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ChemRisk®
A Division of McLaren/Hart
Environmental Engineering

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Dr. Hasmukh C. Shah, PhD
Chemical Manufacturers Association
Vinyl Chloride Panel
2501 M. Street, N.W.
Washington, DC 20037

Dear Dr. Shah,

Thank you very much for your hospitality during our recent visit to Washington to present a seminar about our work on Vinyl Chloride risk assessments with PB-PK models.

I am enclosing with this letter (1) an expense report since you were kind enough to offer to pay my travel expenses up to $600.00 (CMA contract VCRC-1.0-CONS REITZ), and (2) a hardcopy of the slides I used during my presentation.

I took the liberty of reducing the slides by 50% and printing them two/page. I think they are all still quite legible, but if you prefer I would also be happy to send you a full size copy.

It was a real pleasure to meet you yesterday, and to interact with your Vinyl Chloride panel. If there are any occasion where McLaren/Hart could be of service to the CMA's Vinyl Chloride panel, we would be delighted to discuss these with you.

Please make the expense check payable to me personally, since I charged all the expenses to my personal American Express Card, and please send the check to:

Dr. Richard H. Reitz
McLaren/Hart, ChemRisk Division
4105 Chelsea Ct.
Midland, MI 48640.

Again, it was a real pleasure to meet you and I look forward to seeing more of you in the future.

Sincerely,

Richard H. Reitz

Richard H. Reitz, PhD, DABT
Principal Health Scientist

P.S. Please feel free to distribute the slides to your committee. I ask only that they acknowledge the source of the material.

Also – I will send you a copy of our manuscript on VC as soon as it is submitted for publication.

Dick

SEMINAR TOPIC #1

Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model.

Richard H. Reitz
McLaren/Hart, ChemRisk Division

Physiologically-based pharmacokinetic (PB -PK) models have been proposed as tools for facilitating the extrapolation of animal cancer tests to humans. For instance, several of us (Reitz, Andersen, Gargas, Clewell) developed a risk assessment for methylene chloride which used PB -PK modeling to extrapolate between species, across different routes of exposure, and from high dose to low dose. This risk assessment predicted considerably less risk to humans than earlier procedures, and the PB-PK risk assessment was consistent with epidemiology studies for methylene chloride (which are generally accepted as negative).

Because the epidemiology studies for methylene chloride are negative (as the PB -PK model predicted they would be), they do not provide an opportunity for comparing cancer rates in humans with predictions derived from the PB -PK model. However, there is one industrial compound (vinyl chloride, VC) which has been shown to produce measurable increases in the incidence of liver angiosarcoma in both rats and humans. In order to determine whether risk assessments based on PB -PK adjustments of dose adjustments are too conservative, not conservative enough, or about right, we have developed a PB -PK model for VC and predicted the risk to humans based on rat studies.

The VC model for rats and humans was developed from several in vivo and in vitro data sets. Both the rat and human models were then validated with independent studies of VC metabolism in the appropriate species (i.e. the validation studies were not used in development of the model itself). Then PB -PK model was combined with the multistage model of Crump & Howe (GLOBAL83) to predict the incidence of liver angiosacroma produced in humans. The human studies included more than 12,000 workers exposed to VC occupationally over a period of several decades.

The risk assessment based on the PB -PK model predicted considerably less risk than would be calculated by default (nonpharmacokinetic) procedures. However, the incidence of angiosarcoma actually observed in human subjects was still considerably lower than predicted by the PB -PK/multistage model, suggesting that if the results obtained with VC are typical, risk assessments combining PB -PK and multistage modeling likely overpredict, rather than underpredict, human risk.

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