INTEGRATED PROBABILISTIC AND DETERMINISTIC MODELING TECHNIQUES IN ESTIMATING EXPOSURE TO WATER-BORNE CONTAMINANTS: PART 2: PHARMACOKINETIC MODELING

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ABSTRACT

The Total Exposure Model (TEM) uses deterministic and stochastic methods to estimate the exposure of a person performing daily activities of eating, drinking, showering, and bathing (see part 1). There were 250 time histories generated, by subject with activities, for the three exposure routes, oral, dermal, and inhalation, and these were input to the physiologically based pharmacokinetic (PBPK) model, via ERDEM (Exposure Related Dose Estimating model). The chemicals modeled were trichloroethylene (TCE), trichloroacetic acid (TCA), and dichloroacetic acid (DCA). Time histories of concentrations and Areas Under the Curve (AUC) were determined for the liver, kidney, and venous blood. They were combined to determine the distribution at each time step and hence define the 5th, 50th and the 95th percentiles. The important pathways and the basis for their predominance are shown. Thus highly variable exposures can be related to actual dose to various organs of the human body.

DISCLAIMER

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INDEX TERMS

Human Activities, VOCs and SVOCs, Exposure Assessment, Pharmacokinetic Modeling, Modeling Indoor Pollutants

INTRODUCTION

Scientists have been working to develop techniques for analyzing and representing residential water use and the subsequent exposure to waterborne contaminants. In this work the main chemical concerns are water borne contaminants. The Total Exposure Model (TEM) was used to estimate the exposure pattern of these contaminants. Then the Exposure Related Dose Estimating Model (ERDEM) is run to determine the concentrations, area under the curve (AUC), and amount in urine for the chemicals and their metabolites in the liver, kidney, and venous blood. There were 250 exposure patterns determined from TEM for an adult male and they have been run through ERDEM. Parameter values are taken from values suggested by Abbas and Fisher, 1997, Fisher, et al, 1998, and Clewell, et al, 2000. Some values were then adjusted using ERDEM in order to fit data for the first subject reported by Fisher, et al, 1998.

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WATER USE EXPOSURE MODEL

A water use exposure model, TEM (Total Exposure Model, discussed in Part 1) was developed by Dr. Charles Wilkes. TEM models the exposure of subjects to chemicals in water through ingestion, inhalation and dermal contact. Activities considered in this modeling approach include showering, bathing, hand washing, toilet use, clothes washing, dish washing, and direct and indirect consumption of water and beverages. The pattern of use is determined by activity pattern studies such as NHAPS, (Kliepeis, et al 1996, Tsang, et al 1996).

EXPOSURE RELATED DOSE ESTIMATING MODEL

The ERDEM model is a Physiologically Based Pharmacokinetic (PBPK) Model (developed using the ACSL[1] engine) that takes input from up to eight exposure routes with multiple chemicals in each scenario of an exposure route. Inputs may also be time histories of the exposures. There may be multiple chemicals and multiple metabolites of each. All chemicals and metabolites are treated as circulating. The static lung models the exchange between the blood and air. A two compartment gastro-intestinal tract is modeled. Outputs can be time histories of any of the variables (specified in a special history file). Plots or even ASCII time histories can be generated for post processing and analysis. The outputs from the 250 model runs for this study were generated as ASCII time histories and run through a special SAS program for analysis and curve generation

PBPK MODEL PARAMETERS FOR TCE, TCA, AND DCA AND METABOLITES

The parameter values were chosen from the work of others but some elimination and metabolism parameters were adjusted with ERDEM model runs using data reported by Fisher, et al, 1998. The volumes and blood flows are given in Table 1 for the compartments used in the simulation. The remaining 9% is the blood residing in the blood vessels (not shown in Table 1). The alveolar ventilation rate was input from the TEM model as a time history of up to seven activities and then converted to an approximate cardiac output by multiplying by the factor 0.854 (based on the relative values used in earlier male trichloroethylene modeling, Fisher, et al, 1998).

Table1: Volume and Blood Flow

Compartment Name	Tissue Volume (% Body Wt)	Blood Flow(% Card.Output)
Dermis	9[a]	4.8[d]
Fat	17[b]	4.8[b]
Liver	2.6[b]	24.0[b]
Static Lung	1.4[b]	
Kidney	0.4[b]	19.7[b]
Rapidly Perfused Tissue	4.6[b]	27.5[c]
Slowly Perfused Tissue	56[c]	19.2[b]

a. McDougal, et al,1990,value reduced to 9%.
b. Fisher, et al, 1998.
c. Value reduced to account for the Dermis.
d. Estimated from Corley, et al, 1990.

