

AIR FORCE RESEARCH LABORATORY



**Development of a Physiologically-Based
Pharmacokinetic Model of Trichloroethylene and
Its Metabolites for Use in Risk Assessment**

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FOR THE DIRECTOR

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14. ABSTRACT A physiologically based pharmacokinetic (PBPK) model was developed which provides a comprehensive description of the kinetics of trichloroethylene (TCE) and its metabolites, trichloroethanol (TCOH), and trichloroacetic acid (TCA), in the mouse, rat, and human, for both oral and inhalation exposure. The model includes descriptions of the three principal target tissues for cancer identified in animal bioassays: liver, lung, and kidney. Dose metrics that can be calculated with the model for cancer risk assessment include the area under the concentration curve (AUC) for TCA in the plasma or liver, the peak concentration and AUC for chloral (CHL) in the tracheo-bronchial region of the lung, and the production of a thioacetylating intermediate from dichlorovinylcysteine (DCVC) in the kidney. Additional dose metrics that can be calculated for noncancer risk assessment include the peak concentrations and AUCs for TCE and TCOH in the blood, as well as the total metabolism of TCE divided by the body weight. There is currently no adequate data available with which to confidently parameterize a description for another metabolite of interest, dichloroacetic acid (DCA). Model predictions of TCE, TCA, and TCOH concentrations in rodents and humans are consistent with a variety of experimental data, suggesting that the model should provide a useful basis for evaluating cross-species differences in pharmacokinetics for these chemicals. In the case of the lung and kidney target tissues, however, only limited data are available for establishing cross-species pharmacokinetics. As a result, PBPK model calculations for these dose metrics are highly uncertain.					
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PREFACE

The U.S. Air Force (USAF) and the U.S. Environmental Protection Agency (USEPA) jointly sponsored a scientific workgroup to develop a harmonized PBPK model for TCE and its metabolites based on the full range of available science and data. This workgroup was composed of scientists from the USAF and EPA, with technical expertise from Toxicology Excellence for Risk Assessment (TERA) and other scientists under contract to the USAF. The results of this joint USAF-USEPA workgroup served as important input to ongoing TCE risk assessment activities, including a multi-agency consultation with the National Academy of Sciences on TCE science issues. This project was sponsored by AFIOH/RSRE with Brian Howard serving as the Air Force program manager.

Work was conducted under Department of the Air Force Contract No F33615-00-C-6060 and subcontracts to ENVIRON and the University of Georgia. Dr. David R. Mattie served as the Contract Technical Monitor for the U.S. Air Force, Air Force Research Laboratory, Applied Biotechnology Branch (AFRL/HEPB, Wright-Patterson AFB, OH) and Dr. Darol Dodd served as Program Manager for the ManTech/GEO-CENTERS Joint Venture Contract (F33615-00-C-6060).

Harvey J. Clewell, formerly at ENVIRON Health Sciences Institute, is currently employed at CIIT Centers for Health Research, Research Triangle Park, NC.

USAF and USEPA staff have provided technical input to this project's development, but it does not necessarily reflect the views or policies of the USAF or the USEPA, and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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ABBREVIATIONS

ACSL	Advanced Continuous Simulation Language
ADH	Alcohol Dehydrogenase
AUC	Area Under the Concentration Curve
BSA	Body Surface Area
CHL	Chloral
CV	Coefficients of Variation
CYP	Cytochrome P450
DCA	Dichloroacetic Acid
DCVC	Dichlorovinylcysteine
GSH	Glutathione
GST	Glutathione Transferase
MCA	Monochloroacetic Acid
MFO	Mixed Function Oxidase (P450)
PBPK	Physiologically Based Pharmacokinetic
TCA	Trichloroacetic Acid
TCE	Trichloroethylene
TCOH	Trichloroethanol
UGT	UDP Glucuronosyl Transferase

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DEVELOPMENT OF A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL OF TRICHLOROETHYLENE AND ITS METABOLITES FOR USE IN RISK ASSESSMENT

INTRODUCTION

Physiologically-based pharmacokinetic (PBPK) modeling is widely held to be a useful methodology for improving the accuracy of chemical risk assessment. The goal of PBPK modeling is to simulate the uptake, distribution, metabolism, and elimination of a chemical in an organism, using as realistic a description of the relevant physiology and biochemistry as is necessary and feasible. For its use in risk assessment, PBPK modeling attempts to describe the relationship between external measures of exposure (e.g., amount administered or concentration in air) and internal measures of biologically-effective dose (e.g., amount metabolized or concentration of an active metabolite in the tissue displaying the toxic response) in both the experimental animal and the human.

The most recent EPA cancer risk estimates for trichloroethylene (TCE) were derived in part using PBPK models. In particular, risks of liver cancer based on tumors in mice were estimated using two different PBPK models,^{1,2} as well as with "calibrated" versions of these two models using re-estimated parameters obtained from Markov chain Monte Carlo analysis.^{3,4} The purpose of the study reported here was to develop a single harmonized PBPK model for TCE that included as complete a description as possible of all of the metabolites and target tissues that may be relevant to the toxicity and carcinogenicity of TCE, and to characterize the accuracy and reliability of the resulting model in providing dosimetry estimates in support of a risk assessment for TCE.

Requirements for a PBPK Model to Support TCE Risk Assessments

Recent quantitative cancer risk estimates for TCE have been based on animal bioassays, specifically liver and lung tumors in mice and kidney tumors in rats, as well as on human epidemiological studies. In the case of the human studies, PBPK modeling can be used to perform route-to-route extrapolation.

For each of the three rodent target tissues, liver, lung, and kidney, there is evidence that the carcinogenicity of TCE may be associated with one or more of its metabolites: trichloroacetic acid (TCA) and dichloroacetic acid (DCA) in the liver, CHL in the lung, and 1,2-DCVC in the kidney. Thus, to be useful in a comprehensive cancer risk assessment for TCE, a PBPK model should include at least three target tissues: liver, lung, and kidney, along with a description of the kinetics of the metabolites that may play a role in the carcinogenic activity.

Several target tissues have also been identified for the noncancer toxicity of TCE, including the liver, kidney, CNS, immune system, and developing fetus. As in the case of the carcinogenicity of TCE, several of these noncancer endpoints appear to be associated with exposure to the metabolites of TCE rather than to the parent chemical itself. For example, trichloroethanol (TCOH), the major metabolite of TCE, has been suggested to be responsible for the observed neurological effects of chloral hydrate.

Previous PBPK Modeling of TCE

A number of PBPK models have been developed for TCE. However, most have only been parent chemical models; that is, they provide a pharmacokinetic description of TCE itself, but do not include an explicit description of the pharmacokinetics of any of the metabolites. Therefore, these parent chemical models cannot be used for predicting tissue exposure to specific metabolites.

