancer deaths occurred in the lowest silica and highest asbestos exposed group. Therefore "confounding by asbestos exposure is a very unlikely explanation for the observed dose-response relation" (Checkoway et al., 1998).

Note that similar prevalence of pleural abnormalities in the two DOH (date of hire) groups does not assure there was not confounding by asbestos exposure. Pre-1930 hires with lung cancer were in the high silica exposure group; the lack of lung cancer cases in the low silica/high asbestos exposure group may mean there was not confounding. But it is probable there was exposure misclassification, since asbestos exposures are largely unknown prior to 1930.

A second concern is exposure misclassification of cristobalite exposures, particularly prior to 1930 (Merliss, 1998). Silica exposure estimates prior to 1948 were based on extrapolation and an arbitrary scaling factor. This put most of pre-1930 hires in the highest silica exposure category. But the dominant product prior to 1930 was an uncalcined product, which is mostly amorphous silica and only small amounts of quartz (<5%). Some calcining began in 1923, with limited quantities beginning in 1925, and until 1930 comprised about 40% or less of production. Thus, silica exposures could be overestimated in the E-R analysis. Checkoway et al. contend these facts were taken into account and that the "true association" was underestimated rather than exaggerated. But "it is not possible to predict with any accuracy whether these exposures were underestimated or overestimated" (Checkoway et al., 1998).

Note that exposure overestimates reduce the perceived toxicity and underestimates exaggerate the risks. At any rate, uncertainty in the pre-1930 exposure classifications for asbestos and silica can be removed by excluding these workers. This was done in the 1988 reanalysis (Checkoway et al., 1996) because asbestos was definitely used but "specific jobs and exposure levels could not be identified" (Gibbs, 1998).

A third concern is confounding from smoking, which was considered but was thought "unlikely" to be the "sole or predominant explanation for the observed

association." This judgment was based on similar prevalence of smoking in the two highest-exposure groups (86% vs. 83%) but with a decided difference in RRs (1.26 vs. 2.15) (Checkoway et al., 1997). Data for 50% of the cohort were stratified by categories of cumulative exposure with smoking prevalences of 63%, 82%, 80%, 86%, and 83%, respectively. Using the Axelson method to adjust for smoking effects and using a 20-fold difference between smokers and nonsmokers, the RR in the highest exposure category was calculated to decrease from 2.15 to 1.67 (Checkoway et al., 1997).

This information allows calculation of a revised E-R trend that adjusts for exposure misclassification and asbestos confounding by excluding pre-1930 hires, and indirectly adjusts for smoking following the method demonstrated by the authors in the previous paragraph. Results are summarized below with a 15-year exposure lag.

Asbestos and silica exposure misclassification among pre-1930 hires is eliminated by exclusion, and indirect adjustment used by the authors to adjust for smoking further reduces confounding in this cohort (Checkoway et al., 1997), as demonstrated in the table below and shown in Figure 11.

mg/m³-years	Total cohort[n] RR(95% CI)	Exclude pre-1930 hires[n] RR (95% CI)	% smoker	RR_{conf}	RRs (95% CI)*
0.25	[22] 1.00	[22] 1.00	0.63	—	1.00
0.8	[12] 0.96 (0.47–1.98)	[12] 0.96 (0.47–1.98)	0.82	1.28	0.75 (0.37–1.55)
1.6	[9] 0.77 (0.35–1.72)	[9] 0.77 (0.35–1.72)	0.80	1.25	0.62 (0.28–1.38)
3.55	[14] 1.26 (0.62–2.57)	[14] 1.26 (0.62–2.57)	0.86	1.34	0.94 (0.46–1.92)
34	[20] 2.15 (1.08–4.28)	[12] 1.74 (0.85–3.46)	0.83	1.29	1.35 (0.66–2.69)

*Adjustment for smoking (Checkoway et al., 1985).
RRconf = [(RRsm − 1) (Psm/e) + 1)] / [(RRsm − 1) (Ssm/ne) + 1]
where RRconf = RR due only to confounding by smoking
RRsm = RR associated with smoking = 20
Psm/e = proportion of smokers among the exposed group
Psm/ne = proportion of smokers in the nonexposed (reference)
RRadj = RRobs / RRconf

The risk assessment (Rice et al., 2001) was based on the updated total cohort of DE workers (Checkoway et al., 1997). The concerns about exposure misclassification of asbestos and silica among pre-1930 hires, and confounding by smoking are applicable to both analyses of the total cohort (Checkoway et al., 1997; Rice et al., 2001), the pooled analysis (Steenland; Mannetje et al., 2001) and conclusions of IARC (IARC, 1997, 2009; Steenland; Mannetje et al., 2001).

The least confounded E-R analysis excludes pre-1930 hires and adjusts for smoking. This E-R shows point estimate below 1.0 except for the highest exposure category of >5.0 mg/m³-years where there are 12 lung cancer cases and an adjusted RR of 1.35 (0.66–2.69) (Figure 11). Results from this analysis do not support the hypothesis that cristobalite exposure causes lung cancer.

2.2.2. Pottery cohorts (Chen et al., 2007; Cherry et al., 1998; Ulm et al., 1999; Mundt et al., 2011)

Two of the 10 least confounded cohorts (IARC, 1997) studied were of pottery workers. One was a study of a UK pottery (Cherry et al., 1998) with several preliminary reports (Cherry et al., 1996, 1997, 1998). The report available to IARC (1996) was a nested case-control study of 52 lung cancer cases employed ≥10 years with 3–4 controls (Cherry et al., 1996). Lung cancer risk was associated with smoking, average intensity of >200 μg/m³, and maximum peak exposures ≥400 μg/m³ among workers in firing and post-firing occupations where the authors thought cristobalite exposures occurred. IARC (1996) interpreted this as a positive finding, and was a major factor in changing the IARC vote to sufficient evidence for carcinogenicity with the caveat that excesses were not found in all studies. This preliminary report was reanalyzed with more detailed and somewhat different results (Cherry et al., 1998), and is the analysis used by IARC (2009) and included in the pooled analysis.

Another least confounded study was of Chinese pottery workers. The study available to IARC (1996) (McLaughlin et al., 1992) was included in the pooled analysis, with a UR of 1.004 (0.97–1.04) (Steenland; Mannetje et al., 2001). The cohort was then updated with improved exposure data and a revised analysis that adjusted for confounding PAH exposures (Chen et al., 2007).

IARC (2009) included a German study of pottery and stone workers (Ulm et al., 1999). A recent study of German Porcelain workers (Mundt et al, 2011) was not available to IARC (2009).

2.2.2.1. UK pottery (Cherry et al., 1998) (Figure 12). IARC (1986) concluded there was limited evidence in humans that silica was a carcinogen. This conclusion led to a search for a silica-exposed cohort in the UK, and resulted in a mortality study of potteries (Winter et al., 1990) based on periodic medical surveys in 1931–1984. A subset of this cohort was formed from pottery, refractory, and sandstone industries at Stoke-on-Trent and identified via the medical surveillance program. Preliminary results on exposure, radiographic, and mortality findings were published (Burgess et al., 1997; Cherry et al., 1997; McDonald et al., 1997) and used by IARC (1996).

The cohort comprised 5115 men born in 1916–1945 with no known prior exposure to asbestos or foundry work and <1 year's exposure to other dusts. Fifty-two lung cancer cases were matched with three to four controls on DOB and date of first exposure. ORs (with 90% CI) from conditional logistic regression were stratified into dichotomous high and low exposures and presented as unadjusted or adjusted for smoking and radiographic changes. There were no associations with cumulative exposure ≥4 mg/m³-year (OR = 0.51; 0.24–1.11) or tenure ≥20 years

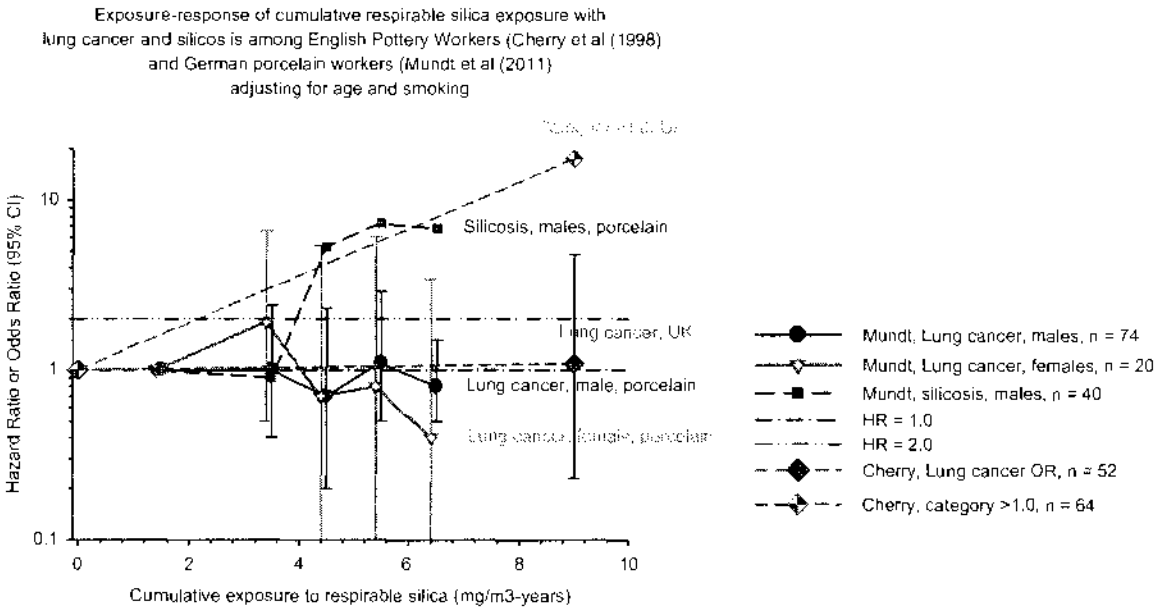

Figure 12. UK pottery.

(OR = 0.38; 0.18-0.78). There were significant associations with mean intensity ≥0.2 mg/m³ (OR = 1.88; 1.06-3.34) and maximum exposure ≥0.4 mg/m³ when exposure was confined to firing and post-firing operations (OR = 2.16; 1.11-4.18).

The authors (Cherry et al., 1997) concluded cumulative silica exposure was unrelated to lung cancer risk. After accounting for smoking and radiographic changes, neither duration nor mean exposure showed a "clearly positive relation." They estimated an OR of 2.17 (90% confidence interval [CI] 1.16-4.07) for cases working in firing and post-firing jobs. Temperatures ranged from 1000°C to 1400°C, with 8% cristobalite in pottery samples. Excesses of lung cancer in workers exposed to heated quartz as in diatomaceous earth (Checkoway et al., 1997) and refractory brick manufacture (Merlo et al., 1991) led Cherry et al. to conclude that "the only risk factor identified in this study was work in firing or post firing occupations."

Preliminary results (Cherry et al., 1997) were used by IARC (1996), but a more complete analysis was published in a subsequent report (Cherry et al., 1998). Added details included (a) a total of 195 controls, all of whom had to be smokers because all 52 cases had been smokers; (b) elimination of participants with silica exposures in the sandstone or refractory industries where there were no exposure estimates; (c) at least 10 years exposure beginning prior to 1960; (d) a conversion factor of 1 mppcf = 0.09 mg/m³ respirable dust; and (e) recording of work in firing and post-firing because of potential exposure to cristobalite or tridymite produced by sustained heat >1000°C.

In the cohort portion of this study, 1985-1992, SMRs were calculated using national expected rates from England/Wales and regional rates from Stoke-on-Trent, which materially reduces SMRs.

Cause of death	Observed	SMR/national	SMR/local
All causes	470	1.46 (1.33-1.60)	1.15 (1.05-1.26)
Lung cancer	68	1.91 (1.48-2.42)	1.28 (0.99-1.62)
NMRD	57	2.87 (2.17-3.72)	2.04 (1.55-2.65)

In a subcohort of 1080 workers selected for radiographic analysis, overall prevalence of small opacities ≥1/0 was 5.9%; a third of these were category ≥2/1. Prevalence of small opacities in smokers was about twice that of nonsmokers. Prevalence of small opacities increased with cumulative exposure (Figure 12). ORs for radiographic small opacities ≥1/0 by exposure and adjusted for smoking were significant for cumulative and mean concentrations but not for duration.

Exposure index	Radiographic opacities ≥ 1/0 OR (95% CI), adjusted for smoking
Cumulative (mg/m³-year)	1.37 (1.24-1.53)
Mean (0.1 mg/m³)	2.66 (1.94-3.66)
Duration (10 years)	1.08 (0.83-1.40)

In the nested lung cancer case-control study (Cherry et al., 1998), no case was recorded as a never smoker. Known nonsmokers were excluded as controls. Cases had significantly fewer ex-smokers (9.6%) than controls (26.2%) and heavier smokers, with 27% ≥20 cigarettes/day compared to 13% of controls. E-R analyses by conditional logistic regression showed no associations with cumulative exposure or tenure, but a significant ($p < .008$)

association with mean concentration. Lung cancer death occurred on average 18 years after last pottery employment, so there was little difference in ORs at different lag periods. Results with a 10-year lag are presented here.

	Lung cancer mortality	
Exposure index	OR (unadjusted)	OR (adjusted for smoking)
Cumulative	0.93 (0.79–1.09)	1.02 (0.86–1.21)
Duration	0.67 (0.47–0.95)	0.75 (0.48–1.18)
Average	1.67 (1.18–2.35)	1.66 (1.14–2.41)

The preliminary analysis (Cherry et al., 1997) showed that when peak and heated silica exposure were dichotomous variables, they were statistically elevated. In the detailed analysis (Cherry et al., 1998), mean concentration was entered as a continuous variable and ORs were no longer statistically significant. The authors suggested the continuous analysis did not change "results to an important extent."

Exposure index	OR, continuous	OR, dichotomous
Maximum, ≥0.4 mg/m³	1.29 (0.47–3.55)	2.16 (0.98–4.74)
Heated silica (firing and post-firing)	1.64 (0.68–3.94)	2.19 (1.06–4.51)

This study was not included in the pooled analysis (Steenland; Mannetje et al., 2001) because of different criteria for case-control matching. Results were said to be considered indirectly in that the regression results from the case-control data appeared to be compatible with the results of the pooled analysis. But matching was redone in the pooled analysis so it is not clear why rematching could not have been redone in this study.

The authors of the extended analysis (Cherry et al., 1998) concluded the "association between risk of lung cancer and quantitative estimates of silica exposure supports the SMR analysis and implies that crystalline silica may well be a human carcinogen." The authors' conclusion is based on average exposure (mg/m³), as there clearly was no association with cumulative exposure.

Comments on UK pottery (Cherry et al., 1998)

The preliminary study was important in the IARC (1997) conclusion because of the 2.2-fold excess risk among workers exposed to heated quartz, with mention of cristobalite by both the authors and IARC. A similar association with cristobalite in the DE study (Checkoway et al., 1996) led to the conclusion that there was *sufficient evidence* that quartz or cristobalite from occupational sources are carcinogenic. That conclusion would not have been accepted without the caveat that carcinogenicity is "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" (IARC, 1997). The follow-up of the preliminary UK pottery study showed there was no association with cumulative exposure, but it was not available to IARC. The critique in this paper suggests no association in the DE cohort either. Thus the further analysis and follow-up of two "cristobalite" study results have not confirmed the IARC (1997) conclusion of "sufficient" evidence for silica carcinogenicity based on these two studies.

There are several possible sources of confusion relating to the occurrence of cristobalite. Cristobalite is clearly formed in calcining DE. At temperatures of 1100°C (2012°F) and greater, a portion of quartz may be converted to cristobalite. Formation of cristobalite is affected by a number of factors, including the speed of the temperature changes and how long the pots are held at high temperatures.

In the potteries a little cristobalite may be useful, but too much cristobalite is disastrous, making the pot brittle or wrinkled. The maximum temperature in the bottle kilns of Staffordshire was 1000–1250°C and maintained for 2–3 hours (www.thepotteries.org). Under these conditions and with batch firings, there may have been a few percent of quartz converted to cristobalite. With modern tunnel kilns, about 1% cristobalite might be formed and another 1–2% if fired twice. It appears that cristobalite was considered to be present based on a 1959 Factory Inspectorate Report; other than that no measurements were taken. From an industrial hygienist's point of view, <5% cristobalite in the aerosol formed after firing would not be considered significant unless there were extremely high respirable dust exposures (personal communication, Bob Glenn). Cumulative respirable dust exposures were below 10 mg/m³-years and were 4–6 times lower than DE and Chinese potteries. The health significance of cristobalite in large quantities (DE) or small quantities in high-temperature pottery is unclear, as the more detailed E-R analysis did not find an association in either exposure situation.

A conclusion contrary to that of the authors (Cherry et al., 1998) is considered more plausible if cumulative exposure is considered a more appropriate indicator of silica effects than mean exposure. Comments are categorized into eight groups below.

a. Some of the author's adjustments for confounding from smoking appear implausible. Cases had a higher prevalence (67%) of current smokers than controls (57%), but fewer former smokers (10% vs. 26%). Smoking adjustments increased ORs for cumulative exposure (from <1.0 to >1.0) and duration, but slightly reduced them for mean exposure. It is not clear why the direction of the adjustment differs by exposure metric, or why ex-smokers have stronger effects for cumulative and duration than smokers despite the larger proportion of smokers. These data suggest

adjustments would produce small reductions in the ORs, not a relatively large increase. If true, there is a suggestion of positive bias in the adjusted OR with cumulative exposure and duration of exposure.

A similar finding was found in the preliminary analysis where smoking adjusted ORs were larger for cumulative exposure and duration, but smaller for mean intensity and maximum exposure. Some explanation of these unexpected effects of adjustments for smoking would be helpful.

b. Preliminary results used only two exposure categories (Cherry et al., 1996). The revised analysis (Cherry et al., 1998) provides more relevant results because there is less exposure misclassification (and greater precision). Two categories (high and low) of exposure have limited value, as there are only two points in an E-R trend. Because of the wide range of exposure in each category, there will inevitably be some exposures in the low-exposure group that are closer to intermediate than low exposure; likewise in the high-exposure group there will be misclassification of exposure and reduced precision. For example, high (low) exposures in the low (high)-exposed category are closer to intermediate than either high or low. With three exposure categories misclassification still occurs, but the bias is reduced and precision increased because of reduced exposure range in each exposure category. Increasing the number of exposure categories continually reduces this bias, until eventually the variable becomes continuous (as in the revised analysis).
c. The exposure index is validated by the strong associations between silicosis (measured as rounded opacities on radiographic chest films and both cumulative and mean intensity indices) (Figure 12). Thus the lack of E-R association appears to be real, and not attributable to invalid exposure indices.
d. Case-control results were said to confirm the results of SMR analysis. The SMR analysis, using national rates for expected, showed high mortality (1.46 for all causes; 1.91 for lung cancer). Mortality was still increased but not as much using local rates (1.15 for all causes; 1.28 for lung cancer). The high lung cancer SMR using the national population as controls is consistent with an E-R trend, but the lower lung cancer SMR using the local population as controls is inconsistent with a trend. The regional population in the SMR analysis is more like the controls in the case-control design than the national population and these results are consistent with no E-R trend in the case-control analysis. Confirmation of mortality SMRs is not possible via the lung cancer case-control analysis. The 1.3-fold increased lung cancer SMR using the local population as controls may be consistent with the lack of an E-R trend in the case-control study, but is not confirmatory. I interpret these data as indicating a high mortality and lung cancer risk in Stoke-in Trent relative to the UK population. The E-R data based on cumulative respirable silica exposure "imply" that silica probably is *not* a human carcinogen.
e. The cristobalite–lung cancer hypothesis derived from the preliminary results regarding cristobalite from cohorts of the UK pottery (Cherry et al., 1997), diatomaceous earth (Checkoway et al., 1997), and Chinese pottery (McLaughlin et al., 1992) are not confirmed in the revised updates or extended analysis of UK pottery workers (Cherry et al., 1998), after consideration of exposure misclassification and adjustments for smoking in the diatomaceous earth cohort (Gibbs, 1998; Merliss, 1998) and this report, and among Chinese pottery workers after adjustments for PAHs and smoking (Chen et al., 2007).

The excess of lung cancer among workers exposed to diatomaceous can largely be accounted for by exposure misclassification and confounding from smoking (this report). The positive E-R trend among Chinese pottery workers was due to confounding from PAHs. An alternative hypothesis that has not been tested for the UK pottery workers is the possibility of PAH from heating the kilns. Coal was the fuel used in the UK potteries, so it seems plausible coal would be a source of PAHs. Also reducing exposure misclassification via continuous exposure variables rather than categorical reduced risk of lung cancer reduced estimated risk.

Cristobalite exposure is not well established. Analysis for cristobalite was conducted on pottery samples showing 8% cristobalite. Some environmental samples were analyzed for cristobalite, but none were "identified specific to the firing and post-firing process." Cristobalite exposures were most probable in the earlier years when high temperatures conducive to formation of cristobalite continued for several days. Thus a more reliable test of the cristobalite hypothesis may be lost in the destroyed records of the earlier workers.

f. Because work history records were supposed to be destroyed after death, records of 32 of 88 (36%) lung cancer cases were unavailable and could not be included in the case-control study. These would be early deaths and if there were nonrandom removal and destruction of records, it could lead to severe confounding. The authors tried to minimize this possibility in three ways:

   i. The cohort study population was confined to deaths after 1984, which removes possible confounding for the cohort but not the case-control study population.
   ii. In the pneumoconiosis subcohort, results were similar when those with and without destruction of records were included. This would be more convincing if the same analysis had been conducted in the lung cancer case-control study.
   iii. In the case-control study, all extant records were used, so nonrandom removal of records is unlikely

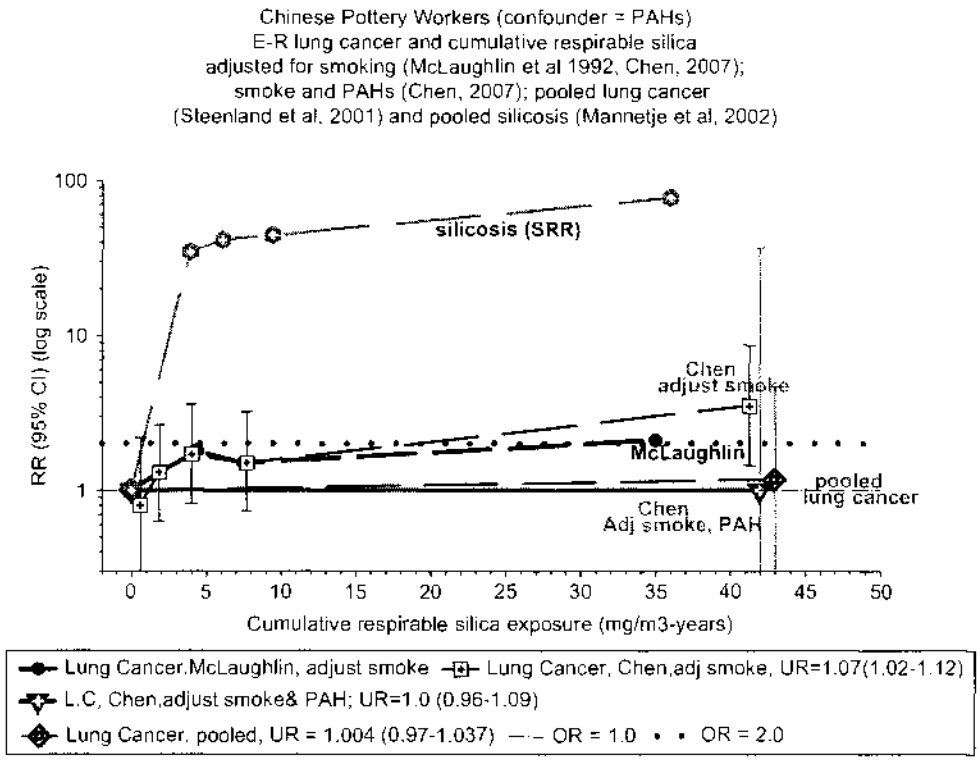

Figure 13. Chinese pottery.

in this analysis. Comparison of all extant death certificates with those whose work histories were destroyed showed pottery work recorded on 52% of the former and 48% on the latter. Also, only 3/32 (9%) excluded lung cancer cases had mention of silicosis on their death certificates. The authors conclude that "this did not suggest important bias in destruction" of records.

However, use of the death certificate is not a strong confirmatory test, as half the cases known to have worked in the pottery had no pottery work recorded on their death certificate.

It is not clear why the small proportion of death certificates with mention of silicosis is suggestive of no important bias. NMRD mortality was raised, but based on radiographs this is unlikely to be due to silicosis. About 6% of the pneumoconiosis subcohort had category ≥1/0 rounded opacities. The prevalence of abnormal radiographs was somewhat higher among those born earlier, started work earlier, and opacities were detected earlier (shorter durations of exposure) than those with normal radiographs. Smoking doubled (OR = 2.28) the risk of small opacities, but firing jobs did not (OR = 0.83). Twelve percent of deaths were diagnosed as NMRD. It is not clear how these facts prove or disprove bias. The question of possible bias from destruction of records remains an unanswered question that might partly explain the increased SMRs for lung cancer.

g. Ranking the importance of exposure metrics is an important question for interpreting results of this study. Cumulative exposure traditionally has been considered the more relevant exposure metric for chronic disease, more so than average exposure or duration of exposure. The association with average exposure appears to be due to a higher proportion of short-term (<5 years) cases than controls.

Clearly there was no association with either cumulative exposure or duration of exposure. This is because a higher proportion of cases had shorter durations of exposure (<5 years), and a lower proportion of cases had long tenure than controls. Half of controls had worked >20 years compared to 38% of cases. Average exposures were 21% higher for those with <20-year duration. Cases and controls had similar proportions working 5–15 years. The higher proportion of cases than controls among those with <5-year tenure indicates that increased risk is among "short-term" workers.

