

Cancer risk assessment for crystalline silica to implement California's Hot Spots Act

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Crystalline silica has been identified as a probable human carcinogen. To assess the potential for adverse health effects due to environmental exposures to respirable crystalline silica, a quantitative estimate of carcinogenicity has been made using incidence data from three studies in which long-term silica inhalation caused lung tumors in rats. The uncertainties in risk assessment in general and in the risk assessment for silica in particular are discussed.

Key terms carcinogen, multistage model, risk assessment, silica, uncertainty.

California's Air Toxics Hot Spots Information and Assessment Act of 1987 requires industrial facilities to quantify routine air emissions of designated chemicals, to perform a risk assessment if the emissions may affect public health, and to notify the public of significant risks. Because the International Agency for Research on Cancer identified crystalline silica as a probable human carcinogen (class 2A) since there was sufficient evidence from laboratory animals and limited human evidence (1), crystalline silica became subject to the Hot Spots Act. Its inclusion led to need for a quantitative estimate of its carcinogenicity. This paper reviews the methods and results of a quantitative risk estimate and discusses the uncertainties and needs for future research.

Methods

Because of difficulties in quantitating workplace exposures, human data on the carcinogenicity of crystalline silica were not readily amenable to quantitative risk assessment. (However see Goldsmith et al, this issue.) Therefore, three inhalation studies on rats were used (table 1). In addition, data from intratracheal instillation were considered for comparison.

Dagle et al (2) exposed three-month-old Fischer-344 rats to $51.6 \text{ mg} \cdot \text{m}^{-3}$ Min-U-Sil 5 quartz 6 h a day, 5 d a week for up to 24 months. Subgroups of five animals per sex were withdrawn at 4, 8, 12, and 16 months and observed until death or killed at 24 months. The average length of exposure to quartz was assumed to be 12 months. Ten of 53 exposed females had epidermoid (squamous-cell) lung carcinomas. Three animals with tumors were in the five animals withdrawn after only four months of exposure. One of 47 exposed males had an epidermoid carcinoma of the lung.

Holland and his co-workers (3, 4) exposed 60 female Fischer-344 rats, nose only, for 6 h a day, 4 d a week, for 83 weeks, to $12 \text{ mg} \cdot \text{m}^{-3}$ Min-U-Sil quartz dust aerosol with a mean geometric

particle size of $2.0 \pm 0.2 \mu\text{m}$ (70% respirable). Twenty total tumors (6 adenomas, 11 adenocarcinomas, and 3 squamous-cell carcinomas) were observed in 18 animals, of which six (the adenomas) were not malignant. Thus between 12 (if two animals had two different malignant tumors) and 14 (if all malignant tumors were in different animals) rats had malignant tumors. For risk assessment the value of 13 was selected. [Page 271 of the paper states: "In three cases, both adenocarcinomas and epidermoid carcinomas were present in the same lung, in one instance in the same lobe (Fig. 26—6)" (3). If so, then a total of $11 + 6 = 17$ animals, not 18 as stated in the paper, would have tumors.]

Muhle et al (5) exposed groups of eight-week-old Fischer-344 rats to DQ12 silica, which contained 87% crystalline alpha-quartz, 6 h a day, 5 d a week, for 24 months (whole-body exposure). The concentration was $1 \text{ mg} \cdot \text{m}^{-3}$ with 74% respirable. Four of 50 males and 8 of 50 females developed malignant lung tumors. There was one malignant lung tumor in the 100 controls (sex not specified). (See Muhle et al, this issue, for added details.)

Holland et al (6) gave weekly intratracheal instillations of 7 mg of Min-U-Sil quartz for 10 weeks to Sprague-Dawley rats. The animals developed both fibrosis (15 of 36 animals) and carcinomas (5 of 36 animals) of the lung. Groth et al (7) deposited a single dose of 20 mg of Min-U-Sil silica into male Fischer-344 rats. Of the 67 treated rats, 30 developed lung adenocarcinomas. The doses were assumed to be equivalent to a similar inhalation dose spread out over the animals' lifetimes.

