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Concordance of Rat- and Human-based Risk Estimates for Particle-related Lung Cancer

E. D. KUEMPEL[1]*, R. J. SMITH[1], D. A. DANKOVIC[1], A. J. BAILER[1,2] and L. T. STAYNER[1]

[1]National Institute for Occupational Safety and Health, Risk Evaluation Branch, 4676 Columbia Parkway, M.S. C-15, Cincinnati, OH 45226-1998; [2]Miami University, Department of Mathematics and Statistics, 123 Bachelor Hall, Oxford, OH 45056, USA

In this study we use existing data in both rats and humans exposed to respirable, poorly soluble particles to compare the dose–response relationships for lung cancer. Exposure–response data for lung cancer were available in both species for crystalline silica and in rats for coal dust and titanium dioxide. Tumorigenic doses (TDs) associated with specified levels of excess risk (e.g. 1%) were computed, using multistage models in rats and relative rate models in humans. The rat-based and human-based TDs for crystalline silica are reasonably concordant (i.e. TD ratios near 1.0) for several dose metrics, including average internal dose in the lungs. The rat-based TDs associated with a 1% excess risk of lung cancer (TD_1) (extrapolated to humans, assuming a 45 yr working lifetime exposure) are point estimates from 0.007 to 0.24, 2 to 91 and 1.7 to 444 mg/m^3, respectively, for crystalline silica, coal and titanium. The rat-based TD_1 values for silica, coal and titanium dioxide are consistent with the relative toxicity of these airborne particulates and with results from epidemiological studies. These findings provide some support for the continued use of risk assessment models based on rat bioassay data for particulates when human data are not available.

Keywords: risk assessment; inhaled particles; lung cancer; interspecies comparison

INTRODUCTION

Risk assessment often relies on animal bioassay data to predict disease risk in humans. This requires extrapolation from animals to humans and often from higher animal doses to lower human doses. Few human exposure–response data are available to assess the validity of these assumptions, especially for poorly soluble, respirable particles. Animal studies have shown that rats develop lung cancer following chronic inhalation of poorly soluble, respirable particles (e.g. diesel exhaust particulate, carbon black, titanium dioxide, silica and talc) (International Life Sciences Institute, 2000). These lung tumors occur at lung burdens high enough to cause overloading of alveolar macrophage-mediated clearance. Rats have been shown to exhibit a greater pulmonary response than other rodents with overloading doses of particles and it has been hypothesized that a pro-inflammatory environment in the alveoli may make the rat sensitive to developing epithelial hyperplasia and neoplastic changes (Oberdörster, 1994; International Life Sciences Institute, 2000). Although the rat is frequently used to assess the toxicity of inhaled materials, questions arise as to how the rat data on respirable, poorly soluble particles should be used in human health risk assessment. For example, what information do we have on the relative sensitivity of rats and humans to equivalent doses of respirable particles? What do we know about the mechanisms leading to lung cancer in particle-exposed rats and do these mechanisms also exist in humans?

The overloading of lung clearance has not been directly observed in humans, although reduced clearance rates have been measured in retired coal miners (Freedman and Robinson, 1988). Significantly elevated pulmonary inflammation has been observed in the bronchoalveolar lavage fluid of humans occupationally exposed to coal or silica particles (Lapp and Castranova, 1993; Vallyathan *et al.*, 2000). Although the relationship between lung particle dose and inflammation has not been quantitatively compared in rats and humans, qualitatively similar responses are observed (Castranova, 2000). An excess risk of lung cancer mortality has been demonstrated for occupational exposure to respirable

*Author to whom correspondence should be addressed.
Fax: +1-513-533-8224; e-mail: ekuempel@cdc.gov

crystalline silica (Rice *et al.*, 2001; Steenland and Sanderson, 2001), but not to respirable coal mine dust (Miller and Jacobsen, 1985; Kuempel *et al.*, 1995) or titanium dioxide (Chen and Fayerweather, 1988). Lung diseases other than cancer (e.g. fibrosis and chronic obstructive pulmonary disease) have also been associated with occupational exposures to respirable particles, including silica, coal and titanium dioxide. It is not clear from these findings whether only certain types of respirable particles are carcinogenic in human lungs or whether dose is a critical factor. Since crystalline silica is more toxic than coal dust or titanium dioxide, the pathological precursors to tumor development (e.g. chronic pulmonary inflammation) may arise at lower exposures to silica than to the other, less toxic particles.