Whether increased risk of "short-term" workers applies to those with 1–5-year tenure as well as <1-year tenure is not well established. But the higher proportion of short-term workers among cases than controls potentially biases results, especially if cases also start out in jobs with higher exposures. Matching on date of hire was ±3 years, which also might explain

in part the higher exposures among short-term cases compared to short-term controls.

h. These limitations and lack of E-R association with cumulative exposure detracts from the silica (cristobalite)–lung cancer hypothesis. The evidence for a causal association is equivocal at best, and needs more evidence to be convincing.

2.2.2.2. Chinese pottery workers (Chen et al., 2007; McLaughlin et al., 1992) (Figure 13) The Chinese pottery E-R study was a case-control study (McLaughlin et al., 1992) nested in a cohort (Chen et al., 1992) comprised of eight pottery factories and workers with ≥1 year's employment in 1972–1974, with follow-up to 1989. The case-control study had 62 male Chinese cases and 238 controls, and after adjustment for age and smoking showed a nonsignificant negative E-R lung cancer trend, with ORs of 2.0, 1.7, and 1.5 for low, medium, and high cumulative total dust. There was a nonsignificant positive E-R trend for PAHs, with ORs of 1.8, 1.5, and 2.1 in these same exposure categories and a correlation of $r = .56$ between silica and PAH. Adjustment for PAHs "did not reduce" but "slightly raised rather than lowered the ORs for exposure to silica." They concluded risk of lung cancer was not significantly increased (McLaughlin et al., 1992).

IARC (1997) concluded this was one of the 10 least confounded studies, leading to their conclusion of sufficient evidence of carcinogenicity. Potential PAH confounding was ignored, and the "least confounded" characterization may be based on the observation that "pottery factories had the least amount of exposure to agents that might confound the association with silica," despite negative E-R trends for arsenic, PAH, and radon among tungsten miners and positive trend for PAH in potteries (McLaughlin et al., 1992).

The pooled analysis (Steenland; Mannetje et al., 2001) showed a nonsignificant positive trend (UR = 1.004 [0.97–1.037]) and cited Chen (Chen et al., 1992) as the data source. PAHs were recognized as potential confounders but no adjustments were made for confounders (Steenland; Mannetje et al., 2001) and thus the pooled analysis appears to bias the E-R trend upward.

Chen et al. extended follow-up to 1994 for seven of the pottery factories in the original cohort (Chen et al., 2007). The update doubled the number of cases from 62 to 120 and controls from 238 to 459. A purpose of the updated/revised study was to improve individual exposure information to better separate effects of silica from those of confounding exposure of PAHs in the pottery factories.

Reduction of confounding in the revised/improved analysis was attempted by

i. complete reconstruction of individual work histories and exact average exposure values for each facility, job, and calendar year instead of seven crude exposure categories;

ii. calculation of respirable silica exposure using a conversion factor between total dust and respirable silica; and

iii. use of conditional logistic regression that allows control of residual confounding via regression (Chen et al., 2007).

Chen et al. showed clear E-R relationships between lung cancer and smoking (OR = 10.9 for 35–180 pack-years); lung cancer and PAHs (OR = 1.3 [1.11–1.54] per 100 μg/m³-year); and lung cancer and respirable silica adjusted for smoking but not adjusted for PAHs (UR = 1.1 [1.02–1.12] and OR = 3.5 [1.45–8.66] for the 5th quintile of 10·72 mg/m³-years). After adjustments for *both* smoking and PAHs, the lung cancer and cumulative respirable silica E-R trend disappeared, with ORs <1.0 in all exposure categories, an OR of 0.9 (0.19–4.32) in the high-exposure group, and UR = 1.00 (0.96–1.09) (Figure 13) (Chen et al., 2007).

IARC (2009) noted results from the original study were confirmed by the follow-up (Chen et al., 2007) and that adjustment for PAHs reduced the E-R trend to the null. IARC (2009) noted that PAHs were highest in this group of pottery workers compared to other Chinese industrial groups (mean, 199 μg/m³-years compared to 26.7 and 24 μg/m³-years among iron/copper and tungsten, respectively) (Chen et al., 2007). The correlation of 0.56 between silica and PAH exposure was noted by IARC, implying it may be too high to assess individual effects. The Working Group also noted that in the original analysis "adjusting for PAHs slightly raised rather than reduced the silica exposure RRs," the opposite of the revised analysis (Chen et al., 2007). Verbal comments of Working Group Members suggested this was a weakness of the updated study, and suggestive that the results of McLaughlin et al. were favored over the negative results from the updated analysis of Chen et al.

Comments on China pottery (Chen et al., 2007)

A significant effort was made to collect and analyze the exposure data collected since the 1950s using Chinese methods and converting them to data compatible with those in the literature. Side-by-side sampling and use of historical bulk samples were used to develop conversion factors for total to respirable silica dust were specific to each facility (Zhuang et al., 2001). Because of the extensive historical sample results, the exposure database may be among the best for both silica and confounders (e.g., radon, PAHs, arsenic).

The 2009 IARC Working Group suggested in their summary that the role of silica "must be regarded as unclear" because of confounders in studies of tin miners, Fe/Cu miners, and pottery workers. This is not true for pottery worker based on results indicating no association after careful adjustments for smoking and PAHs using both categorical and continuous analyses where the UR = 1.0 (0.96–1.09) (Figure 13). It is illogical why the result is unclear to IARC, as two different statistical analyses with adjustments for known confounders

and improved exposure estimates clearly showed no association. If PAH and silica exposures were too highly correlated to separate effects, the statistical models would produce inconsistent and unreliable results, as happened in the tin miner analysis. Since this did not happen despite a correlation of at least .56, the burden of proof rests with IARC (2009) to explain why these updated results are unclear.

IARC (2009) also noted the McLaughlin adjustments for PAHs raised lung cancer ORs, whereas the Chen et al. adjustments lowered them. The adjusted results from McLaughlin et al. were not provided, but they appear to be incorrect, as adjusted ORs are in the wrong direction. PAHs are a positive confounder (increases risk of lung cancer and higher exposure among cases than controls), so adjustment for PAH should reduce ORs as seen in Chen et al. (2007).

Chen et al. concluded that this study provides no evidence of a causal relationship between silica and lung cancer among Chinese pottery workers after adjustments for confounding factors (smoking, PAHs). The pooled analysis showed the same E-R trend and IARC (2009) notes the lack of an E-R trend. Note in Figure 13 that adjustment for confounding from PAH changes a significant association to no association. It is not clear why the pooled analysis E-R in the absence of smoking and PAH adjustments was similar to adjusted lung cancer risks (Chen et al., 2007). These data indicate no increased lung cancer risk associated with silica exposure, and the results detract from a causal association of lung cancer and respirable silica.

2.2.2.3. German Pottery Workers (Ulm et al., 1999) A case-control study in the German pottery industry was conducted with 114 cases and 564 controls (Ulm et al., 1999). (Stone and quarry workers and pooled E-R analyses were part of this study and are discussed at appropriate places.) Cases diagnosed in 1980–1994 were selected from insurance institutes and hospital files; compensated silicotics were excluded. Controls were selected from a pottery industry file of preventive check-ups to prevent silicosis and frequency matched on sex, year of birth, and smoking. Complete work histories were ascertained and exposure levels were estimated based on dust measurements or expert opinion of industrial hygienists knowledgeable about the specific workplace situation. Statistical analysis for individual industries was a logistic regression where exposure was divided into low and high levels, with midpoints of 15 mg/m^3 for average and peak exposures, and 2.88 mg/m^3-years for cumulative silica exposure. ORs were adjusted for onset and duration of exposure, latency, year of first exposure, and other potentially risky exposures.

There were no associations between three different exposure metrics and lung cancer. The high exposed groups had ORs of 1.03 (0.49–2.16) for average exposure, 1.05 (0.59–1.86) for cumulative exposure, and 0.75 (0.46–1.24) for peak exposure.

Ulm et al. concluded that "the risk of an association between crystalline silica and lung cancer in the absence of silicosis seems to be very small."

This study was not included in the pooled analysis (Steenland; Mannetje et al., 2001). IARC (2009) appears to consider this a negative study, noting limitations of possible restriction of the exposure range with lack of low exposures and adjusting for duration of exposure and cumulative exposure that might have led to low power and reducing ability to detect a silica effect.

Comments on Ulm et al. (1999)

The unit risks estimated from the dichotomous E-R analysis does not correspond to the categorical result for both industries. For example, the OR is 1.04 in the highest exposure category for all industries (>4.68 with an estimated average of about 16), but in the dichotomous analysis the OR at 16 mg/m^3-years is 2.18. So the categorical results for both industries are used only for illustrative purposes in the figures. Only results from the entire cohort are used as a basis for evaluating causality.

The authors and IARC (2009) noted that exclusion of silicotics may have restricted the exposure range. The authors commented that exposure distribution was not the same as the total workforce. Nevertheless, high exposures occurred. Cases in the 90th percentile had higher average exposures (0.32 mg/m^3) than controls (0.19 mg/m^3). Cumulative exposures of cases and controls were similar with medians of 2.97 and 2.88 mg/m^3-years, respectively. Controls had slightly higher values because they had 3 more years tenure than cases (30 vs. 33 years), but cases had higher 90th percentile but not maximum values; 11.8 versus 7.3 and 25.92 versus 28.08 mg/m^3-years, respectively. Cumulative exposures appear to be comparable to those among UK pottery workers (Cherry et al., 1998).

IARC (2009) noted that exclusion of silicotics produced a "low study power." The number of excluded silicotics was not provided, so the loss in power is not known. However, power is not "low" compared to other pottery cohorts, as there were 114 cases compared to 120 cases in the largest pottery study (Chen et al., 2007) and 52 cases in the UK pottery study (Cherry et al., 1998). These numbers indicate a lack of study power is more of a concern for the UK pottery study than the German study.

IARC (2009) also noted that adjustments were made for "duration of exposure along with cumulative exposure, perhaps reducing the ability to detect an effect of silica exposure." Tenure was adjusted for in all measures of exposure. It seems unlikely to have a large effect, as median, minimum, and maximum durations of exposure were nearly the same for cases and controls (30 vs. 33, 3 vs. 2, and 54 vs. 53, respectively). Nevertheless, adjustment for duration should not have been done and it detracts from the merit of the study.

Another limitation of this study is matching on smoking rather than adjusting for smoking in the analysis. Matching produced a similar small percent of nonsmokers (about 3%). But controls had fewer current smokers (43% vs. 53%), fewer heavy smokers (66% vs. 82%), more ex-smokers (53% vs. 40%), and longer time since quitting smoking (14 vs. 4 years). These differences in smoking bias the ORs high, and may counteract to some extent the downward bias from matching on tenure.

Analysis of E-R trends of pottery and stone/quarry industries separately is of limited value. Exposure was divided dichotomously, high and low, which is inadequate for a reliable evaluation of E-R. Analysis of both pottery and stone/quarry industries by quartiles provided a more informative E-R trend. For the combined E-R analysis the cohort was divided into 4 groups of equal size with a nonsignificant trend ($p = 0.69$) and ORs of 1.0, 0.95 (0.48–1.53), 0.92 (0.44–1.61), and 1.04 (0.53–1.89) from low to high exposures.

2.2.2.4. German Porcelain Workers (Mundt et al, 2011) The objectives of this study were to quantify E-R associations of respirable silica with lung cancer and silicosis mortality, assess whether high silica exposure in the absence of silicosis was carcinogenic, and provide additional data to the controversy regarding carcinogenicity of silica and variable occupational limits.

This is a cohort of 17,644 employees of over 100 plants of the West German porcelain and fine ceramics industry who participated in the medical surveillance program 1985-87 with over 6 months tenure and adequate work history information. Vital status follow-up was through 2005 with 6% lost to follow-up and 9% mortality. There were 74 lung cancer cases among men, 20 among women with SMRs of 0.71 (0.56-0.89) and 0.72 (0.44-1.12) respectively. There were 5 silicosis deaths among men with an SMR of 7.20 (2.32-16.8) (Birk, Mundt et al. 2009; Mundt, Birk et al. 2011).

There were over 8000 exposure samples collected from 1954 to end of follow-up. Side-by-side sampling was employed to convert particle counts to gravimetric measures (Birk, Guldner et al. 2010). Five exposure categories were selected at 3.0 mg/m3-year intervals. Cox proportional hazard models were used for E-R analysis to derive hazard ratios adjusted for sex, smoking, age at hire and tenure. Lung cancer associations were stratified by gender, but full cohort analysis was presented for silicosis.

There were strong associations of silica exposure and radiographic silicosis (n=40) with increased risks occurring above cumulative exposures of 4 mg/m3-yrs and average exposures of 0.1 mg/m3. There were no associations of lung cancer with cumulative and average silica exposure among men or women. With only 20 lung cancer cases, confidence intervals were wide for women and there were only six cases in the highest cumulative exposure category. Nearly half of the 74 cases among men were below 3 mg/m3-years (45), and 25% (16) were in the highest exposure category (Figure 12).

Comments on (Mundt, Birk et al. 2011)

This is one of the largest cohorts of porcelain workers (including potteries or ceramics)or any other type of silica, although not the largest number of lung cancer deaths. About half of the over 17,000 workers are women, although only 21% of the lung cancer cases were women. There is a large significantly increased mortality of silicosis and a strong association with radiographic silicosis that validates the exposure assessments (Figure 12).

A potential weakness is the lack of possible employment in silica-exposed jobs outside the porcelain industry. If so,

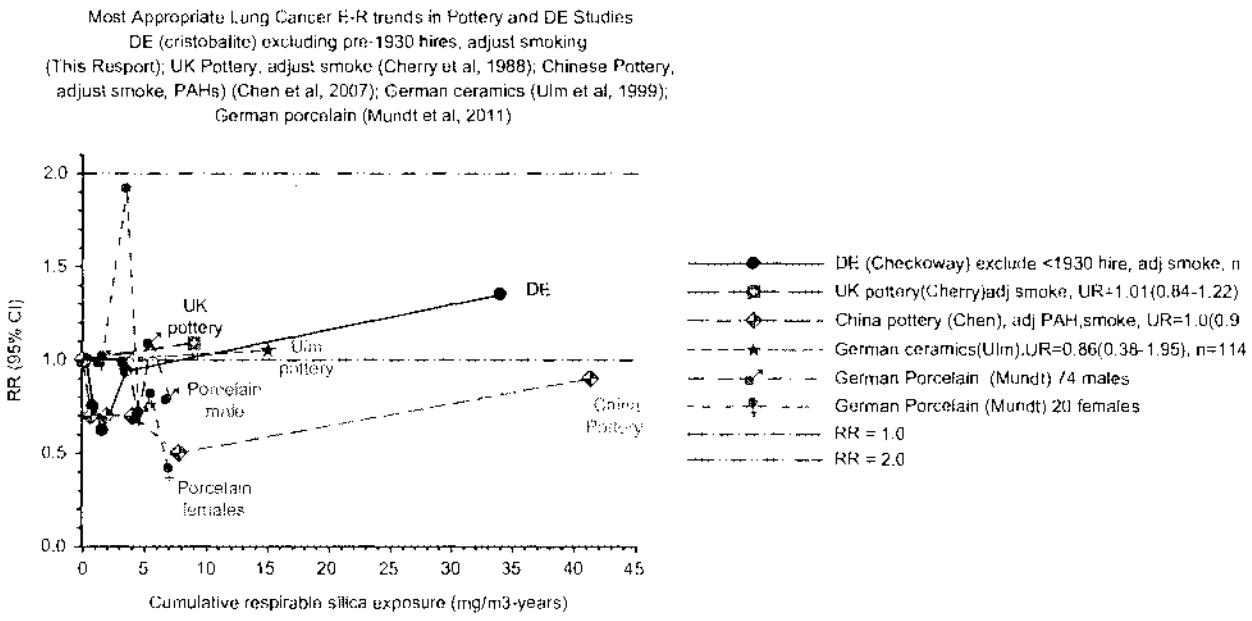

Figure 14. Summary: Potteries and cristobalite (DE).

silica exposure might be under-estimated. But since there was no association of silica exposure and lung cancer, the results further strengthen the conclusion of no etiological association if there was extra-porcelain silica exposure.

A major strength of this study is the extent and quality of the exposure data, including conversion of early particle sample results by employing side-by-side comparisons with current gravimetric results. These sample data covered all 31 years of exposure history from the initiation of the study. Imputation of exposure was confined to 1928-1953, so imputed exposures was confined to about 8 cases of silicosis (20%) and 10 cases if lung cancer (11%). Thus exposure misclassification in these early years "is expected to be modest."

Exposures tended to be low, below the West German standard for silica, and cumulative exposures below 10 mg/m3-years.

2.2.3.Summary of cristobalite (DE), pottery and porcelain worker cohorts (Checkoway et al., 1997; Chen et al., 2007; Cherry et al., 1998; Ulm et al., 1999; Mundt et al., 2011) (Figure 14)

The lack of associations between lung cancer and cumulative silica exposure, average exposure, and peak exposure detract from the silica–lung cancer hypothesis among pottery workers (Figure 14).

IARC (1997) considered potteries among the least confounded studies. Revised analysis of the Chinese pottery study revealed significant confounding exposures to PAHs, which were not adjusted for in the initial analysis. E-R disappeared when PAHs were adjusted for in the updated analysis. Extended analysis of the UK pottery study resulted in no apparent E-R associations with cumulative exposure or with heated quartz thought to be cristobalite.

The cohort exposed to DE is the primary study where exposure is cristobalite produced by calcining diatomaceous earth. After adjusting for smoking and excluding pre-1930 hires because of potential exposure to asbestos and unknown silica exposure, the SMR in the highest-exposure group was reduced to 1.31 and was no longer significant. Since SMRs in all the other exposure categories are <1, the E-R trend disappears. This study was a major contributor to the IARC (1997) conclusion of sufficient evidence of silica carcinogenicity. Removal of bias and confounding produces no significant association and an E-R trend similar to that of US gold miners, where there is consensus that no association exists.

A study of nonsilicotic German ceramic workers and stone workers had only two exposure categories. Both trends were nonsignificant and are shown separately in the discussion of industry groups (Figure 14). But in the final analysis this study is counted as one and shows no E-R association based on the entire cohort.

These results represent consistent patterns that detract from a silica–lung cancer hypothesis:

- Strength of association is consistently weak (RRs <1.5 in DE and potteries) except for 2-fold nonsignificant excess for German ceramics.
- There is a consistent lack of biological gradients, with a flat E-R trend in the largest study with the highest exposure (Chinese cohort) after adjustment for confounding from smoking and PAHs. There was no association in the UK pottery, with most exposures <10 mg/m^3-years. There was a 2-fold increased OR at about 15 mg/m^3-years but the lower confidence interval was nearly zero, and the unit risk was nonsignificant at 1.05 (0.59–1.86).

The summary results for cristobalite and potteries are homogeneous and suggest no associations after adjustments for bias and confounding. Without adjustment for bias both the Chinese and DE cohorts showed positive and significant E-R trends. None of the studies in this industrial category support the silica–lung cancer hypothesis.

2.3.Quarries and stone cutters (Koskela et al., 1994; Steenland; Mannetje et al., 2001; Ulm et al., 1999; Vacek et al., 2010)

This industrial group included several least confounded cohorts, including Danish stone cutters (Guenel et al., 1989), American crushed stone workers (Costello et al., 1995), and German slate quarry workers (Mehnert et al., 1990), for which no E-R analyses were conducted. There are three cohorts with E-R analyses. There are several analyses of Vermont granite shed workers with either or both E-R and intervention design analyses (Attfield et al., 2004; Costello et al., 1988; Davis et al., 1983; Graham et al., 2004; Vacek et al., 2010). The Finnish granite worker cohort has both qualitative and quantitative estimates of exposure. The first E-R analysis (Koskela et al., 1994) used qualitative exposure estimates, whereas quantitative E-R analysis was published as part of the pooled analysis (Steenland; Mannetje et al., 2001). Finally the German cohort contained both ceramic workers and stone workers (Ulm et al., 1999).

2.3.1.Vermont granite workers (Attfield et al., 2004; Graham et al., 2004; Vacek et al., 2010; Vacek et al., 2009) (Figures 15, 16)

The two studies available to IARC (1997) were the initial intervention analysis (Costello et al., 1988) and a proportionate mortality E-R study (Davis et al., 1983). The original cohort (Costello et al., 1988) was updated to 1996, with a similar intervention design comparing mortality of pre-1940 and post-1940 hires (before and after installation of dust controls) (Graham et al., 2004). The updated cohort and exposure estimates (Davis et al., 1983) led to an E-R study used in the pooled analysis (Steenland; Mannetje et al., 2001) and a separate publication (Attfield et al., 2004). Both were available to IARC (2009). A third update of this cohort has been just published and using additional sources to increase complete enumeration of the entire cohort and improved estimates of exposure with both an intervention and E-R analysis (Vacek et al., 2009, 2010).

2.3.1.1. Intervention study of Vermont granite workers (Costello et al., 1988; Graham et al., 2004; Vacek et al.,

2009) This cohort of Vermont granite workers was one of the least confounded studies, as there are no apparent occupational confounders. The cohort consisted of 5414 workers employed in 1950–1982 with at least one chest X-ray (Costello et al., 1988). Shed workers had significantly increased lung cancer and silicosis SMRs of 1.27 (1.03–1.55) and 7.73 (5.47–10.6), respectively. Less emphasis was placed on quarry workers as silicosis mortality increased only 2-fold (SMR = 1.95) and lung cancer was not elevated (SMR = 0.82).

From 1938 to 1940 a program of dust control was instituted that reduced dust levels from an average of 40 mppcf to <10 mppcf by 1955. This reduction essentially eliminated silicosis and TB mortality. Lung cancer was not eliminated among long-term granite shed workers. Pre-1940 hires with 40+-year latency and 30+-year tenure had a lung cancer SMR of 1.81 (1.33–2.41). For post-1940 hires with 25+-year latency and 10+-year tenure, the lung cancer SMR was 1.73 (1.01–2.77). When latency and tenure were comparable, the post-1940 hires with less silica exposure have the higher lung cancer risk. Pre-1940 shed workers with 25–39-year latency and 10–25-year exposure had a lung cancer SMR = 1.27, whereas post-1940 hires with the same latency and tenure had an SMR = 1.91, indicating lung cancer risk did not appear to be related to silica exposure (Costello et al., 1988).

IARC (1997) considered this a positive study because of a "nearly two-fold mortality elevation among long-term granite shed workers" (IARC, 1997). They also commented that the lack of dust exposure data and E-R analysis was a limitation. Note the inconsistency between concluding this is a positive study and the IARC guideline (WHO, 2006) indicating there is a negative E-R association when risk stays the same when exposure is decreased.

Follow-up of this 1988 cohort was extended to 1994 (Graham et al., 2004). The number of lung cancer cases was increased from 118 to 211, and lung cancer SMRs were similar (1.16 vs. 1.18) in the two reports. Silicosis deaths increased from 41 to 53, whereas SMRs for silicosis increased from 6.36 in 1988 to 20.6 in the 2004 study. Comparing lung cancer SMRS of pre- and post-1940 hires with >15-year latency and short, medium, and long tenures shows both pre- and post-1940 hires had increasing lung cancer mortality associated with increasing tenure. But the lung cancer mortality does not appear to be related to silica exposure as post-1940 hires are much less exposed to silica than pre-1940 hires. The reduced silica exposure in post-1940 hires is demonstrated by 7-fold differences in silicosis mortality (SMR = 27.4 [20–36]) among 50 pre-1940 hires and 3.98 (0.82–11.6) among 3 post-1940 hires. The three post-1940 silicosis deaths were not associated with Vermont granite exposures. Two had worked previously in granite elsewhere and had only 3- and 7-year tenure in Vermont granite. The third case appears to be a misdiagnosis, as he had seven normal chest X-rays up to 1 year before death. There was a 5-fold difference in prevalence of X-ray silicosis (27% vs. 5.7%). (The differences between pre- and post-1940 silicotics may to some extent be due to shorter latencies and tenure among post-1940 hires, as well as lower exposures.)

Vacek et al. updated by 10 years the 1994 cohort of Graham et al. to 2004, searched all extant records to enumerate all workers, and increased the cohort size to 7688 workers (Vacek et al., 2009). The mortality analysis showed elevated SMRs of 1.08 (1.05–1.12) for 3831 deaths from all causes, 1.37 (1.23–1.52) for 359 lung cancer cases, 1.38 (1.25–1.53) for 377 NMRD cases, and 59.1 (44.5–77) for 55 silicosis cases. The intervention analysis by date of hire (pre- and post-1940) was similar to Graham et al. (2004) but without adjustment for latency and duration of employment. It showed no association with all cause mortality. Lung cancer risk was elevated slightly more in post-1940 hires (SMR = 1.44 [1.27–1.63]) compared to pre-1940 hires (SMR = 1.23 [1.01–1.49]), indicating no association between silica exposure and lung cancer risk. Silicosis risks were reversed from SMR of 82 among pre-1940 hires to 18 for post-1940 hires, indicating a strong association between silica exposure and silicosis. Silicosis risk from pre-1940 Vermont granite exposures may have been even greater, as the six silicosis deaths hired after 1940 appear largely unrelated to Vermont granite exposure. Three cases worked <10 years after 1940. One case had worked 40 years as a stone cutter in Canada and one had no information on previous employment. The two remaining cases began work in Vermont granite industry at the ages of 43 and 52 years.

	Pre-1940	Post-1940
All causes	1.07 (1.02–1.12)	1.10 (1.05–1.14)
Lung cancer	1.23 (1.01–1.49)	1.44 (1.27–1.63)
Silicosis	82.1 (60.7–108.5)	18.0 (6.61–39.2)

Comments on intervention studies (Graham et al., 2004; Vacek et al., 2009)

The importance of intervention study design should not be underestimated, although there are few such studies. There are a number of differences between the first updates of the Vermont granite worker cohort (Attfield, 2004; Graham et al., 2004) and the second follow-up studies (Vacek et al., 2009, 2010) that demonstrate significant limitations in the first group and strengths in the second group for both the intervention and E-R analyses. Finally, the intervention study demonstrates the success of the dust controls implemented in 1938–1940 in essentially eliminating silicosis and indicating silicosis is not associated with lung cancer and the increased risk of lung cancer is most likely attributable to cigarette smoking.