The dose of silica delivered in the three inhalation studies (2, 3, 5) was calculated using the exposure data in milligrams per cubic meter of the respirable silica provided and an allometric equation for rat inhalation (8):

$$I_{\text{rat}} = 0.8 W^{0.8206},$$

where I is the inhalation rate in cubic meters per day and W is the body weight in kilograms. No adjustment was made for particle

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Table 1. Determination of silica potency.

Study	Nominal respirable exposure (mg · m ⁻³)	Animal lifetime dose (mg · kg ⁻¹ · d) ^a	HED ^b (mg · kg ⁻¹ · d)	Tumor incidence	Inhalation unit risk	
					- Surface area correction	+ Surface area correction
Dagle et al, female rats (2)	51.6 0	4.90	0.703	10/53 0/47	2.0 × 10 ⁻⁵	1.4 × 10 ⁻⁴
Dagle et al, male rats (2)	51.6 0	4.47	0.759	1/47 0/42	5.0 × 10 ⁻⁶	2.9 × 10 ⁻⁵
Holland et al, female rats (3)	12 0	1.08	0.16	13/60 0/54	9.8 × 10 ⁻⁵	6.8 × 10 ⁻⁴
Muhle et al, male and female rats (5)	1 0	0.133 ^c	0.021	12/100 1/100	4.1 × 10 ⁻⁴	2.6 × 10 ⁻³
Muhle et al, female rats (5)	1 0	0.14	0.020	8/50 0/50	6.1 × 10 ⁻⁴	4.2 × 10 ⁻³

^a For the purpose of the calculations the body weight of all the female rats was taken to be 0.207 kg, the average body weight of quartz-exposed females in the Dagle et al study (3). The daily air intake of a rat was calculated from the formula $I(\text{m}^3) = 0.8\text{bw}^{0.8206}$ (8). The body weight used for the males was 0.342 kg, the average body weight of quartz-exposed males in the Dagle et al study (3).

^b HED = human equivalent dose, calculated by dividing the animal dose by $(\text{bw}_{\text{human}}/\text{bw}_{\text{rat}})^{1/3}$.

^c The group was evenly divided between males and females. The authors did not group the results by sex, but stated that there were four malignant lung tumors in the males and eight in the females.

retention in the lung. For example, if a female rat weighs 0.207 kg, then:

$$I_{\text{rat}} = 0.22 \text{ m}^3 \cdot \text{d}^{-1},$$

$$\begin{aligned} \text{Animal dose} &= \frac{12 \times 0.70 \times 0.22 \times 6/24 \times 4/7 \times 581/683}{0.207} \\ &= 1.085 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}. \end{aligned}$$

A human equivalent dose was also calculated using a body surface area scaling factor (9, 10):

$$\text{Human equivalent dose} = \frac{1.085}{(70/207)^{1/3}} = 0.156 \text{ mg/kg} \cdot \text{d}.$$

The computer program GLOBAL 86, which fits the linearized multistage model to the experimental data (10, 11), was used. Its mathematical expression is:

$$P(d) = 1 - e - (q_0 + q_1d + q_2d^2 + \dots + q_kd^k),$$

where $P(d)$ is the lifetime probability of developing a tumor at dose d , q_0 is a constant that accounts for the background incidence of cancer, and $q_1, q_2, \dots, q_k$ are coefficients that allow the data to be expressed to various powers of the dose to obtain the best fit (10). The program computes maximum likelihood estimates (MLE) and upper 95% confidence limits (UCL) of risk associated with a particular dose. The model is based on several assumptions about carcinogenesis. Cancer is assumed to be an irreversible process which originates in single cells and involves numerous biological stages. The rate of occurrence at each stage varies linearly with dose. The output of the GLOBAL 86 program in units of $(\text{mg} \cdot \text{kg}^{-1} \cdot \text{d})^{-1}$ was converted to units of $(\mu\text{g} \cdot \text{m}^{-3})^{-1}$ by assuming that a 70-kg person inhales 20 m³ of air per day.