The partition coefficients used in the ERDEM model runs are shown in Table 2.

[1] Advanced Continuous Simulation Language, owned by Aegis Technologies.

Table 2: Partition Coefficients for TCE and It's Metabolites in the Human Male

Compartment to Blood or Air	TCE[a]	TCA[a]	TCOH[a]	DCA, Mouse[c]	TCOG, Mouse[c]
Arterial Blood to Air	11.15				
Dermis to Venous Blood	1.38[b]				
Fat to Venous Blood	52.34				
Kidney to Venous Blood	1.08	0.66	2.15	0.8	1.4
Liver to Venous Blood	4.85	0.66	0.59	0.8	0.6
Rapidly Perfused to Venous Blood	4.85				
Static Lung to Arterial Blood	0.39	0.47	0.66	0.16	1.1
Slowly Perfused to Venous Blood	1.38	0.52	0.91	0.43	1.1

a. Fisher, et al, 1998
b. Value chosen the same as the Slowly Perfused Tissue.
c. Abbas and Fisher, 1997

METABOLISM, ELIMINATION, GI, AND SKIN PERMEATION PARAMETERS

There are five metabolisms in the Liver that are modeled for TCE and TCOH (Table 3). Elimination is modeled for TCA and DCA (Table 4). Urine flow is modeled for TCA, DCA, and TCOG (also in Table 4). The skin permeation coefficient and the gastro-intestinal tract parameters (stomach to portal blood, stomach to intestine, and intestine to portal blood) are all given in Table 4. The results of ERDEM model runs for inhalation exposures with these values provides a good fit with experimental values (A in the figures from data of Abbas and Fisher) of concentration in the blood and urine measurements for TCE, TCOH, TCA, DCA, and TCOG. Metabolism and urine parameters were fit for subject 1 (Abbas and Fisher) and then scaled by body weight for the other subjects. Figures 1 and 2 show subject 2 results for TCE and TCA.

Table 3: Parameters for Metabolites of TCE

Parent Chemical	Metabolite	Saturable Metabolism		Linear Metabolism
		Vmax,mg/h/kgBW[a]	Km,mg/L[a]	Linear rate const.
TCE	TCA(0.1)	0.6	10.8	
TCE	TCOH(0.9)	5.4	10.8	
TCOH	TCA			7.0[a]
TCOH	DCA	0.1[b]	10[b]	
TCOH	TCOG	30.0	160.0	

a. Values determined from fitting to experimental data from Fisher, et al, 1998.
b. Clewell, et al, 2000.

Table 4: Elimination rates, Urine Flow, Skin and GI Parameters

Chem	Liver Lin Elim Rate Const(1/hr)	Urine Rate Const(1/hr)	Skin Perm. Coef. (cm/hr)	Stomach to Intest. Rate const.(1/h)[e]	Stom-Portal Blood Rate const (1/hr)[e]	Intest-Portal Blood Rate const (1/hr)[e]
TCE	N/A	N/A	0.0157[d]	2.18	13.65	0.044
TCA	0.2[a]	0.519[b]	3.58E-6[d]	2.18	13.65	0.044
DCA	7.0873[c]	0.00795[c]	1.84E-6[d]	2.18	13.65	0.044
TCOG	N/A	40.0[a]	N/A	N/A	N/A	N/A

a. Determined from fit to experimental data from Fisher, et al, 1998.
b. Estimated from the urine data for subject 1 of Fisher, et al, 1998
c. Clewell, et al, 2000

d. JN Mcdougal, personal communication.

e. Abbas and Fisher, 1997 for the mouse, corn oil gavage. GI parameters modified based on Staats, et al, 1990 for water..