This intervention study design compared mortality before and after installation of dust controls. It is the only intervention study design among studies of silica and lung cancer. An intervention study design is the most

powerful design for determining causal associations or effectiveness of dust controls. If silica exposure causes an increased risk of lung cancer, one expects lung cancer mortality to decrease among post-1940 hires since exposure decreased. Comparison of pre- and post-1940 roughly matched on tenure and latency shows that lung cancer mortality did *not* decline in post-1940 hires. Lung cancer mortality increased with increased tenure, but also increased with decreased exposure in both pre- and post-1940 hires. Since all cases with known histories were smokers, it is plausible that tenure is an exposure surrogate for pack-years or years smoked.

This intervention design has comparable weight to the subsequent E-R analyses (Attfield et al., 2004; Vacek et al., 2010). Intervention studies cannot estimate threshold levels if they exist, but it can say that pre-1940 exposures with high silica exposures pose no greater risk of lung cancer than post-1940 exposures with lower silica exposures. It also shows that pre-1940 exposures must have been high based on highly increased risk of silicosis as well as environmental measurements. Post-1940 exposures did not pose an increased risk of silicosis or TB. Elimination of silica-related diseases of silicosis and TB indicates dust controls were effective in decreasing dust levels. No decrease in risk of lung cancer after reduction in silica levels indicates lung cancer is not related to silica exposure, and the absence of silicosis mortality validates the post-1940 reduction in silica exposure. The results of both intervention studies (Graham et al., 2004; Vacek et al., 2010) provide strong evidence against the silica-lung cancer hypothesis.

A limitation is that comparisons before and after intervention should be between groups with equal latency and years exposed. For a chronic disease such as lung cancer both are fairly long. There were proportionally more pre-1940 hires among the cases with 30+-year tenure, whereas post-hire numbers indicate proportionally more cases with shorter tenures. This limitation does not invalidate the conclusion of no association, as the elevated SMRs are significant in both groups with 30+-year tenure.

There is no individual-level E-R analysis. The comparisons by date of hire are similar to group-level ecological comparisons, so there may be some doubt whether lung cancer cases actually had more or less silica exposure. On the other hand, the installation of dust control measures in 1940 occurred over a relatively short time period and produced rather dramatic reductions in dust levels (80–90%) and silicosis, but without apparent reductions in lung cancer risk. The reductions in dust appear to be applicable for all jobs in the sheds. The quantitative estimates of exposure are imprecise, but the large reductions override the imprecision with regard to determining causality.

There are a number of key differences between the intervention study used by IARC (Graham et al., 2004)

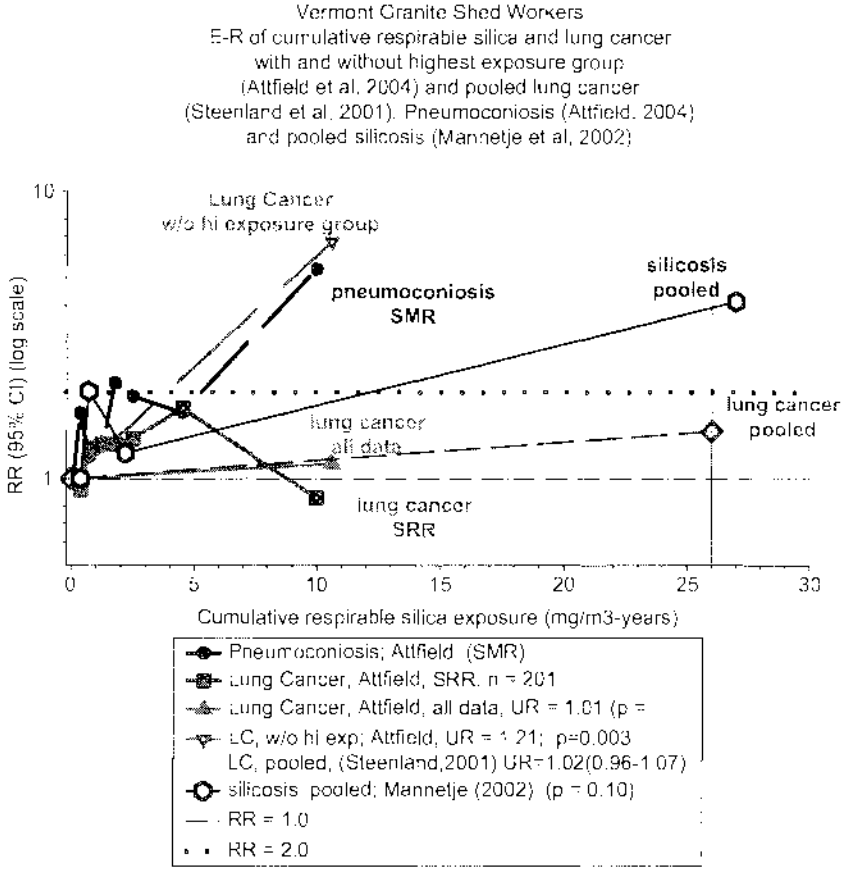

Figure 15. Vermont granite shed (Attfield and Costello, 2005; pooled analysis).

and the updated intervention study (Vacek et al., 2009, 2010). These include the following:

i. 1700 more workers and 10 more years of follow-up (2004 vs. 1994)

ii. More men employed over a wider range of years (1947–1999 vs. 1950–1982)

iii. Inclusion of men who did not participate in Vermont radiographic surveillance program, or 18.3% of all men employed that were not included in the previous updated cohort (Attfield et al., 2004; Graham, 2004)

iv. Corrections in the data were made to exclude 22 workers entered twice, exclude 27 workers employed prior to 1947, include 162 workers who had been considered alive after 1994 but had actually died prior to 1994, and corrections in names, birth dates, social security numbers (SSNs), cause of death (COD), which may have contributed to incomplete mortality ascertainment.

v. Reconstruct work histories so they were complete by adding to the radiographic surveillance program data information from pension records on employment with all other Vermont granite work and work after World War II.

vi. Increase data on exposures by accessing all individual samples (not relying on group data from Davis et al. (Davis et al., 1983), including information from all surveys and reports and consulting with individuals familiar with past and current IH practices who assisted in classifying jobs into group categories and estimating exposures.

2.3.1.2. Exposure-response studies of Vermont granite workers (Attfield et al., 2004; Vacek et al., 2010) Attfield et al. (2004)

The first update of the Vermont granite cohort was also used to assess E-R of silica with lung cancer, pneumoconiosis, TB, kidney cancer, and all causes (Attfield et al., 2004). Dust exposures were based on six environmental surveys conducted in 1924–1977. Cumulative exposure was derived from the job-time exposure matrix used in a proportionate mortality rate (PMR) analysis (Davis et al., 1983) and three time periods were considered: pre-dust control (<1940), intermediate (1940–1950), and post-dust control (>1950). Exposures in the intermediate period were considered midway between pre-1940 and post-1950. RRs were both SMRs and standardized relative risks (SRRs) with 15-year latency or 15-year lag. Since smoking information was incomplete there were no adjustments for smoking.

Attfield et al. present two ways of interpreting the lung cancer E-R. The first interpretation uses all the data and shows the sixth and seventh exposure categories had significantly elevated SMRs of 1.48 (0.97–2.16) in the 2–3 mg/m^3-years exposure category and 1.70 (1.14–2.49) in the 3–6 mg/m^3-years category. In the eighth and highest exposure category the SMR was reduced to 1.16 (0.78–1.66). In the SRR analysis the eighth and highest-exposure group show an SRR = 1.0, with significant elevations in the 6th and 7th exposure categories. The analysis using all the data show nonsignificant trends and no clear E-R relationships. The second analysis excluding high-exposure data shows a steep slope and a clear and strong E-R relationship. The E-R trend becomes highly signifi-

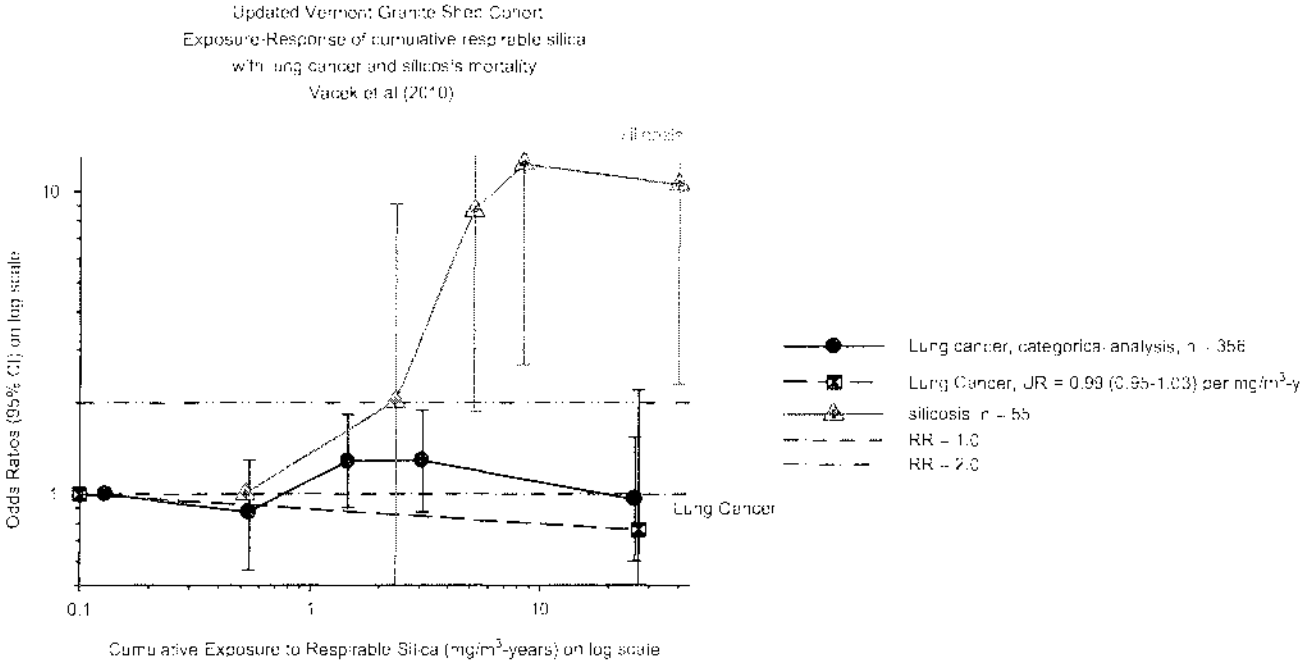

Figure 16. Updated Vermont granite shed cohort (Vacek et al, 2010).

cant, and according to the authors almost monotonic in the SRR analysis (Figure 15).

Attfield et al. (2004) favored the second analysis, which excluded the highest exposure category. From this analysis they concluded these results "indicate the presence of clear exposure-response for lung cancer and silica exposure" in the absence of major occupational confounding. This conclusion is strengthened by the clear positive monotonic E-R trend for pneumoconiosis, but without a reduction in the SMR for the last exposure category. This E-R trend for silica-related diseases such as TB, silicosis, and pneumoconiosis validate exposure estimates. In this case they validate the exposure estimates in all exposure categories, including the highest exposure category.

Follow-up in the pooled analysis was not extended beyond the original termination date of 1982, so there were only 124 lung cancer deaths compared to 201 in Attfield et al, (2004). The UR for lung cancer was 1.015 (0.96–1.07) (Steenland; Mannetje et al., 2001), which is similar to the E-R using all the data and longer follow-up (Attfield et al., 2004). There was also a strong but non-significant ($p = .10$) E-R trend with silicosis in the pooled analysis (Mannetje et al., 2002) (Figure 15).

Vacek et al. (2010)

Vacek et al. (2010) extended the follow-up to 2004 and increased the cohort size 1.4-fold so there were 356 lung cancer cases. In the E-R analyses there is a strong, positive, and highly significant trend for silicosis risk to increase up to about 10 mg/m^3-years, when it begins to level off in the high exposure category (Vacek et al., 2009). There are slightly negative E-R trends for lung cancer in both the categorical and continuous regressions analyses (Vacek et al., 2010) (Figure 16).

The results demonstrate the "absence of an association between silica exposure and lung cancer mortality [which] indicates that the increased mortality from this disease among cohort members is most likely attributable to cigarette smoking or other exposures unrelated to employment in the Vermont granite industry" (Vacek et al., 2009).

Smoking histories were unavailable for most cohort members. Smoking prevalence was 50% among 1457 cohort members interviewed in 1979–1985 in a pulmonary function study (Graham et al., 1994). Smoking prevalence among white US males in 1980 was estimated at 37% (Vacek et al., 2009).

The observation that smoking is correlated with tenure is suggestive that smoking is probably a confounder. The longer one works, the longer one smokes. Smoking-related lung cancer has a long latency, and risk of lung cancer continues to rise as latency increases above 40 years.

Quarry workers showed no excess lung cancer, despite high exposure to silica as shown by excess silicosis and TB (Costello et al., 1988; Graham et al., 2004). This supports the lack of quartz-related lung cancer shown among workers in the granite sheds.

	Lung cancer SMRs by birth year	
Years worked	Birth year pre-1920	Birth year post-1920
<1940	0.99 (0.96–1.02)	0.83 (0.41–1.71)
1940–1999	1.00 (0.98–1.01)	1.01 (1.00–1.03)

The latest intervention study (Vacek et al., 2009) confirms the results from the previous analysis (Graham et al., 2004) where lung cancer risk stays the same (or slightly increases) in post 1940 hires, whereas quartz exposure and silicosis risk decrease markedly.

Multivariate regressions showed no associations for E-R trends pre- and post-1940 (UR = 0.99 [0.96–1.01] and 1.01 [0.995–1.02]), respectively. When stratified by birth before and after 1920 to avoid possible competing risks from silicosis and NMRD, there still were no associations between silica exposure and lung cancer.

Another purpose of this analysis was to examine whether silicosis and TB may have been competing risks biasing lung cancer risk at high exposures. This was an issue in the previous E-R study (Attfield et al., 2004) where it was hypothesized that if age at death was lower for silicosis and TB, then workers with high exposures could die from silicosis and TB before they had the opportunity to develop lung cancer. All TB deaths and all but three silicosis deaths occurred among workers born before 1920. If they are competing risks, E-R trends would be expected to decrease among those born after 1920. The data suggest no competing risk from silicosis and TB, as E-R trends are similar for all time periods except for the lowest coefficient during high-exposure years for those born after 1920. It would have been helpful if ages of death for silicosis and TB had also been provided as they were for lung cancer and NMRD.

Vacek et al. suggest NMRD might be a competing cause of death in both time periods. This is of less concern because lung cancer death usually occurred before NMRD with average ages at death of 67.3 and 74.0 years, respectively.

The intervention studies are consistent in showing no associations of lung cancer and silica exposure. The updated study appears to refute the hypotheses that lung cancer risk is reduced at high exposures because of competing risks of death (i.e., silica, TB, NMRD).

Comments on E-R studies (Attfield et al., 2004; Vacek et al., 2010)

Comments will be divided into sections with a separate discussion for each analysis. The pooled analysis is included in the discussion of Attfield et al. (2004).

Comments on Attfield et al. (2004)

Attfield and Costello give four reasons supporting exclusion of the highest-exposure group and suggested smoking is not a confounder in the E-R analysis nor that smoking is a confounder causing higher lung cancer mortality in post-1940 hires (Attfield, 2004; Attfield et al., 2004).

Excluding highest-exposure group from E-R analysis. A major issue in this study is whether the highest exposure category should be dropped from the analysis. The authors clearly favor this approach for several reasons.

i. Excessive influence of high-exposure group

The high-exposure group was said to be "so heavily influential that it dominates the model fitting. When all data are included, the model using all of the data implies lack of exposure-response. This is clearly contradictory to the findings for the SRRs, which clearly indicate almost monotonically and statistically significant increasing risks of lung cancer with rising silica exposure up until that last group. Hence, we feel that the model fitted to all of the data is not truly representative of the underlying pattern in the results." A downturn at the highest-exposure group is "inconsistent" with a cause-effect relationship.

Comment on excessive influence of highest exposure. A purpose of this study is to test the silica lung cancer hypothesis, not fit the data to support a hypothesis. The idea that this downturn is "inconsistent with a causal association" appears to be an argument from the conclusion, which is wrong. The correct approach is to argue from the data, which are suggestive of a pattern of a lack of an E-R trend.

Results from the intervention studies (Costello et al., 1988; Graham et al., 2004; Vacek et al., 2010) of the Vermont granite cohort clearly indicate no association of lung cancer and silica exposure. The pooled analysis and the updated E-R analysis indicate no association (Costello et al., 1988; Graham et al., 2004; Steenland; Mannetje et al., 2001; Vacek et al., 2009). This evidence suggests the "underlying pattern" of the evidence does not support a causal association between silica exposure and lung cancer.

To be consistent regarding which data to retain requires dropping the highest-exposure group in all E-R analyses such as for kidney cancer, TB, pneumoconiosis, and silicosis where E-R analyses have been conducted. If done for pneumoconiosis, TB, and diseases of the respiratory system appear to become nonsignificant, whereas the lack of association with kidney cancer appears to become positive and significant (Attfield et al., 2004). For silicosis the strong association would largely disappear, as there is a clear upward spike in risk for the highest-exposure group (Figure 15) (Mannetje et al., 2002).

Excluding the highest-exposure group reduces the exposure range. In other studies with categorical analysis excluding the highest exposures change positive associations to no association. These include the DE cohort (Figure 11), the tin miner cohort (Figure 5), South African gold miners (Hnizdo et al., 1997) (Figure 3), and US industrial sand workers (Steenland and Sanderson, 2001) (see Figure 19).

ii. Weak exposure data in high-exposure group

The data in the highest-exposure group were "weakest" because exposure estimates are poorest; and because cohort selection bias, competing risks, and misdiagnosis are likely. One plausible reason for weakness is that since work history data are from cross-sectional surveys, they are truncated at the last survey. Therefore cumulative exposure will be underestimated because exposure after the last survey could not be included.

Comment on weak exposure data. The data and some of the authors' other comments discredit these arguments as implausible. If poor exposure estimates were the cause of the drop-off in lung cancer mortality at the highest exposure levels, one would expect a drop-off in silicosis or pneumoconiosis mortality (and perhaps TB) mortality as well. This did not occur for pneumoconiosis as shown in Figure 15.

The authors commented that "exposures employed in this study are superior in quality to those used in most other occupational exposure-response studies." Industrial hygiene measures were collected in 1924–1977, which included times when exposures were highest. Interpolations of exposure estimates from 1940 to 1950 only were necessary, suggesting this might be a period of greatest weakness of exposure estimates. The strong E-R trends with silicosis and TB "validate the derived cumulative exposure estimates." The supposition that exposure misclassification occurs only at the highest exposure levels is not supported by these facts and the authors validation of the generally high quality of exposure estimates. No documentary evidence is put forward supporting the claim that poor exposure estimates produced decreased lung cancer mortality but not decreased silicosis mortality.

It is not clear that truncation of exposure history after the last survey is a cause of the reduction of risk at the highest exposures. This might be analogous to a lag. There were small reductions of silicosis and lung cancer mortality in the E-R analyses where there was no truncation of work histories (Figure 16) (Vacek et al., 2010), and a sharp increase in pneumoconiosis at the highest exposure with truncated histories (Figure 15).

iii. Healthy worker effect (HWE) and competing risks caused reduced mortality in high-exposure group (Attfield et al., 2004)

Initially they thought highest exposed workers might have had high but short acute exposures producing acute silicosis and premature mortality, and thereby not living long enough to get lung cancer. They rejected this reason because the average age of death among high-exposed workers was similar to those in lower-exposure groups. Because they had entered the cohort with substantial exposures, they were a "highly selected healthy worker group." When TB and silicosis were main health concerns deaths from these causes may have obscured lung cancer as a cause of death.

Comment on HWE and competing risks. The supposition of a healthy worker effect (HWE) and competing risks does not seem adequate to explain the "puzzling" reduction in lung cancer mortality in the highest-exposure group. The SMR for all causes of death was 1.01 (0.97–1.05) overall and 1.22 (1.16–1.28) among pre-1940 hires (Graham et al., 2004). TB and silicosis

SMRs were quite high (17.9 and 27.4, respectively, for pre-1940 hires) and may have obscured lung cancer as a cause of death in some cases. This high mortality is inconsistent with a "healthy worker group." Whether these were competing risks could be tested by determining whether age at death is less among lung cancer deaths than for TB and silicosis. If not, then they should not be competing causes of death. These data were not provided in the report so this speculation cannot be independently evaluated.

iv. Linear E-R at lower exposure levels

At lower exposure levels E-R rises linearly and is similar to other studies (Attfield et al., 2004). The great majority (85%) of the data at lower exposure levels are of current interest today and around recommended exposure limits (~2.25 mg/m^3-years). Within this range the data "are very consistent internally, showing significant excesses rising linearly with increasing exposure." Findings omitting the final exposure group are much more consistent with risk estimates obtained in other studies (e.g., diatomaceous earth [Rice et al., 2001] and industrial sand workers [Steenland and Sanderson, 2001]) than those from the model using all of the data.

Comment on linearity of E-R. The observation on linear E-R is mostly correct (Figure 15). Significant excesses of SMRs occurred for the two penultimate exposure groups at 1.48 and 1.70 with 15-year latency and at 1.88 and 1.64 with 15-year exposure lag. SRRs also showed excesses at the same exposure groups and models: 1.38 and 1.76, and 2.60 and 1.90, respectively.

On the other hand 73% of the data show weak (SRRs <1.5), nonsignificant associations and all the data show nonsignificant trends. Although the highest-exposure group contains only 15% of the cases, it should be weighted more heavily because if there is a causal effect, the highest risk is expected to be in the highest-exposure group unless there are plausible circumstances that reduce that high probability.

Consistency of excess risks from all relevant studies is an important guideline for determining causality. As summarized in this report, E-R trends are consistently lacking with a few exceptions. The authors cited their "positive" results as slightly lower but similar in exposure, RRs, and risk estimates to workers exposed to DE (Rice et al., 2001) and industrial sand (Steenland and Sanderson, 2001).

- In DE the E-R trend shows a possible excess only in the highest-exposure groups, which drops to an insignificant RR of 1.3 after accounting for the exposure misclassification in the pre-1930 hires and indirectly adjusting for smoking. If the highest-exposure group is excluded, there is absolutely no trend and no association as RRs are less than 1.0 except for the nonsignificant RR in the penultimate exposure group (Figure 1). In other words, the analogy with DE shows a different scenario, namely that there is a linear decrease in exposure at lower exposure levels, with the only increased risk at the highest exposure level. The analogy with the risk estimates (Rice et al., 2001) are considered to be overestimates because account was not taken of exposure misclassification and confounding from smoking (see discussion of DE above).
- In the industrial sand study cited (Steenland and Sanderson, 2001) the highest OR is in the highest-exposure group. If the last exposure group is excluded the E-R trend is negative (Figure 19).
- The other industrial sand study (Hughes et al., 2001) was updated and reanalyzed (McDonald et al., 2005). Exposures were higher and the OR was 2.64 at the highest-exposure group of >4.5 mg/m^3-years and 1.8 at about 3.2 mg/m^3-years. Below about 2.5 mg/m^3-years there are no significant risks (ORs <1.2). If the highest-exposure group were excluded, there would still be an E-R trend because of the 1.8-fold OR at about 3 mg/m^3-years (see Figure 20).

Smoking as a confounder (Attfield et al., 2004). Attfield et al. argue that although skeptics continually raise the issue that smoking is a "potential confounder of occupational exposure, there is evidence that it has limited capacity to cause confounding." For confounding to occur, it would have to be correlated with exposure intensity within both the shed and quarries, which is "hard to envisage."

The authors argue there is no foundation for the idea that "the tenure-related trend of lung cancer mortality in workers hired after 1940 is due to excess smoking in that group."

For confounding to occur in the E-R trends, there has to be a difference in smoking rates by exposure group. For internal comparisons, cases and controls are similar because they are from the same population. Generally there are only small differences in smoking rates between exposure groups. Attfield and Costello suggest smoking-related mortality from bronchitis, emphysema, and ischemic heart disease (IHD) is greater among quarry workers than shed workers, suggesting smoking is a greater risk in quarries than sheds.

Comments on smoking. Working populations consistently have higher smoking rates than the general population, from which expected deaths for calculation of the SMR are derived. Thus the absolute value of the SMR generally is confounded by smoking. Without some smoking prevalence data in the cohort and by exposure category it is not possible to assess the potential confounding effect in the SMR point estimate of risk in the cohort analysis.

It is true that in E-R analysis, it is unlikely smoking is a confounder because cases and controls at all exposure levels are similar, including smoking habits. But there are times this is not true, as was shown in the E-R for workers exposed to diatomaceous earth. In this instance the 20% difference in rates between high exposed and low exposed reduced the SMR in the highest exposure category to nonsignificance.

The authors disagreed with the contention that smoking-related causes of death, apart from lung cancer, were more prevalent among shed workers than quarry workers. Therefore the increased lung cancer rates among post-1940 hires would not be due to smoking.

The data do not provide much support about smoking prevalence. The SMRs for IHD (bold in summary below) suggest similar smoking among shed and quarry workers. Data on bronchitis mortality are not shown (Graham et al., 2004), but there are no differences in nonmalignant respiratory disease (NMRD), which includes bronchitis. The rate of emphysema is 2-fold higher among quarry workers, which is suggestive of higher smoking among quarry workers. There were apparent differences in laryngeal, bladder, and esophageal cancers, two favoring greater smoking in shed workers and one showing no difference. However, laryngeal and esophageal cancers have few cases (0 for laryngeal), so the SMRs are not stable and the comparisons are relatively uninformative.

