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Comparative cancer potency for silica from extrapolations of human and animal findings

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The International Agency for Research on Cancer has judged that the evidence for the carcinogenicity of silica in animals is sufficient, and for humans it is limited. With the use of the Global 86 computer model, animal and human cancer potency data were extrapolated and the findings compared. The animal findings were based on inhalation rat studies. The cancer slope factors ranged from 2.3×10^{-5} to 6.0×10^{-3} for $(1\ \mu g \cdot m^{-3})^{-1}$ among three experimental studies. The epidemiologic findings were from gold workers exposed to quartz and diatomaceous earth workers exposed to cristobalite. The cancer slope factors ranged from 6.8×10^{-7} to 1.85×10^{-5} for lifetime exposure to $1\ (\mu g \cdot m^{-3})^{-1}$ of silica dust. Because of the many uncertainties involved in extrapolating to humans from animal data, more rational risk assessments are achieved when data from silica-exposed workers are used than when laboratory findings are relied on.

Key terms cancer risk assessment, comparing rat and human extrapolations, cristobalite, dose-response findings.

Silica exposure is widespread, it has occupational cancer and non-cancer health effects, and it has animal and human data supporting its classification as a toxic substance. Silica dust levels are regulated in workplaces in the United States by the Occupational Safety and Health Administration (OSHA), the time-weighted average (TWA) being 0.1 mg · m^{-3} of crystalline silica over an 8-h day. For two crystalline polymorphs (cristobalite and tridymite), the TWA standard is more strict, 0.05 mg · m^{-3} (1). For both of these standards, the permissible exposure limits are designed to prevent silicosis. The International Agency for Research on Cancer (IARC) evaluated crystalline silica and judged it to be a probable human carcinogen according to findings of sufficient evidence for carcinogenicity in laboratory animals and limited evidence for humans (2). Based in part on IARC's evaluation, California's Proposition 65 Science Advisory Panel judged airborne, respirable crystalline silica to be a carcinogen in 1988 (3). In 1991, silica was listed as a carcinogenic air toxin in the California Toxic Hot Spots legislation, AB 2588 (4). In the language of the Toxic Hot Spots bill, California's air pollution control districts (and other agencies) are required to conduct risk assessments to guide the formulation of policies regarding hazardous ambient air emissions.

As with other airborne respiratory hazards such as arsenic, asbestos, coke oven emissions, and radon, cancer risks have been assessed for ambient environmental exposures (5). This process requires extrapolation of the risks using the cancer potency slope or the geometric means of several slope lines according to established methods (6). This paper contrasts the cancer risk assessments developed for humans and for animals.

Background

The first findings demonstrating that quartz produced tumors were reported by Wagner et al. (Summarized in references 2 and 7.) Wagner and her colleagues showed that intrapleurally injected silica dusts produced histiocytic lymphomas in several strains of rats. Since 1983, silica (as Min-U-Sil and DQ12 quartz) has been shown to be a pulmonary carcinogen in four lifetime rat studies using both intratracheal injection and inhalation methods (8—11). Because the studies by Holland et al (8), Dagle et al (10), and Muhle et al (11) applied inhalation methods to expose the animals to silica (similar to the route of exposure in humans), their findings were used in the extant risk assessment extrapolations (12, 13). (See also Collins & Marty, this issue.) There have also been two epidemiologic studies of white South African gold miners and California diatomaceous earth workers exposed to inhaled silica dust showing dose-response gradients for lung cancer (14, 15). The cancer risk assessment for the human and animal data are presented below.

Assumptions for extrapolating from animals to humans

For all three risk assessment extrapolations from data on rodents, several standard assumptions were used. First, the lifetime silica dust exposure in the experimental studies was converted from micrograms per cubic meter to micrograms per kilogram per day. Thus one assumes that the body weight (BW) of adult female rats is 0.207 kg and that of male rats is 0.342 kg. The daily air intake of a rat (Ira) is assumed to be $0.8 \cdot BW^{(0.8206)}$ (17). The fraction of

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silica aerosol deposited (DF) in the lung is 23% (18). Thus the animal dose (AD) is obtained by multiplying the Ira times the silica dust concentration (Sdc) times the hours exposed per day (Hexp) times days exposed per week (Dexp) times days exposed per exposure period (Mexp) times the respirable fraction (Rspf) times the deposition fraction (DF). This numerator is then divided by the rodent body weight to obtain the animal dose (AD):

$$AD = (Ira \times Scd \times Hexp \times Dexp \times Mexp \times Rspf \times DF)/BW.$$

Thus, to obtain the AD (in milligrams per kilogram per day) for female F344 rats in Dagle et al's study (10), the calculation is as follows:

$$[(0.8)\ (0.207\ kg^{(0.8206)})\ (51.6\ mg \cdot m^{-3})\ (6\ h/24\ h)\ (5\ d/7\ d/week)\ (494/730)\ (100\%)\ (0.23)]/0.207\ kg = 1.52\ mg \cdot kg^{-1} \cdot d^{-1}.$$

To obtain the human equivalent dose (HED) from the animal dose, we assumed that an average human weighs (avg BW) 70 kg and applied a surface area correction factor (SACf) which equals $(avgBW/BW)^{(1/3)}$. Thus the human equivalent dose = AD/SACf, and, continuing the Dagle et al example, SACf = $(70\ kg/0.207\ kg)^{(1/3)}$ = 6.97 and HED = $(1.52\ mg \cdot kg^{-1} \cdot d^{-1})/6.97$ = $0.22\ mg^{-1} \cdot kg^{-1} \cdot d^{-1}$.