Results and discussion

Inhalation unit risks. Carcinogenic potency is expressed as the inhalation unit risk, the theoretical upper bound probability of contracting cancer by breathing 1 $\mu\text{g} \cdot \text{m}^{-3}$ of the material for a lifetime. Table 1 shows the unit risks for silica exposure; they were calculated both with and without a surface area scaling factor. The lowest inhalation unit risk was obtained from male rats in the Dagle study, while the highest was seen in the Muhle study, which

used the lowest silica concentration. The inhalation unit risks varied from $5.0 \times 10^{-6} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ to $2.6 \times 10^{-3} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$. To incorporate as much of the data as possible into the risk number used for the hot spots program, a geometric mean was taken of the four values for risk: Holland, females; Dagle, females; Dagle, males; Muhle, both sexes. This procedure resulted in mean cancer risk values of $4.5 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ without the surface area scaling factor and $2.9 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ with the surface area scaling factor. For comparison, unit risks determined in California's toxic air contaminant program have ranged from $1 \times 10^{-6} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ for methylene chloride to $38 (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ for dioxin.

Theoretical cancer risk for people. The value of $2.9 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ predicts that a person would theoretically incur a 10^{-5} lifetime cancer risk by continuously breathing air containing $0.03 \mu\text{g} \cdot \text{m}^{-3}$ silica, while the value of $4.5 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ estimates a 10^{-5} risk from a silica concentration of $0.2 \mu\text{g} \cdot \text{m}^{-3}$. A worker exposed to the threshold limit value of $100 \mu\text{g} \cdot \text{m}^{-3}$ for a worklife (45 years, 8 h a day, 5 d a week, 48 weeks a year) would incur a theoretical lifetime cancer risk of $100 \times 8/24 \times 5/7 \times 48/52 \times 45/70 \times 2.9 \times 10^{-4} = 4.1 \times 10^{-3}$, a risk that would be difficult to identify in epidemiologic studies of lung cancer in silica-exposed workers.

In California, the most sensitive sex, site, and species is used for cancer risk assessment (12). Since this procedure required a calculation for females only in the Muhle study (5), the potency was calculated using a tumor incidence of either 0/50 or 1/50 for controls. The unit risks were very similar [6.1×10^{-4} and $5.7 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$, respectively, without surface area scaling and 4.2×10^{-3} and 3.8×10^{-3} with surface area scaling]. The higher value of each pair was used for calculating a geometric mean with the results from females in the Dagle et al (2) and Holland et al (3) studies. The risks estimated using only females (and without surface area scaling) had a geometric mean of $1.1 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$. The corresponding values with surface area scaling had a geometric mean of $7.4 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$, values two to three times greater than the preceding ones.

Intratracheal studies with rats. Unit risks were calculated from the intratracheal studies for comparative purposes. From the Groth et al study (7), unit risks of $2.5 \times 10^{-3} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ and $1.5 \times 10^{-2} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ were estimated without and with a surface area

scaling factor. From the Holland et al (6) study, unit risks of $1.8 \times 10^{-4} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ and $1.2 \times 10^{-3} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$ were calculated without and with surface area scaling. These risks may be higher than those from inhalation studies because the nasal passage is bypassed during intratracheal instillation and the dose is given early in the life span.

Inhalation study with mice. Wilson et al (13) exposed female Balb/cBYJ mice by inhalation to up to $1950 \mu\text{g} \cdot \text{m}^{-3}$ Min-u-Sil 8 h a day, 5 d a week for 570 d. Tumor incidence was not increased by silica; at the highest concentration, 4 of 16 animals had lung tumors versus 4 of 13 of the controls. Based on the unit risk from the three studies of female rats and a surface area scaling factor between mice and rats of approximately 2, an approximate unit risk for mice would be $5.5 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1}$. The number of excess tumors predicted in the highest dose group would be $5.5 \times 10^{-5} (\mu\text{g} \cdot \text{m}^{-3})^{-1} \times 1950 \mu\text{g} \cdot \text{m}^{-3} \times 8/24 \times 5/7 \times 16 \text{ mice} = 0.4 \text{ tumors}$. The observed result is consistent both with no effect of silica and with the 0.4 additional tumors predicted.