	Shed		Quarry	
COD	(A&C)	(G&C)	(A&C)	(G&C)
Bronchitis	1.36	—	4.21	—
Emphysema	1.07	1.07	2.06	2.06
IHD	0.87	**0.72**	1.78	**0.72**
NMRD	—	1.45		1.56
Lung cancer	—	1.31		0.74
Laryngeal cancer	1.41	—	0	—
Bladder cancer	1.50	—	0.83	—
Esophageal cancer	.69	—	0.68	—

These arguments do not address the important question being asked: if silica exposure is causing lung cancer, why isn't lung cancer reduced when silica exposure is reduced? Smoking is the most plausible alternative hypothesis and is supported by no known nonsmokers among lung cancer cases.

Comments on Vacek et al. (2010)

Vacek et al (2010) added 1700 more workers, 155 more lung cancer cases, and 10 more years of follow-up to the Attfield et al (2004) cohort.

A major difference was exploration of all extant data to assure more complete enumeration of the cohort, which appears successful because of the large increase in cohort size. The previous cohort (Attfield et al., 2004; Graham et al., 2004) was about 76% as large as Vacek et al. About 18% of workers added in Vacek et al. had not participated in the cross-sectional radiographic surveillance programs prior to 1963 when participation rate was about 96%. There were enumeration errors that led to exclusion of about 263 workers and other errors such as in cause of death (COD) and work history.

There were substantive differences in work history. Both studies relied heavily on the surveillance program. But these data were not available for workers who did not participate in that program. Data from the cross-sectional surveillance program did not include work done after last participation in the program, and often did not include work done before World War II or work for other companies. Vacek et al. accounted for these gaps largely by use of insurance and pensions records.

There were some differences in estimates of exposure, in large part because of differences in JEM. The JEM used by Attfield and Costello (2004) was based on six

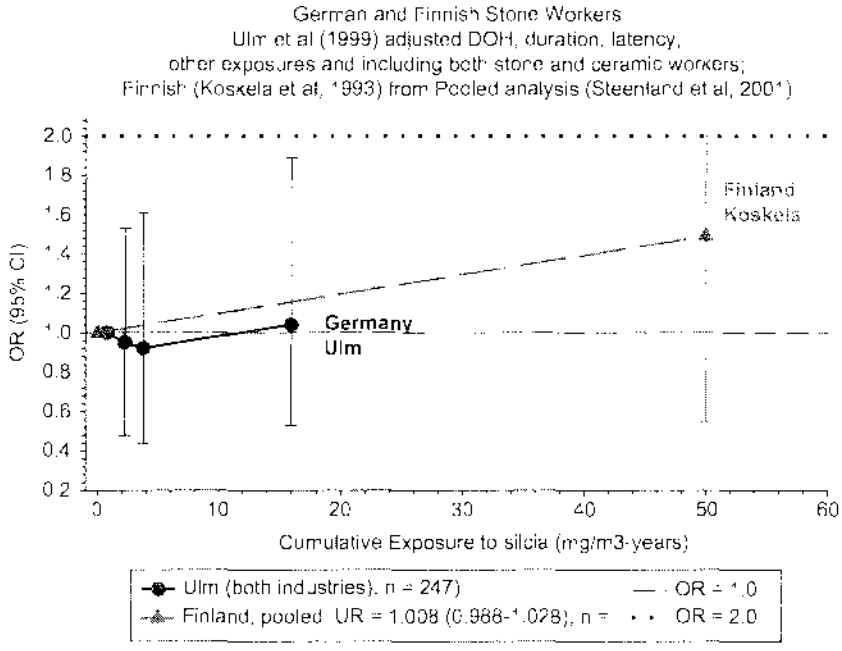

Figure 17. German and Finnish stone workers.

environmental surveys conducted between 1929 and 1982 (Davis et al., 1983). Vacek et al. added other surveys and consulted with individuals familiar with past and current IH practices. The primary differences were in the conversion from mppcf to gravimetric with a factor of 1 mg/m³ per 10 mppcf by Vacek et al. and 0.075 mg/m³ per 10 mppcf by Attfield and Costello. Estimated job concentrations were similar with the exception of the pre-1940 estimates for "channel bar operator." Vacek et al. conducted a sensitivity analysis using four different modifications and reported little effect on associations of quartz exposure with silicosis or lung cancer mortality. Odds ratios ranged from 1.06 to 1.17 per unit increase in cumulative exposure for silicosis and 0.98 to 1.01 for lung cancer. The strong association of silica exposure and silicosis mortality validated the exposure estimates in both studies.

Major strengths of Vacek et al. include complete enumeration of the cohort, use of all available information and careful editing to reduce errors, and longer follow-up to increase number of deaths. The longer follow-up essentially eliminate questions of too short latency as follow-up ended in 2004 or 34 years after 1970 when only 20% of the cohort were hired. The increased number of granite workers revealed potential information bias in the previous studies (Attfield et al., 2004; Graham et al., 2004) and confirm the necessity of relying on the Vacek et al. data set as the most complete and most appropriate for assessing a silica–lung cancer association (Figure 16).

2.3.1.3. Summary of Vermont granite worker studies (Attfield et al., 2004; Graham et al., 2004; Vacek et al., 2009, 2010) (Figures 15, 16) The two intervention studies (Graham et al., 2004; Vacek et al., 2009, 2010) compared pre- and post-1940 hires (high and low exposures) and detract from the silica–lung cancer hypothesis. The primary limitation is the lack of quantitative exposure estimates for individual workers, so to a limited extent this is an ecological or group-level study. But this lack of precision does not reduce the significance regarding the hypothesis about silica carcinogenicity. All post-1940 hires were exposed to markedly reduced silica levels compared to pre-1940 hires. The reduced silicosis mortality among post-1940 hires supports a causal association of silica and silicosis, whereas the lack of a reduction in lung cancer mortality is contrary to a causal association between silica and lung cancer.

The initial published E-R study of Vermont granite workers (Attfield et al., 2004) is indeterminate because of the incompletely resolved question about exclusion of the highest-exposure group. The pooled analysis (Steenland; Mannetje et al., 2001) used all the data without exclusion and showed no apparent association of silica and lung cancer. A larger issue in this cohort is the potential information bias from incomplete enumeration which was revealed by a complete enumeration of the cohort (Vacek et al., 2009). Figure 16 clearly shows (1) a strong association of silicosis with cumulative respirable silica thereby validating the exposure estimates; and (2) *no* association with lung cancer that detracts from the lung cancer-silica hypothesis.

2.3.2.German stone and quarrying industry (Ulm et al., 1999) (Figure 17)

The stone and quarrying portion of this study consisted of 133 cases and 231 controls matched on YOB. They were all nonsilicotics and all male. There were no significant associations with three exposure metrics:

Exposure metric	OR (95% CI)
Time weighted (average intensity) mg/m³	0.81 (0.37–1.77)
Cumulative, mg/m³-years	0.86 (0.38–1.95)
Peak, mg/m³	1.25 (0.58–2.69)

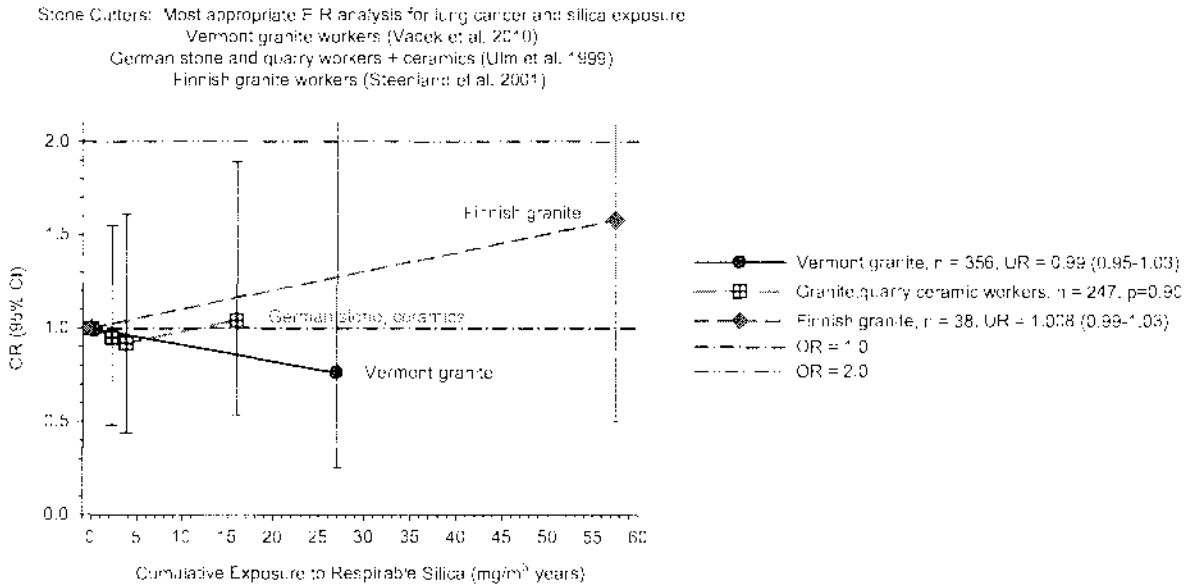

Figure 16. Summary: Quarry workers and stone cutters.

The authors concluded that there was no association between lung cancer and silica exposure (Figure 17). Exclusion of silicotics may have reduced the number of high-exposed workers and therefore reduced the range of exposure and reduced the power for detecting a small risk.

Comments on German quarry workers (Ulm et al., 1999)

Limitations of this study are discussed in the pottery section (Section 2.2.2) of this study. The unit risks estimated from the dichotomous E-R analysis do not correspond to the categorical result for both industries. For example, the OR is 1.04 (0.53–1.89) in the highest exposure category for all industries (>4.68 with an estimated average of about 16 mg/m^3-years) but in the dichotomous analysis the OR at 16 mg/m^3-years is 1.37 (0.002–1100). So the categorical results for the individual industries (stone/quarry and pottery) are too crude to be of much use for describing effects except in a very broad way.

This is a negative E-R study, although there were criticisms. The Working Group (IARC, 2009) noted restriction of study participants to nonsilicotics and adjustments for duration of exposure may have restricted the exposure range and limited the power of the study to detect an association. The criticism of low exposures may be incorrect, as average Vermont granite exposure in the 3rd quartile was 2.2 (Mannetje et al., 2002) compared to a range of 2.89–4.68 mg/m^3-years for the German cohort (Ulm et al., 1999). Maximum cumulative exposure was about 28 mg/m^3-years; 10% of cases had exposure of 12 mg/m^3-years or greater and about 50% of study participants had exposure of 3 mg/m^3-year or more. Mean exposures were largely above the TLV of 0.025 mg/m^3, with 75% of the cases and controls exposed to average exposures >0.03 mg/m^3.

The number of cases is fairly large (247 cases), so lack of power is not a significant limitation in detecting an increased risk with this large number of cases and when the E-R trend is so obviously flat (Figure 17).

These results do not support the silica-lung cancer hypothesis and suggest little or no increased risk of lung cancer at the highest silica exposures in the German stone/quarry industry. Exclusion of this study from the pooled analysis is unfortunate as adjustments for duration could have been removed and eliminated this limitation.

2.3.3.Finnish granite workers (Koskela et al., 1994; Steenland; Mannetje et al., 2001) (Figure 17)

This is a cohort of 1026 Finnish granite workers hired between 1940 and 1971 and working in granite quarries and processing barns in three main granite areas in Finland. Vital status was followed in 1940–1985. Dust exposure measurements were collected in 1970–1972 and 1980–1989 by the Finnish Institute of Occupational Health at the workplaces where occupational histories were obtained from personnel records. These are total dust samples and no estimates of respirable silica were found. Quartz content was 31% in both the grey and red granite areas. The third area had black Vitassaari "granite" composed of 60% plagioclase, 20% augite, 15% fluorite, and 5% hornblende, so it is not granite.

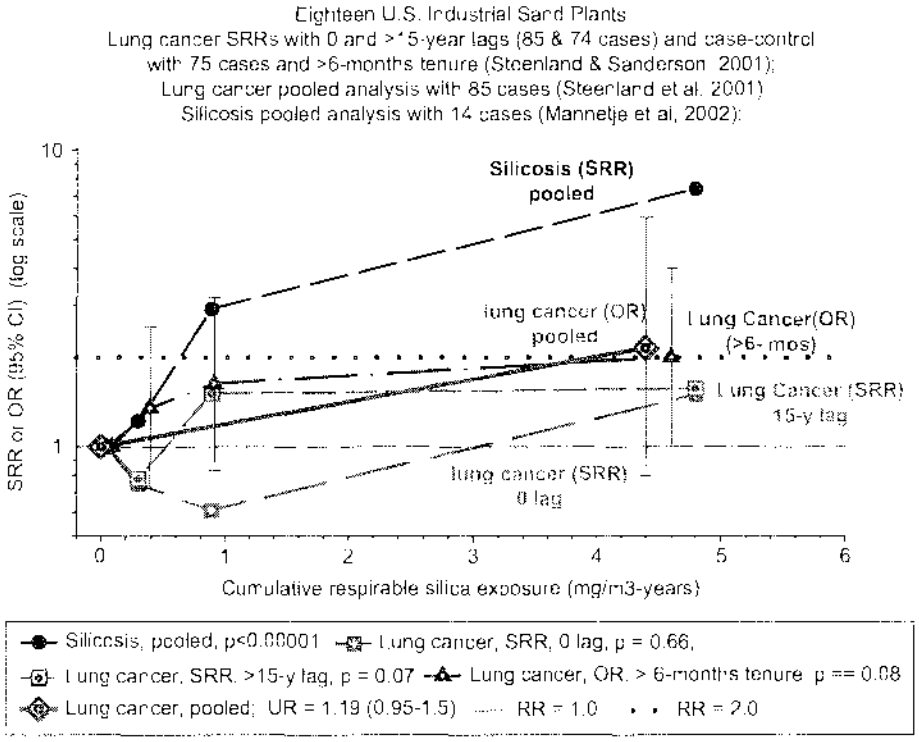

Figure 19. Eighteen US industrial sand plants (Steenland et al., 2001).

This region had only nine deaths and was not analyzed further. Lung cancer SMR was significantly elevated to 1.75 (1.02–2.81) in the grey area. In the red and grey granite areas there were 22 lung cancer cases and an SMR of 1.48 (0.93–2.24) with ≥10-year exposure and ≥20-year latency. There was no E-R analysis.

The data used in the pooled analysis are from a dissertation where follow-up was extended to 1994. Total dust measurements were converted to respirable silica based on Finland regional conversion factors. Cumulative respirable silica exposure estimates for the cohort were a median of 4.63, 3rd quartile of 15.42, and a maximum of 101 mg/m^3-years. There were 14 silicosis deaths in this cohort with 4 deaths in the 3rd quartile and 10 in the 4th quartile indicating a significant trend validating the exposure estimates (Mannetje et al., 2002). The lung cancer SMR was 1.4 (1.0–2.0), with 38 lung cancer cases. A nested case-control study with E-R analysis and quantitative estimates of exposure produced a nonsignificant unit risk of 1.008 (0.998–1.020) (Steenland; Mannetje et al., 2001) (Figure 17). The pooled analysis is considered the most appropriate because of longer follow-up and E-R using quantitative estimates of exposure.

2.3.4.Summary of quarry and stone cutter cohorts (Figure 18)

These studies are among the least confounded regarding occupational exposures, making smoking the primary potential confounding exposure.

None of the latest publications were available to IARC (1997). Early studies of Vermont granite and Finnish granite were considered among least confounded studies. Both were updated, E-R analyses added, and included in the pooled analysis.

Exposures appear adequate for assessing risk as cumulative exposure in high-exposed groups range from about 10 to 50 mg/m^3-years (Figure 18). Exposures were validated by strong associations between pneumoconiosis (or silicosis) and cumulative silica exposures. The cohort of Finnish stone workers had among the highest cumulative silica exposure among all studies yet there is only a slight nonsignificant trend.

The initial E-R Vermont granite study (Attfield et al., 2004) is replaced with the updated cohort (Vacek et al., 2009, 2010), which is a decided improvement because it has complete enumeration of the cohort, complete work history data, 10 years longer follow-up, and large increases in lung cancer cases (n = 356), making it the largest of the 18 cohorts. The intervention study clearly shows silica exposure is not responsible for increased lung cancer risk, which is supported by the E-R analysis.

All three cohorts indicate no associations, as E-R trends are nonsignificant or negative. The pattern from these studies of granite and quarry workers does not support the hypothesis that silica is a lung carcinogen:

- Strength of association is consistently weak. Risk at high exposure is at or below the null in two cohorts with lower cumulative exposures, and around 1.5 at high exposures of about 50 mg/m^3-years. All are statistically nonsignificant.
- There is a consistent lack of biological gradients (Figure 18), which is strong evidence against the silica-lung cancer hypothesis.

2.4.Sand and gravel (industrial sand) (Brown et al., 2005b; McDonald et al., 2005; Steenland and Sanderson, 2001)

There are three new cohorts of industrial sand workers that were not available to IARC (1996); two in the USA (McDonald et al., 2001, 2005; Steenland and Sanderson, 2001)and one in the UK (Brown et al., 2005b). Only one US cohort (Steenland and Sanderson, 2001) was included in the pooled analysis (Steenland; Mannetje et al., 2001). Confounding from occupational sources is minimal, so the primary confounding source is smoking.

2.4.1.US industrial sand workers (Sanderson et al., 2000; Steenland and Sanderson, 2001) (Figure 19)

This is a cohort of 4626 industrial sand workers who had worked for >1 week in 18 plants in 11 states. Follow-up was 1960–1996. There were 109 lung cancer deaths and 100 controls matched on race, sex, date of birth, and survival. E-R was analyzed by conditional logistic regression using cumulative, average, and peak exposures. Indirect control of smoking was based on NIOSH survey data in 1978–1989 on 358 men in four of the largest plants in this study. For E-R analyses 13% of the cohort had to be excluded because they "worked in unknown jobs only." For lung cancer there were 109 cases in the SMR analysis, 85 cases in the SRR and SMR E-R analysis, and 75 cases in the case-control analysis that excluded workers with <6 months' employment.

SMRs were significantly elevated for lung cancer (1.60; 1.31–1.93) with 109 cases, TB (3.39; 1.09–7.92); silicosis (66; 33–119) with 11 cases, and IHD (1.22; 1.09–1.36). In the discussion the authors indicate smoking in this cohort would be expected to increase lung cancer mortality by 10–20%, "which can only partially explain the observed 60% excess." Adjusting for a 20% upward smoking bias to the observed unadjusted overall risk of 1.60 (1.31–1.93) reduces the excess to 1.33 (1.09–1.61). Sensitivity analyses were conducted to adjust for possible confounding effects of smoking using Bayesian and Monte Carlo methodology. These produced an adjusted lung cancer SMR of 1.43 and confidence intervals of 1.12 and 1.15–1.78 respectively (Steenland et al., 2004).

There were significant E-R trends for silicosis (p < .00001), respiratory TB (p = .01), but not lung cancer (p = .66) in the SRR analysis without lags (Figure 19). There was a suggestive trend for lung cancer (p = .07) with a 15-year lag. Silicosis was mentioned in only 2 of the 109 cases of lung cancer, which is about half the expected based on mention of silicosis on all other death certificates. Silicosis is expected to correlate with silica exposure, so "partial confirmation" of the validity

of historical exposure estimates was provided by the significant positive E-R trend for silicosis.

Analysis of lung cancer mortality revealed a 2.4-fold increased mortality for short-term workers (<6 months) that seemed unrelated to occupational exposures. Lung cancer E-R analysis was repeated in the nested case-control study, excluding the short-term workers. This analysis showed "a twofold excess risk for those in the highest quartile" (Figure 19), and the trend was even more pronounced with average exposure. None of these analyses are adjusted for smoking.

The authors concluded these findings "tend to support the 1997 judgment by IARC that crystalline silica is a lung carcinogen."

The pooled analysis (Steenland; Mannetje et al., 2001) reported a similar lung cancer SMR of 1.60 (1.2–1.9), but with 85 cases instead of 109 cases as in Steenland and Sanderson. Unit risk for lung cancer based on 85 lung cancers was 1.19 (0.95–1.50) (Steenland; Mannetje et al., 2001). The E-R trends were similar when there were 15-year lags (Figure 19).

Comments on industrial sand cohort (Steenland and Sanderson, 2001)

Three strengths of this study are noted.

i. It was unlikely there were significant confounding occupational exposures.
ii. The number of lung cancer cases was reasonably large (109 cases) in the cohort analysis. There were 75 lung cancer cases in the case-control analysis when workers with <6 months' tenure were excluded.
iii. Industrial hygiene sampling was available over time. There were 4269 MSHA and company samples collected in 1974–1996; 1974–1988 data were used because end of follow-up was 1988. These data allowed E-R analyses, which are important for two reasons. E-R analyses "are less subject to confounding by smoking than are simple comparisons of lung cancer rates in exposed workers versus the general population because workers with a high exposure may be compared with those with a low exposure who are more likely to share similar smoking and other lifestyle habits. Exposure-response trends, or the lack of them, also provide valuable evidence with which to draw conclusions about whether the agent in question truly causes the disease in question."

Limitations include the following points:

i. There were only limited data on smoking gathered in the 1980s on about 7.5% of the cohort. Using these smoking data and Axelson-type smoking adjustments by age and dichotomous exposure categories produced smoking adjusted RRs of 1.04 and 1.10 at cumulative exposures >0.59 mg/m^3-years for >45 years and <45 years, respectively, compared to RR = 1.0 at <0.59 mg/m^3-years. Unfortunately, smoking adjusted ORs for each exposure category were not calculated, so a smoking adjusted E-R trend is unavailable. IARC (2009) noted a sensitivity analysis (Steenland et al., 2004) adjusting for smoking produced a reduction in overall SMR for lung cancer from 1.60 (1.31–1.93) to 1.43 (1.15–1.78).
Unfortunately there was no adjustment for smoking in the E-R analysis. None of the ORs were significant but the trend in the case-control study was marginally significant. It would have been useful to conduct a sensitivity analysis for smoking effects in the E-R analysis. It's unclear what would happen for an adjusted E-R trend.
ii. Industrial hygiene data were lacking for years 1947–1974. Impinger data were collected in 1946 in 19 plants. All exposures prior to 1946 were assumed to be the same as 1946, and linear extrapolation between 1946 and 1974 was used to estimate exposure in the intervening years. No adjustments were made for plant-specific engineering changes. Conversion from mppcf impinger sample results to respirable mg/m^3 results were conversion factors derived from side-by-side sampling in Vermont granite sheds, North Carolina dusty trades, and taconite mines.
iii. Results are equivocal with regard to a causal association, in part because of the appearance of changing exposure categories. There was no association in the SRR analysis where both TB and silicosis showed strong associations. With a 15-year lag the SRR trend was similar to the trend in the case-control analysis with the same RRs in the penultimate and highest exposure categories (Figure 19). There was a marginally significant E-R trend ($p = .04$) after excluding short-term workers of <6 months, and the lower confidence interval in the highest-exposure group was less than 1.0. A possible reason the E-R trend became statistically significant may be related to changing exposure cut-points, which in the initial analysis were quartiles based on the distribution of *all decedents*. In the case-control analysis quartiles were based on distribution of *all non-cases*. E-R trends in categorical analyses can be influenced by choice of cut-points defining exposure categories and the distribution of exposure cut-points within a category. As a result, the changing choice of cut-points may have influenced the shape and statistical significance of the E-R curve.

The most appropriate result from this cohort is from the pooled analysis because the continuous E-R analysis is not influenced by exposure cut-points.

2.4.2. Updated US sand industry study (McDonald et al., 2005) (Figure 20)

McDonald et al. (McDonald et al., 2001) conducted a cohort study of 2670 men in nine industrial sand plants who were employed before 1980 for ≥3 years. Of the cohort, 2644 (99%) were followed up to 1995 with 1025 deaths. SMRs for those with ≥20-year latency were 1.39 for lung cancer, 1.61 for nonmalignant respiratory disease,

and 37 deaths from silicosis and silico-TB. The increased SMR for lung cancer was due to high rates in four of the nine plants in two states. The authors concluded that the significant SMR in lung cancer could not be attributed to silica because there was no smoking information and no E-R analysis.

A nested case-control study of lung cancer and silicosis was conducted to ascertain quantitative E-R trends after adjusting for smoking (Hughes et al., 2001). There were 32 silicosis cases (57 controls) and 91 lung cancer cases (162 controls) matched on date of birth, date of hire, plant, and survival. Workers with silicosis were hired on average about 10 years earlier than lung cancer cases, and died slightly younger (63 vs. 66). More lung cancer cases smoked (91%) than silicosis cases (85%), and both smoked more than controls (69% and 70%, respectively). Silicosis risk was associated with lagged cumulative and average silica exposure. These results "lend support to the validity...of exposure estimates." Lung cancer risk was related to lagged and unlagged cumulative exposure and unlagged average exposure after accounting for a highly significant smoking exposure.

Subsequently, 6 more years of follow-up through 2000 added 231 total deaths (McDonald et al., 2005), with lung cancer cases increasing from 91 to 105. Objectives were to assess E-R with chronic renal disease and determine whether or not lung cancer and silicosis maintained similar associations as in the initial study. The follow-up included 2452 workers in eight US plants, excluding the Canadian plant with 215 employees. Only those with ≥3-year employment with 1 month employment during 1940–1979 were included in the cohort.

Updated ORs for lung cancer and silicosis were very similar to original results with lung cancer, again related to average and cumulative silica exposure (but not tenure) after adjusting for smoking (Figure 20).

The authors concluded these findings "support a causal relationship between lung cancer and quartz exposure after allowance for cigarette smoking, in the absence of other known carcinogens."

