Lung Dosimetry Models in Rats and Humans: Use and Evaluation for Risk Assessment of Nanoparticles

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ABSTRACT

Lung dosimetry models are useful in the risk assessment of inhaled particles of all sizes by providing a biologically-based, mechanistic approach to predicting the internal dose to the lungs. Human data are limited for the risk assessment of nanoparticles, but dose-response data are available in rats exposed to ultrafine or fine particles. These studies have shown a consistent relationship between the lung dose as particle surface area and pulmonary inflammation and lung cancer in rats. To use these data in risk assessment, a scientifically reasonable approach for extrapolating the rodent data to humans is required, including adjustment for species differences in the relationship between airborne exposures and internal dose. We illustrate the key steps in a quantitative risk assessment, using dose-response data in rats with chronic inhalation exposure to poorly-soluble ultrafine and fine particles. The excess risk estimates are extrapolated from rats to humans using either allometric adjustments or lung dosimetry models. We also compare observed vs. model-predicted lung burdens in rats exposed to fine or ultrafine poorly-soluble particles.. Finally, we describe ongoing research to evaluate and extend current rat and human lung dosimetry models to improve dose estimation of inhaled nanoparticles.

INTRODUCTION

The overall objective of this research is to develop a scientifically reasonable strategy to estimate the risk of exposure to nanoparticles (a.k.a. ultrafine particles)[1] in the workplace. Few studies are available to assess the risk of engineered nanoparticles, including limited toxicological studies and no epidemiological studies. However, established quantitative risk assessment (QRA) methods can be applied to the available animal dose-response data to provide risk estimates of exposure to those compounds, and to provide a basis for comparison and evaluation of possible adverse health risks from exposure to nanoparticles.

QRA is defined as "the estimation of the severity and likelihood of adverse responses associated with exposure to a hazardous agent" (Piegorsch and Bailer 2005). Dose-response assessment, a fundamental component of any QRA, can be performed using statistical and/or biologically-based models. These models provide estimates of the risk associated with a specified dose, or the dose associated with a specified risk. The benchmark dose (Crump 1984) is an example of the latter approach.

In this paper, we illustrate the steps in a QRA to estimate the human-equivalent exposures using rat dose-response data. Both allometric and lung dosimetry model-based methods are illustrated. We also compare the observed and predicted lung burdens in rats and discuss issues and research needs for rat and human lung dosimetry modeling of nanoparticles.

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[1] The terms ultrafine particle and nanoparticle are often used interchangeably, although nanoparticle is a more recent term which is often used to refer to engineered particles. Ultrafines or nanoparticles have primary particle diameters of less than 0.1 μm, and are respirable (i.e., capable of depositing in the gas-exchange region of the lungs), as are fine particles (0.1-2.5 μm) and coarse particles (2.5-10 μm) in humans.

METHODS

The excess risk of lung cancer associated with either the airborne mean particle mass concentration or the retained lung dose was estimated using chronic inhalation data in rats. Excess (or added) risk at dose X, ER(X), is defined here as the difference in the tumor proportion in the exposed, P(X), and the unexposed or control, P(0), rats at the end of a two-year study, i.e., $ER(X) = P(X) - P(0)$. A critical lung dose (i.e., benchmark dose) was identified as the estimated retained dose associated with a specified excess risk (e.g., 0.1%). The benchmark dose (BMD) is defined as ". . . a statistical lower confidence limit on the dose corresponding to a small increase in effect over the background level" (Crump 1984). More recently, the 95% lower confidence limit of the benchmark dose is referred to as the "BMDL" while the point estimate, e.g., maximum likelihood estimate (MLE), is called the "BMD" (U.S. EPA 2003).