The data are quite limited for quantitative comparisons of dose–response in humans and rats exposed to inhaled particles, although some analyses are feasible. In this study we have used the available data to quantitatively compare the exposure–response and dose–response relationships in humans and rats exposed to respirable crystalline silica and then applied the results for rats exposed to respirable titanium dioxide and coal dust to predict tumorigenic dose in humans.

MATERIALS AND METHODS

To evaluate the concordance of risk estimates in rats and humans exposed to respirable particles, we compute the ratio of the tumorigenic doses associated with specified levels of excess risk of lung cancer in each species using available data.

Rat data

The rat studies of chronic inhalation exposure to three types of particles include: respirable crystalline silica (Holland *et al.*, 1986; Muhle *et al.*, 1991), titanium dioxide (Lee *et al.*, 1986) and coal dust (Martin *et al.*, 1977). Lung tumor responses (i.e. proportion of rats with tumors) and inhaled dose levels were used to compute the tumorigenic doses (TDs), as external exposures (mg/day or mg/m^3), associated with various levels of excess risk of lung cancer (e.g. 1%). For crystalline silica the TDs as average internal dose (mg/g lung or m^2/m^2 lung) were also estimated, using a rat lung dosimetry model (Tran *et al.*, 2001) fitted to the Muhle *et al.* (1991) data. A quantal multistage model (Howe and Crump, 1983) was fitted to the rat data (using either external exposure or internal dose) to predict the doses associated with excess risk levels. For quartz and coal one-stage models were fitted because data were available for only two groups (exposed and control). For titanium dioxide multistage models were fitted to male and female rat data, with three dose groups and a control for each.

Human data

Human-based TDs were derived for crystalline silica using human exposure–response data for lung cancer in two recent epidemiological studies (Rice *et al.*, 2001; Steenland and Sanderson, 2001). Poisson regression models and lifetable analyses (that account for competing causes of death) were used to estimate the excess risks of lung cancer in males at age 75 yr associated with average airborne concentrations over a 45 yr working lifetime (ages 20–65) (Committee on the Biological Effects of Ionizing Radiation, 1988). Relative risk models of a linear (Rice *et al.*, 2001) or loglinear (Steenland and Sanderson, 2001) form were used. Age-specific background rates for both lung cancer and competing causes were obtained from the 1992 US vital statistics for all males (National Center for Health Statistics, 1996). TDs as average internal dose (mg/g lung or m^2/m^2 lung) were estimated for crystalline silica using a human lung dosimetry model (Kuempel *et al.*, 2001) calibrated for quartz (Tran *et al.*, 2000).

TDs

The rat TDs based on external exposure (mg/day) were extrapolated to humans using 'classical' allometric scaling factors (based on body weight, body surface area, metabolic rate and air intake) as well as adjustments for species differences in lung mass or alveolar epithelial surface area. These rat-based TD_1 values in humans were then expressed as airborne concentration (mg/m^3) over a working lifetime, by adjusting for the volume of air inhaled per work day. These values were also compared to the current permissible exposure limits (PELs) (OSHA 29 CFR 1910.1000). TD_1 was the focus because 1% lifetime excess risks may be detectable in typical epidemiological studies (Stayner and Smith, 1993). For crystalline silica the ratios of the TDs in rats and humans were computed using both external exposure and internal dose measures. Unlike the external exposure TDs, in which scaling factors were used, the rat TDs based on internal dose were compared directly with humans, since these were based on equivalent tissue dose (as mass, mg/g, or surface area, m^2/m^2).

RESULTS

Figure 1 illustrates that crystalline silica is substantially more tumorigenic than coal or titanium dioxide, with lung tumors occurring at a much lower dose rate in silica-exposed rats. Although the coal and titanium dioxide potency appears similar, the additional dose groups for titanium dioxide suggest a non-linear dose–response effect for that particulate, particularly in female rats.