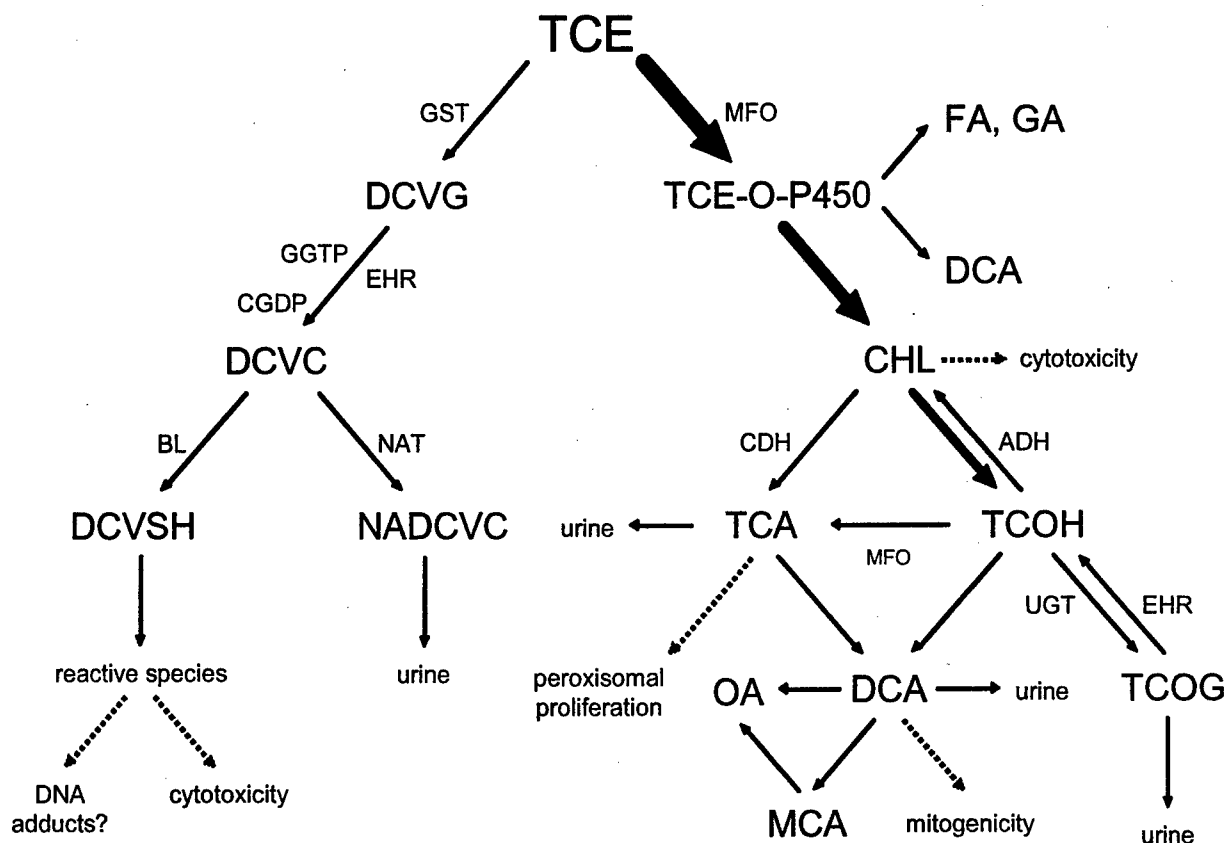
Fisher and coworkers developed a PBPK model for TCE and its principal metabolite, TCA, in the rat and mouse.⁵ These rodent models, together with a similar model of TCE and TCA in the human,⁶ served as the basis for a PBPK-based risk assessment for TCE liver carcinogenicity⁷ based on either average daily total metabolism or average daily AUC for TCA. These models provided the first successful cross-species pharmacokinetic description for a metabolite of TCE. Subsequently, Clewell and co-workers built on the work of Fisher and Allen⁷ by adding limited descriptions of additional metabolites (TCOH, DCA, CHL, 1,2-DCVC) and target tissues (lung and kidney).¹ Fisher and colleagues also continued to elaborate and refine their PBPK models for TCE, focusing on the metabolites of interest for liver carcinogenicity.² Published models include (1) a model of the kinetics of TCE, CHL, TCA, DCA, and TCOH in the B6C3F1 mouse based on data from corn oil gavage exposures,⁸ (2) a model of TCE, TCA, and TCOH in the human based on data from controlled human inhalation exposures,⁹ (3) a model of TCE, TCA, and TCOH kinetics in the rat that considers enterohepatic recirculation of TCA and TCOH following oral or intravenous exposure to TCE,¹⁰ and (4) a model of inhaled TCE and its oxidative metabolites in the B6C3F1 mouse.¹¹ A recent study evaluated various elements of the PBPK description in the rat, including diffusion limited uptake in the fat and liver.¹² Together, these models provide a capability for estimating dose metrics in the mouse, rat, and human in support of a risk assessment for TCE liver carcinogenicity. A potential advantage of these more recent mouse PBPK models^{8,11} is that their calibration includes data on TCA concentrations in the liver. However, since there was no human data on liver concentrations, the human model⁹ could not be similarly calibrated. Therefore, the relationship of liver and blood TCA dosimetry must be inferred from data on plasma binding of TCA.¹³

DESCRIPTION OF THE HARMONIZED PBPK MODEL FOR TCE

PBPK Model Structure

The structure of a PBPK model is necessarily a function of several variables: the physicochemical and biochemical properties of the compound, the physiological and functional properties of the biological system, and the experimental scenarios being investigated. In addition, the model must incorporate information on the various metabolites generated from the compound that are of importance for the intended application. The metabolism of TCE is summarized in Figure 1, which is adapted from the review by Lash *et al.*¹⁴

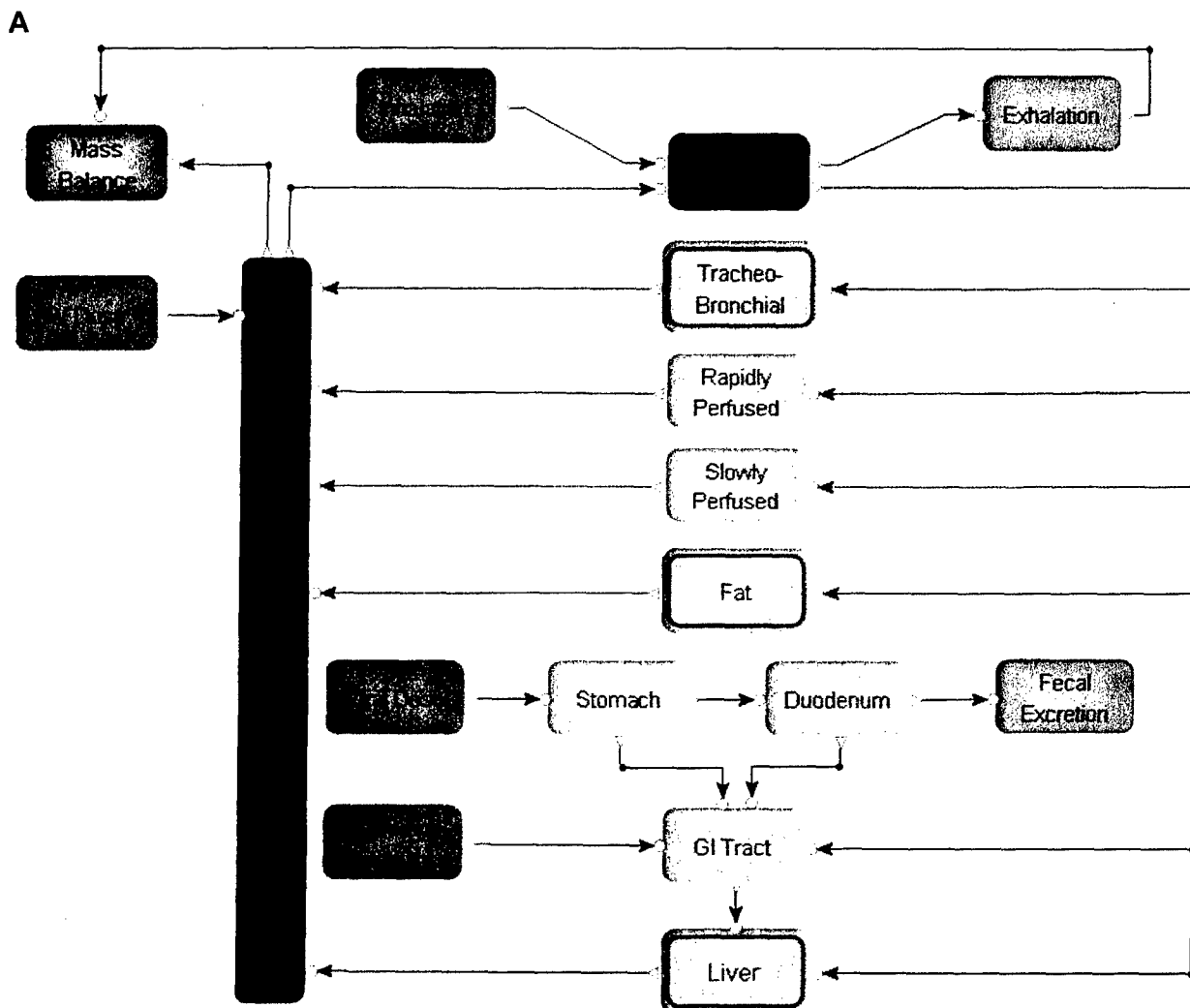
Figure 1. Metabolism of TCE. Abbreviations not given in text: (right pathway) CDH: chloral dehydrogenase (aldehyde oxidase); EHR: enterohepatic recirculation; FA: formic acid; GA: glyoxylic acid; OA: oxalic acid; TCE-O-P450: oxygenated TCE-Cytochrome P450 transition state complex; TCOG: TCOH glucuronide; UGT: UDP glucuronosyl transferase; (left pathway) BL: cysteine conjugate β -lyase; CGDP: cysteinyl-glycine dipeptidase; DCVG: dichlorovinyl glutathione; DCVSH: dichlorovinyl mercaptan; GGTP: γ -glutamyl transpeptidase; NADCVC: N-acetyl dichlorovinylcysteine; NAT: N-acetyl transferase.