Comments on updated US industrial sand worker study (McDonald et al., 2005) and comparison with other US industrial sand study (Steenland and Sanderson, 2001)

IARC (2009) noted the two US studies arose from the same population of workers but the degree of overlap was unknown. The Steenland et al. (2001) study comprised 18 US plants, and 8 of these plants were also in the McDonald et al. case-control study (McDonald et al., 2005). The Steenland cohort included 4027 workers with >1 week's employment in 1987–1988 and adequate exposure information; follow-up was 1960–1996. The McDonald et al. cohort comprised 2455 workers with >3-year employment and ≥1 month's employment in 1940–1979, with follow-up through 2000. Despite the larger size, the Steenland et al. cohort had fewer lung cancer cases (85) than the McDonald et al. cohort (105). Several reasons for this disparity in number of deaths is that the McDonald et al. cohort is older (50% vs. 24% deceased), earlier mean year of hire (1950 vs. 1967), employed earlier in the century (1940–1979 vs. 1987–1988); longer follow-up (60 vs. 9 years or 1940–2000 vs. 1987–1996). These differences indicate limited overlap, suggesting these are essentially separate cohorts separated in time.

There were several differences in exposure estimates between the two US studies. In the McDonald cohort more sampling data were obtained (Rando et al., 2001). For example, they had 14,249 measurements from cyclone and membrane samples from company documents, consultant reports, publications, and government databases. The database is smaller in the Steenland et al. industrial sand study with 2975 samples from MSHA and 1294 from plant data (Sanderson et al., 2000).

The conversion from mppcf to mg/m^3 was also different. In the study of 18 plants the conversion was:

1 mppcf = (100 μg/m^3) × (% quartz in historical samples) (Sanderson et al., 2000)

This conversion was based on estimates from other industries (e.g., Vermont granite) that are not representative of the industrial sand industry.

Conversion in the smaller study was 1 mppcf = 276 μg/m^3 (Rando et al., 2001) based on particle counts by size range from 14 samples from industrial sand plants and reported in a master's thesis (Severns, 1979). Rando et al. showed a geometric mean exposure that was nearly twice as high as that of Sanderson et al.: 42 vs. 25.9 μg/m^3.

There was a large database of environmental silica samples. A problematic factor is converting mppcf to μg/m^3. The most appropriate conversion is the one using side-by-side sampling in the industrial industry (Rando et al., 2001), rather than industries other than industrial sand (Sanderson et al., 2000).

A strength of this study is adjustment for smoking based on records for 91% of cases and controls. It would have been informative to have presented both unadjusted and adjusted results. Another strength is that the analysis was based on workers with 20+-year latency.

Consistency between results from the original and updated analysis strengthens the authors' conclusions of a causal association.

The Steenland et al. cohort was in the pooled analysis, although presumably both could have been included. It would have been appropriate and a significant improvement if both studies had been included, or even better, combined.

2.4.3. UK industrial sand worker cohort (Brown et al., 2005a, 2005b) (Figure 20)

This is a cohort study of 2703 industrial sand workers in seven UK silica sand quarries with >1-year employment 1950 and 1986; follow-up was 1950–2001. There were 764 total deaths, 81 from lung cancer and 91 from NMRD, with SMRs of 0.90 (84–97), 0.99 (0.78–1.24), and 0.91 (0.73–1.12) for men and 0.70 (0.49–0.96), 1.45 (0.40–3.72), and 0.52 (0.11–1.51) for women, respectively.

Internal E-R trends for lung cancer and NMRD were analyzed on a subcohort of 2272 workers with complete

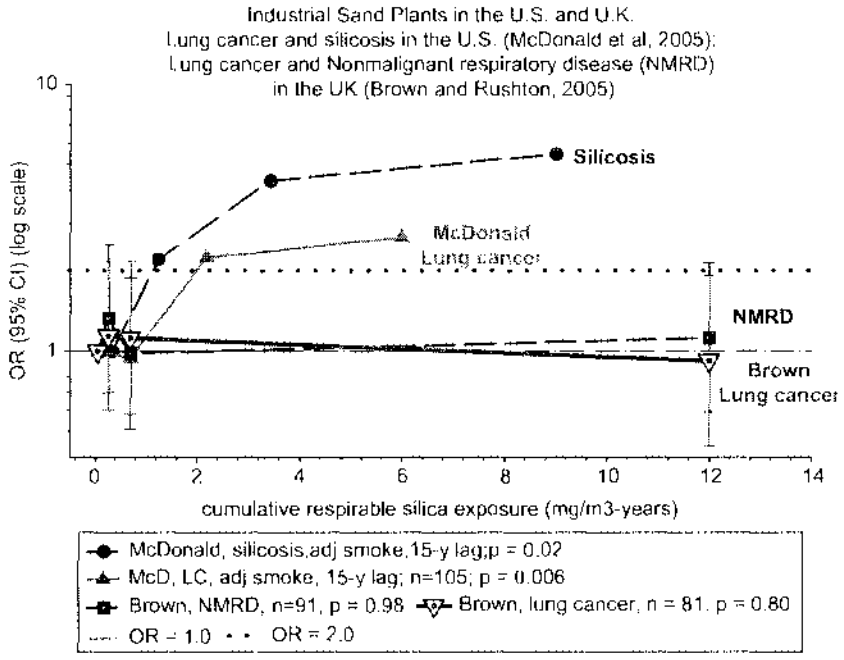

Figure 20. Industrial sand cohorts in USA and UK.

data. Poisson regression was used to adjust for attained age, calendar year, year beginning work, time since first employment, employment status, and cumulative exposure to respirable crystalline silica (RCS).

Cumulative exposure ranged from 0.01 to 23.2 mg/m^3-years, with a geometric mean (GM) of 0.31 mg/m^3-years. There were no E-R trends with cumulative exposure for mortality from lung cancer or NMRD (Figure 20). The authors concluded this "study did not show any consistent relation between RCS exposure (in the absence of other known carcinogens) and the development of lung cancer."

Comments on UK industrial sand study (Brown et al., 2005a, 2005b)

This is clearly a negative study and does not support the silica-lung cancer hypothesis. Several criticisms have been directed toward this study.

i. Low exposures and deficits in expected silicosis mortality

IARC (2009) noted that low exposures in this study reduced its power to detect a silica effect. Exposure levels were rather low, so the negative results are not surprising as exposure may be below a threshold effect level (Steenland, K, 2005). Because silica is "not a strong carcinogen," lung cancer excesses may not increase until after a cumulative exposure of about 2 mg/m^3-years (Steenland; Mannetje et al., 2001). A GM of 0.31 mg/m^3-years in the UK study may mean exposures were too low to detect an increased risk.

But these comments are contradicted by "a similar low overall level of cumulative exposure" in the US study, which showed a strong E-R trend for silicosis, and a lung cancer excess, despite lower exposures among UK workers than US workers (Figures 20, 21).

Brown and Rushton (Brown et al., 2005a) note that "average silica exposure levels were higher than those in US sand workers, although not as high as those in other industrial environments where silica occurs." The GM among UK sand workers was 0.09 (3.9) mg/m^3 (Brown et al., 2005a) or about 3 times greater than the 0.026 (0.011) mg/m^3 in US sand workers in 1974–1996 (Sanderson et al., 2000). Mean exposures were clearly higher in the older US industrial sand cohort as the 75th percentile for average exposure was >0.26 mg/m^3 (Hughes et al., 2001). In the pooled analysis (Steenland; Mannetje et al., 2001) US industrial sand has the lowest cumulative silica exposure, whereas half of the 10 cohorts have cumulative exposures >10 mg/m^3-years and a number of those studies have median average exposures ranging from 0.05 mg/m^3 among US gold miners and granite workers to highs of 0.43 mg/m^3 among Australia gold miners and 0.59 mg/m^3 among Finnish granite workers (Mannetje et al., 2002). Distribution of cumulative exposure is not reported, but among UK industrial sand workers the overall GM was 0.31 mg/m^3-years and in the 4th quartile was 1–23.2 mg/m^3-years (Brown et al., 2005a) compared to >1.23 mg/m^3-years in US sand workers with >6 months' employment (Steenland and Sanderson, 2001).

In US industrial sand studies, there were 11 cases of silicosis and silico-tuberculosis (0.24%) (Steenland and Sanderson, 2001) in one study and 37 cases (1.4%) in the other (McDonald et al., 2005), but only 2 (0.07%) in the UK cohort (Brown et al., 2005b).

Two reasons were offered for these differences: (a) silicosis is rarely mentioned on death certificates in the UK, and (b) exposure was too low to have an effect (Brown et al., 2005b).

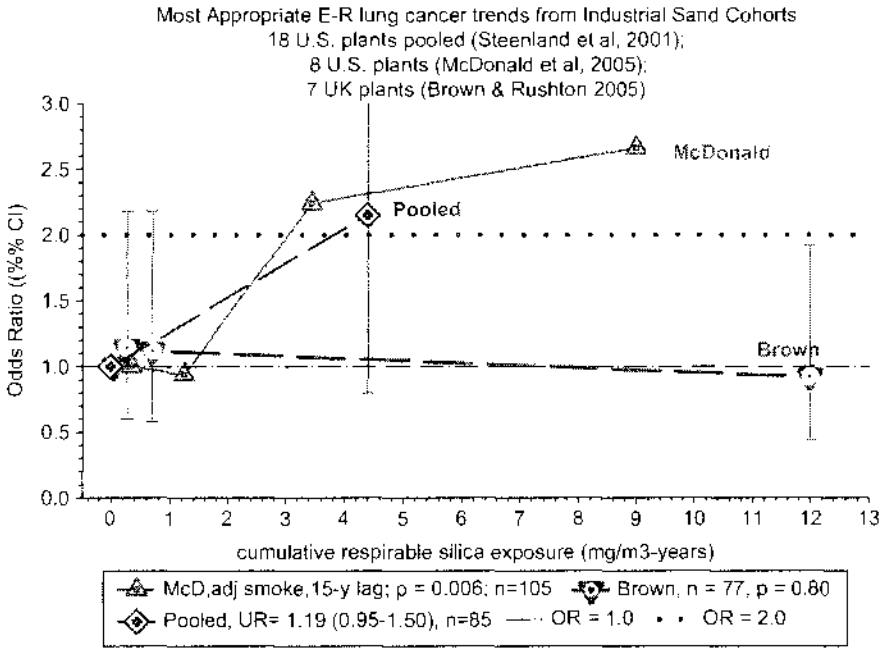

Figure 21. Summary of industrial sand cohorts.

The latter reason seems implausible, as average and cumulative exposures in the UK study were comparable to those in the Steenland study, even though there were fewer cases of silicosis. Two other reasons might be considered. Perhaps there were differences in the silica as the authors discussed with regard to high mortality at quarry 7. Possible differences included a different geology of the quarries, chemical composition of the sand, different methods of extraction and refining, and whether exposure was to aged or freshly cut surfaces of silica. Fresh cut surfaces were produced at quarries 5 (during extraction) and 6 (milling to produce silica flour). But mortality (all cause, lung cancer) was not elevated at these quarries.

Another possible difference is smoking. McDonald et al. (McDonald et al., 2005) found a strong relationship between smoking and silicosis, with the risk of silicosis significantly increased 5-fold (OR=5.09; 1.29–20) for smokers compared to nonsmokers. Brown et al. (Brown et al., 2005b) did not have smoking histories, but believed smoking "did not play a significant role in mortality within the cohort" because mortality was reduced in smoking-related diseases (i.e., SMRs of 0.99 for lung cancer, 0.91 for respiratory diseases, 0.90 for circulatory disease, and 0.93 for IHD among men).

ii. Less follow-up time and inadequate latency

The negative finding was also attributed to only eight lung cancer cases with, 20+-year latency. The overall deficit of lung cancer SMR was because of significant deficits from one quarry in lung cancer mortality (0.27), which also had significant deficits for all-cause mortality (0.81) and all-cancer mortality (0.58), possibly because of less follow-up time and a greater healthy-worker effect (Steenland, 2005).

It is unlikely these are plausible reasons for the negative finding. The quarry with significant deficits in lung cancer SMR (SMR=0.26) only had 12% (n=7) of lung cancer deaths, but 30% (n=228) of all causes (SMR=0.81) and 20% (n=43) of all cancers (SMR=0.74). Shorter follow-up and inadequate latency (<20 years) are implausible reasons for deficits based on data from an internal report (Brown et al., 2003). The average length of follow-up was 28 years with over 80% followed for 20 or more years. The lowest SMRs were in workers with 20+-year employment, and highest mortality tended to be in short-term workers (<5 years): e.g., 1.10 versus 0.69 for all causes, 1.24 versus 0.66 for all cancers, 1.55 versus 0.63 for lung cancer, and 1.08 versus 0.54 for respiratory disease. Those with 40+-year follow-up had lower mortality than those with <20-year follow-up: e.g., 3.61 versus 0.36 for all causes, 3.90 versus 0.36 for all cancers, 4.33 versus 0.33 for lung cancer, and 2.38 versus 0.36 for respiratory disease.

iii. Consistency in epidemiology studies

In commentary on the UK study of industrial sand workers, a broader question was raised (Steenland, 2005) about how "we evaluate consistency in epidemiological studies, and when one might consider that a controversy about a putative carcinogen might be laid to rest." It was considered not unusual for a new study to be negative, "especially when exposure levels are low." Policy makers must judge the weight of evidence as has been done by IARC and the National Toxicology Program (NTP). In light of the large number of studies, it "might be considered high time ...to act without the perennial call that 'more research is needed.'"

But a new study may also be positive, as it was for the two US industrial sand studies, even though exposures

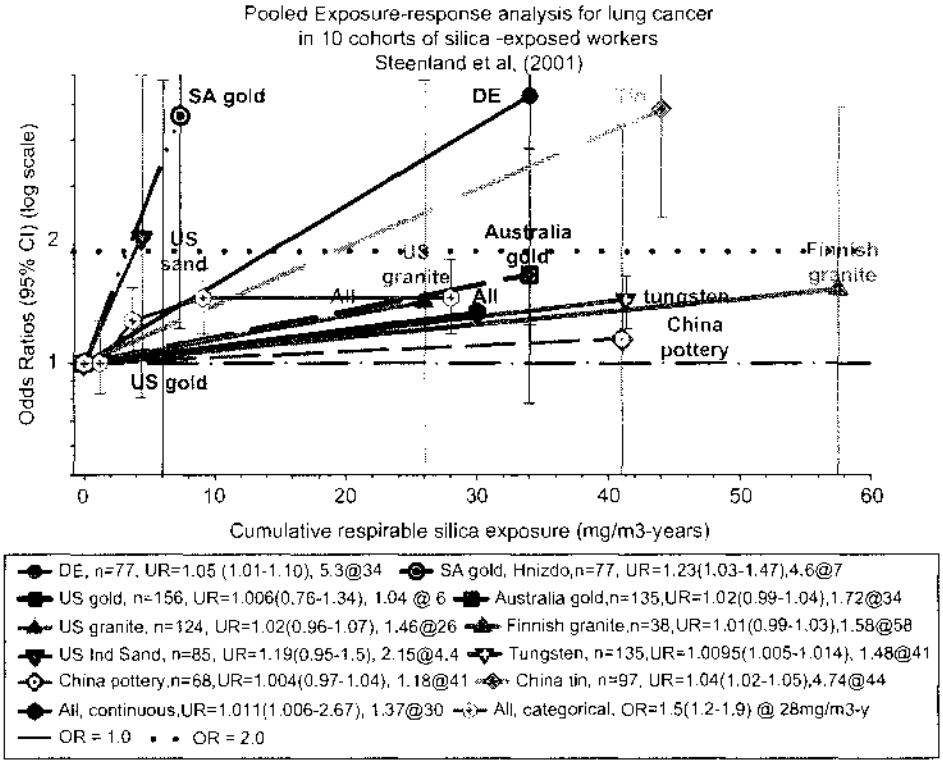

Figure 22. Summary of pooled analysis of 10 cohorts.

tended to be lower than in the UK study, and especially lower in the Steenland et al. cohort (Figure 21). But the fact that the UK study (or the US study) is new does not provide a plausible reason to dismiss either because they are negative or positive. What is perhaps more surprising is that the Steenland et al. cohort was not negative despite being a young cohort with low exposures, short tenure, and short follow-up. One might consider that some of the excess mortality might be from other nonsilica causes because of the mean latency of 17 years (mean years to death from year of first employment), short tenure (8.8 years), and inclusion of potentially short-term workers (only excluded workers with <1-week employment).

2.4.4.Summary of industrial sand studies (Figure 21)

E-R trends for three studies of US and UK industrial sand workers are inconsistent, with one showing a strong E-R trend between lung cancer and cumulative exposure to silica (McDonald et al., 2005), one showing a strong but nonsignificant E-R trend (Steenland and Sanderson, 2001), and one showing no association with a flat E-R slope in UK workers (Brown et al., 2005b).

These industrial sand studies are new and were not available for IARC (1996). They added 272 lung cancer cases to the database. A surprising difference between the US and UK is the absence of a lung cancer response in the UK despite the higher cumulative and mean exposures. The US studies had lower exposures than the UK studies and showed strong associations, whereas there were no associations of silica with NMRD or lung cancer in the UK. Smoking was a potentially important confounder in one study of US workers (McDonald et al., 2005). Limited information on smoking was available on only 10% of US workers in the other study, but no adjustments were made for smoking in the E-R analysis and the authors suggested smoking could not explain all the excess risk (Steenland and Sanderson, 2001). Smoking data were not available in the study of UK workers, but the role of smoking did not appear to be a strong confounder based on low mortality in smoking-related diseases (Brown et al., 2005b).

The inconsistent results from these three studies in the industrial sand industry, two positive (one nonsignificant) and one negative provide limited support for the silica–lung cancer hypothesis (Figure 21).

2.5.Pooled analysis (Steenland; Mannetje et al., 2001)

A pooled analysis converts exposure levels to the same metric and analyzes E-R as one database. The statistical power of a pooled analysis is markedly increased, the range of exposure is wider with more subjects at both lower and higher exposures, and studies are weighted proportional to their sample size. A potential problem with pooled analysis is the selection of studies. Studies with unresolved confounding or bias should not be included in the pool. All relevant studies (positive, negative, equivocal) should be included with regard to quality, but not results.

The pooled analysis of 10 silica-exposed cohorts includes 992 lung cancer deaths (Steenland; Mannetje et al., 2001). The focus was on internal E-R analyses

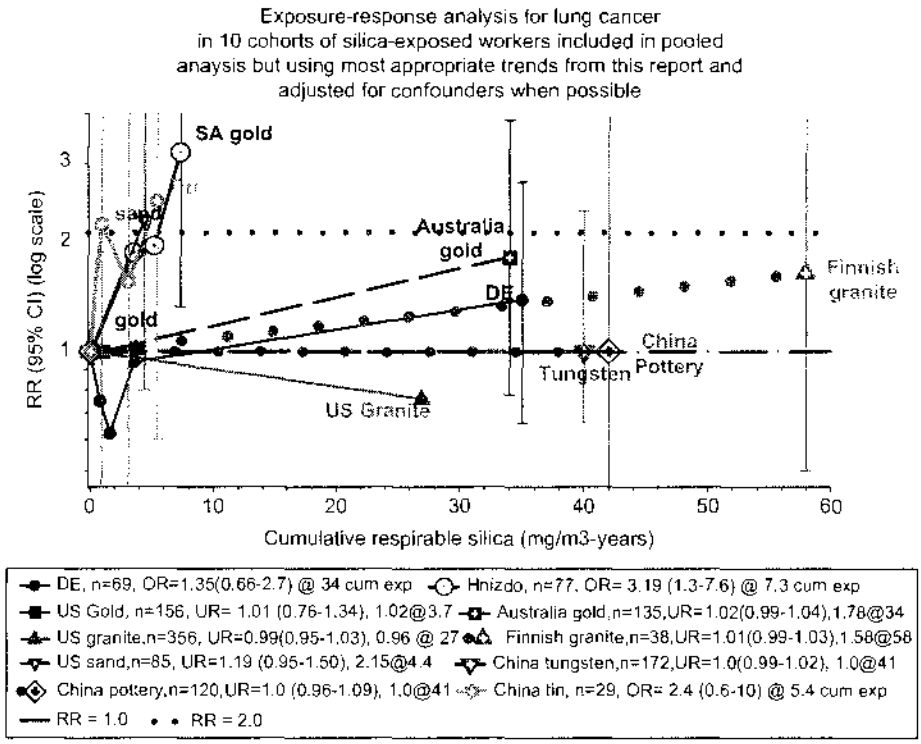

Figure 23. Summary of most relevant E-R trends from 10 cohorts in pooled analysis.

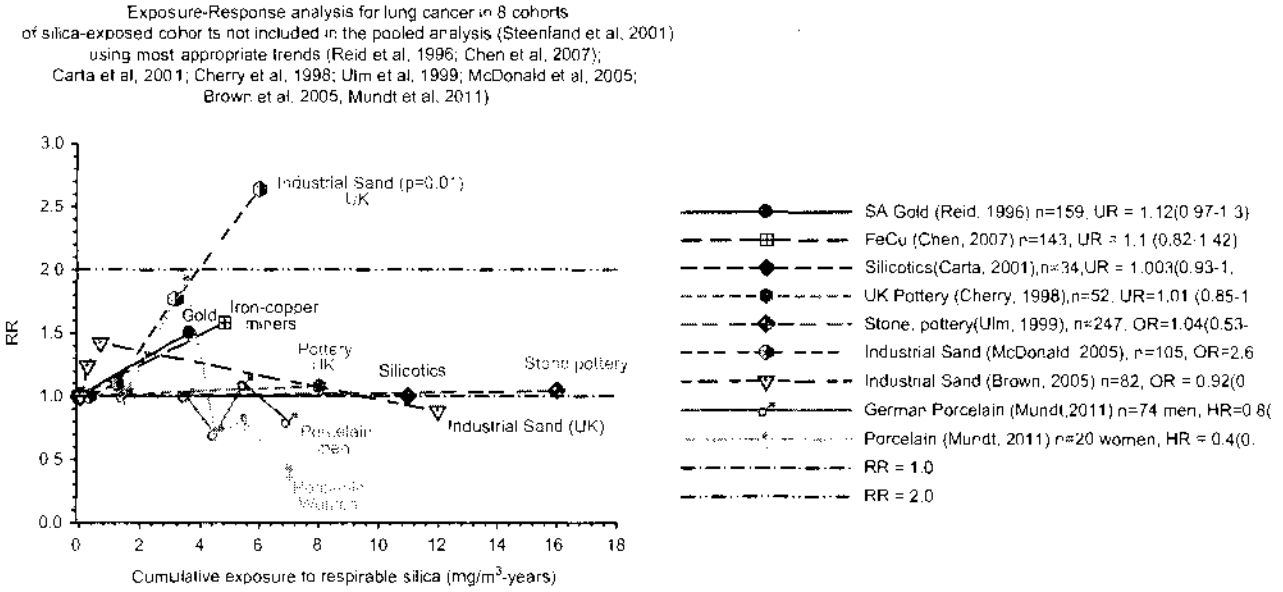

Figure 24. Most appropriate E-R in eight cohorts not included in pooled analysis.

using conditional logistic regressions via nested case-control design. Each case was matched by race, sex, DOB, study, and survival, with 100 controls/study randomly selected from each study. Only exposure variables of cumulative exposure (mg/m^3-years) or average exposure (mg/m^3) were included in the models, "given the matching on confounders." Categorical E-R analyses used quartiles based on distribution of exposure among cases. Adjustments were made for competing risks. There were no adjustments for confounders. E-R for silicosis was analyzed in 5 of the 10 cohorts (Mannetje et al., 2002).

Literature was reviewed to identify all cohorts with quantitative exposure data. Ten of 13 cohorts were selected. Several studies were excluded from the pooled analysis:

a. Dutch ceramic workers (Miejjers et al., 1996) because of confidentiality issues.
b. South African gold miners (Reid et al., 1996) because of data unavailability.
c. UK pottery workers (Cherry et al., 1998) because of different case-control matching criteria. Cherry et al. matched on DOB, date of first employment, and never smokers were excluded because none of cases had been nonsmokers. But in the pooled analysis there is the implication that new matching was done or redone. Since presumably the entire database was available for studies included, it seems possible to match cases and control using their own criteria. It is not clear why this negative study was excluded. Exclusion of this study reduces the significance of the pooled analysis.
d. Coal miners (Miller et al., 1997) because of low silica content of the dust (5%) and different surface properties of silica in some coal mines that appear to reduce toxicity of silica particles coated with clay.
e. Foundries because of likely confounding exposures, including two studies in IARC (1996) (Andjelkovich, D et al., 1994; Xu et al., 1996).

2.5.1.Ten cohorts from pooled analysis (Figure 22)

E-R trends from the pooled analysis of 10 cohorts with 992 lung cancer cases are positive but the authors commented on the heterogeneity of results, as shown in Figure 22. E-R trends are quite steep for China tin miners confounded by arsenic, DE workers (cristobalite) confounded by smoking and exposure misclassification, US industrial sand workers (very steep slope but low exposure), and South African gold miners (Hnizdo et al.). Moderate slopes are displayed for Australian gold miners, US granite shed workers, Finnish granite workers, and Chinese tungsten miners. There were no associations for Chinese pottery workers and US gold miners.

Four studies show strong E-R trends with three significant (South African gold, DE, tin) and one not significant (US industrial sand). The remaining seven studies suggest positive E-R trends that are not significant and the highest ORs at high exposures are less than 2-fold. Combining all 10 cohorts produced a significant positive trend with a UR = 1.011 (1.006–1.015) and a calculated OR = 1.35 (1.19–1.51) at 28 mg/m^3-years (median exposure in the highest exposure category of all cases). The categorical analysis produced an OR of 1.5 (1.2–1.9) for the high-exposure quintile with median exposure of 28 mg/m^3-years (Figure 22).

