December 20, 2006

Awards Committee
Biological Modeling Specialty Section (BMSS)
2007 Society of Toxicology Annual Meeting
Charlotte, North Carolina

Dear Members of the BMSS Awards Committee:

I am happy to write a letter of support for the consideration of Dr. Yuching Yang for the BMSS Student Award. She is currently serving as a post-doctoral fellow at the CIIT Centers for Health Research under my supervision. In this position, she is conducting research on the development and evaluation of biologically based cancer modeling approaches for formaldehyde. While this research requires skills in mathematics and computer programming, the more important factor is the ability to comprehend the biology and toxicology underlying the mode of action for formaldehyde carcinogenesis and to use this information to direct the modeling approach. Yuching has demonstrated great ability and dedication to her work. She has a strong desire to broaden her experience and understanding of toxicology. I believe she will make significant contributions to the work of the Society. Receiving this honor would have a very favorable impact on her professional and personal development. I heartily recommend her for this award.

Thank you for your consideration,

[Signature]

Harvey P. Clewell
Director, Center for Human Health Assessment

HJC:jg
ABSTRACT

Characterization of sensitivity of risk estimates to uncertainties associated with biologically based modeling of formaldehyde carcinogenicity

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Regulatory acceptance of a biologically based dose-response model of formaldehyde-induced rat nasal tumors (Tox Sci 75, 432-47) has been hindered by US EPA concerns regarding the uncertainty of risk predictions obtained with the model. To address these concerns, we developed a novel, sequential Bayesian methodology for conducting a comprehensive, quantitative sensitivity analysis of the biologically based cancer model. A hierarchical Bayesian analysis was performed using the Markov Chain Monte Carlo (MCMC) algorithm to provide a multi-step evaluation of the propagation of uncertainty from the rodent experimental data and modeling to the human extrapolation and risk estimation. The analysis provided posterior parameter distribution estimates consistent with the values used in the original model. In addition, by taking advantage of the Bayesian technique, it was possible to develop an approach to resolve a key issue regarding the choice of historical control data. The analysis demonstrated that the most crucial prediction of the modeling – the existence of a dose-dependent threshold (DDT) for formaldehyde carcinogenicity at an inhaled concentration on the order of 1 ppm in the human – is robust to uncertainties in the model and the underlying data. Most of the uncertainties investigated affect the predictions of residual risk below this threshold, rather than the existence and location of the threshold itself. Even uncertainties amounting to several orders of magnitude did not necessarily change the conclusion that risks below the DDT are negligible.
DISCUSSION

Formaldehyde is a nasal irritant, and inhalation exposure to formaldehyde has been associated with nasal lesions and tumors in rats. A biologically based cancer risk assessment for formaldehyde has previously been described by Conolly et al. (2003) at the CIIT Centers for Health Research. In the present study, the approach used in the original biologically based risk assessment will be carefully evaluated to determine the impact of uncertainties, including assumptions and simplifications made in the modeling approach as well as limitations in the available data, on the predicted risks for human exposure to formaldehyde.

Conolly’s model describes cell proliferation and mutation as a function of formaldehyde flux. The model takes into account the respiratory tract physiology and regional air flow in animals and humans and provides a biological-based respiratory carcinogenic risk assessment for human exposure to formaldehyde. It is considered a more reliable estimate of cancer risk than the use of standard default assumptions, due to the incorporation of all available biological data.

However, the lifetime risk of cancer predicted using this model is much lower than those derived under the current regulatory guideline. Therefore, some concerns have been raised about uncertainty and assumptions in this model by US EPA. To address these concerns, a sequential Bayesian approach is proposed to conduct a comprehensive quantitative uncertainty evaluation of the formaldehyde clonal growth model.

A Bayesian analysis was performed using the Markov Chain Monte Carlo (MCMC) algorithm to provide a multi-step evaluation of the propagation of uncertainty from the rodent experimental data and modeling to the human extrapolation and risk estimation. The analysis provided posterior parameter distribution estimates consistent with the values used in the original model. In addition, by taking advantage of the Bayesian technique, it was possible to develop an approach to resolve a key issue regarding the choice of historical control data.

The analysis demonstrated that the most crucial prediction of the modeling – the existence of a dose-dependent threshold (DDT) for formaldehyde carcinogenicity at an inhaled concentration on the order of 1 ppm in the human – is robust to uncertainties in the model and the underlying data. Most of the uncertainties investigated affect the predictions of residual risk below this threshold, rather than the existence and location of the threshold itself. Even uncertainties amounting to several orders of magnitude did not necessarily change the conclusion that risks below the DDT are negligible.