The steps in a QRA using animal dose-response data, as illustrated in this paper, include the following:

1. Select the animal model, dose metric, and disease response. These analyses are based on data from chronic inhalation studies in rats exposed to fine or ultrafine titanium dioxide (TiO_2), ultrafine carbon black (CB), or ultrafine diesel exhaust particulate (DEP) (Lee et al. 1985; Mauderly et al. 1987; Muhle et al. 1991; Heinrich et al. 1995; Nikula et al. 1995). The dose metric used is either (a) the retained particle surface area dose in rat lungs (which is estimated from the measured mass dose in the lungs and the specific surface area (m^2/g) of the bulk particle material); (b) the retained mass lung dose; or (c) the average airborne exposure concentration in the chronic inhalation study. The response evaluated is lung cancer.
2. Analyze the dose-response relationships to estimate a critical dose, i.e., the dose associated with a specified risk level of an adverse response. The statistical dose-response model used

here is the multistage model to estimate the BMD and BMDL at 10% excess risk of lung cancer, with linear extrapolation to 0.1% excess risk (U.S. EPA 2003).

3. Extrapolate the critical dose (BMD, BMDL) in animals to humans by adjusting for species differences in lung mass or lung surface area. In the absence of other data, an equal response is assumed at an equivalent (or normalized) dose in both species (Brown et al. 2005; Jarabek et al. 2005).
4. Determine the human external exposure (e.g., working lifetime average exposure concentration) that is equivalent to the animal-based critical dose. For the BMD/BMDL based on mean airborne exposure concentrations, the species differences in inhalation rate, lung mass, and exposure conditions are taken into account. For the BMD/BMDL based on retained lung dose, human lung dosimetry models are used to estimate the working lifetime exposure concentrations that would yield those retained doses.

An additional analysis was performed to compare the observed and predicted lung burdens in rats. Three different rat lung dosimetry models (CIIT and RIVM 2002; Tran et al. 2000; and Tran et al. 2001, 2002) were used to predict the rat retained lung mass dose of fine or ultrafine TiO_2, ultrafine CB, or ultrafine DEP. These predicted rat lung burdens were not used in the human risk estimates, but were obtained to provide a preliminary evaluation of how well the current models may predict nanoparticle lung doses.

RESULTS

Table 1 shows the human-equivalent exposure concentration (mg/m^3) (over a 45-year working lifetime) associated with a 0.1% excess risk of lung cancer (QRA Step 4). Among the ultrafine particles, the estimates are within a factor of two, whether from allometric extrapolation or lung dosimetry modeling. For fine TiO_2, the human-equivalent exposure estimates are much

higher (approximately 5-50 fold) than those for any of the ultrafines, using either the allometric extrapolation or the lung dosimety modeling approach.

Table 2 shows results for the evaluation of the observed vs. predicted retained mass lung burdens for the three rat lung dosimetry models. These results show that each of these models predict reasonably well (within a factor of approximately two) the fine or ultrafine particle mass doses retained in the lungs following chronic inhalation at the highest exposure in each study. The retained mass burden of fine TiO_2 was underpredicted by each model, while the lung burden of ultrafine particles tended to be overpredicted.

DISCUSSION

Both of the human lung dosimetry models predicted lower human-equivalent exposure concentrations for fine TiO_2 compared to the allometric approaches (Table 1), suggesting that the human lung dosimetry models are more sensitive to the factors influencing the relationship between respirable particle exposure and internal lung dose in humans. The similar human-equivalent exposure estimates for the ultrafine particles from the allometric extrapolation and the lung dosimetry models suggest that external exposure is a good estimate of the internal dose—which would be expected if there were high lung retention of inhaled ultrafines. These estimates may also reflect some of the complexity of the processes influencing particle size-specific deposition and retention in the lungs, and the capability of the current lung models to predict these processes for ultrafines. For example, in each of these lung dosimetry models, the clearance rate coefficients describe the mass transfer of *all* particles that deposit in a given region of the respiratory tract (e.g., alveolar). However, some experimental studies have shown that the alveolar clearance of ultrafine particles is lower than that for fine particles of equal mass and composition (Oberdörster et al. 1994; Renwick et al. 2004). In contrast, a longer-term (6-month)

study showed that the lung retention of iridium nanoparticles was similar to that of other micrometer-size particles (Semmler et al. 2004)

A comparison of observed and predicted lung burdens in rats chronically exposed to fine or ultrafine poorly-soluble particles showed that each of the models evaluated provided a reasonable prediction (within a factor of two) of the retained lung burden (Table 2) Further evaluation of these models is needed for nanoparticles with varying characteristics (e.g., size, shape, chemical composition, degree of agglomeration).