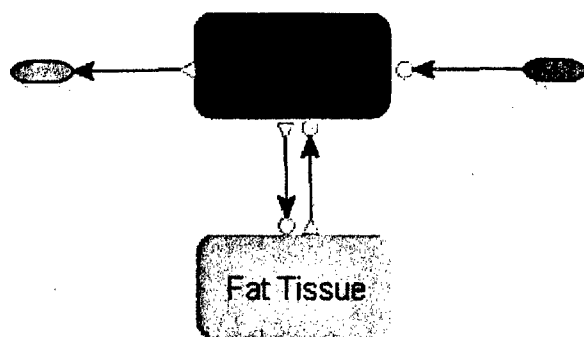
A diagram of the PBPK model developed for TCE and its metabolites is shown in Figures 2 and 3. The model was written in acslXtreme (The Aegis Technologies Group, Inc., Austin, Texas), an implementation of the Advanced Continuous Simulation Language (ACSL). The ACSL source code and command files for the model are included in Appendices A and B, respectively. The parent chemical portion of the model (Figure 2a) includes individual tissue compartments for the liver, GI tract tissue, fat, and tracheo-bronchial region of the lungs. All other tissues are lumped into rapidly perfused (kidney, brain, alveolar region of lungs, etc) and slowly perfused (muscle, skin, etc) compartments. The model has the capability to describe the fat compartment as a diffusion-limited tissue (Figure 2b). The model includes both inhalation and oral routes of exposure. Oral gavage is modeled using a two-compartment description of the gastrointestinal tract in order to better simulate the time course for the uptake of TCE from corn oil gavage. Allometric scaling is used throughout the model (volumes scaled by body weight, flows and metabolic capacities scaled by body weight to the three-quarters power, rate constants scaled by body weight to the negative one-quarter power) to simplify intraspecies and

interspecies extrapolation. Parent chemical dose metrics provided in the model include the concentration of TCE in blood and tissues, as well as the AUC for TCE in the blood.

Figure 2. Model schematics for the parent chemical. (A) General model schematic for parent chemical; (B) Sub-model for fat compartment. These diagrams were taken directly from the acslXtreme graphic model display. The blocks are color coded. (Red: blood compartment. Dark Blue: venous blood compartment. Yellow: tissue compartment. Brown: metabolism compartment. Light Green: bile compartment. Dark Green: dosing compartment. Purple: excretion compartment. Light blue: submodel. Rose: mass balance compartment.)



B



The model includes a number of submodels describing metabolism of TCE as well as downstream metabolism and elimination (Figure 3). These submodels are aimed at providing metabolite dose metrics, including tissue-specific dose metrics for the lung, liver, and kidney target tissues. Except where otherwise noted, Michaelis-Menten kinetics are assumed for all metabolic processes.

Lung Submodel. The tracheo-bronchial region of the lungs, which receives its own arterial blood supply, is described separately to support the modeling of *in situ* metabolism in this region by the Clara cells (Figure 3a). This approach for describing metabolism in the cells lining the airways of the lung was felt to be more biologically accurate than the sequential gas exchange and lung tissue compartments used in the methylene chloride model.¹⁵ However, as long as metabolism in the lung is unimportant for presystemic elimination, as is the case for TCE and methylene chloride, the two descriptions should yield identical results. The dose metrics provided for the lung are the instantaneous concentration and AUC for CHL in the tracheo-bronchial region, which is assumed to be produced by saturable production and clearance of CHL in Clara cells. No systemic circulation of CHL is considered in the model.

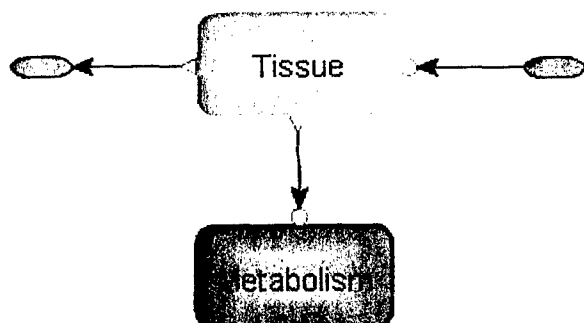
Oxidative Metabolism. Apart from the limited metabolism occurring in the lung, the model assumes that all oxidative metabolism takes place in the liver. The dose metric provided to describe metabolism is the total amount of TCE metabolized divided by the body weight. The model does not actually calculate the formation and metabolism of CHL in the liver, but instead assumes that TCA and TCOH are formed in a fixed yield from the oxidative metabolism of TCE (Figure 3b). In the model, TCOH can subsequently be oxidized to TCA or conjugated with glucuronic acid. Biliary excretion of TCOH glucuronide and enterohepatic recirculation of free TCOH are described, with only the glucuronide being excreted in the urine (Figures 3b-3e). The description of TCA includes compartments for liver, blood, and other tissues, with clearance into the urine from blood (Figure 3f). Binding of TCA in the plasma is modeled using equations derived from experimental data,¹³ and only the free TCA is exchanged with the tissues. Tissue distribution is described using measured partitioning of TCA between tissues and blood.^{8, 9, 16} Measured partition coefficients for total TCA between tissues and blood were 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. An empirical ratio is used to adjust predicted plasma concentrations for comparison with measured blood concentrations. A rudimentary single-compartment description of DCA is included in the model, assuming direct production of DCA from TCE as a constant fraction of the rate of oxidative metabolism (Figure 3g). Dose metrics for use with the liver target tissue include the

concentrations and AUC for TCA in the plasma and liver. The concentration and AUC for TCOH in the blood are also provided as a noncancer dose metric.

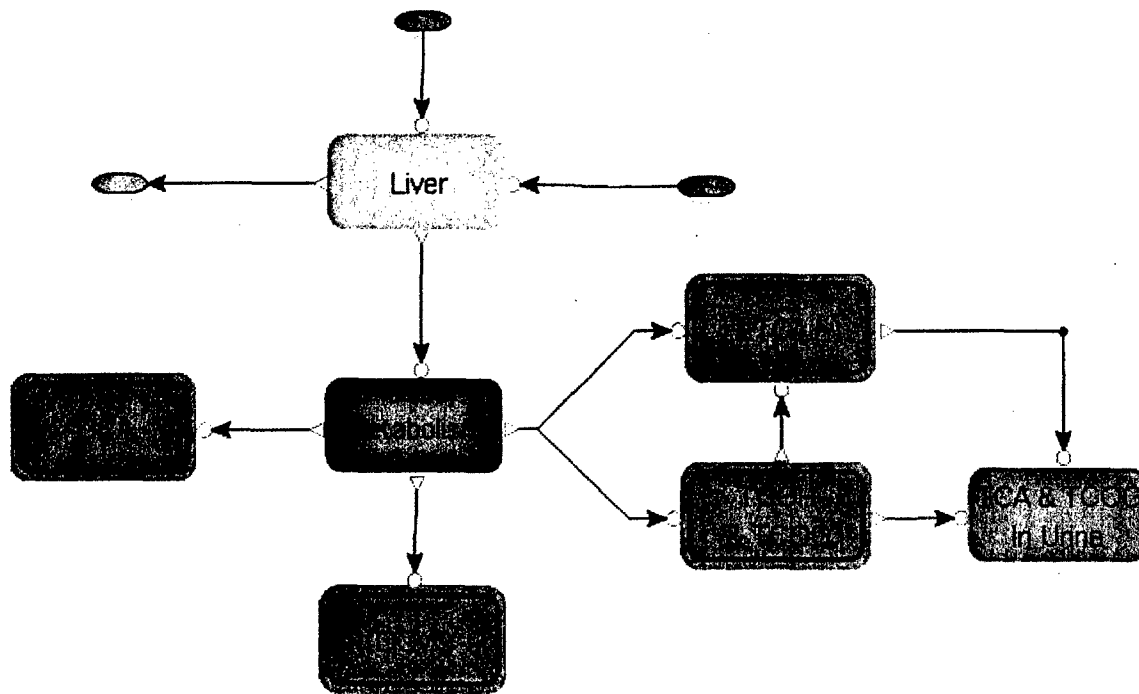
Conjugative Metabolism. The model also includes a linear metabolic pathway representing conjugation of TCE by GST (Figure 3b). The model implicitly assumes that all GSH conjugation of TCE in the liver leads eventually to the appearance of DCVC in the kidney. Clearance of DCVC by N-acetyl-transferase into the urine is also modeled (Figure 3h). The dose metric provided in the model for the kidney is the total production of a thioacetylating intermediate from DCVC, divided by the volume of the kidney.

Figure 3. Model schematics for the metabolites. (A) Sub-model for tracheo-bronchial compartment; (B) Sub-model for liver; (C) Sub-model for TCOH and TCOG; (D) Sub-model for TCOH; (E) Sub-model for TCOG; (F) Sub-model for TCA; (G) Sub-model for DCA; (H) Sub-model for DCVC. These diagrams were taken directly from the acslXtreme graphic model display. The blocks are color coded. (Red: blood compartment. Dark Blue: venous blood compartment. Yellow: tissue compartment. Brown: metabolism compartment. Light Green: bile compartment. Dark Green: dosing compartment. Purple: excretion compartment. Light blue: submodel. Rose: mass balance compartment.)

