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# Silicosis Exposure–Response in a Cohort of Tin Miners Comparing Alternate Exposure Metrics

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**Background.** *The detailed lung radiographic response to silica exposure has not been described. In estimating the exposure–response relationship in silicosis with statistical models, the absence of baseline (unattributable) risk can disable relative-rate estimation or produce widely varying estimates. This obstructs identification of optimum exposure metrics and invalidates comparisons and meta-analyses, which assume a common background rate.*

**Methods.** *A cohort of 3,000 Chinese tin miners with more than 1,000 cases of silicosis was analyzed for the period 1961–1994. Regular surveillance documented three stages of silicosis. To examine the exposure–response relationship, the intercept in relative-rate models was fixed to correspond to 1% of the observed silicosis rate. Exposure metrics for contributions in different time-windows were simultaneously evaluated, as were burden and cumulative burden metrics.*

**Results.** *Silica exposures that most contributed to silicosis onset occurred in the period 5–10 years prior (excess annual rate per 10 mg-year/m$^3$, ER = 0.158, 95% CI = 0.125–0.192, or 16% per year). During 10–20 year prior, the excess rate contribution was much smaller (ER = 0.048, 95% CI = 0.037–0.060) but larger again during 20–30 year prior to onset (ER = 0.112, 95% CI = 0.098–0.126). For advanced silicosis, all time periods contributed about equally to the rate of onset.*

**Conclusions.** *Reliable estimates of parameters were observed, demonstrating exposure contributions over time. Burden metrics with different half-lives suggested some reversibility for silicosis onset with a half-life of 20 years. Advanced silicosis was best predicted with a cumulative burden metric which was consistent with prior observations that previously deposited silica continues to cause pulmonary damage.*
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***KEY WORDS: burden; cumulative exposure; exposure response; occupational disease; vanishing baseline***

## INTRODUCTION

Silicosis is a form of pneumoconiosis, a dust-induced lung disease, resulting from inhalation of silica. It has an early presentation sometimes referred to as ''simple silicosis'' or perhaps more appropriately ''chronic, uncomplicated silicosis'' [Greaves, 2000] where the X-ray picture shows discrete radiographic nodules without obvious respiratory impairment. At a later stage, ''conglomerate silicosis'' or ''progressive massive fibrosis'' (PMF) [Peters, 1986] the X-ray picture is one of coalescing nodules associated with fibrotic masses and widespread

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destruction of lung architecture leading to respiratory failure and other fatal sequelae [Greaves, 2000].

A detailed examination of the structure of the silicosis exposure–response relationship using multiple regression methods is thwarted by the essential absence of non-attributable cases—zero baseline risk—as with any pathognomonic disease (i.e., occuring almost exclusively in association with a specific exposure). Other examples include: aplastic anemia (certain chemotherapeutic drugs), bronchiolitis obliterans (artificial butter flavorings), and Reye's Syndrome (aspirin in children). Examples of occupational diseases with small or unobservable baseline risk include: silicosis (silica), mesothelioma (asbestos), aplastic anemia (benzene), and angiosarcoma of the liver (vinyl chloride). Relative-risk estimates are fundamentally grounded on the baseline (intercept) estimate. Relative-rate regression models with sparse or absent non-attributable cases can produce unstable or near-zero estimated baseline risk and unbounded effect estimates. Baseline instability is further compounded when important age confounding (common with environmental exposures) or age interactions may be present, requiring estimation of the age-dependence of baseline risk. The problem is acute when attempting to evaluate alternate exposure metrics in the same study population.

Investigators typically address the problem of vanishing baseline risk by defining the lowest exposure stratum in a categorical analysis as the comparison or reference group [e.g., Mannetje et al., 2002]. This would mean attributable cases are present in the reference category, which would tend to cause underestimation of relative and attributable risks; this approach could still be subject to instability, and precludes examination of the exposure response at low concentrations. Another standard approach would be to utilize additive absolute rate rather than relative rate models, but these have convergence problems that are particularly severe when evaluating multiple, collinear predictors as could occur in a detailed examination of the form of the exposure–response relationship. Modeling exposure response from a mid-range reference point, for example exposure offset by the population mean exposure, would permit reliable estimation in that region and would perhaps suffice for etiologic investigations—demonstrating an association—but would not be useful for low-dose examination as typically needed in risk assessment [Park et al., 2002].

In this work, the problem of vanishing baseline risk was addressed by fixing the intercept in a Poisson rate regression model context to a small value corresponding to a rate 1% of that of the observed cases [Park, 2012]. The incidence of three stages of silicosis, diagnosed on the basis of X-ray chest films, was then analyzed in a large cohort of Chinese tin miners [Chen et al., 2001, 2006] with a special focus on the structure of the exposure–response relationship.