Uncertainties in risk assessment. There are many uncertainties in risk assessment (14): (i) selection of test species, (ii) different susceptibility between the sexes, (iii) measure of dose, (iv) tumor response in test species (eg, variability in tumor diagnosis), (v) statistical variability in tumor response data in test species, (vi) selection of a specific dose-response model (linearized multistage versus other), (vii) calculation of uncertainty in dose-response (use of 95% upper confidence limit versus maximum likelihood estimate), (viii) interspecies extrapolation method, (ix) expression of human dose (concentration at contact site versus dose to target tissue) and (x) description of target humans (variation in sensitivity in human population due to age, sex, genetics, etc). In addition there are uncertainties specific to a risk assessment for silica. Silica is carcinogenic in rats by inhalation (table 1) and in rats and other animals by injection into lung and pleura (1). It is also able to cause mammalian cell transformation, an in vitro analog of cancer induction (1).

Dose-response. When this risk assessment was carried out, a dose-response study in the rat had not been done in a single laboratory. The three positive inhalation studies with rats do not exhibit a dose-response relationship among themselves (figure 1). The tumor responses at three different levels of silica were similar (16, 19, and 22% malignant tumors). In the Dagle study (2), there were varying lengths of exposure to quartz, and therefore the difficulty in comparing the studies is increased. However, the fact that quartz is not metabolized and may provide a persistent "foreign body" stimulus once it is deposited in the lungs may make the application of traditional dose-response concepts to silica-based carcinogenesis more problematic.

In a recent study, female Wistar rats were exposed to two levels of silica (6 and $30 \text{ mg} \cdot \text{m}^{-3}$) for only 29 d at 6 h a day early in life (15). After 24 months the lung tumor responses to the two levels of silica were not very different ($6 \text{ mg} \cdot \text{m}^{-3}$ silica, 37 of 85 rats; $30 \text{ mg} \cdot \text{m}^{-3}$ silica, 43 of 85 rats; controls, 0 of 85 rats). Attempts to apply the linearized multistage model to the data did not yield an acceptable fit.

Surface area scaling. Since most toxicants must cross a surface to exert a toxic effect or act at a cell surface receptor, a surface area scaling factor is routinely used in animal-to-human extrapolation (10). Thus the estimation of higher cancer risks for humans than would be predicted without scaling is consistent with the concept that humans are more sensitive to toxicants than ani-

mals. However, use of surface area scaling may not be appropriate for silica because it is a particle and causes cancer only in the tissue it first contacts, the lung. It is worth noting that Goldsmith et al (this issue) have predicted a lower cancer risk based on epidemiologic data than we predicted using rodents.

Greater tumor incidence among females. Another uncertainty is the observation that silica-induced lung tumors are more likely (5) or much more likely (2) to be induced in female rats. Women are considered to be more susceptible to silicosis than men (16). Whether women are at greater risk than men for lung tumors after silica exposure is not clear (17, 18).

Malignant and benign tumors. Only malignant tumors were used in the calculations. A more health protective approach would be to combine benign and malignant tumors if histological evidence indicates that the benign tumor may become malignant. Holland et al (3) reported six adenomas. Muhle et al (5) reported six benign lung tumors. Omitting benign tumors results in an underestimation of cancer risk.

Single species data. More confidence in an animal-based risk assessment would derive from the presence of positive tumor incidence data for more than one species. However, hamsters test negative by inhalation (6) and by intratracheal instillation (6, 19, 20). The mouse has not been adequately tested (13, 21).

Silicosis as a necessary precursor to cancer. Perhaps the greatest uncertainty results from the possibility that cancer, as a sequel to silica exposure, may only occur after the nonmalignant disease silicosis is induced. In workers, lung cancer due to silica exposure usually occurs after silicosis (18, 22). In lung pathology (23), scar cancer is a recognized entity, occurring in conjunction with fibrosis, possibly because the hyperplasia involved in fibrosis may lead to an increased probability of a mutation leading to neoplasia. However, Holland et al (6) have stated that "While most of the evidence points to a preexisting scar that may later give rise to a neoplasm, there is some evidence that suggests that certain pulmonary tumors, particularly adenocarcinomas, create a localized fibrotic response during active growth of the tumor [p 493]."