Research is needed in several areas to address gaps identified in lung dosimetry modeling and to better predict the risk of occupational exposure to nanoparticles. The specific aims of ongoing research to develop lung dosimetry and risk assessment approaches for nanoparticles include: (1) estimate disease risk as a function of particle composition and size, using existing data and models; (2) revise and extend the current rat lung dosimetry models to include particle size- and composition-specific particle clearance from the lungs and translocation beyond the lungs; (3) quantitatively evaluate the model structures and the population variability in parameter values, including deposition and clearance; (4) validate the revised and extended rat lung dosimetry models using data from ongoing studies; (5) extrapolate the validated rat model to extend the human lung dosimetry model to include key processes for nanoparticle clearance and tranlocation; and (6) estimate the internal dose and disease risk associated with occupational exposures to nanoparticles.

CONCLUSIONS

Established QRA methods, such as those described in this paper, can be used to estimate the risk of occupational exposures to fine and ultrafine particles, and to provide a scientific basis for evaluating the possible risk of exposure to engineered nanoparticles. The method used to

extrapolate the rat data to humans influences the estimate of dose, and therefore risk. Validation of lung dosimetry models is needed for nanoparticles of varying physicochemical properties, and extension of these models is needed to describe the translocation of nanoparticles beyond the lungs as observed in rodent studies.

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Table 1. Airborne Particle Concentrations (8-hr TWA) over a 45-year Working Lifetime Associated with 0.1% Excess Risk of Lung Cancer in Humans.

Substance[†]	Human-Equivalent Exposure Concentration (mg/m^3)			
	Allometric Adjustment – BMDL as Air Mass Concentration[*]		*Lung Dosimetry Model – BMDL as Mass Lung Dose*[*]	
	Lung mass extrapolation factor	**Lung surface extrapolation factor**	**MPPD/ICRP models (CIIT & RIVM 2002)**	**Interstitial/ sequestration model** [‡]
TiO_2 (ultrafine)	-	-	0.14	0.073
CB (ultrafine)	0.19	0.11	0.24	0.12
DEP (ultrafine)	0.28	0.17	0.28	0.18
TiO_2 (fine)	8.7	5.1	1.3	0.68

[*] BMDL: Lower 95% confidence limit of benchmark dose (from multistage model, deg. 3). See Methods for details.
[†] DEP: diesel exhaust particulate; CB: carbon black.
[‡] Kuempel et al. (2001a); Tran and Buchanan (2000).

Table 2: Ratio of Predicted/Observed Mass Particle Burden in Rat Lungs

Substance[*]	Two-cpt model: MPPD with inhal adj (CIIT & RIVM 2002)	Nine-cpt model for low toxicity dust (Tran et al. 2000)	Four-cpt model for high toxicity dust (Tran et al. 2001, 2002)
TiO_2 (ultrafine)	1.5	0.92	1.3
CB (ultrafine)	2.0	1.6	2.0
DEP (ultrafine)	1.4	1.1	1.4
TiO_2 (fine)	0.46	0.36	0.43

[*] Highest dose in each study: TiO_2 (ultrafine), CB (carbon black), DEP (diesel exhaust particulate) (Heinrich et al. 1995) (female rats); TiO_2 (fine) (Lee et al. 1985) (average lung burdens of male and female rats).
Abbreviations: cpt: compartment. Inhal adj: inhalation adjustment.

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As before, thank you for supporting the Conference.

Warm regards,

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