## METHODS

### Study Population

The study population was all workers employed for at least 1 year during 1960–1994 at any of four Chinese tin mines. Follow-up started January 1, 1961 or 1 year after date of hire (whichever came later) and ended with date of silicosis diagnosis, date lost to follow-up or death, or December 31, 1994 (whichever came first). Silicosis outcomes, defined in Chinese Silicosis Stages 1–3, were based on annual radiographic (X-ray) examinations among active miners, and X-rays every 2–3 years among former miners. The Chinese Stage 1 radiographic silicosis criterion is approximately equivalent to the International Labor Organization (ILO) 1/0 radiographic silicosis film category [Hodous et al., 1991].

In general, all stages of silicosis were diagnosed under this system with some exceptions: some workers at the start of follow-up had already been diagnosed with some stage and so were excluded from models for that stage; for some workers, the first diagnosis was stage 2 or 3, or they had diagnoses at stages 1 and 3 only, due to rapid progression and the length of time between assessments. In the few latter cases, a date for stage 2 was imputed as mean of dates for stage 1 and 3. Many miners continued in employment after being diagnosed—even as Chinese Stage 3—but were probably moved to lower exposure jobs. For example, 82% of those diagnosed with Stage 1 continued in employment, for an average of 8.4 years. This analysis is based entirely on administrative surveillance data collected by mining enterprises, as required by regulation. Institutional Review Board approval was obtained from Tongji Medical College and the National Institute for Occupational Safety and Health. Participant informed consent was not required.

The work history available for the tin miners specified job assignments in 1-month increments for employment at the study mines. Employment at other mines, usually prior to working in the study mines, was reported in annual increments. An exposure matrix was available specifying estimated mean respirable silica exposure levels and mean hours worked per day for each job title at intervals of 1–3 years in calendar time from 1950 to 1994 [Chen et al., 2001, 2006].

In order to model rates of onset, all observation time was classified in 10-day units by outcome (1 = silicosis diagnosis, otherwise 0), age and calendar time (5-year intervals), gender (0 = male, 1-female), and level of exposure metric (in 50 levels, logarithmically spaced). The person-time weighted mean exposure metric of each classification cell was used in regression analyses.

## Exposure Metrics

Based on current understanding of the underlying pathophysiology in silicosis, we postulated that the traditional cumulative exposure metric may not be the optimum predictor of silicosis onset [Greaves, 2000]. This metric is appropriate only if an exposure effect is (a) immediate, (b) additive over time, (c) has no dose–rate effect (linear in current exposure level), and (d) is irreversible: the contribution to future risk is constant over time. Cumulative exposure was calculated as follows:

$$\text{cumulative exposure}: \quad \text{cumSil}(t) = \Sigma_k[\text{Sil}_k \times \text{dur}_k] \quad (\text{in mg-year}/\text{m}^3)$$

where, $\text{Sil}_k$ is concentration in $\text{mg}/\text{m}^3$ in time interval k with duration $\text{dur}_k$ (in this study, 10-day units of observation, expressed in years) and $k = 1,\ldots N(t)$. To investigate dose–rate effects, metrics were also calculated as sums over time of silica concentration raised to the 0.5 and 2.0 powers, as in $\Sigma_k\ [\text{Sil}_k{}^{0.5} \times \text{dur}_k]$ and $\Sigma_k\ [\text{Sil}_k{}^{2.0} \times \text{dur}_k]$.

Since cumulative exposure represents a simple time-integration of exposure, its calculation does not take into account when a prior exposure occurred; equivalent cumulative exposures could have very different time-courses of exposure. The long residence time of deposited silica and known progression of the disease even after considerable time has elapsed since termination of exposure suggested that metrics incorporating residence time might be more appropriate. To examine this time-dependence, cumulative exposure was also calculated in six time windows prior to observation [Finkelstein, 1991], expressed as intervals in years: 1–(0,2], 2–(2,5], 3–(5,10], 4–(10,20], 5–(20,30], 6–(30+]. Additionally, a burden and cumulative burden metric were calculated:

$$\text{burden}: \quad B(t) = \sum_k[\text{Sil}_k \times \text{dur}_k \times (0.5)^{(t-t\_k)/T^{half}}] \quad \text{in mg-year}/\text{m}^3$$