Figure 2 shows the ratios of the TD_1 values for crystalline silica in rats and humans. A ratio of 1.0

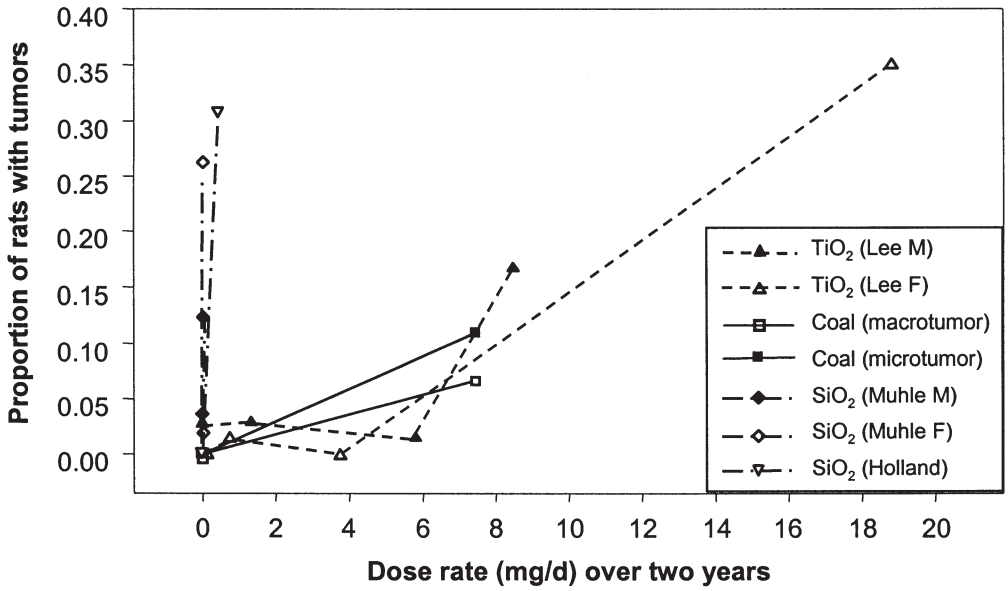

Fig. 1. Lung tumor response in rats after chronic inhalation of respirable particles.

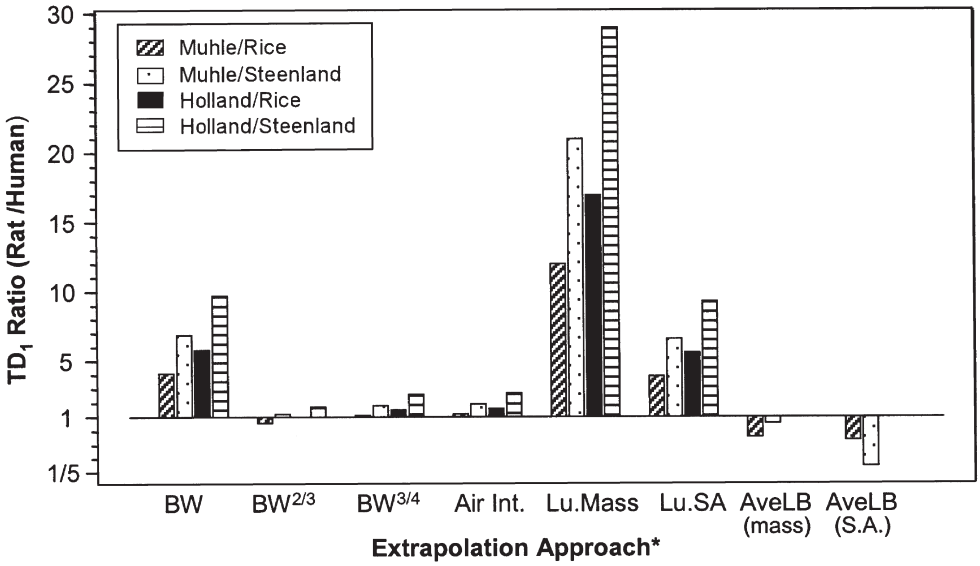

Fig. 2. Ratio of rat-based to human-based tumorigenic doses associated with 1% excess risk of lung cancer from working lifetime exposures to respirable crystalline silica. External dose rate, allometric scaling factors: body weight (BW); surface area ($BW^{2/3}$); metabolic rate ($BW^{3/4}$); air intake; lung mass; lung alveolar epithelium surface area. Internal dose, average lifetime lung burden: AveLB (mass) or AveLB (S.A.).