A few occupational studies indicate that cancer may occur in the absence of silicosis (18, 24, 25). But the induction of lung

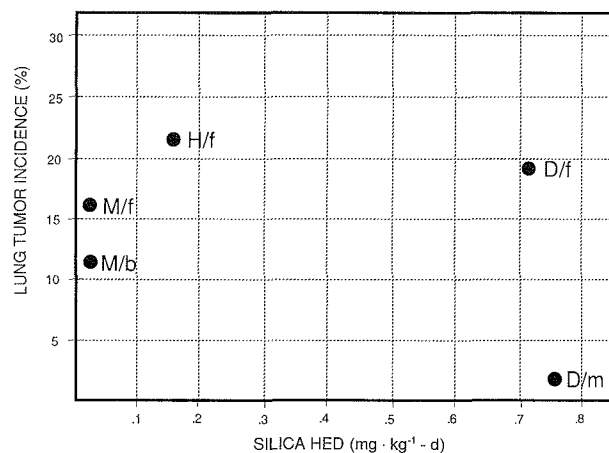


Figure 1. Lung tumor incidence versus silica dose. Human equivalent doses (HED) of silica were calculated as shown in table 1 and plotted against tumor incidences from the animal studies (see the text). [M = Muhle et al study (5), H = Holland et al study (3), D = Dagle et al study (2), f = females, m = males, b = both sexes]

cancer without silicosis is controversial (22, 26, 27). Epidemiologic studies of silica are often complicated by confounding exposures to asbestos, radionuclides, polycyclic aromatic hydrocarbons (PAH) if diesel equipment is used, arsenic, and cigarette smoke. Occurrences of silicosis due to chronic environmental exposures are rare and not fully validated (28, 29).

In the three rat studies, many more animals had fibrosis than cancer. It was not mentioned if there were any rats that had cancer without fibrosis. Holland et al (3) stated that "Most animals surviving beyond 400 days of exposure exhibited pronounced pulmonary fibrosis . . . [p 276]." Muhle et al (30) reported that 92% of their silica-exposed rats had a moderate degree of fibrosis by the end of the study. Silica-induced tumors occur later in life. No lung tumors were observed in studies involving 2300 female Wistar and Sprague-Dawley rats exposed to up to 50 mg of silica when the exposure lasted 12 months or less (A Brammertz, University of Aachen, unpublished results). Holland et al (3) indicated that the first lung tumor was observed after 651 d of exposure, although the paper states that the first tumor in any exposed group appeared at approximately 17 months.

Intratracheal instillation studies of silica indicate that rodents vary in their susceptibility to silica-induced fibrosis. The mouse is less susceptible than the rat (31) and the hamster is much less susceptible than the rat (4, 19, 20). If fibrosis is a mandatory step in the pathway to silica-induced cancer, it might explain why hamsters exposed to silica have tested negative for cancer induction.

If silicosis, a nonmalignant disease, must occur before cancer occurs, there would be a threshold for silicosis and consequently for subsequent lung cancer (as suggested by Klein & Christopher, this issue). Thus low environmental levels, below the threshold concentration, would pose no cancer risk. The standard application of the linearized multistage model may, therefore, be inappropriate. Silica would not be an initiator of carcinogenesis, but rather a promoter or cytotoxic agent (32).

Differential retention of silica. The potential difference in the retention of silica between rat and human lungs (27) has not been addressed in this report. Our risk assessment was a preliminary one carried out to implement the California Hot Spots Act and, although it was done according to standard procedures, it did not receive extensive peer review. If particle retention in humans and rats is similar, a correction would not be needed.