$$\text{cumulative burden}: \quad \text{cum}B(t) = \sum_k[B(t_{-k})] \quad \text{in mg-year}^2/\text{m}^3$$
$$= \sum_k\left\{\sum_{l<k}\left[\text{Sil}_l \times \text{dur}_i \times (0.5)^{(t\_k-t\_l)/T^{half}}\right]\right\}$$

where, $k = 1,\ldots N(t)$, and t_k is time at kth interval. Burden at time, t, is the time-weighted sum of all prior exposure contributions each with an exponentially declining weight since time of exposure, with half-life $T_{half}$. For example, following three time units, with exposure levels X = a, b, c and half-life = 1 time unit, the exposure metrics would be:

| | Time period | | |
|---|---|---|---|
| Metric | 1 | 2 | 3 |
| Silica conc. | a | b | c |
| cumSil | a | a + b | a + b + c |
| B | a | a/2 + b | a/4 + b/2 + c |
| cumB | a | a + (a/2 + b) | a + (a/2 + b)+(a/4 + b/2 + c) |

In the limit, as $T_{half}$ becomes very large, burden becomes cumulative exposure—all prior exposures are summed with equal weight. Burden could have a simple interpretation—the remaining mass of deposited material undergoing first-order clearance kinetics, or it could represent some adverse physiological condition that declines over time. Cumulative burden is the summation of burdens over time; it has been proposed previously [Jahr, 1974], and is also known as "effective dose" or "area under the curve (AUC)" [Links et al., 2001; Kriebel et al., 2007]. With a small half-life, corresponding to a burden persisting largely over only one time interval in the above summations, cumulative burden approaches equivalence with cumulative exposure. In the limit of large $T_{half}$, cumulative burden becomes the total exposure-weighted residence time with no clearance or decline. A display of these three metrics for a hypothetical exposure history is presented in Figure 1.

## Models of Exposure Response

Poisson regression [Frome and Checkoway, 1985] was used to model rates of onset using Epicure statistical software [Preston et al., 1993]. In fitting models in the usual manner, there was considerable evidence of instability including failures to converge and widely varying effect-estimates for similar exposure metrics despite very abundant data (>800 cases). This was because of vanishing baseline risk; silicosis presumably arises only from exposure to silica. Constraining the model intercept [Park,

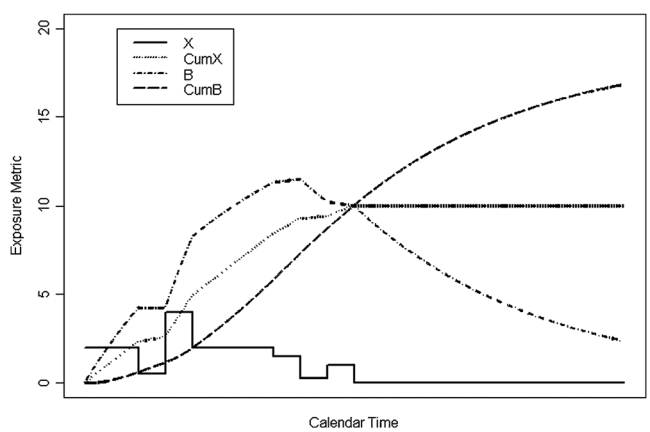


**FIGURE 1.** Exposure metrics derived from a hypothetical 40-year exposure history (half-life = 20 years, vertical axes re-scaled to converge at end of exposure).

2012] enabled model fits even with multiple co-linear terms. For these analyses, the intercept was fixed at $-9.01 = \ln(0.01 \times 866/71{,}513)$, corresponding to 1% of the observed crude rate for the 866 new Chinese Stage 1 cases observed during 71,513 person-years of observation (up to Stage 1).

An additive relative rate model was specified as follows:

$$\begin{aligned}\text{rate} &= [\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \\ &\quad \times [1 + \beta \times \text{MetX}] \text{ or rate ratio} \\ &= 1 + \beta\text{MetX}\end{aligned}$$

where: $\alpha_0$ is the fixed intercept parameter, age is in 5-year increments and centered at age 55, gender (gen) is coded 0 = male, 1 = female, and MetX is an exposure metric. $\beta \times$ MetX is the excess rate ratio (ERR), and the excess rate in this model would be: ER = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times \beta \times$ MetX.