Last we assumed a standardized human inhalation rate of 20 m^3 of air per day and a 70-year lifetime exposure (16) for those living where ambient silica levels are the greatest. Table 1 summarizes the cancer risk from the extrapolation of experimental findings to 1 $\mu g \cdot m^{-3}$ of ambient silica.

Extrapolation methods

To conduct a cancer risk assessment, the linearized multistage model, developed by Crump and his colleagues in the form of the GLOBAL 86 program (18), was used to estimate the cancer potency slope for silica. This model has been used by the California Environmental Protection Agency and the Department of Health Services and the United States (US) Environmental Protection Agency for previous cancer health risk assessments. The program uses the animal tumor incidence data to compute maximum likelihood estimates (MLE) and upper 95% confidence limits (UCL). The upper 95% confidence limit is regarded as the upper limit of the estimated risk and, because of the nonthreshold assumption regarding carcinogens, the MLE and upper 95% confidence limits are linear at low doses (18). When the upper 95% confidence limit is estimated at an exposure value of 1 $mg \cdot kg^{-1} \cdot d^{-1}$ (the "unit" cancer risk level in public health extrapolations), it is defined as the q1* or cancer potency slope (CPS). The q1* results are converted from milligrams per kilogram per day to micrograms per cubic meter (used for inhalation risk assessments) by first multiplying the CPS value by 20 m^3 of air per day, multiplying that product by $10^{-3}\ mg \cdot \mu g^{-1}$, and dividing the whole product by 70 kg, the average weight of an adult.

The following equation gives the cancer potency slope (q1*) from the Dagle et al female rat tumor study (10) in micrograms per cubic meter per day for an adult who is a lifetime resident in a location where there is mean exposure to 1 $\mu g \cdot m^{-3}$ ambient silica dust, as

$$\text{unit cancer risk} = (q1^*)\ (20\ m^3 \cdot d^{-1})(10^{-3}\ mg \cdot \mu g)/(70\ kg)$$

or

$$(0.36)\ (20)\ (0.001)/(70) = 1.0 \times 10^{-4}\ (\mu g \cdot m^{-3})^{-1}.$$

Table 1. Summary of risk assessment calculations for rat inhalation studies. HED = human equivalent dose, CPS = cancer potency slope or q1*, ICPS = inhalation cancer potency slope or q1* converted to airborne exposure.

Research	Sex	HED ($mg \cdot kg \cdot d^{-1}$)	CPS $(mg \cdot kg \cdot d^{-1})^{-1}$	ICPS $(\mu g \cdot m^{-3})^{-1}$
Dagle et al (10), Min-U-Sil quartz	Male	0.240	0.08	2.9×10^{-5}
	Female	0.220	0.36	1.0×10^{-4}
Holland et al (8), Min-U-Sil quartz	Female	0.050	3.83	1.1×10^{-3}
Muhle et al (11), DQ12 quartz	Male	0.046	10.73	3.1×10^{-3}
	Female	0.043	20.89	6.0×10^{-3}

Another way of describing this information is that the adult lifetime excess of cancer risk from inhalation of 1 $\mu g \cdot m^{-3}$ of silica based on the Dagle et al study (10) of female rats is 1 in 10 000.

Risk assessments from animal and human dose-response gradients

To find the individual cancer risk from lifetime exposure to silica levels, one multiplies the unit cancer risk factor by the measured silica concentration:

individual lifetime cancer risk = silica exposure × unit cancer risk [q1*].

The cancer potency or unit risk factor estimated by Goldsmith et al (13) ranged from 2.3×10^{-5} (based on data from male rats in Dagle et al's study) to 6.0×10^{-3} (based on data from female rats in Muhle et al's study) for a $(1\ \mu g \cdot m^{-3})^{-1}$ for lifetime air exposure to respirable silica dust. These findings are similar to those estimated by the California Environmental Protection Agency's Office of Health Evaluation and Assessment, which range from $2.9 \times 10^{-4}\ (\mu g \cdot m^{-3})^{-1}$ (without correction for surface area differences between rodents and humans) to $4.4 \times 10^{-5}\ (\mu g \cdot m^{-3})^{-1}$(with surface area correction). (See Collins & Marty, this issue.) Brantner & Klein (12) also conducted a cancer risk assessment for silica exposure based on the same three animal studies. They derived a single CPS of $3.55 \times 10^{-5}\ (\mu g \cdot m^{-3})^{-1}$ for quartz. Another interpretation of these findings is that, if lifetime exposure to quartz is 1 $\mu g \cdot m^{-3}$, then the cancer risk will be greater than 1 in 100 000, and a Proposition 65 warning about cancer risk is required to be posted by the source of the emissions (3).