indicates exact concordance of the point estimates and suggests similar sensitivity in rats and humans for that dose metric. Ratios near 1.0 are observed for several extrapolation approaches, including the TDs based on external dose (mg/d), with the rat-based TDs adjusted for metabolic rate [i.e. $(BW_{hum}/BW_{rat})^{3/4}$], body surface area [i.e. $(BW_{hum}/BW_{rat})^{2/3}$] and air intake. The ratios of rat to human TDs based on internal dose (estimated average lung burden) are also close to (and less than) 1.0. In contrast, the ratios using the rat TDs based on external dose adjusted for body weight, lung surface area and lung mass are ~3–30, implying that humans are more sensitive than rats by these metrics.

Table 1 shows for silica, coal and titanium dioxide the range of rat-based TD_1 values estimated using

Table 1. Rat-based tumorigenic doses associated with a 1% lifetime excess risk (TD_1 values)[a] of lung cancer in human males, compared with occupational exposure limits

Particle type	TD_1 MLE (mg/m^3)	TD_1 95% lower confidence limit (mg/m^3)	Permissible exposure limit (mg/m^3)[b]
Crystalline silica	0.007–0.24	0.0045–0.17	~0.1[c]
Coal dust	2.3–91	1.3–40	~2[c]
Titanium dioxide	1.7–444	1.3–98	15, 5[d]

[a]TD_1 values are point estimates; ranges reflect different extrapolation approaches, dose metrics, models and sex of rat.
[b]OSHA (29 CFR 1910.1000).
[c]Respirable mass fraction, dependent on percentage of crystalline silica.
[d]The PEL for titanium dioxide is 15 mg/m^3 as a total mass fraction; the PEL for the respirable fraction of particles not otherwise regulated (PNOR) is 5 mg/m^3.

the different extrapolation approaches, model forms (including one-stage and multistage models for titanium dioxide) and sex of rat. The maximum likelihood estimate (MLE) TD_1 values for respirable coal ranged from just above the PEL to 45 times greater. The MLE TD_1 values for respirable titanium dioxide ranged from ~3 times lower than the PEL for respirable particles not otherwise regulated to >80 times greater. In contrast to the TD_1 values for coal and titanium dioxide (which tended to be much greater than the PEL), the TD_1 values for crystalline silica ranged from far below the PEL (14 times lower) to only 2 times greater. The human-based TD_1 values for crystalline silica (0.025–0.042 mg/m^3 MLE) are similar to the rat-based TD_1 values shown in Table 1.

DISCUSSION

The comparison of the rat- and human-based TDs for lung cancer risk from crystalline silica exposure suggests reasonable concordance across species, given the uncertainties inherent in interspecies extrapolation. These TD comparisons indicate how well human disease risk might be estimated using the rat data and a given extrapolation method or dose metric. These results may also reflect the relative sensitivity of each species to developing lung tumors from inhaled particles as measured by a given dose metric. The results show that the internal average lung dose in rats, a dose metric expected to be closely associated with lung disease development, provides a better prediction of the silica-related lung cancer risk in humans than does the administered external dose rate in rats adjusted for species differences in lung mass or surface area.

Although human studies were not available for comparison with the rat-based TD estimates for lung cancer in humans occupationally exposed to coal or titanium dioxide particles, the rat-based analyses provide some useful information. For crystalline silica the current PEL is within the range of TD_1 estimates (as mg/m^3). This finding is consistent with the statistically significant exposure–response effect for lung cancer in silica-exposed workers. Similarly, the TD_1 estimates for coal dust and titanium dioxide, which are generally near the PELs to many times greater, are in agreement with the absence (to date) of detectable excess lung cancer morality risk in workers exposed to these particulates. These findings are also consistent with the much greater toxicity and tumorigenicity of crystalline silica than coal or titanium dioxide in rats. However, given the extremely limited data overall (e.g. one dose group only for silica and coal), additional studies are needed to confirm these findings.

CONCLUSIONS

The rat-based models provide reasonably concordant estimates of human lung cancer risk from crystalline silica for several dose metrics, including average internal particle dose in the lungs. The lower TDs for crystalline silica in both rats and humans are consistent with its greater toxicity and tumorigenicity compared with coal dust and titanium dioxide.

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