2.5.2.Ten cohorts using most appropriate E-R trends from this report (Figure 23)

These cohorts contrast results from the pooled analysis (Figure 22) with individual results from the same cohorts with 1237 lung cancer cases and using the most appropriate E-R trend available derived from the analysis in this report (Figure 23). E-R trends from the pooled analysis were used for Finnish granite workers, US gold miners, Australian gold miners, and US industrial sand workers (Steenland and Sanderson, 2001). The categorical data from South African gold miners was used instead of the continuous data from the pooled analysis. More appropriate data selected to replace the pooled data included the improved updated results for US granite (Vacek et al., 2010) and two studies of China tungsten and pottery workers adjusted for confounding and with improved exposure estimates (Chen et al., 2007). Data from the DE cohort (Checkoway et al., 1997) were adjusted for exposure misclassification and smoking (this report), and analysis of tin miners was restricted to the Limu mine to ameliorate confounding from arsenic (Chen et al., 2002).

These results show a relatively homogeneous outcome of two studies, with strong, positive E-R associations (South African gold mine, industrial sand) and one (Limu tin miners) with a suggestive E-R trend based on high ORs but unstable, nonmonotonic, and nonsignificant E-R trend. All are at low exposures, and only the Hnizdo et al. study of South African gold miners was statistically significant. Four studies showed no E-R associations (US granite, US gold, tungsten, and pottery) or moderate nonsignificant E-R trends (Finnish granite, DE, Australia gold) (Figure 23). Overall there are no apparent associations and flat E-R trends in 7 of the 10 cohorts selected from studies with the least bias or confounded, longest follow-up, and better exposure data.

IARC (2009) concluded that the "strongest evidence supporting the carcinogenicity of silica on the lung comes from the pooled and meta-analyses. The pooled analysis demonstrated clear exposure-response."

A more systematic review of these 10 cohorts suggests a consistent finding of *no clear exposure-response* associations (Figure 23).

2.5.3.Seven additional cohorts of silica-exposed workers (Figure 24)

There are seven cohorts of silica-exposed that were not in the pooled analysis. These studies show one clear and significant E-R trend (US industrial sand). There are four studies with flat E-R trends showing no associations (UK pottery, UK industrial sand, German stone/quarry/pottery workers, and Sardinia silicotic miners). There are two equivocal studies with possible but nonsignificant E-R trends (South African gold miners, Fe/Cu miners) (Figure 24). These "excluded" studies suggest a consistent and homogeneous pattern of weak or negligible strength of association and lack of E-R trends.

The pooled results are incomplete as eight cohorts are missing (Figure 24) and contains at least four studies that may be biased or confounded (DE, tin, Vermont granite, China pottery). Limitations of the pooled analysis are that new and updated studies were not or could not be included (US granite, Chinese miners/potteries, US and UK industrial sand workers and German porcelain workers); no adjustments for confounding were made,

some cohorts were not included (Sardinia silicotics, South Africa gold miners, German stone/quarry/pottery workers, Fe/Cu miners), and some studies should not have been included because of confounding (China tin miners).

IARC (2009) characterized the pooled analysis as representing the "strongest evidence supporting the carcinogenicity of silica." Results from the pooled analysis do not provide strong evidence for the silica-lung cancer hypothesis because all the available cohorts with E-R evidence from the literature are not included; biased and confounded data from several cohorts are included or not adjusted; and there is not a consistent finding of E-R trends, as a majority of the 10 studies show no apparent E-R association.

3.0.Overall summary

This report has attempted to include relevant cohorts with quantitative E-R analyses where confounding and bias are unlikely to have a major effect on results.

Studies with E-R analyses were divided into four industrial groupings for preliminary consideration. The quality of data from each cohort was assessed and summarized and a judgment made as to what evidence is most appropriate in preparation for evaluating all this evidence and making a judgment about the strength or weight of this evidence regarding carcinogenicity. This overall summary consolidates the rationale and selection of the most appropriate E-R evidence. This body of evidence is compared to IARC and the pooled analysis, and assess the weight or "strength" (WHO, 2006) of the evidence.

3.1.Mining (Figure 10)

There are eight miner cohorts with E-R analyses. There are four E-R studies of gold miners (Figure 4), plus two large studies without formal E-R analysis but showing no difference in mean exposure of cases and controls (Hessel et al., 1986, 1990). These case-control studies from necropsy files have 364 cases and are considered negative studies. The other four cohorts are not gold miners, but are mining tungsten, Fe/Cu, tin, and a variety of minerals (Figure 9).

US gold miners. The Homestake mine is now closed and has been studied numerous times. The first E-R study (Steenland et al., 1995b) included a cohort analysis and a nested lung cancer case-control study. The cohort analysis showed a slight nonsignificant excess risk in the highest exposure category, and the nested case-control study showed a negative E-R trend (results not shown). The cohort was updated 6 years for the pooled analysis, which increased the number of cases from 115 to 156 and produced similar results with a unit risk of 1.006 (0.76-1.34) (Steenland; Mannetje et al., 2001). The pooled E-R is used because of longer follow-up, larger number of cases and no occupational confounding (Figure 1).

Australia gold miners. The original study (de Klerk et al., 1998) reported no E-R association based on a qualitative exposure-score. Radon exposures were negligible. Exposure was quantified for the pooled analysis and produced similar results with 135 cases and a unit risk of 1.016 (0.99-1.04) (Steenland; Mannetje et al., 2001).

South African gold miners (Hnizdo et al., 1997). There are 77 cases and significantly positive E-R trends (Figure 3). There was possible confounding from radon but inclusion and exclusion of this cohort in the pooled analysis did not affect the outcome. The unit risk (UR) from the pooled analysis was 1.23 (1.03-1.47) and produced an OR = 4.63(1.24-16.7) at 7.3 mg/m^3-years that was higher than the 3.19 (1.3-7.6) from highest-exposure group in the categorical analysis. The lower slope in the original categorical analysis may be due to adjustments for smoking and is the reason for selecting the original publication (Hnizdo et al., 1997). These results are similar to the other South African E-R study (Reid et al., 1996) except for the high-exposure group (Figure 3).

South African gold miners (Reid et al., 1996). There are 159 cases and a positive but nonsignificant E-R trend similar to Hnizdo et al. (1997) at the lower exposure levels (Figure 3). Adjustments for smoking increased the UR from 1.08 to 1.12, indicating smoking was a negative confounder and cases smoked less than controls, which seems unlikely. This is considered an equivocal positive study. Exposures are low with nonsignificant RRs of 1.52 (0.89-6.5) and 1.32 (0.80-1.96) at 3.7 mg/m^3-years with and without adjustments for smoking (Figure 4).

Results are mixed for the gold miner studies. Two South African studies show positive trends (Hnizdo et al., 1997; Reid et al., 1996) and two show no difference in exposure of cases and controls (Hessel et al., 1986;, 1990). The cohorts from Australia and the USA (Steenland; Mannetje et al., 2001) show no apparent associations (Figure 4).

Chinese tin miners (Figure 5). McLaughlin et al. (1992) reported a positive E-R trend ($p = .004$) after adjustment for smoking. There were also positive trends for arsenic ($p = .004$) and PAH (*NS*). This cohort with 97 cases was included in the pooled analysis, showing a strongly positive association and a unit risk of 1.04 (1.02-1.05) without adjustment for any confounders. Chen et al. (2007) reported a unit risk of about 1.06 (1.02-1.11) for silica and lung cancer after adjusting for smoking but not arsenic. There was no E-R analysis adjusting for arsenic because reliable results could not be produced "due to the strong correlation (colinearity) between the cumulative exposure to respirable silica and arsenic." IARC (IARC, 1997, 2009) agreed with this assessment, but the pooled analysis included this study and found a significantly positive UR = 1.036 (1.021-1.052) attributable in part at least to arsenic (Steenland; Mannetje et al., 2001).

Chen and Chen (2002) split this cohort of four tin mines into two groups. The tin mine located in Limu

had low arsenic exposures, 29 lung cancer cases, and no significant associations ($p = .65$) of lung cancer with total dust, or with silicosis and lung cancer ($p = .46$). The Limu tin mine results adjusted for smoking are considered appropriate for assessment of silica effects although the results are unstable because of the small size of this cohort in the one mine (Figure 5).

Chinese Fe/Cu miners (Figure 6). The original analysis showed no E-R trend adjusted for smoking, but confounding from PAHs and radon was possible although the associations with lung cancer were nonsignificant (McLaughlin et al., 1992). Chen et al. (2007) revised the case-control analysis and with 75 cases found a positive E-R trend after adjustment for smoking. Adjustments for smoking, radon and PAHs reduced lung cancer risk to below the null, except for an OR of 1.4 (0.33–5.50) at about 4 mg/m^3-years. Chen et al. estimated the unit risk to be 1.1 (0.82–1.42), which is used in the weight of evidence, although it appears high compared to the categorical analysis (Figure 6).

Chinese tungsten miners (Figure 7). This is among the least confounded studies (no occupational confounders and adjusments for smoking), is among the larger studies ($n = 172$), and is a study with high exposures. The midpoint in the last exposure quintile is 41 (10–72) mg/m^3-years (Chen et al., 2007), whereas in the pooled analysis (Mannetje et al., 2002) the midpoint was about 134 mg/m^3-years, between the maximum of 232 mg/m^3-years and average of 30 mg/m^3-years in the 3rd quartile. In the pooled analysis there were only 135 cases, with a unit risk of 1.0095 (1.005–1.014) without adjustments for smoking (Steenland; Mannetje et al., 2001). However smoking was not a confounder as unit risks were 1.00 (0.99–1.02) both with and without adjustment for smoking (Chen et al., 2007). The E-R trend from Chen et al. (2007) is used because there are more cases than in the pooled analysis (172 vs. 135), it is consistent with the quintile analysis and original analysis (McLaughlin), and because revised and improved exposure estimates were used (Figure 7).

Sardinia miners with compensated silicosis (Carta et al., 2001) (Figure 8). This is a case-control study of 34 lung cancer cases with silicosis. There were significant associations of lung cancer with radon, smoking, and airflow obstruction. There was no association of lung cancer and cumulative exposure to silica or severity of silicosis, as the unit risk was 1.003 (0.92–1.09) after adjustment for confounders. IARC (2009) remarked that the study was small. Nevertheless the confidence intervals for lung cancer are narrow suggesting a stable negative result (Figure 8).

There are four studies where exposure is to minerals other than gold (Figure 9). Two studies clearly show no associations, and the other two are equivocal without either a clear negative or positive trend.

There are a total of 10 mining studies, including two negative studies of South African gold miners where controls had higher average exposure than cases (Hessel et al., 1986;, 1990). For the other eight cohorts, only three have high exposures greater than 10 mg/m^3-years and those with high silica exposure show no E-R association with lung cancer. The remaining five cohorts have low exposures of less than 10 mg/m^3-years but heterogeneous E-R trends, with ORs ranging from a low of 1.02 (0.39–2.6) to a high of 3.2 (1.3–7.6) at 6–7 mg/m^3-years. The latter study of South African gold miners (Hnizdo et al., 1997) is the only statistically significant study among the mining cohorts, although the other South African gold miner cohort shows a suggestive but nonsignificant E-R trend (Reid et al., 1996). The Chinese tin miner cohort is the smallest study and is of limited value because of unstable rates. Confounding from arsenic was presumed to not materially affect results, although trends appeared similar to tin miners exposed to higher concentrations of arsenic. Four studies (tungsten miners, US and Australian gold miners, and Sardinian silicotics) clearly detract from the silica–lung cancer hypothesis. One South African gold miner cohort (Hnizdo et al.) supports the silica lung cancer hypothesis, whereas the other three cohorts are equivocal (Figure 10).

3.2. Diatomaceous earth and potteries (Figure 14)

There are five cohorts in this industrial group. One is the cohort of diatomaceous earth (DE) workers (Checkoway et al., 1997) exposed to cristobalite, which can be produced under certain conditions when diatoms are heated. The remaining are potteries located in the UK (Cherry et al., 1998), China (Chen et al., 2007), and Germany (Ulm et al., 1999; Mundt et al., 2011) where quartz is heated when firing the ceramic bodies in the kilns.

DE (Checkoway et al., 1997) (Figure 11). The original and pooled analyses produced positive significant E-R trends, but had potential confounding that was adjusted in this report by indirectly adjusting for smoking and excluding pre-1930 hires to eliminate potential asbestos confounding and misclassification of exposure. These adjustments produced the most appropriate E-R trend and reduced estimated risks to below the null.

This study is important because exposure is predominately to cristobalite after calcining processes takes place, which may be more fibrogenic than quartz, and because it was decisive factor in the 1997 IARC conclusion. The number of cases is relatively small ($n = 69$) (Figure 11).

UK pottery (Cherry et al., 1998) (Figure 12). There is a strong association with silicosis (UR = 1.37 [1.24–1.53], but no association with lung cancer (UR = 1.01 [0.84–1.22]). The preliminary results from this cohort suggested excess risk from workers around the kiln and potentially exposed to cristobalite. The seemingly consistent results from DE and this preliminary result were major factors leading to the 1997 IARC conclusion that silica and its polymorphs were carcinogenic. The follow-up (Cherry et al., 1998) provided a more substantive analysis and did not substantiate the cristobalite association (Figure 12).

Chinese pottery (Chen et al., 2007) (Figure 13). The initial analysis (McLaughlin et al., 1992) showed a positive but nonsignificant trend with possible confounding from PAHs. Chen et al. (2007) updated the cohort and

improved exposure estimates. With 120 lung cancer cases they found significant confounding effect of PAHs that produced a spurious significant E-R trend. Adjustments for smoking and PAHs produced a flat E-R curve with a UR = 1.0 (0.96–1.09). The pooled analysis had 68 lung cancer cases, no adjustment for PAHs or smoking, and a positive nonsignificant UR of 1.004 (0.97–1.037). It is not clear why there was no association given the large confounding effect of PAHs in Chen et al. (2007). Silica exposure is among the highest among silica-exposed cohort with maximum exposures over 60 mg/m^3-years. Chen et al. provides the most appropriate evidence (Figure 13).

German pottery (Ulm et al., 1999). This cohort is comprised of ceramic workers and stone/quarry workers. The analysis by industry group is limited to a dichotomous E-R with only two high- versus low-exposure groups. The appropriate result from this cohort is the E-R trend from both industry groups, which shows no association, with an OR = 1.04 (0.53–1.89) at about 16 mg/m^3-years high-exposure category (Figure 14).

In summary, there are no significant or clear-cut associations between silica and lung cancer in the industry group of DE and potteries, the only group with exposure to cristobalite (Figure 14).

German Porcelain (Mundt et al., 2011) (Figure 12). There is a strong association with silicosis that may not be a linear E-R relationship despite the relatively low silica exposures. Diagnosis was based on a consensus of two readers and rounded opacities of ILO category 1/1 or greater. No silicosis cases were observed below 3 mg/m^3 years cumulative exposure. There were no associations of lung cancer and silica exposure for either men or women. Overall about half of the cohort were women, but there were only 20 lung cancer cases compared to 74 among the men. Possible cristobalite exposure was not mentioned, and there were no apparent workplace confounders.

3.3. Quarry and stone cutters (Figure 18)

There are three cohorts from Vermont, Finland, and Germany. The Vermont granite shed workers is a recent update that supersedes all previous studies of this cohort. The Finnish cohort became eligible for this report because of a quantitative E-R analysis in the pooled analysis. The German cohort contains both pottery workers plus stone and quarry workers.

Vermont granite shed cohort (Vacek et al., 2010) (Figures 15, 16). The updated cohort increased lung cancer cases from 201 to 356 by closing the information bias with complete cohort enumeration. Exposure estimates were improved (Vacek et al., 2010) by using all available sample data compared to Attfield and Costello (1995). The intervention part of this study showed no increase in lung cancer after the large reduction in silica exposure that occurred after installation of dust controls around 1940. This important finding is consistent with the E-R portion that showed no association, with a unit risk = 0.99 (0.95–1.03) (Figure 16). The updated results validate each other in showing no associations between lung cancer and silica exposure and supersede previous studies (Attfield et al., 2004; Graham et al., 2001) because this is the first study to use all data sources for complete enumeration of the cohort. The pooled analysis (Steenland et al., 2001)have these same limitations but still show no associations with a UR of 1.015 (0.96–1.07).

Finnish granite workers (Koskela et al., 1994) (Figure 17). This is a cohort with 38 lung cancer cases but no E-R analysis in the original publication. For the pooled analysis vital status was extended 9 years to 1994 and quantitative exposures estimated. Exposures were high at ~50 mg/m^3-years and no association of lung cancer with silica exposure was found, with a unit risk of 1.008 (0.988–1.03).

German stone workers (Ulm et al., 1999) (Figure 17). There are no associations of lung cancer and silica exposure overall or in either the stone/quarry or the ceramic cohort. The stone/quarry analysis has limitations in the dichotomous E-R analysis so both industries are considered one study. The combined cohort UR = 1.02 (0.67–1.55).

In summary, there were no associations between lung cancer and silica exposure in these cohorts where there are no known occupational confounders (Figure 18) and low, intermediate, and high exposures (see Figure 26).

3.4. Industrial sand (Figure 21)

Three new cohorts exposed to industrial sand have been added to the data since the 1997 IARC monograph (Brown et al., 2003, 2005a, 2005b; McDonald et al., 2001; Steenland and Sanderson, 2001). Two cohorts were available for the pooled analysis (McDonald et al., 2001; Steenland and Sanderson, 2001), but only the Steenland and Sanderson version was used because of "considerable overlap." All three cohorts were described in the latest IARC Working Group results (2009).

US cohort from 18 industrial sand plants (Steenland and Sanderson, 2001) (Figure 19). The original study used SMR, SRR, and case-control analyses to assess E-R trends. The criterion for including cases and controls was changed with the change in study design from cohort to case-control. There are no known confounding work exposures. The pooled analysis uses a consistent analytical method and showed a strong association of silicosis mortality and silica exposure validating exposure estimates. There were 85 lung cancer, a unit risk of 1.19 (0.95–1.50), and low exposures (<5 mg/m^3-years). Results from both studies are similar but only the pooled analysis is statistically significant (Figure 19).

Updated cohort of eight US industrial sand plants (McDonald et al., 2005) (Figure 20). This cohort study extended vital status 6 years to 2000, added 20 lung cancer cases for a total of 105, and confirmed the original findings (Hughes et al., 2001) supporting a causal association between lung cancer and quartz exposure after adjustments for smoking. The cohort was slightly larger than

the other US sand study and had a steeper E-R trend, with OR = 2.64 at the high category of about 6 mg/m^3-years.

UK cohort of seven industrial sand plants (Brown et al., 2005b) (Figure 20). This is the smallest industrial sand cohort with 82 lung cancer cases but the one with the highest exposures. There were no associations of silica with NMRD or lung cancer, with the lung cancer OR = 0.92 (0.44–1.92) at about 12 mg/m^3-years and a p value of .80 for E-R trend.

In summary, the two industrial sand cohorts in the US show positive E-R trend that support the silica–lung cancer hypothesis. The UK cohort produced no associations of lung cancer and silica exposure despite higher exposures to silica (Figure 21).

3.5. Comparison of IARC (1997, 2009), pooled analysis, and this report (Table 1)

Results from this review are summarized and compared to results from 10 "least confounded" studies of IARC (1997), 10 cohorts where individual study results are pooled for an overall E-R analysis (Steenland; Mannetje et al., 2001), 14 cohorts discussed by the IARC Working Group (2009), and 18 studies evaluated in this review (Table 1).

IARC (1997). The basis for an IARC judgment is somewhat speculative because IARC does *not* explicitly indicate whether a specific study supports or does not support an association between silica and lung cancer. Their judgment regarding chance, bias, and confounding on specific studies is generally not known. An exception is the exclusion of the Chinese tin miner cohort (McLaughlin et al., 1992) because of arsenic confounding. But the IARC consensus on a positive but not statistically significant E-R trend, for example, is unknown. IARC (1997) indicated there were 10 "least confounded examinations of an association between silica exposure and cancer risk," and not all demonstrated excess risk. "In some studies, increasing risk gradients have been observed in relation to dose surrogates" that "could not be explained by confounding or other biases." This evidence led the Working Group to conclude that "overall the epidemiological findings support increased lung cancer risks" from silica. "Support" is uncertain and undefined because a majority of the studies suggest no E-R association between lung cancer and silica exposure.

IARC (1997) largely based their conclusion of *sufficient evidence* of silica carcinogenicity in humans on 10 "least confounded" industrial cohorts. The source of this conclusion is unclear, as only two of the five cohorts with E-R analysis or intervention design showed a positive association (30% of cases). So a majority of E-R studies were negative (or would be if bias had been considered). Several negative studies should have been included but were not included by IARC.

Several limitations have been noted in the IARC conclusion. One is that from one to four cohorts could have been added to the IARC list. The Chinese tungsten miner cohort was among the least confounded, but inexplicably was not included among the 10 studies. The Chinese Fe/Cu cohort was not included, although there was no more potential confounding from PAHs and radon in this cohort than potential confounding from PAHs in the pottery cohort (McLaughlin et al., 1992), which was included. The UK pottery cohort was an extended abstract with only preliminary analysis. These preliminary results were superseded by a more complete E-R analysis using cumulative silica exposure where the cristobalite risk was not confirmed. In the DE cohort, the Working Group did not consider possible effects of confounding from asbestos or misclassification of silica and asbestos exposure in the pre-1930 hires. These factors are considered in this review and transformed the DE study into a negative study.

Four studies (tungsten, Fe/Cu, and the two South African gold miner studies) could be added to the "least confounded" cohorts; half of these are considered positive (South African gold miner cohorts, Hnizdo, and Reid). These additions produce a total of nine quantitative E-R or intervention studies and 400 additional lung cancer cases that doubles the number to 864 cases, 70% in negative studies.

In summary, IARC (1997) considered nine studies (excluding studies of silicotics). Five of these were E-R studies with 424 cases. Based on the information available at the time, 2 are considered to show positive E-R trends with 30% of the cases. The other three were negative studies with negative to slight positive but non-significant slopes. A more critical review of confounding in the DE cohort might have led to a different conclusion, and subsequent analysis of the UK pottery produced a different negative association. If all the available E-R studies had been considered, there were 9 studies with 824 cases. Based on the available evidence at the time, it appears 3 were positive studies with 25% of cases and 6 were negative studies with flat or non-significant trends and 75% of the cases. The tin cohort is confounded and is not included in any of these totals (Table 1). Based on both the 5 and 9 E-R studies available to IARC (1997), it is my conclusion that the weight of evidence is more supportive of a conclusion of limited or inadequate evidence of silica carcinogenicity, rather than a conclusion of sufficient evidence in humans. This conclusion remains the same whether based only on information available at the time or on a post-hoc conclusion from more detailed analysis, updates or control of confounding (Table).

Pooled analysis of 10 cohorts (2001) (Table 1). The pooled analysis (Steenland; Mannetje et al., 2001)

E-R cohort	IARC (1997) conclusions	Post hoc conclusions
US gold	Negative	Negative
Vermont granite	Negative	Negative
DE	Positive	Negative (- bias)
UK pottery	Positive	Negative (+ analysis)
China pottery	Negative	Negative
Tungsten	Negative	Negative
Fe/Cu	Negative	Negative
Hnizdo gold miner	Positive	Positive
Reid gold miner	Negative	Positive
$N = 9$	3 = positive	2 = positive

Table 1. Summary of comparison of E-R results from IARC (1997, 2009), pooled analysis (Steenland et al., 2001), and this report.