The goal was to investigate a variety of definitions for the exposure metric, MetX, variously taking into account partitioning into silica exposure windows, body burden, and residence time. Log-linear models of the form $\exp(\alpha + \beta \times \text{MetX})$ were observed to fit less well and were not extensively used. The statistical significance of terms in the model was derived from the likelihood ratio test comparing likelihoods between nested models. If $G^2 = -2\ln(\text{LR})$, where LR is the ratio of the likelihoods with and without addition of k exposure terms, $G^2$ under the null hypothesis would behave as a chi-square statistic with k-degrees of freedom. Comparative model fit was based on the difference in $-2\ln$ (Likelihood) for two competing models (with same number of terms), which is an underestimate of the difference that would be observed in a nested model comparison (i.e., compared to a model containing all the variables from the two contrasted models). If L(A) is the likelihood for a model with a set of predictors, A, L(B) for predictors B, and L(A,B) for the predictors union(A,B), then $-2\ln[\text{L(B)}] \geq -2\ln[\text{L(A,B)}]$, or $2\ln[\text{L(B)}] \leq 2\ln[\text{L(A,B)}]$ and therefore $\{-2\ln[\text{L(A)}]\} - \{-2\ln[\text{L(B)}]\} \leq \{-2\ln[\text{L(A)}]\} - \{-2\ln[\text{L(A,B)}]\}$, the latter being the basis for testing the significance of model fit improvement adding predictors {B} to the model with predictors {A}. Therefore, $\{-2\ln[\text{L(A)}]\} - \{-2\ln[\text{L(B)}]\}$ provides an underestimate of the statistical significance of the improvement with {B}. When comparing models A and B with the same number of terms, and identical terms except for one, observing $\{-2\ln[\text{L(A)}]\} - \{-2\ln[\text{L(B)}]\}$ equal to 3.84 would correspond to $P < 0.05$ for the improvement in fit adding terms B to model with terms A; >20.0 would correspond to $P < 10^{-5}$ for the improvement in fit adding terms B to A.

# RESULTS

## Study Population

Person-years (85,585) of follow-up (up to Chinese Stage 3) were available for study among 3,004 men (93%) and women (7%) employed for at least 1 year during 1960–1994 at any of four Chinese tin mines (Table I). Incident cases of Chinese Stage 1, 2, or 3 silicosis numbered, respectively, 866, 464, and 122. Mean duration in study mines was 27 years (sd:7.4); time-averaged mean respirable silica exposure was 0.187 mg/m$^3$ and mean cumulative exposure at end of follow-up was 2.92 mg-year/m$^3$. Silicosis cases on average were first exposed 4 years earlier than non-cases and were 5 years older at start of follow-up which on average was in the year 1962 (Table II). Chinese Stage 2 and 3 silicotics were exposed on average 1–2 years less than non-cases.

## Exposure Response

Although duration of silica exposure was a highly significant predictor of Chinese Stage 1 silicosis onset ($\chi^2 = \Delta - 2\ln(\text{L}) = 4{,}866$, 1 df), simple cumulative exposure was a considerably better predictor ($\chi^2 = 5{,}423$, 1 df) (''linear,'' Table III). Model fit was less good calculating the cumulative metric with square root ($\chi^2 = 5{,}287$, 1 df) or square ($\chi^2 = 5{,}169$, 1 df) of silica air concentration, corresponding respectively to negative and positive dose–rate effects (''square root, square,'' Table III). When the cumulative exposure metric was partitioned into six time-prior-to-observation windows, the model fit was

**TABLE I.** Chinese Tin Miner Cohort: Details

| | |
|---|---|
| Workers, n[a] | 3,004 |
| Follow-up: min(date first observed) | 01–01–61 |
| max(date last observed) | 12–31–94 |
| Number of silicosis cases, published[b] | 1015 |
| Number of Chinese Stage 1 silicosis cases, analyzed[c] | 866 |
| Number of Chinese Stage 2 silicosis cases, analyzed[c] | 464 |
| Number of Chinese Stage 3 silicosis cases, analyzed[c] | 122 |
| Person-years of follow-up (up to Stage 3), year | 85,585 |
| Mean worker duration in study mines, year (SD) | 27.4 (7.4) |
| Mean respirable silica exposure[d], mg/m$^3$ | 0.187 |
| Mean cum. respirable silica exposure[e], mg-year/m$^3$ (SD) | 2.92 (2.42) |

[a] All workers with ≥1 year duration in study sites during 1960–1994.
[b] Chen et al. [2001]; silicosis criterion: Chinese Stage 1 (similar to ILO 1/0).
[c] Not all cases of silicosis were incident during period of follow-up or had a date for first attaining Stage 1 status.
[d] Time-weighted average across all employment.
[e] At end of follow-up.

