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Response to Dr. Morfeld's Letter

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To the Editor

We thank Dr. Peter Morfeld for his interest in our article and for his thoughtful comments.

The aim of our article is to illustrate available quantitative methods for using chronic bioassay data in risk assessment of inhaled particles including nanoparticles. We illustrate these methods using rat dose-response data for lung tumors following chronic inhalation to poorly soluble fine and ultrafine particles.

Our choice of animal model was informed by the finding that for most of the particles that are known or suspected human carcinogens, the rat chronic inhalation studies also found elevated lung tumors, while the mouse and hamster studies often did not, making them "false negatives" (Mauderly, 1997). Two expert advisory panels recommended the rat as the best available animal model for predicting the hazard and risk of inhaled particles and fibers in humans (Vu et al., 1994; ILSI, 2000). These evaluations also point out that the rat is more responsive to inhaled particles than is the mouse or hamster. Typically, the most sensitive species is used in hazard and risk assessment unless adequate data are available to determine otherwise.

Although it is useful to compare the dose-response relationships among rodents, as Dr. Morfeld suggests, it is most relevant to examine how well the animal data relate to humans. Qualitatively, the rat and human lung responses to inhaled particles are quite similar (Castranova, 2000). Quantitative comparisons of rat and human dose-response data of quartz or diesel exhaust particulate exposure show the rat-based risk estimates for lung cancer were not substantially greater, and were sometimes lower, than the human-based risk estimates (Stayner et al., 1998; Kuempel et al., 2001, 2002). In addition, coal miners with pneumoconiosis were found to have elevated lung cancer mortality (Morfeld et al., 2002), and ambient fine particle air pollution has been associated with elevated lung cancer mortality risk in humans (Pope et al., 2002). These studies provide additional evidence for using the rat model to estimate human risk of lung cancer from inhaled particles.

This being said, we agree that model validation is essential and that it reduces uncertainty in risk assessment. We have also found that the critical dose or risk estimates can vary considerably depending on the models used to describe the exposure, dose, and response relationships (Kuempel & Tran, 2002). It is interesting that Dr. Morfeld mentions threshold models, as we recently evaluated the fit of several threshold models to the rat chronic inhalation data of titanium dioxide dose and lung tumor response (Dankovic et al., in press). Although each of the models provided similar statistical fit, we found that the data were not sufficient to empirically differentiate between the threshold and non-threshold models. Thus, biological mechanism data are needed to inform the selection of statistical models, or to develop biologically based models (Tran et al., 2002), which can provide a mechanistic framework for using species-specific data in extrapolation of animal-based risk estimates.

We agree with Dr. Morfeld that it is preferable to adjust for survival time when using animal bioassay data in risk assessment (e.g., time-to-tumor analysis). Early mortality could have the effect of underestimating the health risks based on a data analysis that does not account for survival differences.

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