Silica as a toxic air contaminant. The inhalation unit risks for silica were put on a list of screening cancer potency values for the hot spots program (33). These values were not as highly peer reviewed as the unit risks developed by the Environmental Protection Agency and by California regulatory programs such as the toxic air contaminant program (34) and Proposition 65 (35). With the use of screening cancer potency values (33), some dusty facilities had high theoretical cancer risks due solely to their silica emissions. Some of the public interpreted the risk assessment results as certain cancer cases. Because of the preliminary nature of the unit risk factors, it was recommended that the use of the silica risk assessments be deferred until more extensive peer review could be obtained; that review is now underway.

Research needs

Respirable crystalline silica meets the criteria for a carcinogen (1, 18). Numerical estimates of its carcinogenicity based on inhalation studies with rats involve considerable uncertainty. Most

naturally occurring silica particles are too large to be respirable. Human activities like mining and sand blasting often make them respirable. The potential for cancer risk must be dealt with rationally, even when the scientific data currently available are limited. Some specific areas for research to clarify some uncertainties in the risk assessment for silica include proper inhalation concentration-response studies with both rats and mice; mechanistic studies of silica's toxicity at the cellular and molecular level to determine if it is an initiator, a promoter, a cytotoxic agent, or has multiple roles; and analysis of epidemiologic studies to derive an inhalation unit risk number and to correlate it with the risk numbers derived from animals, as done by Goldsmith et al (this issue). The National Institute of Environmental Health Sciences in the United States has been asked to address some of the research questions that can be answered using laboratory animals.

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References

1. International Agency for Research on Cancer (IARC). Silica and some silicates. Lyon: IARC, 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, vol 42.
2. Dagle GE, Wehner AP, Clark ML, Buschbom RL. Chronic inhalation exposure of rats to quartz. In: Goldsmith DF, Winn DM, Shy CM, editors. Silica, silicosis, and cancer: controversy in occupational medicine. New York (NY): Praeger, 1986:255-66.
3. Holland LM, Wilson JS, Tillery MI, Smith DM. Lung cancer in rats exposed to fibrogenic dusts. In: Goldsmith DF, Winn DM, Shy CM, editors. Silica, silicosis, and cancer: controversy in occupational medicine. New York (NY): Praeger, 1986:267-80.
4. Johnson NF, Smith DM, Sebring R, Holland LM. Silica-induced alveolar cell tumors in rats. *Am J Ind Med* 1987;11:93-107.
5. Muhle H, Takenaka S, Mohr U, Dasenbrock C, Mermelstein R. Lung tumor induction upon long-term low-level inhalation of crystalline silica. *Am J Ind Med* 1989;15:343-6.
6. Holland LM, Gonzales M, Wilson JS, Tillery MI. Pulmonary effects of shale dusts in experimental animals. In: Wagner WL, Rom WN, Merchant JA, editors. Health issues related to metal and nonmetallic mining. Boston (MA): Butterworth, 1983:485-96.
7. Groth DH, Stettler LE, Platek SF, Lal JB, Burg JR. Lung tumors in rats treated with quartz by instillation. In: Goldsmith DF, Winn DM, Shy CM, editors. Silica, silicosis, and cancer: controversy in occupational medicine. New York (NY): Praeger, 1986:243-53.
8. Environmental Protection Agency. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati (OH): Office of Health and Environmental Assessment, 1988. EPA 600/6-87/008.
9. Mantel N, Schneiderman MA. Estimating safe levels, a hazardous undertaking. *Cancer Res* 1975;35:1379-86.
10. Anderson EA, the Carcinogen Assessment Group of the US EPA. Quantitative approaches in use to assess cancer risk. *Risk Analysis* 1983;3:277-95.
11. Howe RB, Crump KS, Van Landingham C. GLOBAL 86: a computer program to extrapolate quantal animal toxicity data to low doses. Ruston (LA): Clement Associates, 1986.
12. California Department of Health Services. Guidelines for chemical carcinogen risk assessments and their scientific rationale. Sacramento (CA): Health and Welfare Agency, 1985.
13. Wilson T, Scheuchenzuber WJ, Eskew ML, Zarkower A. Comparative pathological aspects of chronic olivine and silica inhalation in mice. *Environ Res* 1986;39:331-44.
14. Frederick CB. Limiting the uncertainty in risk assessment by the development of physiologically based pharmacokinetic and pharmacodynamic models. *Toxicol Lett* 1993;68:159-75.