**TABLE II.** Attributes of Chinese Tin Miners at End of Follow-Up for Three Stages of Silicosis

| | Mean | | | | | |
|---|---|---|---|---|---|---|
| | Chinese Stage 1 | | Chinese Stage 2 | | Chinese Stage 3 | |
| | Cases | Non-cases | Cases | Non-cases | Cases | Non-cases |
| Year first exposed | 1954.0 | 1958.3 | 1952.4 | 1957.5 | 1950.9 | 1956.9 |
| Year first observed | 1961.4 | 1962.2 | 1961.2 | 1962.1 | 1961.1 | 1962.0 |
| Year last observed | 1976.2 | 1991.6 | 1974.6 | 1991.4 | 1974.3 | 1991.1 |
| Age first observed | 34.5 | 29.3 | 36.5 | 30.3 | 37.0 | 31.1 |
| Duration since first exposed | 22.2 | 33.3 | 22.2 | 33.9 | 23.4 | 34.2 |
| Duration exposed | 14.7 | 14.4 | 13.4 | 14.9 | 12.2 | 14.8 |

further improved, especially if the period 2 years prior to observation was omitted and, again, was best without a dose–rate effect (Table III). Including the window, 0–2 years generated problematic model convergence and the term was negative as was the next term, for 2–5 years, suggesting that onset of disease is causing termination of exposure. The contributions of cumulative exposures from different time windows varied widely and highly significantly. The largest contribution came during the period 5–10 years prior to observation ($\beta = 129.5$ relative to imposed BL risk, per mg-year/m$^3$) followed by the period 20–30 years ($\beta = 91.5$) (Table III). Omitting the term for time period 2–5 years, had no effect for the Chinese Stage 1 model, but omitting the term for the period 30+ years reduced model fit. ($\chi^2 = 5{,}554$ vs. 5,593; Table IV). A test for rejecting homogeneity of window contributions for the best Stage 1 model was highly significant. ($\chi^2 = 5{,}593$ vs. 5,423, 3 df, $P < 10^{-10}$; Table V).

Chinese Stages 2 and 3 onset also were well predicted by cumulative exposure, especially omitting the last 2 years of exposure prior to observation (Table IV). For these stages, model convergence was not attained using the highly correlated partitioned cumulative exposures unless periods 1 (0–2), 2 (2–5) and 6 (30+) were omitted. Chinese Stage 2 also exhibited variation in rate of onset for contributions from different time windows (Table IV,

**TABLE III.** Chinese Stage 1 Silicosis Relative Incidence Rate Models With Duration Exposed, Cumulative Silica Exposure, Partitioned Cumulative Exposure, and Dose–Rate Effect Based on Square Root or Square of Silica Exposure Intensity

| | Square root | | Linear | | Square | |
|---|---|---|---|---|---|---|
| | β | Wald statistic | β | Wald statistic | β | Wald statistic |
| 1 | Δ deviance[a] = 4,861 | Δ deviance = 4,866 | Δ deviance = 4,861 | | | |
| Duration (year) | 12.2 | 22.93 | 12.2 | 22.94 | 12.2 | 22.93 |
| 2 | Δ deviance = 5,287 | Δ deviance = 5,423 | Δ deviance = 5,169 | | | |
| cumSil | 30.1 | 23.25 | 55.0 | 23.39 | 106.5 | 23.22 |
| 3 | Δ deviance = 5,189 | Δ deviance = 5,593 | Δ deviance = 5,362 | | | |
| cumSil (2,5][b] | nc | | −0.42 | −0.15 | 51.2 | 1.57 |
| cumSil (5,10] | | | 129.5 | 9.24 | 201.4 | 8.45 |
| cumSil (10,20] | | | 39.3 | 8.23 | 83.0 | 9.78 |
| cumSil (20,30] | | | 91.5 | 16.05 | 188.3 | 18.00 |
| cumSil (30+] | | | 8.21 | 2.57 | 16.2 | 3.41 |

nc, non-convergent model.

Models: rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta \times \text{duration}]$.

rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta \times \text{cumSil}]$.

rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta_1 \times \text{cumSil}(2,5] + \beta_2 \times \text{cumSil}(5,10] + \beta_3 \times \text{cumSil}(10,20] + \beta_4 \times \text{cumSil}(20,30] + \beta_5 \times \text{cumSil}(30+]$.

Intercept, $\alpha_0$, fixed at $-9.01 = \ln(0.01 \times 866/71{,}513)$ corresponding to 1% of observed crude rate for Stage 1 cases.

[a]Δ deviance—relative to baseline model with age, gender.

[b]cumSil(a,b]—cumulative exposure accruing in time period >a and ≤b; cumulative exposure (linear) in mg-year/m$^3$; exposure time-windows (years prior to observation): 1: (0,2], 2: (2,5], 3: (5,10], 4: (10,20], 5: (20,30], 6: (30+].

