

Charge Questions
TCE Harmonized Model Peer Consultation
June 29, 2004

The 2001 draft EPA risk assessment of TCE used a number of PBPK models for TCE and its metabolites as part of its quantitative risk assessment. In particular, PBPK models were used for developing human equivalent dose metrics from rodent studies, conducting human route-to-route extrapolation, and characterizing human variability. There were a number of uncertainties surrounding the different models and the data used to develop them. The accompanying document describes a draft PBPK model that attempts to harmonize previous models as well as incorporate new scientific data. Input on this draft model is being solicited from a panel of experts on TCE, PBPK modeling, and the kinetics issues relevant to the TCE assessment. Additional background on the model development is provided in the accompanying model documentation.

For all of the charge question issues, the panel is being queried re what is possible given the available data. The peer consultants are asked to focus on providing any information and insight they have regarding additional data sources and approaches to the modeling, given the available data. We are not looking for input as to the structure of the ideal model if all desired data were available, although one of the charge questions does address key data gaps.

1. Are there additional studies or data (either published or unpublished) that should be incorporated into the model development?
2. Was the glutathione conjugation pathway portion of the model appropriately addressed? Consider both the model structure and the parameterization of the model. Given the available data, is the model structure adequate to describe this pathway? The proposed model assumes that all glutathione conjugate formation results in DCVC in the kidney, and that metabolism of DCVC in the kidney is either by beta-lyase to a reactive metabolite or by N-acetyl transferase to a nontoxic metabolite that is excreted in the urine. Is a more complete description needed for this pathway? Are there other data on the metabolism of trichloroethylene (TCE) by the glutathione pathway that should be included? Is metabolism of DCVC in the kidney by flavin mono-oxygenases (FMO) an important factor? Should excretion of DCVC from the kidney into the urine be included? Is there too much uncertainty in this aspect of the model to consider its use to estimate kidney dose metrics for a TCE risk assessment? If so, what would be a reasonable approach for estimating kidney dose metrics?
3. Is the model of chloral in the lung adequate? Chloral is generated in both the lung and the liver, but the authors included only chloral generation in the lung in the model. Is this appropriate? The authors noted in the discussion that local generation of chloral appears to be the dominant source of the lung concentrations of chloral observed in the mouse, since the concentrations of chloral in the lung following oral dosing with TCE were much greater than the concentrations in the blood (from metabolism in the liver). This suggests that not

including systemic chloral in the model may not be a problem. In addition, systemic chloral was not included in the model due to the inability to implement that portion for the human model. Would including systemic chloral for the animal model, but ignoring it for the human model be conservative or non-conservative? Was the choice not to include systemic chloral an appropriate judgment? The issue has been raised regarding whether there are dose-dependent differences in the degree of local versus systemic generation of chloral. This issue arises based on analogy to styrene, for which local metabolism makes a higher contribution at lower concentrations, and has a lower contribution at higher concentrations, due to saturation of local metabolism (Sarangapani et al. 2002). Since the data on TCE found that local generation of chloral dominates at the high concentrations used in the animal study, and the model authors noted that local metabolism will also dominate for humans at the low environmental exposures of interest, they were less concerned about saturation of local metabolism for TCE. Do you agree with the authors' decision? Is the proposed approach for modeling of local chloral production and clearance an acceptable approach, given the available data and what is known about interspecies scaling of aldehyde dehydrogenase (ALDH) kinetics in the lung?

Are you aware of data on the relationship between CYP2E1 and ALDH levels in human vs. mouse lungs that can be used in the model? Is there too much uncertainty in this aspect of the model to consider its use to estimate lung dose metrics for a TCE risk assessment? If so, what would be a reasonable approach for estimating lung dose metrics?

4. The authors have noted difficulties in the modeling of dichloroacetic acid (DCA), due to a number of factors. In some analyses, DCA was formed from TCA as an artifact, so DCA levels measured do not reflect true *in vivo* levels. In addition, because the metabolism of DCA is self-inhibitory, DCA data after multiple dosing in experimental animals would be needed to characterize the DCA generation from TCE. Data on DCA production from TCE in humans are also limited. When DCA production was modeled as a fraction of the rate of metabolism by the P450 pathway in the liver, using the empirical volume of distribution and half life, the predicted time-course for DCA after TCE dosing was not consistent with the best available data (Abbas and Fisher, 1997). Even for these data, which were collected in such a way as to minimize *ex vivo* conversion of TCA to DCA, the concentrations of DCA paralleled those of TCA, suggesting that DCA was being generated from TCA at a level of about 2%. The authors have therefore concluded that it is not currently feasible to confidently model the production of DCA from TCE *in vivo*. Is there a way of describing DCA production and metabolism, given the currently-available data? Is there too much uncertainty in this aspect of the model to consider its use to estimate liver dose metrics for a TCE risk assessment? If so, what would be a reasonable approach for characterizing dose metrics for DCA?
5. TCA binding in the blood is modeled using empirical equations derived from *in vitro* studies. Measured partition coefficients for total TCA between tissues and blood are then converted to partitions for free TCA between tissues and plasma, assuming that all TCA in the tissue is free and using an estimate of the free fraction in plasma from the *in vitro* binding studies. Is this appropriate, given that the fraction bound may not be a constant? Was the calculation of

serum vs. blood concentrations appropriately addressed? Does DCA binding in the blood need to be considered? If so, how?

6. Overall, is the PBPK model structure correct? Is the model adequate for describing the toxicokinetics of TCE and its metabolites for the purposes of the TCE risk assessment? In particular, can the model adequately describe all of the data sets with a consistent set of model parameters? Were the correct metabolites modeled?
7. Are there any other changes you would recommend to the model structure or parameterization? For example, the general TCE model has the capability to describe the fat compartment as a diffusion-limited tissue, but this option was not exercised. Was this an appropriate choice? Is the enterohepatic circulation of TCOH appropriately described?
8. Should the kinetic parameters be calibrated? Should they be re-estimated using Markov Chain Monte Carlo? How many data sets should be used? Which are the key data sets? Are there alternative approaches that should be considered?
9. What key studies would you recommend to fill data gaps?

References:

Abbas, R. and Fisher, J.W. 1997. A physiologically based pharmacokinetic model for trichloroethylene and its metabolites, chloral hydrate, trichloroacetate, dichloroacetate, trichloroethanol, and trichloroethanol glucuronide in B6C3F1 mice. *Toxicol. Appl. Pharmacol.*, 147:15-30.

Sarangapani, R., Clewell, H.J., Cruzan, G., and Andersen, M.E. 2002. Comparing respiratory-tract and hepatic exposure-dose relationships for metabolized inhaled vapors: a pharmacokinetic analysis. *Inhal Toxicol* 14(8):835-854.