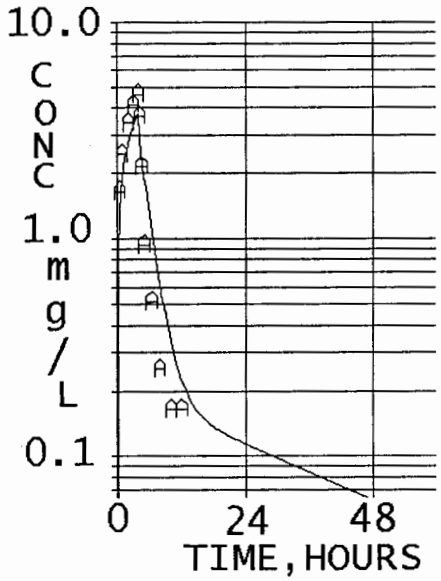

Figure1: Concentration of TCE in Venous Blood for Subject 2 Versus Measured Data

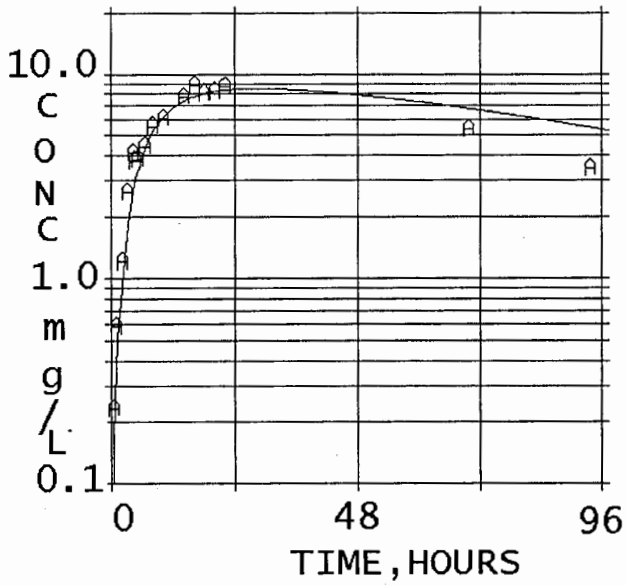

Figure 2: Concentration of TCA in Venous Blood for Subject 2 Versus Measured Data

EXPOSURE INPUTS AND PARAMETER SETTINGS

There were two exposure scenarios, one with 0.1 mg of TCE in the water and the other with the addition of 0.03 mg of TCA and DCA. The subjects were exposed to these chemicals by inhalation of the volatilized TCE from the water, by ingestion of fluids, and by dermal contact. The TCE in inhaled air was modeled by using the TEM model to determine 250 inhalation patterns over a 24-hour period. The 250 dermal and ingestion exposures were also modeled by TEM for TCE, TCA and DCA. The concentration of the TCE given by TEM for ingestion is reduced due to volatilization by 22% for drinks taken directly from the faucet (direct consumption) and by 75% for drinks taken after some processing of water from the faucet (indirect consumption). There is no loss due to volatilization for TCA and DCA.

RESULTS FROM ERDEM MODEL RUNS

The three routes, dermal, ingestion, and inhalation, were modeled separately and all together for 0.1 milligrams/Liter of trichloroethylene (TCE) in the water. The 250 output time histories from ERDEM were input to a SAS© program to determine the percentiles at each time step. The 5th, 50th, and 95th percentiles were plotted at each time step. There were time histories of concentration and area under the concentration-time curve (AUC) generated for the kidney, liver, and venous blood for TCE and the metabolites, DCA, TCA, TCOH, and glucuronidated TCOH – referred to as TCOG. Time histories were generated also for exhaled air and for total amount in the urine for TCA, DCA, and TCOG. The chemicals TCA and DCA at concentrations of 0.03 milligrams/Liter were added to the water and separate time histories were generated from the TEM model for ingestion and dermal. There is no inhalation exposure to TCA and DCA due to low volatilization. The presence of DCA due to metabolism of TCE is minute and is only of consequence when it is already present in the water. TCA is a substantial metabolite of TCE. Thus the presence of TCA in the water may

not cause a significant increase in the AUC of TCA. The dominance of the inhalation route is dependent on the volatility of the chemicals in the water.