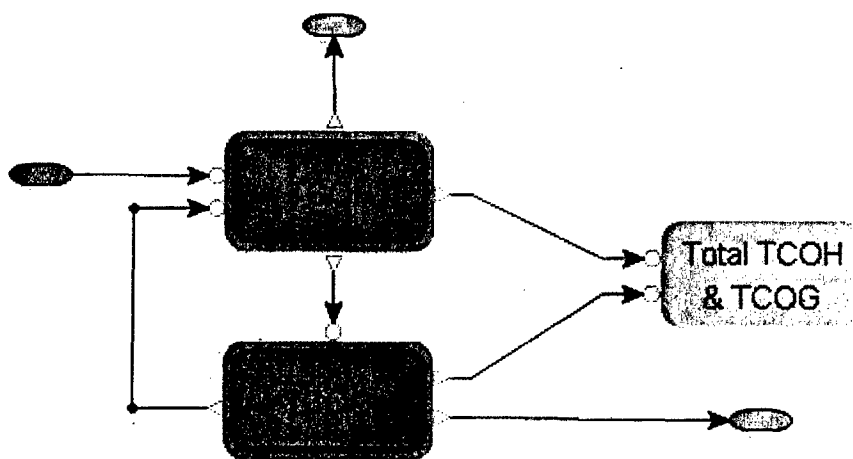
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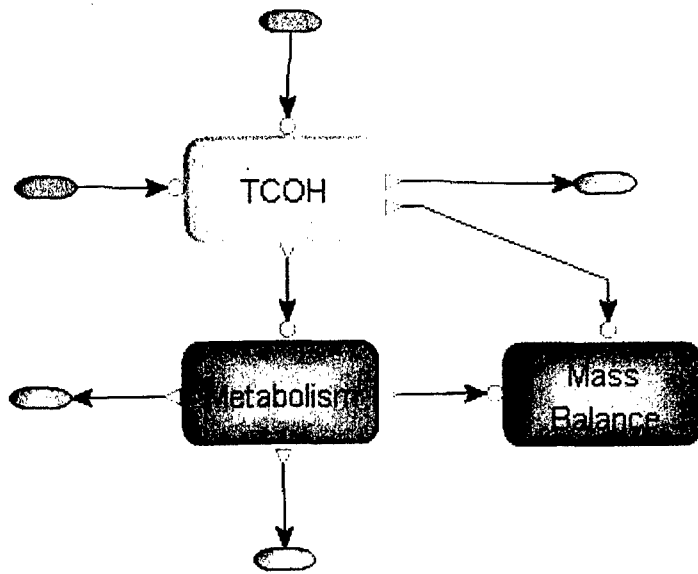
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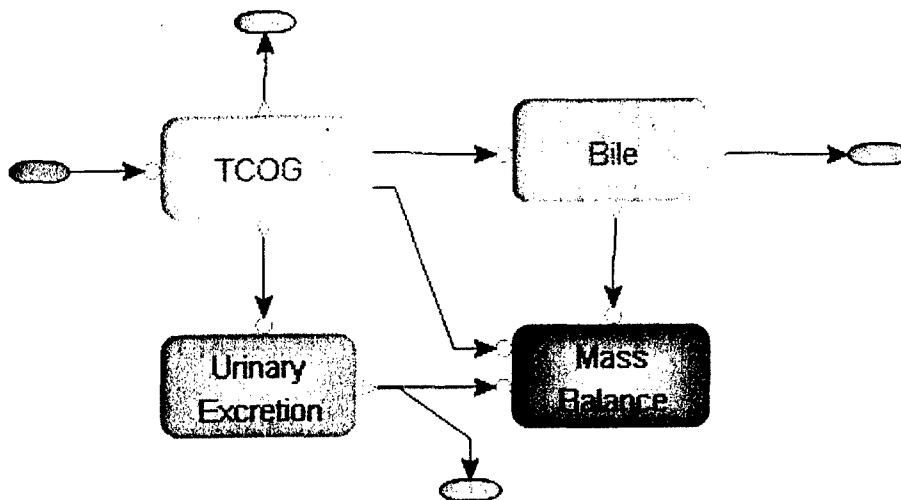
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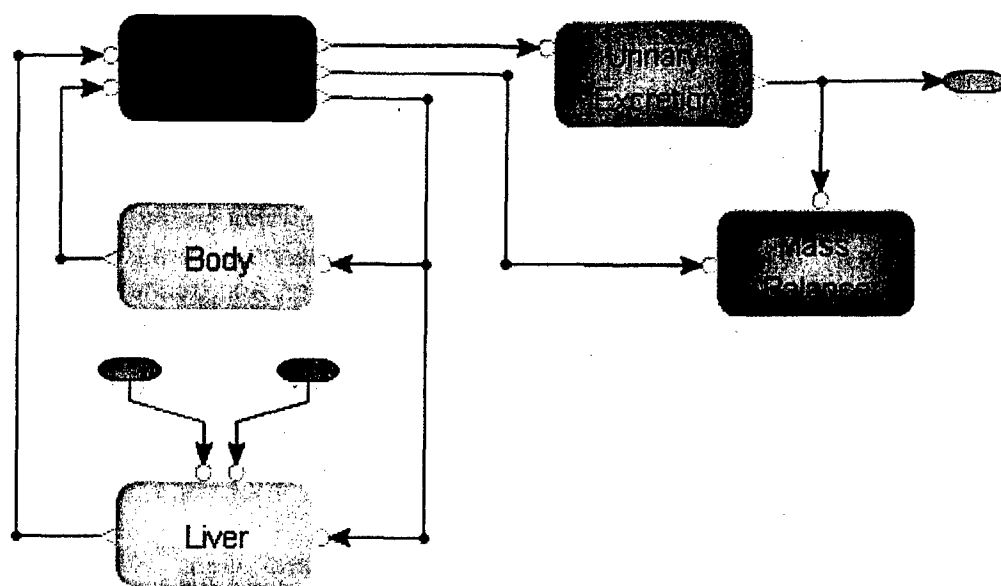
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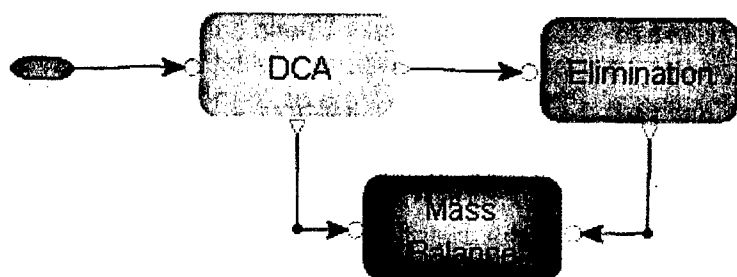
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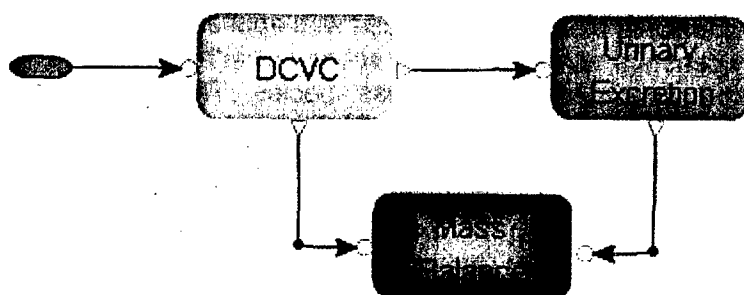
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PBPK Model Parameters

The parameters for the model and their source references are listed in Table 1; they are discussed in the following section.

Parameters for the Parent Chemical. The physiological parameters, with two exceptions, were based on the recommendations of the ILSI Risk Science Institute Working Group on Physiological Parameters.¹⁷ The exceptions were the cardiac output in the mouse and the alveolar ventilation in the human, which were based on the recommendations of Arms and Travis.¹⁸ In the model, the tissue volumes and blood flows for the gut, liver, and tracheo-bronchial region are subtracted from the values shown for "all rapidly perfused tissues" to obtain the parameters for the rapidly perfused tissue compartment shown in Figure 2, and those for the fat are subtracted from the values shown for "all slowly perfused tissues" to obtain the parameters for the slowly perfused tissue compartment. The kidney volume shown in Table 1 is used only in calculations for the kidney dose-surrogate; as shown in Figure 2, the kidney is not described separately in the parent chemical model.