15. Spiethoff A, Wesch H, Wegener K, Klimisch H-J. The effects of Thoro-trast and quartz on the induction of lung tumors in rats. *Health Phys* 1992;63: 101—10.
16. Katsnelson BA, Polzik EV, Privalova LI. Some aspects of the problem of individual predisposition to silicosis. *Environ Health Perspect* 1986;68: 175—85.
17. Katsnelson BA, Mokronosova KA. Non-fibrous mineral dusts and malignant tumors: an epidemiological study of mortality. *J Occup Med* 1979;21: 15—21.
18. Goldsmith DF. Silica exposure and pulmonary cancer. In: Samet J, editor. *Epidemiology of lung cancer*. New York (NY): Marcel Dekker, 1994:245—98.
19. Renne RA, Eldridge SR, Lewis TR, Stevens, DL. Fibrogenic potential of intratracheally instilled quartz, ferric oxide, fibrous glass, and hydrated alumina in hamsters. *Toxicol Pathol* 1985;13:306—314.
20. Niemeier RW, Mulligan LT, Rowland J. Cocarcinogenicity of foundry sand in hamsters. In: Goldsmith DF, Winn DM, Shy CM, editors. *Silica, silicosis, and cancer: controversy in occupational medicine*. New York (NY): Praeger, 1986:215—227.
21. McNeill DA, Chrisp CE, Fisher GL. Pulmonary adenomas in A/J mice treated with silica. *Drug Chem Toxicol* 1990;13:87—92.
22. Pairon JC, Brochard P, Jaurand MC, Bignon J. Silica and lung cancer: a controversial issue. *Eur Respir J* 1991;4:730—44.
23. Spencer H. Scar cancer of the lung. In: Spencer D, editor. *Pathology of the lung*. 4th edition. New York (NY): Pergamon, 1985:885—92.
24. Hnizdo E, Sluis-Cremer GK. Silica exposure, silicosis and lung cancer: a mortality study of South African gold miners. *Br J Ind Med* 1991;48:53—60.
25. Checkoway H, Heyer NJ, Demers PA, Breslow NE. Mortality among workers in the diatomaceous earth industry. *Br J Ind Med* 1993;50:586—97.
26. Heppleston AG. Silica, pneumoconiosis, and carcinoma of the lung. *Am J Ind Med* 1985;7:285—94.
27. Holland LM. Crystalline silica and lung cancer: a review of recent experimental evidence. *Reg Toxicol Pharmacol* 1990;12:224—37.
28. Norboo T, Angchuk PT, Yahya M, et al. Silicosis in a Himalayan village population: role of environmental dust. *Thorax* 1991;46:341—3.
29. Saiyed HN, Sharma YK, Sadhu HG, et al. Non-occupational pneumoconiosis at high altitude villages in central Ladakh. *Br J Ind Med* 1991;48:825—9.
30. Muhle H, Bellman B, Creutzenberg O, et al. Pulmonary response to toner upon chronic inhalation exposure in rats. *Fundam Appl Toxicol* 1991;17: 280—99.
31. Hatch GE, Raub JA, Graham JD. Functional and biochemical indicators of pneumoconiosis in mice: comparison with rats. *J Toxicol Environ Health* 1984;13:487—97.
32. Williams GM, Weisburger JH. Chemical carcinogenesis. In: Klaassen CD, Amdur MC, Doull J, editors. *Casarett and Doull's toxicology: the basic science of poisons*. 3rd edition. New York (NY): MacMillan, 1986:99—173.
33. California Air Pollution Control Officers Association (CAPCOA). Air toxics "hot spots" program, risk assessment guidelines for AB2588. Sacramento (CA): CAPCOA, Risk Assessment Committee, 1991.
34. Mrak E. Managing risk in a technical society: the Tanner Bill in California. *Reg Toxicol Pharmacol* 1985;5:410—5.
35. Pease WS, Zeise L, Kelter A. Risk assessment for carcinogens under California's proposition 65. *Risk Anal* 1990;10:255—71.