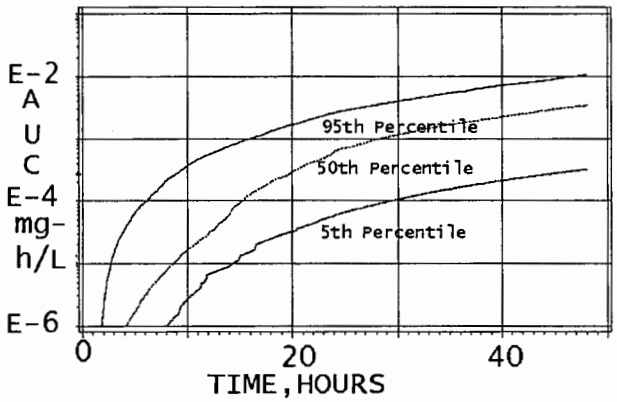

Figure 3: AUC of TCA in Venous Blood for Dermal Exposure

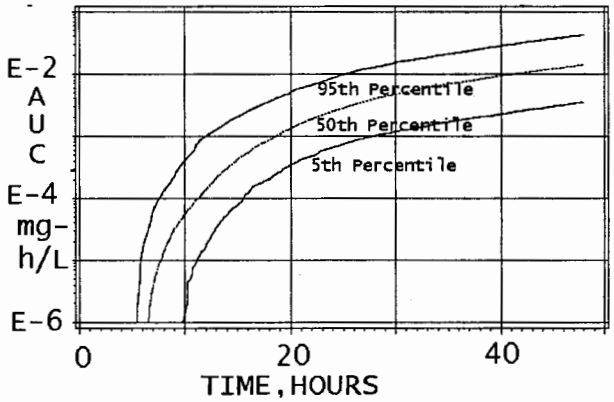

Figure 4: AUC of TCA in Venous Blood for Ingestion Exposure

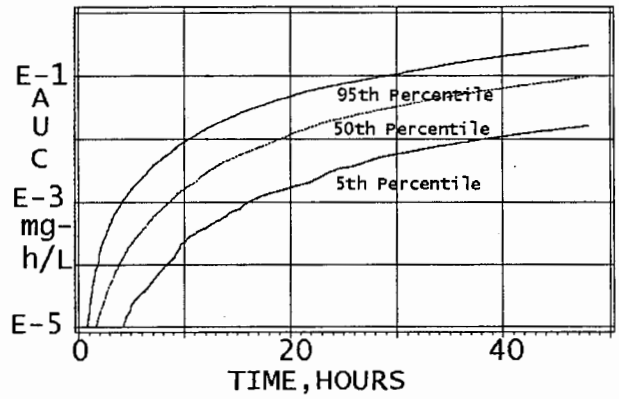

Figure 5: AUC of TCA in Venous Blood for Inhalation Exposure

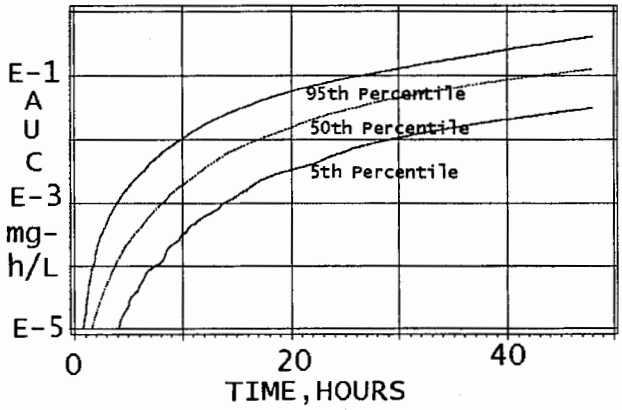

Figure 6: AUC of TCA in Venous Blood for All Exposures

RANGE OF 5TH AND 95TH PERCENTILES

The range of the 5th and the 95th percentiles for the AUC of TCA in Venous Blood for exposure to 0.1 mg/L of TCE are:

1. Dermal - 0.0004 to 0.01 mg-h/L - a factor of 25, Figure 3.
2. Ingestion - 0.0043 to 0.053 mg-h/L - a factor of 12.3, Figure 4.
3. Inhalation - 0.014 to 0.038 mg-h/L - a factor of 27.1, Figure 5,
4. All three routes - 0.04 to 0.5 mg-h/L - a factor of 12.5, Figure 6.

The inhalation and dermal routes are highly variable depending on the activities of the subject, while the drinks of water taken via the ingestion route are more likely to occur many times throughout the day. Thus the AUC for all three routes is less variable than the dermal and inhalation routes due to less variability in the AUC for the ingestion route.

FACTORS AFFECTING THE DOSE FOR EACH PATHWAY

The absorption of chemical by the inhalation route is affected by the activity pattern of an individual, volatility of the chemical(s) in the water, and the blood to air partition coefficient. The rate that the chemical enters the blood is dependent on the lung to blood partition coefficient. Similarly, the absorption of chemical by the ingestion route is affected by the ingestion pattern of the individual as well as the gastro-intestinal tract parameters for that chemical. The absorption of chemical by the dermal route in ERDEM is dependent on the permeation coefficient for the chemical. The rate of release into the blood is dependent on the

partition coefficient from skin to blood.

CONCLUSIONS

This work demonstrates the utility of coupling an exposure model with a pharmacokinetic model to help determine the importance of different exposure factors and patterns on the toxicologically relevant dose. Due to inherent non-linearities in the pharmacokinetics there is often not a direct linear relationship between exposure and dose. Exposure models, such as TEM, are able to give estimates of exposure that take into account the impact of human activities and the natural trans-media relationships of chemicals such as TCE. Coupling these results with a well-formulated pharmacokinetic model, as we have done here, enables the risk assessor to begin to make the connections between source, exposure, and relevant dose.

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16. Abstract **ABSTRACT**

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