Cohort, reference	10 least confounded studies and 9 E-R studies (IARC, 1997)	Pooled analysis (Steenland; Mannetje et al., 2001) of 10 E-R cohorts	16 cohorts cited with E-R analysis (IARC, 2009)	This report, 18 cohortswith most appropriate E-R analysis
US gold (Steenland et al., 1995a)	SMR = 1.31 (0.88–1.87) at 48,000 dust-day (p = .21 for trend); n = 115, Negative	UR = 1.006 (0.76–1.34), Add 4 years of follow-up n = 156, Negative	SMR = 1.31 (0.87-1.89) at >48,000 mppcf-years n = 115, Negative	(Steenland; Mannetje et al., 2001) UR = 1.006 (0.76–1.34) n = 156, Negative
Danish stone (Guenel et al., 1989)	No ER analysis SIR = 2.00 (1.49–2.69) Positive	—	—	—
Vermont granite (Costello et al., 1988)	Intervention designSMR pre- and post-1940 hires (high vs. low exposure): 1.81 (1.33–2.4) vs. 1.73 (1.01–2.8) N = 118, Negative	Attfield (personal communication) UR = 1.015 (0.96–1.07) n = 124, Negative	(Attfield et al., 2004) UR = 1.01 (0.31-3.35)n = 201 Without high-exposure group UR = 1.21(1.2-1.22)Unresolved (Graham et al., 2004)Intervention Negative	(Vacek, P et al., 2010) UR = 0.99 (0.95–1.03) n = 356, Negative Intervention:Lung cancer SMRPre-1940 hire: 1.23 (1.01–1.49) Post-1940 hire: 1.44 (1.27–1.63) Negative
Crushed stone (Costello et al., 1995)	No ER analysis SMR 3.54 granite Positive	—	—	—
Diatomaceous earth (DE) (Checkoway et al., 1997)	RR = 2.74 (1.38–5.5) in highest exposure category N = 77, Positive	UR = 1.05 (1.007–1.10) N = 77, Positive	UR = 1.06 (1.01–1.11) is same with or without adjusting for asbestos ER association n = 77, Positive	Calculated OR = 1.35 (0.66–2.69) at 34 mg/m³-years; adjusted for smoke, no pre-1930 hires n = 69, Negative
Refractory brick (Dong et al., 1995)	No ER analysis SRR = 1.49 (1.15–1.9) Positive	—	—	—
Refractory brick (Merlo et al., 1991)	No ER analysis SMR = 1.51 (1.00–2.2) Positive	—	—	—
UK pottery (Cherry et al., 1997)	OR = 1.88 at >200 μg/m³ avg; 2.16 (1.1–4.2) at >400 μg/m³ max no assoc with μg/m³-years N = 52, Positive	—	(Cherry et al., 1998) UR = 1.01 (0.85–1.19) n = 52, Negative	(Cherry et al., 1998) UR = 1.01 (0.85–1.19), adjusted for smoking n = 52, Negative
Chinese pottery (McLaughlin et al., 1992)	OR = 1.5 at high exposure (NS) n = 62, Negative	UR = 1.004 (0.97–1.04) N = 68, Negative	(Chen et al., 2007) OR = 0.9 (0.19–4.32) at 41mg/m³-years n = 120, Negative	(Chen et al., 2007) UR = 1.0 (0.96–1.09), adjusted for PAH, smoking n = 120, Negative
Registered silicotics	Positive studies	—	—	—
Cohorts not among IARC 1997 least confounded cohorts				
Silicotic miners (Carta et al., 2001)	—	—	SMR = 1.35 (0.73–2.51) at >10 mg/m³-years n = 34, Negative	UR = 1.003 (0.93–1.09); adjusted for smoking, COPD, radon, ILO n = 34, Negative
SA gold (Hnizdo et al., 1991)	RR = 2.92 (1.02–8.4) at 7.3 n = 77, Positive	UR = 1.23 (1.03–1.47) n = 77, Positive	OR = 3.19 (1.3–7.6) at >6.3 mg/m³-years n = 78, Positive	Pooled analysis: UR = 1.23 (1.03–1.47) n = 77, Positive
SA gold (Reid and and Sluis-Cremer 1996)	UR = 1.12 (0.97–1.3) Possible overlap, radon confounding N = 143, Negative	—	—	UR = 1.12 (0.97–1.3); adjusted for smoking, no significant overlap N = 143 Positive or ±
Australia gold (de Klerk et al., 1998)	UR = 1.00 (0.988–1.004)E-R by exposure score-year n = 138, Negative	De Klerk (personal communi-cation) UR = 1.016 (0.99–1.04) n = 135, Negative	UR = 1.00 (0.988–1.004)E-R by exposure score-year n = 138, Negative	Pooled analysis:UR = 1.016 (0.99–1.04) n = 135, Negative
Chinese tungsten (McLaughlin et al., 1992)	OR = 0.5 at high exposure (p = .01) n = 93, Negative	UR = 1.0095 (1.005–1.014) Significant E-R = positve ?? n = 135, Negative	(Chen et al., 2007)OR = 1.0 (0.55–1.66) at 41 mg/m³-years N = 172, Negative	(Chen et al., 2007) UR = 1.0 (0.99–1.02); adjusted for smoking n = 172, Negative
China tin (McLaughlin et al., 1992)	Confounded by arsenic Biased and not used, n = 87, Not considered	UR = 1.04 (1.006–1.04)n = 97Confounded by arsenic Should be excluded, Positive	(Chen et al., 2007) Unresolved arsenic confounding Not considered	(Chen et al., 2002) OR = 2.4 (0.6–10.2) at 5.4 mg/m³-yearsLimu mine low As; unstable n = 29, Equivocal ±

Table 1. continued on next page

Table 1. Continued.

Cohort, reference	10 least confounded studies and 9 E-R studies (IARC, 1997)	Pooled analysis (Steenland; Mannetje et al., 2001) of 10 E-R cohorts	16 cohorts cited with E-R analysis (IARC, 2009)	This report, 18 cohortswith most appropriate E-R analysis
Chinese Fe/Cu miners (McLaughlin et al., 1992)	OR = 0.7 at 30 (NS)n = 87, Negative	—	(Chen et al., 2007)OR = 1.4 (0.33–5.50) at 4 mg/m³-years n = 143, Negative	(Chen et al., 2007) UR = 1.1 (0.82–1.42); adjusted for PAH, radon, smoking n = 143, Negative
Cohort, reference	10 least confounded studies and 9 E-R studies (IARC, 1997)	Pooled analysis (Steenland; Mannetje et al., 2001) of 10 E-R cohorts	16 cohorts cited with E-R analysis (IARC, 2009)	This report, 18 cohortswith most appropriate E-R analysis (19 ER curves)
Finnish granite (Koskela et al., 1994)	No ER analysisIncreased SMR in grey granite	Koskela (personal communi-cation) UR = 1.008 (0.99–1.03) n = 38, Negative	(Koskela et al., 1994)No quantitative ER analysis Increased risk associated with tenure	Pooled analysis UR = 1.008 (0.99–1.03) n = 38, Negative
German stone/ potteryAll included in analysis(Ulm et al., 1999)	NA	—	OR = 1.04 (0.53–1.89) at >4.68 mg/m³-years N = 247, Negative	OR = 1.04 (0.53–1.89) at 16 mg/m³-years n = 247, Negative
US industrial sand (Steenland and Sanderson, 2001)	NA	UR = 1.19 (0.95–1.50) n = 85, Positive	RR = 1.57 at >1.28 mg/m³-years (p = .07) n = 75, Positive	Pooled analysis UR = 1.19 (0.95–1.50) N = 85, Positive
US industrial sand (McDonald et al., 2005)	NA	—	OR = 2.64 at >4.5 mg/m³-years (trend p = .06) n = 105, Positive	OR = 2.64 at 6 mg/m³-years (p = .06) n = 105, Positive
UK industrial sand (Brown et al., 2005)	NA	NA	RR = 0.88 (0.45–1.73) at >1.0 mg/m³-years; p = .79 n = 82, Negative	RR = 0.92 (0.44–1.92) at 12 mg/m³-years (p = .80); adjusted for latency, DOH, quarry n = 82, Negative
German Porcelain (Mundt et al., 2011)	NA	NA	NA	RR = 0.08 (0.5–1.5) (M); 0.4 (0.1–3.4) (F) @ >6 mg/m³-years; n = 99; negative
Subtotals, excluding pooled analysis	5 ER cohorts studies, n = 425, 2 = positive (30%) 9 total ER studies, n = 824 3 = positive (25%)	10 ER cohorts: n = 992; 4 = positive (24%); 6 = negative (76%)	14 ER studies: n = 16394; 4 = positive (20%); 10 = negative (80%)	18 ER studies: n = 2141; 3 = positive (12%); 2 = equivocal (8%); 14 = negative (80%)

Note. NA = not available; positive = association supporting silica-lung cancer hypothesis; negative = no association, does not support silica-lung cancer hypothesis; underline = most appropriate ER.

was conducted in part because of limitations in the IARC (1997) evidence. The "very supportive findings from individual studies" was countered by no cancer excesses in some studies; conclusions remained controversial (Hessel et al., 2000); exposure measures differed between studies; and E-R trends were not always consistent where E-R analyses were conducted. Among the IARC least confounded E-R studies there were 5 that provided evidence useful for evaluating causality. Two of these were considered positive and consistent with a causal association. This is clearly not a majority, and subsequent analyses suggest no association between silica and lung cancer.

The pooled analysis included four of IARC (1997) least confounded cohorts (US gold, Vermont granite, DE, and Chinese pottery). All showed weak trends; only the DE trend was significant. Three E-R studies not included by IARC among the least confounded studies were added to the pooled analysis (Hnizdo South African gold, Chinese tungsten, and tin). Two showed significantly positive E-R trends. However the tin miner cohort was confounded by arsenic so a silica effect could not be determined and this study was not considered by IARC (1997). Three studies previously considered added quantitative exposure estimates and E-R analyses (Australia gold, Finnish granite, and US granite). E-R analyses produced weak positive but nonsignificant trends and are considered negative studies. A completely new cohort of US industrial sand workers that showed a strong but nonsignificant positive E-R trend was also added. Overall, the pooled analysis showed positive E-R association in all 10 cohorts, 4 of which were statistically significant (DE, South African gold, US industrial sand, China tungsten and tin) (Table 1, Figure 22). This report agreed with the pooled analysis results on eight of the studies, but disagreed on DE and China tin cohorts because of confounding.

The pooled analysis is an excellent idea and produced three E-R analyses that have not reported elsewhere (Australia gold, Finnish stone, US gold). Limitations of this analysis include lack of adjustment for confounding and the inclusion of the Chinese tin miner cohort with confounding arsenic exposures. Another limitation is that IARC (2009) considered at least five additional studies (UK pottery, Sardinia miners, Fe/Cu miners, German stone/potteries, and McDonald et al. US industrial sand).

The pooled analysis (Steenland; Mannetje et al., 2001) had 10 cohorts, a UR = 1.011 (1.006–1.015) and a categorical OR = 1.5 (1.2–1.9) at the highest exposure quintile, with a median of 28 mg/m^3-years.

It is not clear how much the pooled analysis contributes to the weight of evidence regarding causality, or how strong the evidence is that IARC (2009) relied upon to support their conclusion. The strength of evidence from the pooled analysis is limited for several reasons.

i. The tin miner cohort results should be excluded because of confounding from arsenic.
ii. There are nine cohorts with 895 lung cancer cases and only four with statistically significant E-R trends and 426 lung cancer cases.
iii. There were five studies cited by IARC (2009) that were not included in the pooled analysis. These excluded studies are UK pottery, Sardinian silicotic miners, Fe/Cu miners, German stone/pottery workers, and US McDonald industrial sand, with 581 lung cancer cases. Four negative studies with 476 cases outweigh the one positive study with 105 cases (Table 1).

IARC (2009) (Table 1). IARC (2009) had all the data available for this report except they did not consider the tin and South African Reid gold cohorts and did not cite the Finnish granite study reported only in the pooled analysis. Two studies were not yet published, the updated Vermont granite shed cohort (Vacek et al, 2010) and the German porcelain industry cohort (Mundt et al., 2011) (Table 1). The E-R evidence was essentially the same for IARC (2009), as the evidence from the Vermont granite shed cohort has generally been negative with the exception of the Davis et al. proportional mortality study since the first intervention study in 1988 (Costello) through the intervention and E-R analyses in 2005 (Graham, Attfield). The 2010 study reported a significantly negative trend with complete enumeration versus a nonsignificant trend. The Working Group concluded there was *sufficient evidence* supporting carcinogenicity and the strongest evidence was from the pooled analysis and meta-analyses. Visual scanning (Figures 22–26) and quantitative analysis of the evidence (Table 2) does not support the IARC (2009) conclusion.

Overall IARC (2009) cited 14 E-R studies. Based on the data they used, four studies (Checkoway et al., 1997; Hnizdo et al., 1997; McDonald et al., 2005; Steenland and Sanderson, 2001) supported the silica–lung cancer hypothesis (Table 1). The majority of studies did not support the hypothesis. IARC (2009) did not include a positive South African gold mine study (Reid and Sluis-Cremer, 1996), which would have led to 5 positive studies out of 16 total studies. Overall the majority of this evidence cited by IARC (2009) does not support the silica–lung cancer hypothesis.

Current review (Figures 23–26, Table 1). This report included 18 cohorts with 2141 lung cancer cases and 19 quantitative E-R analyses that support a conclusion of no apparent causal association between lung cancer and silica exposure based on E-R evidence.

Three studies with 267 (13%) cases had strong associations (Hnizdo gold miners, McDonald, and Steenland industrial sand workers). Two studies with 172 (8%) cases had suggestive but nonsignificant positive E-R trends (Linu tin and Reid gold miners). The remaining 14 negative E-R analyses with 1702 (79.5%) lung cancer cases do not support the silica–lung cancer hypothesis. Overall there is a negative E-R trend (coefficient = –0.012 or UR = 0.99) based on a weighted regression using the ORs of workers at greatest risk (highest exposure) in each

study (Figure 26). This evidence is consistent with and supported by the most appropriate E-R trends of each study (Figure 25, Table 1). This evidence in large part is consistent with the results reviewed by IARC and to a lesser extent the data from the pooled analysis.

These results are inconsistent with the conclusions of IARC and from the pooled analysis, but are consistent with the evidence cited by IARC where a majority of the evidence is negative and *not* supportive of the silica–lung cancer hypothesis. Note that the major substantive difference in the data is with regard to the DE cohort, which is considered a positive study by IARC and pooled analysis. It is considered a negative study based on adjustments for exposure misclassification in the pre-1930 hires and confounding from smoking at higher exposure levels.

Cohort	IARC (1997)	Pooled (2001)	IARC, 2009
US Gold	Negative	± UR = 1.006 (0.76–1.34)	Negative
Vermont granite	Negative	± UR = 1.015 (0.96–1.07)	Negative
DE	Positive	+ UR = 1.05 (1.007–1.097)	Positive
UK pottery	Positive	—	Negative
Chinese pottery	Negative	+ UR = 1.004 (0.97–1.037)	Negative
Sardinia silicotic miners	—	—	Negative
SA gold (Hnizdo)	Positive	+ UR = 1.23 (1.03–1.47)	Positive
SA gold (Reid)	Negative		
Australia gold		± UR = 1.016 (0.99–1.04)	
Tungsten	Negative	+ UR = 1.0095 (1.005–1.014)	Negative
Tin	Confounded	+ UR = 1.036 (1.0121–1.052)	Confounded
Fe/Cu	Negative	—	Negative
Finnish granite	—	+ UR = 1.008 (0.988–1.028)	—
German stone/ pottery	—	—	Negative
Industrial sand (Steenland)		+ UR = 1.19 (0.95–1.50)	Positive
Industrial sand (McDonald)			Positive
Industrial sand (UK)			Negative

+ = equivocal or positive trend but not significant; + = positive study; – = not considered.

4.0. Conclusions (Table 1, Figures 23–26)

The evidence from the most appropriate E-R analyses indicates a minority of studies support the silica lung cancer hypothesis, whereas a large majority of studies and cases do *not* support an association between cumulative exposure to respirable silica and increased risk of lung cancer. The basis for this conclusion is a consistent lack of clear exposure-response trends in industries where silica exposure occurs, and is summarized in Figures 23 to 26 and Table 1. The data used in these tables and figures were selected after consideration of potential roles of chance, bias, and confounding; consideration of the shape and slope of the E-R trends; and consideration of the quality of each study (e.g., exposure assessment and range, number of cases). The evidence supporting this conclusion is not substantively different from the evidence used by IARC and in the pooled analysis (IARC, 1997, 2009; Steenland; Mannetje et al., 2001) where a different conclusions were reached.

IARC (2009) concluded there was sufficient evidence that silica caused lung cancer with a focus on studies with quantitative E-R analyses. The rationale for the IARC conclusion was based largely on the pooled E-R analysis of 10 major studies and the same conclusion was reached from both.

The pooled analysis combined data sets that produced a "relatively shallow exposure-response-trend" with a unit risk = 1.011 (1.006–2.84). These overall results "tend to support" a conclusion that silica is an occupational carcinogen.

Individually and after consideration of subsequent analyses, results from the pooled analysis provides less support than IARC gave them. The tin cohort in the pooled analysis was clearly confounded by arsenic and should have been excluded. Four studies have clear positive E-R slopes (DE, South African gold, tungsten, and tin) (Figure 22). The relatively shallow slope for the tungsten miner cohort is statistically significant but is inconsistent with a later study having more cases, improved exposure estimates and a flat slope where UR = 1.0 (0.99–1.02) (Chen et al., 2007). Australian gold miners have a steeper but insignificant E-R slope compared to tungsten miners, UR = 1.02 (0.99–1.04) versus UR = 1.02 (1.01–1.014), respectively, in the pooled analysis. Both are considered negative studies. Despite the same number of lung cancer cases and shallower slope, the tungsten E-R trend is statistically significant and has narrower CI. The US industrial sand has a steep slope that is not significant.

Data from four cohorts in the pooled analysis are considered the most appropriate E-R data available (US and Australian gold miners, Finnish granite workers, and US industrial sand), three of which are not positive.

Six of the studies from the pooled analysis are replaced by more appropriate data. The steep E-R trend for Chinese tin miners is due to confounding from arsenic. Limiting the cohort to the Limu mine (Chen et al., 2002) where there is no apparent arsenic confounding produces an unstable but suggestive E-R relationship, with the second and fourth quartiles having ORs >2.0 whereas the OR in third quartile is 1.5. The E-R trend for DE workers (Checkoway et al., 1997) appears to be due to smoking and misclassification of exposure in pre-

1930 hires, which when corrected shows no E-R trend. The significant E-R trend of Chinese tungsten miners is contradicted by the Chen et al. (2007) analysis that found a unit risk of 1.0 (0.96–1.09) and had 37 more lung cancer cases, although follow-up dates were the same. The categorical analysis from the South African gold miner cohort (Hnizdo et al., 1997) is adjusted for smoking. The updated US granite worker cohort (Vacek et al., 2010) improved exposure estimates, enumerated the complete cohort, extended follow up for 10 more years, and added 232 lung cancer cases and over 2000 new cohort members and so is selected over the unpublished earlier analysis or subsequent more complete published analysis by Attfield.

The revised evidence for these 10 cohorts (Figure 23) shows three studies with ORs above 2-fold at low exposures less than 10 mg/m^3-years. South African gold and US industrial sand cohorts were the only

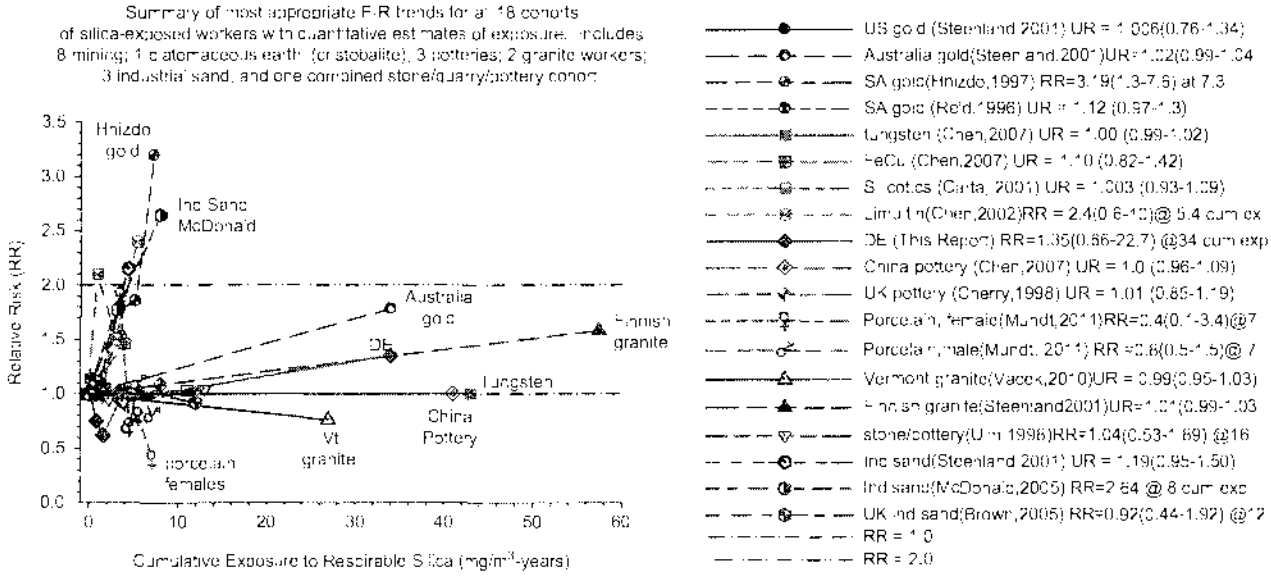

Figure 25. Summary of most appropriate E-R of 18 silica-exposed cohorts.

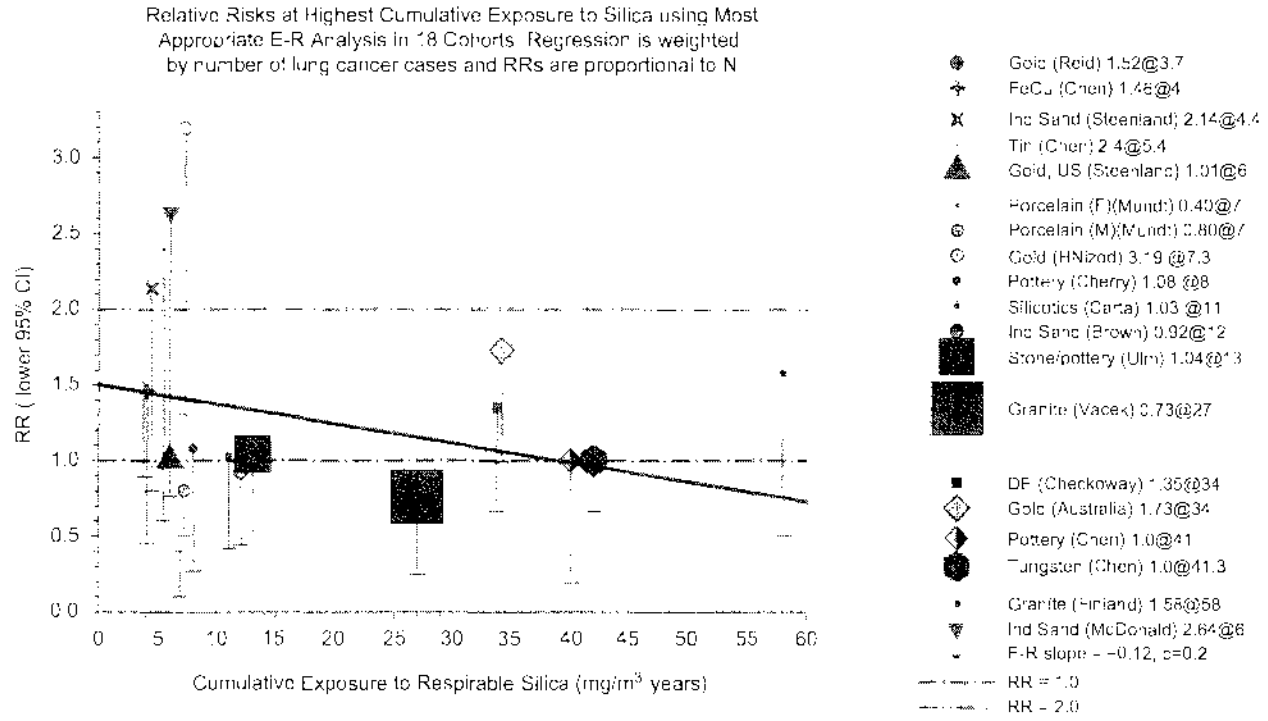

Figure 26. RRs and E-R in highest exposure categories among 18 silica exposed cohorts.

ones with strong associations and only one was statistically significant (South African gold). The tin miner results could be chance findings. The remaining seven cohorts show weak or no associations; four of these E-R trends are flat (pottery, tungsten, granite, gold) and the granite shed result is a significantly negative E-R trend (Figure 23). These results contradict the evidence from the pooled analysis (Figure 22), which was said to "support the decision by the IARC to classify inhaled silica in occupational settings as a carcinogen" (Steenland; Mannetje et al., 2001).

Seven E-R studies could not be included in the pooled analysis but were available for IARC (2009) consideration (Figure 24). One study of US industrial sand workers showed a strong association (McDonald et al., 2005), whereas a South African gold miner cohort (Reid et al., 1996) showed a weaker nonsignificant E-R trend. Four of the seven cohorts showed no associations with flat E-R curves, three of which occurred at higher concentrations of 10-20 mg/m^3-years. The remaining Fe/Cu cohort showed no apparent association at low exposure. These results are inconsistent with the IARC carcinogenic classification for inhalable silica (Figure 24). Two studies were not available for IARC (2009). These were the updated Vermont granite cohort (Vacek et al, 2010) and the German porcelain industry cohort (Mundt et al., 2011).

Results using the most appropriate E-R analyses from all 18 cohorts and 19 E-R trends are shown in Figures 25 and 26. Two features of this evidence clearly stand out from this analysis.

1. There are two groups of studies with opposite results. There is a small group of positive studies with clear E-R trends and strong associations. A larger group of negative studies show no E-R associations (flat or negative E-R slopes) and no excess risks at high exposures. A small intermediate group has shallow E-R slopes and weak associations with ORs about 1.5 or less at high exposures (Figure 25).
   The group of five positive studies (2 are equivocal, tin and Reid SA gold) is consistent with the silica–lung cancer hypothesis and show steep E-R slopes and strong associations at about 2-fold or greater increased risk. These studies include two cohorts of South African gold miners, two cohorts of US industrial sand workers, and tin miners from a single mine. The ORs are 3.19, 1.52, 2.64, 2.15, and 2.4 at low exposures of 7.3, 3.7, 6, 4.4, and 5.4 mg/m^3-years, respectively. Only one of the gold miner cohort (Hnizdo et al., 1997) and one of the industrial sand cohorts (McDonald et al., 2005) are statistically significant. The OR from the tin miner study is unstable because of small numbers.
   The second group of 14 negative studies is not supportive of the silica–lung cancer hypothesis. Four studies have negative slopes (US granite, UK sand and German porcelain workers, both men and women). RRs are less than one at highest exposure levels of about 2, 12 and 7 mg/m^3-years respectively. Two studies have flat E-R slopes, both with URs = 1.0 (tungsten miners and China pottery workers). Four studies have very shallow slopes with URs = 1.01, 1.006, 1.016, 1.003 (i.e., UK pottery, US and Australian gold miners, Sardinia miners, respectively). The remaining four cohorts are somewhat intermediate with weak strength of association (ORs less than 1.5 at maximum exposure) and shallow E-R slopes. They do not support the silica–lung cancer hypothesis but provide only limited weight against a carcinogen classification.