The partition coefficients for TCE were obtained from the work of Fisher and Allen;⁵⁻⁷ the partition coefficients for the gut and tracheo-bronchial tissues were assumed to be the same as those reported for the richly perfused tissues. The oral uptake parameters were estimated from data on the appearance of TCE and its metabolites in the blood following gavage in mice and rats. For some parameters, identified in Table 1, values chosen for calculating risk assessment dose metrics were different from those chosen to reproduce pharmacokinetic data. For example, human dose metrics were calculated using a value for alveolar ventilation of 24, which corresponds to the EPA's standard assumption of a total ventilation rate of 20 m³/day. Similarly, animals used in pharmacokinetic studies tend to have lower average body weights than animals used in cancer bioassays, so body weights appropriate to each case were used in the model.

Parameters for Oxidative Metabolism. Initial values for the metabolic parameters for TCE were obtained from the work of Fisher and Allen;⁵⁻⁷ however, the metabolic and clearance parameters for TCA and TCOH were derived primarily on the basis of fitting the pharmacokinetic data depicted in the figures. Since the model contains a large number of metabolic and clearance parameters, many of which are highly correlated, the parameter values estimated by this process (i.e., the kinetic parameters for TCA and TCOH) cannot be considered to be unequivocally identified. However, an additional biological constraint was applied by attempting to ensure that parameters are relatively constant across exposure scenarios within a given species, and (to the extent justified by the experimental data) across species. This constraint greatly reduces the likelihood that alternative parameterizations could demonstrate equivalent success in reproducing the entire body of data. Another constraint on the parameterization not obvious from the figures is the fact that of the total TCOH extractable from the blood, roughly 80% is present as free TCOH in the human,¹⁹ while roughly 70-85% is present as the glucuronide in the rodent.^{20, 21} In the figures in this paper, the model concentrations shown represent either free TCOH or the total of TCOH plus its glucuronide, corresponding to the experimental data provided.

It is informative to note the departures from simple allometric expectations that were required on the basis of the experimental data across species. As with most other xenobiotics, the mouse shows a relatively greater, and more variable, capacity (VMC) for oxidative metabolism of TCE than the rat and human. Moreover, the Km for oxidative metabolism of TCE in the human appears to be roughly an order of magnitude larger than in the rodents. A striking difference between humans and rodents, which was clearly demanded by the experimental data, was that

the oxidation of TCOH to TCA appears to be a relatively high affinity, low capacity process in the rodent but low affinity, high capacity in the human. It may be that this disparity reflects the involvement of different enzymes (e.g., MFO in the rodent vs. ADH in the human). The result of this species difference is that although the model uses a similar value across species for PO (based on the initial split of TCA and TCOH from CHL), the apparent ratio of TCA to TCOH predicted (and observed) over the entire time-frame of an exposure to TCE is much higher in the human than in the rodent. The apparent capacity for glucuronidation of TCOH in the human, on the other hand, is much lower than in the rodent, as reflected in the greatly different ratios of free TCOH to glucuronide in the blood, mentioned above.

Parameters for Lung Metabolism. The parameters in the PBPK model for predicting the lung dose metric are the capacity and affinity for the production of CHL, and the capacity and affinity for its clearance. In the model, the production of CHL in the tracheobronchial region was assumed to be associated with the P450 activity in that tissue. This is the assumption that was made in the pharmacokinetic risk assessment for methylene chloride.¹⁵ The approach used in that risk assessment was also used to obtain the parameters in this case: the affinity in the lung was assumed to be the same as in the liver for the same species, and the relative capacity of the lung compared to the liver was determined on the basis of P450 activity measured with standard substrates.¹⁵ Based on these data, P450 activity falls off much more rapidly with body weight than would be expected from allometric considerations. No data was available on the clearance of CHL in the lung across species, therefore it was assumed to be a low affinity, high capacity enzyme system such as ADH. The parameters in the PBPK model were chosen such that concentrations of CHL in the lung of the mouse predicted by the model were consistent with those observed in experimental studies.⁸ It was further assumed that the clearance of CHL in the lung scales across species according to allometric expectations (i.e., by body weight to the 3/4 power). This assumption leads to much lower CHL concentrations in the lungs of rats and humans compared to mice for the same TCE exposure conditions. An alternative assumption was that the activity of the enzyme responsible for the clearance of CHL scales in the same way as P450; this assumption leads to similar concentrations of CHL in the lungs of mice, rats and humans for the same TCE exposure conditions.

Parameters for Conjugative Metabolism. The parameters in the PBPK model for predicting the kidney dose metric are the production of DCVC by the GST pathway, its activation by beta-lyase, and its clearance by N-acetyl-transferase. First-order rate constants are used because the production of metabolites by the GST pathway is quite low, and saturation of enzyme capacity is unlikely. The capacity and affinity of beta-lyase in the kidney have been measured in both rats and humans.²² This data was used to estimate the apparent first-order rate constants used in the model. No data was available on the activity of beta-lyase in the mouse, so the relationships between beta-lyase metabolic parameters in mice and rats reported for trichlorovinylcysteine derived from perchloroethylene²³ were assumed to apply for DCVC as well. For N-acetyl-transferase, only specific activity data across species is available.²⁴ These data were converted to the corresponding rate constants by assuming the affinity of N-acetyl-transferase for DCVC is the same as that measured for beta-lyase in the same species. This assumption is supported by the similarity of the affinities of N-acetyl-transferase and beta-lyase for DCVC in the rat: 3.3 mM and 1.6 mM, respectively.^{22, 25}

Finally, measurements of oxidative and conjugative metabolites in the urine following TCE exposure²⁶ were used to obtain estimates of the GST pathway rate constant. The oxidative pathway was represented by total excretion of TCA plus TCOH, while the conjugative pathway was represented by excretion of 1,2-DCVC. Data from the same study on excretion of 2,2-DCVC was not used. Unlike 1,2-DCVC, there was no evidence of a dose-response for 2,2-

DCVC as a function of TCE exposure in humans or rodents; similar amounts of 2,2-DCVC were excreted for TCE exposures ranging from 40 to 160 ppm. The results of this analysis¹ indicated that the model could be made to agree quite well with the urinary data when allometric scaling was assumed for conjugative metabolism.

Table 1: Model Parameters

Parameter	Mouse			Rat			Human		
	Value	Reference	Value	Value	Reference	Value	Reference	Value	Reference
BW	Body Wt (kg)	0.035 ¹	EPA default USEPA (U.S. Environmental Protection Agency (USEPA) 1988)	0.35 ¹	EPA default	70.0 ¹	ICRP (International Commission on Radiological Protection (ICRP) 1975)		
QCC	Cardiac output	18.0	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	15.0	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	13.0	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QPC	Pulmonary ventilation	30.0 ²	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	24.0 ³	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	18.0	Astrand and Rodahl (Astrand and Rodahl 1970)		
QFatC	Fat	0.07	Rat value	0.07	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.052	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QGutC	Gut	0.141	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.162	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.181	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QLivC	Liver	0.02	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.021	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.046	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QRapC	Rapidly perfused tissues	0.713	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.594	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.699	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QSlowC	Slowly perfused tissues	0.287	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.406	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.301	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
QTBC	Tracheo-bronchial	0.005	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.021	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.025	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
VBldC	Blood	0.049	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.074	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.079	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
VBodC	Total body	0.2	Fit to data from Fisher <i>et al.</i> (Fisher, Gargas <i>et al.</i> <i>et al.</i> 1991)	0.2	Fit to data from Fisher <i>et al.</i> (Fisher, Gargas <i>et al.</i> <i>et al.</i> 1991)	0.2 ³	Fit to data from Muller <i>et al.</i> (Muller, Spassovski <i>et al.</i> 1974), (Muller, Spassovski <i>et al.</i> 1975)		
VFatBldC	Fraction of fat that is blood	0.02	Human value	0.02	Human value	0.02	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
VFatC	Fat	0.07 ³	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.07	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.214	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		
VGutC	Gut	0.042	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.027	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)	0.017	Brown <i>et al.</i> (Brown, Delp <i>et al.</i> 1997)		