**TABLE IV.** Silicosis Relative Incidence Rate Models With Duration Exposed, Cumulative and Partitioned Cumulative Silica Exposure by Chinese Silicosis Stage (C)

| | C.Stage 1 (n = 866) | | C.Stage 2 (n = 464) | | C.Stage 3 (n = 122) | |
|---|---|---|---|---|---|---|
| | β | Δ dev[a] (df) | β | Δ dev (df) | β | Δ dev (df) |
| Duration (year) | 12.2 | 4,866 (1) | 5.08 | 2,049 (1) | 1.15 | 295 (1) |
| cumSil | 55.0 | 5,423 (1) | 21.9 | 2,588 (1) | 4.66 | 455 (1) |
| cumSil (2,30+][b] | 55.6 | 5,434 (1) | 22.1 | 2,601 (1) | 4.71 | 460 (1) |
| cumSil (2,5] | −0.42 | 5,593 (5) | – | nc | – | nc |
| cumSil (5,10] | 129.5 | | | | | |
| cumSil (10,20] | 39.3 | | | | | |
| cumSil (20,30] | 91.5 | | | | | |
| cumSil (30+] | 8.15 | | | | | |
| cumSil (2,5] | −0.42 | 5,457 (4) | – | nc | – | nc |
| cumSil (5,10] | 109.3 | | | | | |
| cumSil (10,20] | 44.31 | | | | | |
| cumSil (20+] | 56.27 | | | | | |
| cumSil (2,30] | 74.9 | 5,501 (1) | 30.7 | 2,705 (1) | 6.51 | 460 (1) |
| cumSil (2,5] | −0.42 | 5,554 (4) | – | nc | – | nc |
| cumSil (5,10] | 133.8 | | | | | |
| cumSil (10,20] | 39.5 | | | | | |
| cumSil (20,30] | 94.6 | | | | | |
| cumSil (5,30+] | 56.8 | 5,423 (1) | 22.5 | 2,611 (1) | 4.83 | 466 (1) |
| cumSil (5,10] | 129.5 | 5,593 (4) | – | nc | – | nc |
| cumSil (10,20] | 39.3 | | | | | |
| cumSil (20,30] | 91.6 | | | | | |
| cumSil (30+] | 8.13 | | | | | |
| cumSil (5,10] | 109.2 | 5,457 (3) | 39.51 | 2,625 (3) | 6.19 | 472 (3) |
| cumSil (10,20] | 44.3 | | 27.64 | | 7.71 | |
| cumSil (20+] | 56.3 | | 18.24 | | 3.45 | |
| cumSil (5,30] | 76.7 | 5,489 (1) | 31.4 | 2,714 (1) | 6.67 | 467 (1) |
| cumSil (5,10] | 133.6 | 5,554 (3) | 46.4 | 2,725 (3) | 7.52 | 468 (3) |
| cumSil (10,20] | 39.5 | | 24.2 | | 7.64 | |
| cumSil (20,30] | 94.6 | | 34.1 | | 5.89 | |

nc, non-convergent model.
Models: rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta \times \text{duration}]$.
rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta \times \text{cumSil}]$.
rate = $[\exp(\alpha_0 + \alpha_1 \times \text{age} + \alpha_2 \times \text{gen})] \times [1 + \beta_1 \times \text{cumSil}(2,5] + \beta_2 \times \text{cumSil}(5,10] + \ldots \beta_5 \times \text{cumSil}(30+]]$.
Fixed intercept = −9.010.
[a]Δ dev—change in deviance relative to baseline model (including age, gender); nc, non convergent model.
[b]cumSil(a,b]—cumulative exposure accruing in time period >a and ≤b; cumulative exposure in mg-year/m$^3$.

models with windows for the years 5–30+ prior to observation) and with significant heterogeneity ($P = 0.004$; Table V). For Chinese Stage 3, the 5–10, and 10–20 year windows contributed comparable risk but the period more than 20 year prior to onset contributed about half as much risk per unit cumulative exposure, which was a marginally significant difference ($P = 0.05$).

The annual excess rate of silicosis onset was calculated. For example, in men aged 55 with 10.0 mg-year/m$^3$ silica exposure during 5–10 year prior to onset, the excess rate of Chinese Stage 1 onset was 0.158, or 16% of workers per year (Table V, model 2). This was a high but observable exposure in this population (mean final silica cum. exposure = 2.9 mg-year/m$^3$.