The experimental findings from Muhle et al (11) have the greatest cancer potency slope and the lowest dose, while the results from Dagle et al (10) show the shallowest slope with the greatest dose. The latter result may be a function of the high dose levels, 51.6 $mg \cdot m^{-3}$, used in the Dagle et al study. (This level of exposure likely exceeds the maximum tolerated dose for rats.) Goldsmith et al (13) excluded these high dose levels, and a clear dose-related gradient emerged for the remaining animal data. The finding suggests that, although these separate studies show that silica is a carcinogen in rodents, overall, there appears to be some dose-related gradient except at high doses.

Epidemiologic studies of silica-exposed workers

The epidemiologic findings among white South African gold miners (14) and among California diatomaceous earth workers (15) demonstrated dose-response lung cancer findings for quartz exposure. Applying methods designed by Nurminen et al (19),

Table 2. Cancer potency slopes and inhalation unit risk factors calculated from epidemiology studies of silica-exposed workers.

Researcher	Mineralogical species	CPS[a, b] $(mg \cdot kg \cdot d^{-1})^{-1}$	ICPS[c] $(\mu g \cdot m^{-3})^{-1}$
Hnizdo & Sluis-Cremer (15)[d]	Silica	3.09×10^{-4}	6.75×10^{-5}
Checkoway et al (16), total cohort	Cristobalite	8.43×10^{-3}	1.83×10^{-7}
Checkoway et al (16), smokers	Cristobalite	1.16×10^{-2}	2.53×10^{-7}

[a] The cancer potency slopes (CPS) are for an assumed work lifetime of 40 years.
[b] The lifetime adjusted CPS corrects for the partial exposure in occupational settings: lifetime CPS = crude CPS × (8 h/24 h) (5 d/7 d) (50 weeks/52 weeks) (40 years/70 years).
[c] Inhalation cancer potency slope.
[d] Adjusted for smoking.

Ruble & Goldsmith (20) developed estimations of cancer potency slope from epidemiologic dose-response findings. They applied historical dust exposure levels from Hnizdo & Sluis-Cremer (15) and estimated from the work of Checkoway et al (15) with a 15-year lag time for the total cohort and for smokers. The number of person-years at risk for each dust exposure concentration was used as a denominator to fit the requirements for the Global 86 model (20). Adjustments were also made to reflect the less than lifetime exposure consistent with workplace (ie, 40 years' employment, 8-h workshifts, 50 h workweeks, and 50 weeks per year). As shown in table 2, the cancer slope factors ranged from 6.8×10^{-7} to 1.85×10^{-5} for lifetime exposure to 1 $(\mu g \cdot m^{-3})^{-1}$ of silica dust.

Discussion

Because of the many uncertainties in extrapolating to humans from animal data (21, 22), more rational risk assessments are achieved when data from silica-exposed workers are used than when laboratory findings are relied on. Cancer potency estimation from silica-exposed workers produces shallower slope extrapolations than from rats and thus enables risk managers to develop recommendations having less uncertainty in the quantification of risk.

There is no disputing the ability of silica to cause silicosis (23, 24). Noncancer risk extrapolation focuses on the likelihood of silicosis among workers exposed to quartz dust over a work life (19). The US Environmental Protection Agency (25) and Gift & Faust (26) reviewed the silicosis epidemiology literature to determine the acceptability of studies for calculating an ambient silica regulation. The no observed adverse effect levels (NOAEL) were very close, between 0.05 $mg \cdot m^{-3}$ to 0.3 $mg \cdot m^{-3}$, and the reference concentrations (RfC) ranged from 0.03 $\mu g \cdot m^{-3}$ to 2.06 $\mu g \cdot m^{-3}$ (26). Taking the lowest RfC and applying it to the aforementioned cancer risk values means that lifetime ambient exposure of 0.03 $\mu g \cdot m^{-3}$ would not result in an excess risk beyond acceptable levels based on human extrapolation, but may result in excess cancer when animal methods are used.

Concluding remarks

The extrapolation procedures for assessing risk for crystalline silica seems very straight-forward and compelling as a means to protect public health. However, there have been objections raised to extrapolation from animal studies (27) because all the positive studies were not done using the same protocol and because these studies were not initiated to evaluate the cancer hazards from silica. There is the possibility that costly emissions controls may be required that do little to reduce public lung cancer risk. Goldsmith (22) and Hertz-Picciotto (21) raised the issue of whether using animal data is appropriate when there are high-quality epidemiologic data demonstrating dose-response gradients. Despite the fact that extrapolations from experimental studies may provide greater cancer potency for equivalent exposure, extrapolations from human findings should be seriously considered for risk assessment purposes. This approach should be adopted because these data reflect the species (humans) for which the risk assessment is directed and because the measured lung cancer risks resulted from actual workplace exposures. In addition these findings represent risks in the realm of human exposure and the biological process, while there have been no demonstrated respiratory cancer risks from environmental silica exposures. More research is needed on cancer risk assessment methods, an activity which may lead to extrapolations that are more rationally based on epidemiologic findings.

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