VKidC	Kidney	Brown et al. (Brown, Delp et al. 1997)	0.017	0.007	Brown et al. (Brown, Delp et al. 1997)	0.004	Brown et al. (Brown, Delp et al. 1997)
VLivC	Liver	Brown et al. (Brown, Delp et al. 1997)	0.055	0.034	Brown et al. (Brown, Delp et al. 1997)	0.026	Brown et al. (Brown, Delp et al. 1997)
VRapC	Rapidly perfused tissues	Brown et al. (Brown, Delp et al. 1997)	0.217	0.213	Brown et al. (Brown, Delp et al. 1997)	0.192	Brown et al. (Brown, Delp et al. 1997)
VSlwC	Slowly perfused tissues	Brown et al. (Brown, Delp et al. 1997)	0.619	0.664	Brown et al. (Brown, Delp et al. 1997)	0.651	Brown et al. (Brown, Delp et al. 1997)
VTBC	Tracheo-bronchial	Brown et al. (Brown, Delp et al. 1997); Clewell et al. (Clewell, Gentry et al. 2000)	0.0007	0.0005	Brown et al. (Brown, Delp et al. 1997); Clewell et al. (Clewell, Gentry et al. 2000)	0.0008	Brown et al. (Brown, Delp et al. 1997)
VDDCAC	DCA	Schultz et al. (Schultz, Merdink et al. 2002)	0.5	0.5	Saghir and Schultz (Saghir and Schultz 2003)	0.26	Curry et al. (Curry, Chu et al. 1985)
VDTCOHC	TCOH	Clewell et al. (Clewell, Gentry et al. 2000)	0.65	0.65	Clewell et al. (Clewell, Gentry et al. 2000)	0.65	Clewell et al. (Clewell, Gentry et al. 2000)
PB	Blood/air	Fisher et al. (Fisher, Gargas et al. 1991)	14.0	18.5	Fisher et al. (Fisher, Gargas et al. 1991)	9.2	Allen and Fisher (Allen and Fisher 1993)
PFat	Fat/blood	Fisher et al. (Fisher, Gargas et al. 1991)	36.0	27.5	Fisher et al. (Fisher, Gargas et al. 1991)	73.0	Allen and Fisher (Allen and Fisher 1993)
PGut	Gut/blood	Fisher et al. (Fisher, Gargas et al. 1991)	1.8	1.3	Fisher et al. (Fisher, Gargas et al. 1991)	6.8	Allen and Fisher (Allen and Fisher 1993)
PLiv	Liver/blood	Fisher et al. (Fisher, Gargas et al. 1991)	1.8	1.3	Fisher et al. (Fisher, Gargas et al. 1991)	6.8	Allen and Fisher (Allen and Fisher 1993)
PRap	Rapidly perfused/blood	Fisher et al. (Fisher, Gargas et al. 1991)	1.8	1.3	Fisher et al. (Fisher, Gargas et al. 1991)	6.8	Allen and Fisher (Allen and Fisher 1993)
PSlw	Slowly perfused/blood	Fisher et al. (Fisher, Gargas et al. 1991)	0.75	0.5	Fisher et al. (Fisher, Gargas et al. 1991)	2.3	Allen and Fisher (Allen and Fisher 1993)
PTB	TB/blood	Fisher et al. (Fisher, Gargas et al. 1991)	1.8	1.3	Fisher et al. (Fisher, Gargas et al. 1991)	6.8	Allen and Fisher (Allen and Fisher 1993)
PAFatC1	Takeup	Set to over ride two-compartment fat	10.0	10.0	Set to over ride two-compartment fat	10.0	Set to over ride two-compartment fat
PAFatC2	Release	Set to over ride two-compartment fat	10.0	10.0	Set to over ride two-compartment fat	10.0	Set to over ride two-compartment fat

PBodTCA	Body/free plasma	0.76	Abbas and Fisher (Abbas and Fisher 1997); Lumpkin et al. (Lumpkin, Dallas et al. 2003)	0.51	Jepson et al. (Jepson, Hoover et al. 1994); Lumpkin et al. (Lumpkin, Dallas et al. 2003)	1.9	Fisher et al. (Fisher, Mahle et al. 1998); Lumpkin et al.
PLIVTCA	Liver/free plasma	1.14	Abbas and Fisher (Abbas and Fisher 1997); Lumpkin et al. (Lumpkin, Dallas et al. 2003)	0.76	Jepson et al. (Jepson, Hoover et al. 1994); Lumpkin et al. (Lumpkin, Dallas et al. 2003)	2.5	Fisher et al. (Fisher, Mahle et al. 1998); Lumpkin et al. (Lumpkin, Dallas et al. 2003)
VMaxC	Oxidative capacity (mg/hr)	32.7 ³	Fisher et al. (Fisher, Gargas et al. 1991)	11.2 ³	Fisher et al. (Fisher, Gargas et al. 1991)	12.0 ³	Allen and Fisher (Allen and Fisher 1993)
KM	Oxidative affinity (mg/L)	0.25	Fisher et al. (Fisher, Gargas et al. 1991)	0.25 ³	Fisher et al. (Fisher, Gargas et al. 1991)	1.5	Allen and Fisher (Allen and Fisher 1993)
kDCVCC	Production of DCVC/hr	0.015 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.015 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.015 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
FracDCA	Fractional split of TCE to DCA	0.04	Fit to data from Templin et al. (Templin, Parker et al. 1993)	0.04	Mouse value	0.004	Fit to data from Fisher et al. (Fisher, Mahle et al. 1998)
FracTCE	Fractional split of TCE to TCA	0.035	Fit to data from Prout et al. (Prout, Provan et al. 1985)	0.04 ³	Fisher et al. (Fisher, Gargas et al. 1991)	0.08 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
VMaxClaraC	VMax	3.0	Clewell et al. (Clewell, Gentry et al. 2000)	0.3	Clewell et al. (Clewell, Gentry et al. 2000)	0.0045	Clewell et al. (Clewell, Gentry et al. 2000)
KMClara	KM	0.25	Clewell et al. (Clewell, Gentry et al. 2000)	0.25	Clewell et al. (Clewell, Gentry et al. 2000)	1.5	Clewell et al. (Clewell, Gentry et al. 2000)
VMaxClearC	VMax for chloral clearance	250.0	Clewell et al. (Clewell, Gentry et al. 2000)	250.0	Clewell et al. (Clewell, Gentry et al. 2000)	250.0	Clewell et al. (Clewell, Gentry et al. 2000)
KMClear	KM for chloral clearance	250.0	Clewell et al. (Clewell, Gentry et al. 2000)	250.0	Clewell et al. (Clewell, Gentry et al. 2000)	250.0	Clewell et al. (Clewell, Gentry et al. 2000)
kDissoc	Protein/TCA dissociation constant (μmole/L)	46.1	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	383.6	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	174.6	Lumpkin et al. (Lumpkin, Dallas et al. 2003)
NumSites	Number of binding sites per class protein	0.17	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	1.49	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	2.97	Lumpkin et al. (Lumpkin, Dallas et al. 2003)
ProtConc	Protein concentration (μmoles/L)	196.0	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	190.0	Lumpkin et al. (Lumpkin, Dallas et al. 2003)	239.0	Lumpkin et al. (Lumpkin, Dallas et al. 2003)
VMaxTCOHC	VMax for oxidation to TCA	1.0 ^{3,4}	Clewell et al. (Clewell, Gentry et al. 2000)	0.12 ^{3,4}	Clewell et al. (Clewell, Gentry et al. 2000)	25.0 ^{3,4}	Clewell et al. (Clewell, Gentry et al. 2000)

KMTCOH	KM for oxidation to TCA V _{Max} for	0.25 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.25 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	250.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
V _{Max} GlucC	glucuronidation to TCOG	100.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	100.0 ^{3,4}	Clewell et al. (Clewell, Gentry et al. 2000)	5.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
KMGluc	KM for glucuronidation to TCOG	25.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	25.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	25.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kNATC	Clearance of DCVC by NAT	0.5 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	1.1	Clewell et al. (Clewell, Gentry et al. 2000)	19.0	Clewell et al. (Clewell, Gentry et al. 2000)
kKidCytoC	Kidney cytotoxicity from DCVC	0.4 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	17.0	Clewell et al. (Clewell, Gentry et al. 2000)	37.0	Clewell et al. (Clewell, Gentry et al. 2000)
kAS	Stomach to gut	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kTSD	Stomach to duodenum	10.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	10.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	10.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kAD	Duodenum to liver	0.6 ³	Fit to data from Prout et al. (Prout, Provan et al. 1985)	0.3 ³	Fit to data from Templin et al. (Templin, Stevens et al. 1995)	1.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kTD	Fecal excretion	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kBileC	Biliary excretion of TCOG	1.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	1.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	1.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kEHRC	Enterohepatic recirculation of TCOH	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ^{3,4}	Clewell et al. (Clewell, Gentry et al. 2000)	0.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
kClearDCAC	Clearance of DCA	1.0	Schultz et al. (Schultz, Merdink et al. 2002)	1.3	Saghir and Schultz (Saghir and Schultz 2003)	1.9	Curry et al. (Curry, Chu et al. 1985)
kUmTCAC	Urinary excretion of TCA	0.3 ³	Fit to data from Fisher et al. (Fisher, Gargas et al. 1991)	0.3	Fit to data from Fisher et al. (Fisher, Gargas et al. 1991)	0.2 ³	Fit to data from Muller et al. (Muller, Spassovski et al. 1974), (Muller, Spassovski et al. 1975)
kUmTCOGC	Urinary excretion of TCOG	0.5 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	0.5 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)	3.0 ⁴	Clewell et al. (Clewell, Gentry et al. 2000)
FracPlas	Fraction of blood that is plasma	0.58	Human value	0.58	Human value	0.58	ICRP (International Commission on Radiological Protection (ICRP) 1975)
TCAPlas	To convert TCA in plasma to TCA in blood	0.76	Personal communication with Jeff Fisher	0.76	Personal communication with Jeff Fisher	0.76	Personal communication with Jeff Fisher

¹ Used study specific values when available.