2. The second observation is with regard to the distribution of studies by range of cumulative exposures. There is a tendency for studies with higher exposures to have weak or nonexistent associations. The negative E-R trend (UR = 0.99) from the weighted regression supports that impression (Figure 26).
   Studies can also be classified in low-, intermediate-, and high-exposure categories. There are ten E-R curves in the low-exposure category of less than 10 mg/m^3-years, four studies in the intermediate category of 10–30 mg/m^3-years, and five studies in the high category of more than 30 mg/m^3-years (Figure 26).
   All of the 3 positive and 2 equivocal studies are in the low exposure group below 10 mg/m^3-years. RRs at high exposures are >1.5 (Reid) and four have maximum RRs >2.0 (2 US industrial sand, Limu tin and SA gold). There are a total of 439 (20.5%) cases and a weighted average RR of 2.26. There are 5 negative E-R trends and 445 lung cancer cases in the low exposure group. Both sexes in the porcelain cohort had maximum RRs below 1.0. RRs were 1.02 and 1.08 for UK pottery and US gold, with Fe/Cu miners having a high RR of 1.4, for a weighted average of 1.08. Over half (10/19) of the E-R trends and 41% of the 2141 lung cancer cases were in the low cumulative silica exposure group, with an overall weighted RR of 1.67. A RR this high is suggestive of a possible weak association (Figure 26).
   In the intermediate exposure category there are 4 negative E-R studies with 719 (34%) lung cancer cases. Two studies have RRs less than 1.0 (US granite, UK industrial sand) and 2 have RRs of 1.04 and 1.03 (German stone/pottery and Sardinia silicotics). The weighted average RR is 0.89, indicative of no association with silica (Figure 26).
   In the high exposure category there are 5 negative E-R studies with 534 (25%) lung cancer cases. Three studies have RRs ranging from 1.35 to 1.73 (DE, Australian gold miners, Finnish granite workers) and two studies have flat curves and RRs of 1.0 (China pottery workers and tungsten miners). The average weighted RR is 1.27 in the high exposure category, indicative of no association for workers in the high exposure category (Figure 26).

This evidence from the 18 E-R cohorts with the most appropriate results is summarized as

Industry/Reference	N*	High CE+	RR high cumulative exposure group (95% CI)	E-R?#	Causal?
Diatomaceous earth (Checkoway et al., 1997)/adjusted	69	34	1.35 (0.66–2.69)	No	No
China pottery (Chen et al., 2007)	120	41	1.0 (0.28 1.66)	No	No
UK pottery (Cherry et al., 1997)	52	8	1.08 (0.27 4.02)	No	No
German stone, pottery (Ulm et al., 1999)	247	13	1.04 (0.53-1.89)	No	No
US gold miners (Steenland et al., 1995) via pooled	156	3.5	1.02 (0.39–2.61)	No	No
Australian gold miners (de Klerk et al., 1998) via pooled	135	35	1.73 (0.71–3.79)	No	No
South African gold miners (Hnizdo et al., 1997)	77	7.3	3.19 (1.3 7.6)	Yes	Yes
South African gold miners (Reid et al., 1996)	159	3.7	1.52 (0.89 6.45)	±	±
South African gold miners (Hessel et al., 1986)	133	—	—	No	No
South African gold miners (Hessel et al., 1990)	231		—	No	No
Chinese iron/copper miners (Chen et al., 2007)	143	4	1.4 (0.35–5.50)	No	No
Chinese tungsten (Chen et al., 2007)	172	41	1.0 (0.55–1.66)	No	No
Linu Chinese tin miners (Chen et al., 2002)	29	5.4	2.4 (0.6 10.2)	±	+
Sardinia silicotic granite, miners (Carta et al., 2001)	34	11	1.03 (0.42–2.50)	No	No
US Granite (Vacek et al., 2010)	356	27	0.76 (0.25–2.22)	No	No
Finnish granite (Koskela et al., 1994) via pooled	38	58	1.58 (0.50 4.89)	No	No
US Industrial sand (Steenland, 2001) via pooled	85	4.4	2.15 (0.80 5.94)	Yes	Yes
US Industrial sand (McDonald et al., 2005)	105	6	2.64 (p=.02)	Yes	Yes
UK industrial sand (Brown et al., 2005b)	82	12	0.92 (0.44–1.92)	No	No
German Porcelain (Mundt et al, 2011)	74M	7	0.80(0.5-1.5)	No	No
	20F	7	0.40(0.1-3.4)	No	No

* = number of lung cancer cases; + = cumulative exposure at high exposure levels or high-exposure category; # = exposure-response where yes = clearly positive; + = suggestive of no, but equivocal; no = clearly no E-R.

The weight of evidence is now evaluated by Hill's guidelines of strength of association, biological gradients, consistency, and consideration for roles of chance, bias, and confounding.

Strength of association. A strong association is considered greater than 2-fold. A RR of 1.5-2 is considered moderately weak and less than 1.5 weak. Weak associations are considered not likely to be supportive of causal associations as they are potentially more affected by residual confounding. In these E-R studies, strength of association is evaluated for the workers at highest risk, namely those with the highest exposure.

The weighted average RR for all studies combined is 1.51, suggesting an overall moderate strength of association (Figure 26). As shown in the table below, strengths of association are consistently weak or negligible and become weaker as exposure increases (Figure 26). These data are consistent in not supporting the Strength of Association guideline. This evidence therefore does not support a causal association between silica and lung cancer.

	Strength of association at highest exposure levels				
	Strong	Moderate	Weak to no association		
	RRs >2	RRs 1.5 2	RRs 1.2–1.5	RRs 1–1.2	RRs ≤1.0
No. of studies (%)	4 (24)	3 (18)	2 (12)	4 (24)	4 (24)
No. of cases (%)	296 (14)	316 (15)	212 (10)	489 (24)	730 (26)

Exposure-response or biological gradient. A positive biological gradient (or E-R trend) is strong evidence of a causal association. Statistical significance is a factor, but a clear positive, nearly monotonic trend is more important. Selection of the most appropriate E-R trend was based on several factors, including the latest analysis, the best exposure data, and the lack of potential confounding and bias.

Eighteen cohorts had quantitative data evaluating E-R trends. These most appropriate trends are shown in Figures 25 and 26 and Table 1. The data in Figure 25 indicate a relatively clear separation between five studies with steep slopes and strong E-R trends at low exposures and the remainder of the studies showing little or no evidence of E-R relationship at both high and low exposures. This evidence is consistent with the negative E-R trend where higher risks are found in studies with low exposures and risk decrease as exposure increases (Figure 26).

These visual presentations are consistent with numerical estimates of these same data as demonstrated in the table below. These data indicate a consistent pattern of no biological gradients. Over two thirds of the studies show no E-R trends, nearly one quarter show equivocal but not definitive trends and only two (10%) show clear strong

trends and at low exposures. The table below shows the consistent lack of positive exposure-response trends.

	Strong E-R trends	Suggestive nonsignificant trends	No apparent E-R trends
No. of studies (%)	2 (12)	3 (18)	12 (71)
No. of cases (%)	182 (8.9)	257 (12.6)	1604 (79)

Consistency. Consistent results showing strong associations and clear E-R trends support a causal conclusion. Consistent findings of weak associations and clear lack of E-R trends or indeterminate or equivocal trends do not support a causal association.

Data from 18 cohorts show a consistent pattern of weak associations and a consistent pattern of weak and negligible E-R trends, as demonstrated visually in Figures 23 to 26 and quantitatively in Tables 1.

Temporality. This requirement for determining a causal association appears to be met. For occupational lung cancer about 20 years should elapse after first exposure. One study adjusted for latency (Ulm) and for another study latency periods ranged from 18 to 50 years (Koskela). In nested case-control studies, follow-up periods ranged from 22 to 61 years except for two (Hnizdo, Fe/Cu) with 16 and 17 years follow-up. However, bias is unlikely with matching on age or date of hire.

The evidence is summarily reviewed in Figures 25 and 26 and Tables 1. These data and the following listing show that the weight-of-evidence does not support but instead detracts from the hypothesis that there is a causal association of lung cancer and silica exposure. The evidence is suggestive of a lack of carcinogenicity between occupational exposure to silica and lung cancer.

In sum there are consistent patterns showing *no* increased risk of lung cancer at the highest exposure and a majority of studies with *no* increases in risk as exposure increases. Carcinogenicity was detected in only two industrial circumstances where increased risk could not be explained by bias, confounding, or chance. Results from original E-R studies available to IARC (2009) are similar to the most appropriate data selected in this review. Both data sets consistently shows no associations between silica exposure and lung cancer. Both detract from the silica–lung cancer hypothesis despite the IARC (2009) conclusion of *sufficient* evidence supporting a causal association of lung cancer and silica exposure.

The Working Group conducted a perfunctory review and did not graphically review the overall database to assess consistency of strong associations or biological gradients. Too much reliance was placed on the author's conclusion from the pooled analysis without evaluating each cohort and the data in the seven cohorts not included in the analysis. Whether one uses the "appropriate" trends selected in this review or the exposure-response trends directly from the literature,

Industry/ Reference	N*	High Exposure mg/m³-years	RR in high-exposure group (95% CI)	ER ???	Causal???
Diatomaceous earth (Checkoway et al., 1997)/ adjusted	69	34	1.35 (0.66–2.69)	No	No
China pottery (Chen et al., 2007)	120	41	1.0 (0.28–1.66)	No	No
UK pottery (Cherry et al., 1997)	52	8	1.08 (0.27–4.02)	No	No
German stone, pottery(Ulm et al., 1999)	247	16	1.04 (0.53–1.89)	No	No
US gold miners (Steenland et al., 1995a) pooled	156	6	1.04 (0.19–5.81)	No	No
Australian gold miners (de Klerk et al., 1998) pooled	135	35	1.73 (0.71–3.79)	No	No
South African gold miners (Hnizdo et al., 1997)	77	7.3	3.19 (1.3–7.6)	Yes	Yes
South African gold miners (Reid and Sluis-Cremer, 1996)	143	3.7	1.52 (0.89–6.45)	±	±
South African gold miners (Hessel et al., 1986;, 1990)	364	--	—	No	No
Chinese iron/ copper miners (Chen et al., 2007)	143	4	1.46 (0.45–4.06)	No	No
Chinese tungsten (Chen et al., 2007)	172	41	1.0 (0.55–1.66)	No	No
Limu Chinese tin miners (Chen et al., 2002)	29	5.4	2.4 (0.6–10.2)	±	±
Sardinia silicotic granite, miners (Carta et al., 2001)	34	11	1.03 (0.42–2.50)	No	No
US granite (Vacek et al., 2010)	356	27	0.76 (0.25–2.22)	No	No
Finnish granite (Koskela et al., 1994) pooled	38	58	1.58 (0.50–4.89)	No	No
US Industrial sand (Steenland and Sanderson, 2001) pooled	85	4.4	2.15 (0.80–5.94)	Yes	Yes
US Industrial sand (McDonald et al., 2005)	105	6	2.64 (p = 0.02)	Yes	Yes
UK industrial sand (Brown et al., 2005b)	82	12	0.92(0.44–1.92)	No	No
Porcelain workers (Mundt et al, 2011)	74M	7	0.8 (0.5-1.5)	No	No
	20F	7	0.4 (0.1-3.4)	No	No

* = number of lung cancer cases; + = cumulative exposure at high exposure levels or high-exposure category;
presence of E-R trends rated as yes = clearly positive;
± = suggestive of no, but equivocal; no = clearly no association;
pooled = results from Steenland; Mannetje et al. (2001).

the weight of evidence is *not sufficient* to support a silica lung cancer hypothesis.

The weight-of-evidence from epidemiology studies does not support the silica-lung cancer hypothesis. The consistent lack of E-R associations is inconsistent with and detracts from the IARC conclusion of sufficient evidence that silica is a lung cancer carcinogen.

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Declaration of interest

The author, John Gamble, prepared the manuscript after attending the IARC Monograph 100C workshop in Lyon, France, 16–24 March 2009, on silica as an industry observer. He wrote a report summarizing the workshop and his preliminary analysis/review of silica epidemiology was reported to his sponsors, National Stone, Sand and Gravel Association and the American Chemical Council. This article is a more detailed analysis of this preliminary analysis, and was done independently and without financial support to the author, who has sole responsibility for the writing and content of the paper.

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Table A-1. Summary of least confounded studies.

Reference/ Country	Study base/ Follow-up	Lung Cancer RR(95% CI) and/orE-R – mg/m3-d	IARC or author Comments (*my comments*)
South Dakato gold miners(Steenland, K et al. 1998a)	3328 gold miners1940-90	SMR: (115): 1.13(0.94-1.36) 0.16 0.8 1.6 5.5 1.17 1.01 0.97 1.31	Negative trend in case-control
No follow-up			
Danish stone workers (Guenel, P et al. 1989)	2071 stone workers(incidence 1943-84	2.00(1.49-2.69) Skilled 1.81 (1.16 2.70) unskilled	SIR, adjusted smoking
Vermont granite (Costello, J et al. 1988)	5414 shed & quarry1950-1982	<1940 DOH, 40+ latency, 30+ tenure: 1.81(1.33-2.41) >1940 DOH, 25+ latency, 10+ tenure: 1.73(1.01-2.77)	2-fold SMR among long-term workers indicates increased risk; Lack of E-R limits conclusions
(Graham, W et al. 2004) Not in IARC table	5408 shed & quarry1950-1996	<1940, 25-39 latency, 10-29 tenure: 0.95(0.31-2.2) >1940; 25-39 latency, 10-29 tenure: 1.54(1.04-2.2)	Similar risks by duration & latency before & after dust suppression indicates quartz not risk factor
(Attfield, M et al. 2004)	1950-1994	0 0.25 0.5 1.0 1.5 2.0 3.0 6.0 SMR: 0.77 0.89 1.35 1.27 1.33 1.48 1.70 1.16	Clear E-R up to highest exposure; statistical significance unless highest exposure group included
Crushed stone (Costello, J et al. 1995)	3246 stone workers1940-1980	20+y latency, 10+ tenure: 7 / 1.98 – 3.54(1.42-7.29)	
Diatomaceous Earth (Checkoway, H et al. 1996)	2266 workers in 1 plant1942-87.	Intensity-yrs:≤50 50-99 100-199 ≥200 1.0 1.37(0.61-3.08) 1.8(0.82-3.9) 1.79(0.77 4.2)	pre-1930 hires excluded; adj asbestos, age, calendar year, duration of follow-up, ethnicity
(Checkoway, H et al. 1997)	7 more yrs follow-up; 2342 workers1942-1994, includes pre-1930 hires	Mg/m3 yrs <0.5 0.5 1.1 1.0 1.07(0.53 2.2) 0.55(0.23-1.32) 2.1 - >5.01.19(0.59 2.4) 2.11(1.07 4.11)	includes pre 1930 hires, adjusted for age, calendar year, duration of follow-up, ethnicity;Significant SMR in high exposure group
(Checkoway, H et al. 1998)	Excluded pre-1930 hires; 1942-1994	> 5.0 mg/m3-yrs – 1.31 (0.71-2.33)	adjusted for smoking;, high exposure not significant
Chinese Refractory Brick (Dong, D et al. 1995)	6266 refractory brick workers; 11470 nonsilicotic steel worker controls; follow-up through 1985	Silicotics: 35/ 16.7 – 2.10 (1.46-2.92)Non-silicotics: 30/17.5 – 1.11(0.75-1.58)	"modest increasing trend of lung cancer was found with radiographic profusion category"
Italian refractory brick (Merlo, F et al. 1991)	1022 brick workers employed 1954-77; follow-up through 1986	SMR: 28/18.5 = 1.51(1.0 2.2)20+ y latency;<20 years: 8 / 4.6 = 1.75(0.75-3.46)>20 years: 13 / 6.5 = 2.01 (1.07 3.44)	"nearly two-fold increased risk among long-term workers"mortality almost due to workers hired <1957
UK Pottery (Cherry, N et al. 1996)	52 cases employed 10+ years, nested in cohort of 5115 pottery workers	Association with smoking but not cumulative exposure;Average exposure: >200 ug/m3: OR – 1.88 (1.06-3.34)Peak > 400 ug/m3: OR – 2.16 (1.11 4.2)	peak exposure risk limited workers in firing & post-firing occupations.
(Cherry, N et al. 1998)	Re-analysis of Cherry et al (1996) with quantitative E-R(avg = ug/m3; cumulative = ug/m3-yrs)	Cumulative silica dust, continuous = 1.01 (0.85-1.19) Average concentration = 1.67 (1.13-2.47)	Adjusted for smoking amount (all smokers), no mention of confounders, probable exposure cristobalite
Chinese Pottery (McLaughlin, J et al. 1992)	62 cases &238 matched controls from pottery; nested in (Chen, J et al. 1992); employed 1972-1974, follow-up until 1990; exposure – ug/m3-yrs	0 low(8.7) medium(26) high(>221) 1.0 1.8(1.04 2.9) 1.5 (0.99 2.2) 2.1 (0.80 4.1)	adjusted age & smoking; trend p >0.5IARC 2009: r = 0.56 silica & PAHs, "adjustment for PAHs reported to raise silica RRs,
(Chen, W et al. 2007)	120 cases & 459 matched controls; extended follow-up to 1994; mg/m3-y; table only; no discussion in text	0 1.1 2.6 5.4 1 0.7(0.25-2) 0.7(0.3 1.8) 0.7(0.3 2.2) -10.1 - 720.5(0.25-1.8) 0.9 (0.19 4.3)	adjusted for PAHs where OR = 1.4 (1.02-1.94) per 100 ug/m3-y. "pottery workers had the highest PAH levels over all industrial groups. Adjustment for PAHs...led to a silica exposure RR of 1.1(1.02 1.12) dropping to 1.0 (0.96-1.09). [The Working Group noted ...in the prior analysis ...adjusting for PAHs slightly raised rather than reduced silica exposure RRs."

Table A-2. Characteristics of South African gold miner studies

	(Hessel, P et al. 1986)	(Hessel, P et al. 1990)	(Reid, P et al. 1996)	(Hnizdo, E et al. 1997)
Follow-up	1979-83	1974-1979, 1984-1986	1970-1990	1968-1986
Location	All South Africa gold mines		Transvaal	Sample of all miners
N cases	133	231	143	78
DOB	Average ~ 1917	Avg ~1908-1921	1916-1930	1916-1925
Eligibility	Pension fund, >15-yrs tenure, >1000 dusty shifts (~4-yrs)	Necropsy file with ~86% WM gold miners, >1000 shifts,	39-54 gold miner working on 1/1/1970; medical exam 1969 certifying able to work; ≥85% work as gold miner, ≥15% UG	miners selected for study of respiratory disorder, age 45-54 in 1968-71, >10-years UG
Controls	266 Matched DOB, tobacco from pension fund	318 Matched age at death from necropsy file	286 randomly selected on YOB, survival of case from cohort of 4925 miners	386 matched YOB, survival of case from cohort of 2260 miners
Analysis	No differences between cases & controls on cumulative exposure, tenure, average intensity, number shifts of high dust		5-year lag, regression	Conditional logistic regression adjusted for packyears

Table A-3. Comparison of Mining studies from pooled analysis (Steenland, K, Mannetje, A et al. 2001) and published literature (sometimes adjusted for smoking or occupational exposures).

Study	mg/m³-yr:hiexpos group	Pooled Analysis(95% CI)	OR Peer-reviewed studies; RR (95% CI) in highest exposure category	Comment
US Gold Miners(Steenland, K et al. 1995a)	5.5(1.9-9.03)	1.03(0.22-4.94)	SMR: 1.31 (0.88-1.87); Negative, non-significant trend in case-control study; Cases vs controls cumulative exposure -1.14 vs 1.24 mg/m³-yrs	Pooled analysis added 6-years to follow-up; RRs appear to have declined with further follow-up; No association but exposures are on the low side. Data from pooled analysis used because of added follow-up
Australian Gold miners(de Klerk, N et al. 1998)	Median 11.4	1.27 (1.12-1.62) (@ 15 mg/m³-y	exposure metric = exposure-score year; RR = 1.003(0.999-1.005) after adjustment for smoking, bronchitis	Pooled results most appropriate analysis because quantitative exposure metric
SA Gold miners(Hnizdo, E et al. 1997)	25% >6.3 mg/m3-y lagged 20-y	5.96 (1.29-22.3) @ 8 mg/m3-y	3.19 (1.3-7.6) @ >6.3; adjusted for smoking	Lagged 20-years & adjusted for smoking; possible confounding from radon (~1.2-1.3 RR) based on uranium miners
SA gold miners (Hessel, P et al. 1986; 1990)	exposures not in mg/m3-yrs	---	E-R trends not analyzed although quantitative estimates of cumulative exposure were the same for cases and controls.	No apparent association with silica exposure but limited as only mean exposure estimates of cases & controls were evaluated.
SA gold miners(Reid, P et al. 1996)	Typical ~ 3.7 mg/m3-y	---	1.33 (0.80-1.96) @ 3.7, lagged 5-yrs 1.52 (0.89-2.64) adjusted for smoking	Exposure levels low, perhaps because based on mass from thermal precipitator,
Chinese tungsten(Chen, J et al. 1992; Chen, W et al. 2007)	41 (10-72) Median = 4.8 (0-72.4)	1.48 (0.81-1.76) @ 41 mg/m3-y	Categorical: 1.0 (0.55-1.66) Regression: 1.0 (0.66-2.25) Adjusted for smoking	Adjusted for smoking, no other relevant confounders.
Chinese Fe-Cu(Chen, J et al. 1992; Chen, W et al. 2007)	4.7 (2.6-6.8) Median = 0.2 (0-6.8)	---	Categorical: 1.4 (0.33-5.5) @ 2.6-5.40 Regression: 1.46 (0.45-4.07) Adjusted for smoking, PAHs & radon	RR for radon (yes/no) = 1.2 (0.64-2.42)
Chinese tin miners(Chen, J et al. 1992; Chen, W et al. 2007)	23 (10.1-35.4) median = 2.6 (0-35.4)	2.28 (0.62-3.24)	unadjusted: for arsenic: Categorical: 3.3 (1.66-6.61) Unreliable results when adjusted for arsenic	This study should be excluded because high collinearity of silica and arsenic making statistical model results unreliable; unable to assess independent effects of silica and arsenic.

Table A-4. Comparison of Cristobalite and Heated Quartz (potteries) results from pooled analysis (Steenland, K, Mannetje, A et al. 2001) and published literature (sometimes adjusted for confounders in original analysis and/or in this paper). No adjustments in the pooled analysis. (See Figure 22).

Study	mg/m³-yr: hiexpos group	Pooled Analysis OR (95% CI)	Peer-reviewed published Studies; OR (95% CI)	Comment
DE (Checkoway, H et al. 1997): [this paper]	34 (5-63)	5.47 (1.27-23)	Original: 2.15 (1.08-4.28)Adjusted: 1.31 (0.71-2.2)	Exclude <1930 hires that adjusts asbestos, silica exposure misclassification, adjust smoking
China Pottery:(Chen, J et al. 1992): *(Chen, W et al. 2007)*	40 (10-72)	1.16 (0.82-4.19)	1.0 (0.55-1.66)	Adjusted for smoking & carcinogenic PAHs
UK Pottery(Cherry, N et al. 1998)	7 (>6)	---	1.07 (0.32-3.38)	Adjusted for smoking, 10-year lag
German Ceramics(Ulm, K et al. 1999)	15 (2.9-27)	---	1.05 (0.59-1.86)	Adjusted for age & year of 1st exposure, duration, latency; other exposures; matched on smoking

Table A-5. Comparison of Quarry and stone workers results from pooled analysis (Steenland, K, Mannetje, A et al. 2001) and published literature (sometimes adjusted for confounders in original analysis or in this paper. No adjustments in the pooled analysis.

Study	mg/m³-yr:hi expos group	Pooled Analysis OR (95% CI)	Peer-reviewed studies; RR (95% CI) in highest exposure category	Comment
Vermont granite:(Attfield, M et al. 2004)	10.6 (5-?)	1.17 (0.66-2.11)	Latency > 15 years SRR = 1.18 SMR = 1.16 (0.78-1.66) Exposure lagged 15 years SRR = 1.18 SMR = 1.12 (0.74-1.62)	Pooled analysis added exposure estimates to cohort (Costello, J et al. 1988); published paper used similar exposures but based on extended follow-up (Graham, W et al. 2004)
Finnish stone (Koskela, R et al. 1994)	32 (>28.1)	1.29 (0.68-2.45)	---	E-R analysis of lung cancer not published independently.
Sardinian quarry & mining (Carta, P et al. 2001)	30 (>20)	---	SMR; 2.08 (0.88-4.91) Regression: 1.05 (0.10-3.65)	SMR = 20+ y latency; no adjustment for confounders: Regression adjusted for smoking, airflow obstruction, radon., silicotics included quarry, mining (metal, coal)
German stone & quarry, pottery (Ulm, K et al. 1999)	15 (2.88-27)	---	0.86 (0.38-1.95)	Adjusted for age at hire, year 1st exposure, duration of exposure, latency, additional exposure in workplace; nonsilicotics.

Table A-6. Comparison of Industrial Sand results from pooled analysis and published literature.

Study	mg/ m³-yr:hiexpos group	Pooled AnalysisOR (95% CI)	Peer-reviewed studies; RR (95% CI) in highest exposure category	Comment
US(Steenland, K and Sanderson, W 2001)	>1.28>1.23@ 5mg/m3-y	2.43 (1.28-7.52)	≥1.28: SMR: 2.25 (1.51-3.23); 15-y lag: 2.38 (1.41-3.80) SRR: 1.50 1.01-2.15) 1.57 (0.89-2.83) SMR, >6 mo 2.25 (1.48-3.27)≥1.23 OR >6 mo: 1.70 (0.88-3.25) 15-y lag:2.00 (1.0-4.01)	
US(Hughes, J et al. 2001)Updated version(McDonald, J et al. 2005)	Median = 7.1	---	6 exposure categories:OR: no lag; >6 mg/m3-y: OR = 1.9; lag 15 yr: OR = 1.84 exposure categories: original OR updated OROR, no lag:@>4.5 (7.1 median) 2.58 2.6415-y lag@ >3.3 (median 6.2): 2.07 2.66	Adjusted smokingShould use *a priori* categories = >6 mg/m3-y
UK(Brown, T et al. 2005)	> 1 mg/m3-y	---	OR: adjusted age, period from 1st employment, employment status, quarry: 0.92 (0.44-1.92)	