## Burden and Cumulative Burden Metrics

Cumulative metrics of the form burden (half-life = 20 20 years, $\chi^2 = 5{,}446$) and cumulative burden (half-life = 1 year, $\chi^2 = 5{,}429$) both predicted Chinese Stage 1 onset

**TABLE V.** Excess Annual Rate, ER, With Cumulative Exposure by Chinese Silicosis Stage, Final Models

| | | β | Wald statistic | ER[a] | Wald 95% CI | Δ dev (df)[b] |
|---|---|---|---|---|---|---|
| | | | Chinese stage 1 (n = 866) | | | |
| 1 | cumSil (5,30+][c] | 56.8 | 23.1 | 0.069 | 0.64–0.75 | 5,423 |
| 2 | cumSil (5,10] | 129.5 | 9.2 | 0.158 | 1.25–1.92 | 5,593 |
| | cumSil (10,20] | 39.3 | 8.2 | 0.048 | 0.37–0.60 | |
| | cumSil (20,30] | 91.6 | 16.1 | 0.112 | 0.98–1.26 | $P_H$[d] $< 10^{-10}$ |
| | cumSil (30+] | 8.1 | 2.6 | 0.010 | 0.02–0.18 | |
| | | | Chinese stage 2 (n = 464) | | | |
| 3 | cumSil (5,30] | 31.4 | 16.9 | 0.038 | 0.34–0.43 | 2,714 |
| 4 | cumSil (5,10] | 46.4 | 6.1 | 0.057 | 0.39–0.75 | 2,725 |
| | cumSil (10,20] | 24.2 | 7.5 | 0.030 | 0.22–0.37 | |
| | cumSil (20,30] | 34.1 | 11.5 | 0.042 | 0.35–0.49 | $P_H = 0.004$ |
| | | | Chinese stage 3 (n = 122) | | | |
| 5 | cumSil (5,30] | 6.7 | 8.7 | 0.0082 | 0.06–0.10 | 467 |
| 6 | cumSil (5,10] | 6.2 | 2.4 | 0.0076 | 0.01–0.14 | 472 |
| | cumSil (10,20] | 7.7 | 4.8 | 0.0094 | 0.06–0.13 | |
| | cumSil (20+] | 3.5 | 5.0 | 0.0042 | 0.03–0.06 | $P_H = 0.05$ |

Fixed intercept = −9.010.
[a]ER—excess annual rate at 10.0 mg-year/m$^3$ in window in men age 55; ER = [exp(−9.01)] × [$\beta_i \times 10$].
[b]Δ dev—change in deviance relative to baseline model (including age, gender).
[c]cumSil(a,b]—cumulative exposure accruing in time period >a and ≤b.
[d]$P_H$: *P*-test for homogeneity across cumulative exposure windows, for example, model 2 versus model 1.

better than simple cumulative exposure ($\chi^2 = 5{,}423$), suggesting some reversibility but also continuing impact during the first year following exposure. (Table VI). Chinese Stage 2 showed the same pattern while Chinese Stage 3 showed only a progressive pattern with a half-life in the vicinity of 5 years ($\chi^2 = 457$ vs. 452; Table VI) Thus, the rate of Stage 3 onset increases even after exposure has stopped, over several years.

## DISCUSSION

In this study, examination of features of the silicosis exposure–response relationship was made possible by addressing low or absent baseline risk using a fixed model-intercept, and some discernment of the silicosis exposure–response structure was attained. Use of this procedure may be advantageous even when observable, low; baseline outcome risk is present, given the central role of baseline cases in constructing relative rate estimates. A substantial part of the estimation variance in age-adjusted relative rate models could arise from sparse representation of non-attributable cases across age. Major improvement might be realized in studies with limited statistical power.

The fixing of the intercept to a small number is quite a robust choice. For example, choosing 0.1% for baseline cases instead of 1% had a small impact on the differences

**TABLE VI.** Burden and Cumulative Burden Metrics for Chinese Silicosis Stages 1–3

| | Burden, B[a] | | | | cumSil | Cumulative burden, cumB (AUC) | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Half-life, year** | **5** | **10** | **15** | **20** | **∞/0** | **1** | **5** | **15** | **25** |
| Δ deviance (1 df)[b] | | | | | | | | | |
| Stage 1 | 5,112 | 5,398 | 5,438 | 5,446 | 5,423 | 5,429 | 5,401 | 5,335 | 5,308 |
| Stage 2 | 2,397 | 2,577 | 2,601 | 2,605 | 2,588 | 2,597 | 2,591 | 2,551 | 2,534 |
| Stage 3 | 374 | 437 | 447 | 451 | 452 | 455 | 457 | 448 | 444 |