² 18.0 was used for open chamber simulations. 30.0 was used for closed chamber simulations.

³ Different values were needed to fit some data sets.

⁴ Value from Clewell et al. (Clewell, Gentry et al. 2000) was fit to data.

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RESULTS

The predictions of the PBPK model for the experimental data sets used in its development are shown in Figures 4-17. The order of the figures follows the order of use of the data in model development. Mouse data sets are shown first, followed by rat and human.

Figure 4 shows the ability of the model to simulate the chamber concentration time-course in gas-uptake studies conducted with male (a) and female (b) B6C3F1 mice. These data were used to obtain initial estimates of the kinetic parameters for TCE.⁵ The resulting estimates of V_{maxC} were 32.7 mg/hr/kg^{3/4} for the male and 23.2 mg/hr/kg^{3/4} for the female. Fractional fat volumes of 0.05 and 0.1 were also estimated for males and females, respectively, based on the early uptake in these studies. It was only possible to determine that K_m was probably less than 1 µg/L. Estimates of the other kinetic parameters were obtained using data on concentrations of TCE and its metabolites in male mice following oral gavage in corn oil²⁷ and water²⁰ vehicles.

The resulting fits of the model to the data are shown in Figures 5 and 6. In fitting these two data sets, it was only necessary to use different values for three of the model kinetic parameters. The simulation of the corn oil gavage data was obtained with $k_{AD}=0.3$, $V_{maxC}=50$, and $V_{maxTCOHC}=2$, while the aqueous vehicle data was best simulated with $k_{AD}=1.0$, $V_{maxC}=60$, and $V_{maxTCOHC}=0.5$. For both data sets, it was also necessary to reduce QPC to 18 L/hr/kg^{3/4}, rather than the value of 30 L/hr/kg^{3/4} used in the closed chamber studies. The rest of the model parameters were as shown in Table 1.

Figure 4. Comparison of predicted and experimental chamber concentrations of TCE in male (A) and female (B) B6C3F1 mice exposed to TCE in a closed, recirculating chamber. Kinetic data are taken from Fisher *et al.*⁵

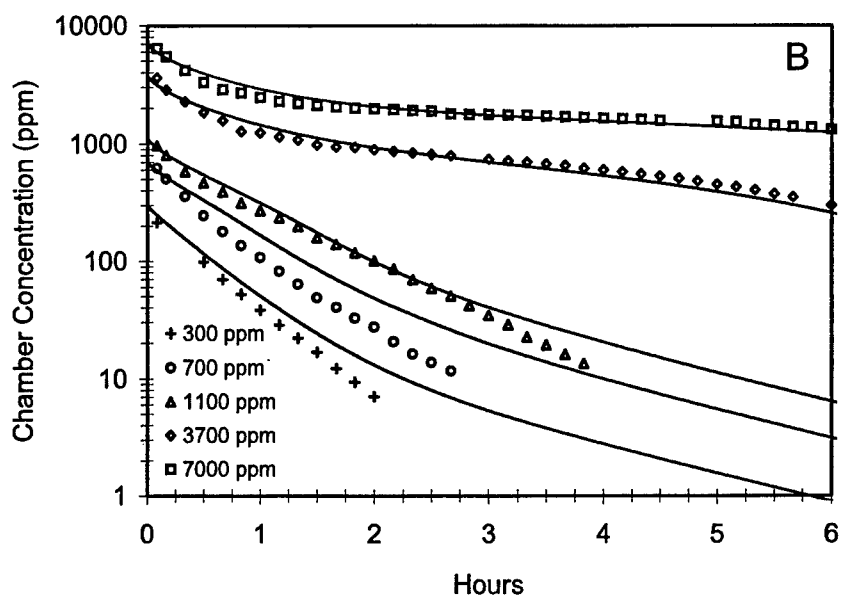
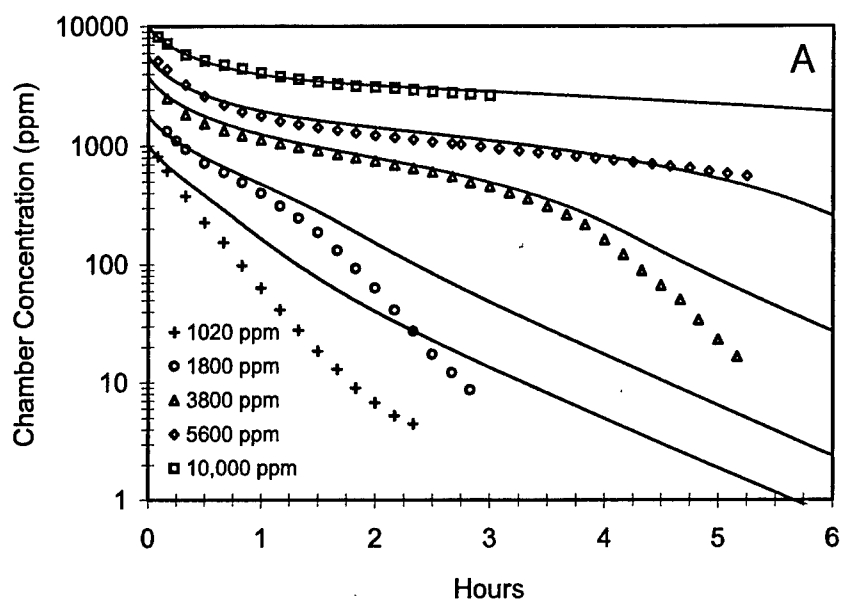


Figure 5. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following corn oil gavage with 1000 mg/kg TCE in mice. Kinetic data are taken from Prout *et al.*²⁷

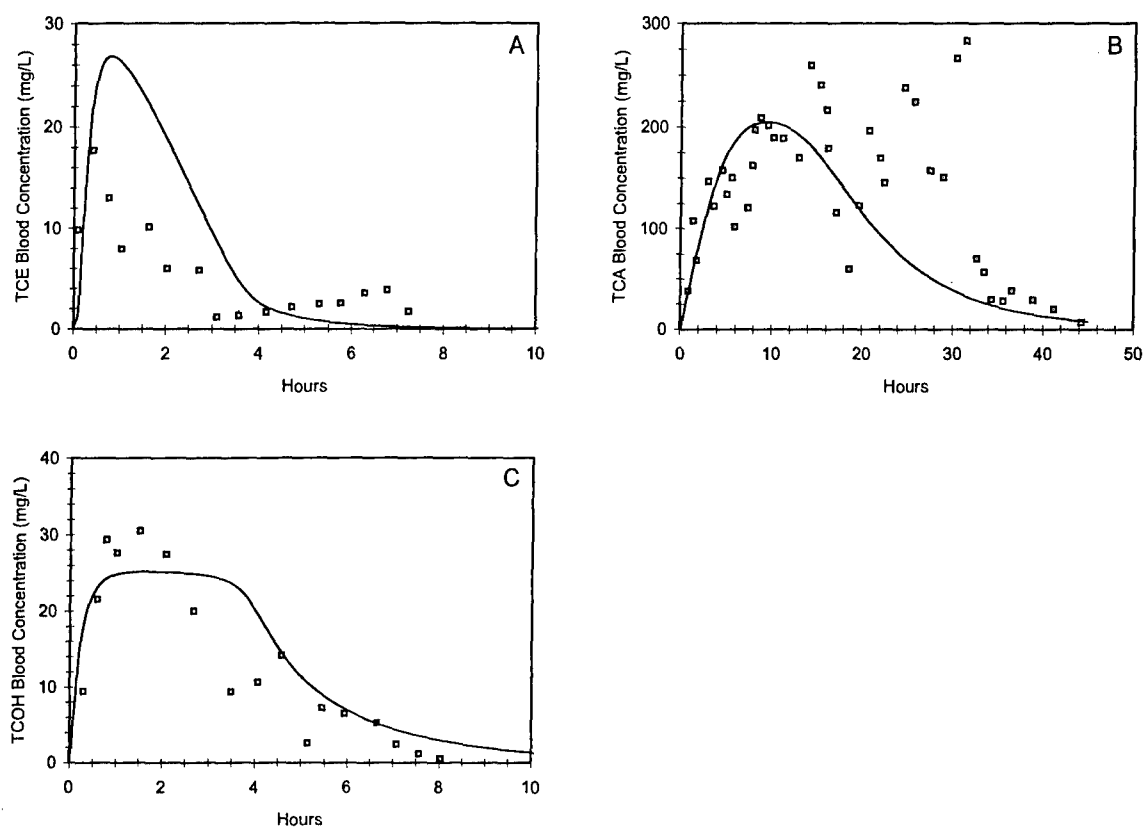


Figure 6. Mean observed and predicted blood concentrations of (A) TCE and metabolites (B) TCA, (C) TCOH and (D) DCA following an oral dose of 499 mg/kg TCE in B6C3F1 mice. Kinetic data are taken from Templin *et al.*²⁰