[a]Models: rate = [exp($\alpha_0 + \alpha_1 \times$ age + $\alpha_2 \times$ gen)] × [1 + $\beta \times$ B].
rate = [exp($\alpha_0 + \alpha_1 \times$ age + $\alpha_2 \times$ gen)] × [1 + $\beta \times$ cumSil].
rate = [exp($\alpha_0 + \alpha_1 \times$ age + $\alpha_2 \times$ gen)] × [1 + $\beta \times$ cumB];
reference model: rate = [exp($\alpha_0 + \alpha_1$age + $\alpha_2$gen)]; AUC, "area under the curve."
[b]Δ deviance—relative to baseline model with age, gender.

in deviances for competing metrics. Thus, comparing cumulative duration versus cumulative silica exposure yielded deviance differences of 557 [Table III, models 1 and 2 (linear)] versus 560, respectively, for the 1% and 0.1% fixed baselines. Comparing cumulative duration versus the five time windows for exposures prior to 2 years before observation yielded deviance differences of 727 [Table III, models 1 and 3 (linear)] and 730, respectively, for the 1% and 0.1% fixed baselines.

Although rate-ratio estimates are specific to the baseline risk chosen, attributable or excess rates should be generalizable to other populations. The excess relative rate coefficient is estimated assuming 99% of the silicosis cases are attributable to silica, instead of 100%. This should induce a small systematic bias in this linear relative rate model. By enabling more detailed examination of an exposure–response, this method potentially would enhance mode of action or mechanistic insight and assist moving beyond phenomenological or ''black box'' epidemiology.

## Interpretation of Silicosis Findings

The analyses using partitioned cumulative exposure clearly demonstrate that some time-varying processes are at play leading to conditions that are diagnosed as early silicosis on X-ray film. Complicating the picture is the apparent removal from exposure of insipient cases. This would normally happen if an appropriate surveillance system were in place, which would be the purpose for the periodic X-rays that were taken at yearly intervals among employed miners in this study. The negative effects of exposure in the years just prior to observation indicate that this selection out of exposure may have been operating for as many as 5 years, or more, prior to silicosis diagnosis. Some impairment may precede a positive radiographic picture in silicosis [Wagner et al., 1993] but the parallel progression of radiographic opacities and pulmonary impairment has not been adequately studied. In a study of Chinese refractory brick workers exposed to silica, even those without a silicosis diagnosis had lower than expected pulmonary function and 30% reported symptoms of dyspnea (shortness of breath) [Wang and Yano, 1999].

The pattern of exposure response showing two periods of high exposure-effect on incidence of Chinese Stage 1 or Stage 2 diagnosis, for the years 5–10 and 20–30 prior to observation, suggests that two processes are contributing to the X-ray picture, perhaps a preliminary inflammatory process followed by fibrotic structural changes. The date of onset distribution in this cohort, relatively uniform over the first 20 years of follow-up (1960–1979) but then doubling during 1980–1984 is consistent with the two-process model being proposed here, resulting from high exposures in the 1950s, but variable case-detection efficiency (variable surveillance effort over time) cannot be ruled out as a contributing explanation. Variable detection efficiency could cause some cases to be identified at a more advanced progression.

The observed changes in diagnostic potential may reflect transport of silica between tissue compartments: alveolar, tracheobronchial, interstitial, and lymph node [Tran and Buchanan, 2000]. Based on coal miner studies [Kuempel et al., 1997], the first-order kinetics of particle clearance in the lung has been described under varying conditions of clearance overload [Kuempel, 2000]. Clearance from the alveolar to interstitial compartment [Kuempel, 2000] appears to have a half-life of about 5 years (rate coefficient, $K \sim 0.0005$/day), which perhaps corresponds to the decline in diagnostic risk by 10 years following an exposure contribution.

These results imply that radiographic sensitivity for diagnosing Chinese Stage 1 silicosis may decline with time since exposure in some periods, also suggested by the observation that the best single predictor was not cumulative exposure but rather burden with a 20 years half-life. One implication that might be explored is for silicosis diagnostic criteria to be expanded to include symptomatic and ventilatory measures.

The results are consistent with a progressive component being present, manifest as increasing rate of diagnosis after 20 years of exposure, perhaps the same process that is well-recognized in the PMF stage of silicosis after sustained high silica exposures [Peters, 1986]. Thus, a worker with a 10-year exposure period would experience increasing risk of Chinese Stage 1 silicosis diagnosis beginning about 5 years after first exposed and the risk would decline at 15 years but then increase again for the period 20–30 years post first exposure.

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