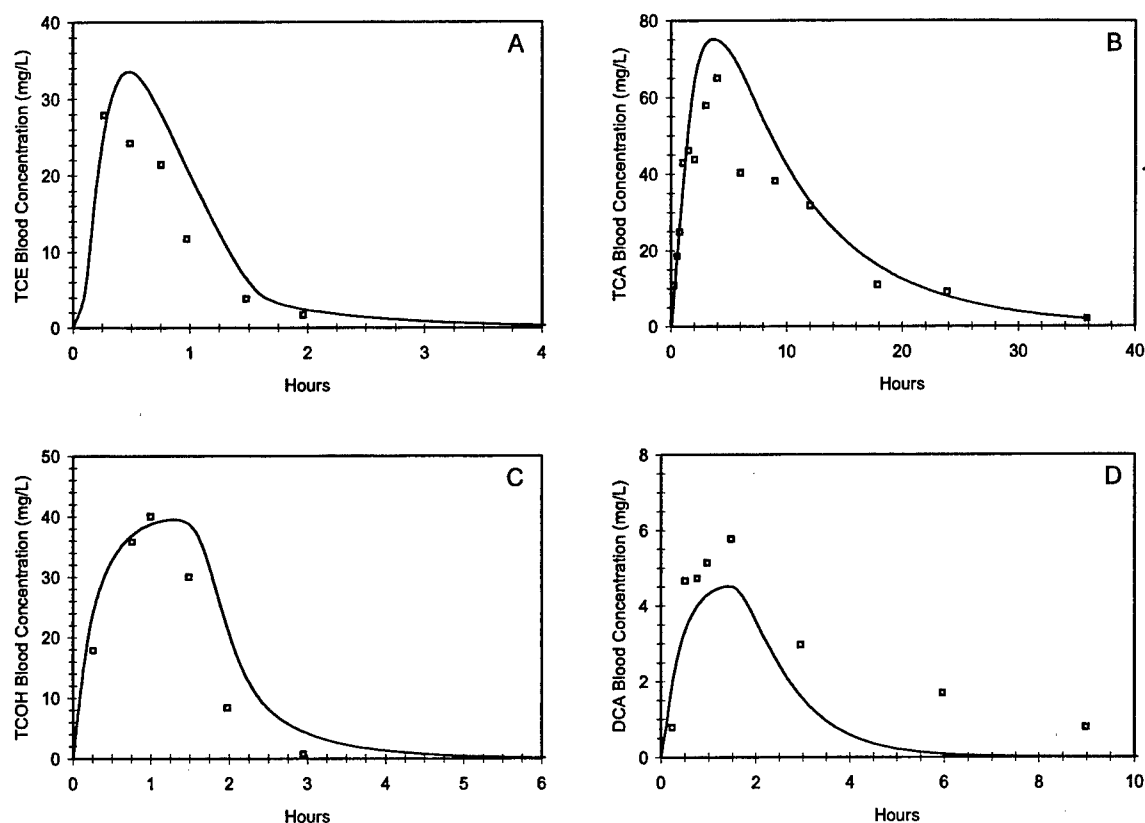


Figure 7 shows the predictions of the model for inhalation exposures to TCE in male and female mice.⁵ All of the model parameters in this case were those shown in Table 1, except that for the females the value of V_{maxC} was reduced to 23.2 mg/hr/kg^{3/4} and the urinary excretion rate constant for TCA, k_{UrTCA} , was doubled to 0.6 kg^{1/4}/hr. The lower value of QPC mentioned above was also used. Validation of these mouse parameter values, shown in Figure 8 was performed using the more recent inhalation data of Greenberg *et al.*¹¹.

Finally, the model parameters in Table 1 were tested by using them in the model to predict the time-course for TCE and TCA in a number of tissues for comparison with the corn oil gavage data collected by Abbas *et al.*⁸; the results of the prediction are displayed in Figure 9. The blind predictions of the model are generally within a factor of two of the data, although the model tends to underestimate TCE concentrations at early times. The model also overestimates liver concentrations of TCA to a much greater extent than blood concentrations, suggesting that the *in vitro* partitioning of TCA may not accurately predict its distribution *in vivo*.

Figure 7. Comparison of predicted and experimental concentrations of TCE in blood and TCA in plasma in B6C3F1 mice exposed to TCE by inhalation. The figures show TCE-blood and TCA-plasma concentrations in (A) male mice exposed for 4 hr to 110 ppm TCE vapors and (B) female mice exposed for 4 hr to 368 ppm TCE vapors. Kinetic data are taken from Fisher *et al.*⁵

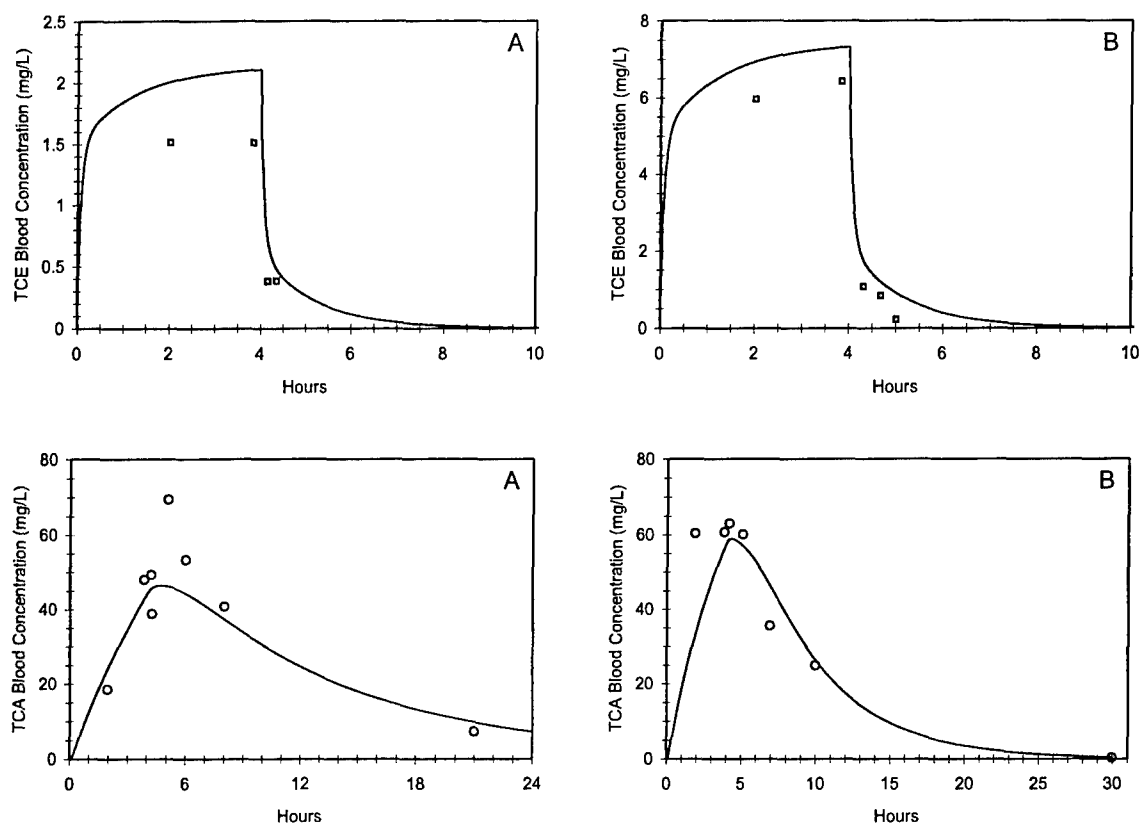


Figure 8. Comparison of predicted and experimental concentrations of TCE, TCOH, and TCA in blood in male B6C3F1 mice exposed for 4 hr to 600 ppm TCE by inhalation. Kinetic data are taken from Greenberg *et al.*¹¹

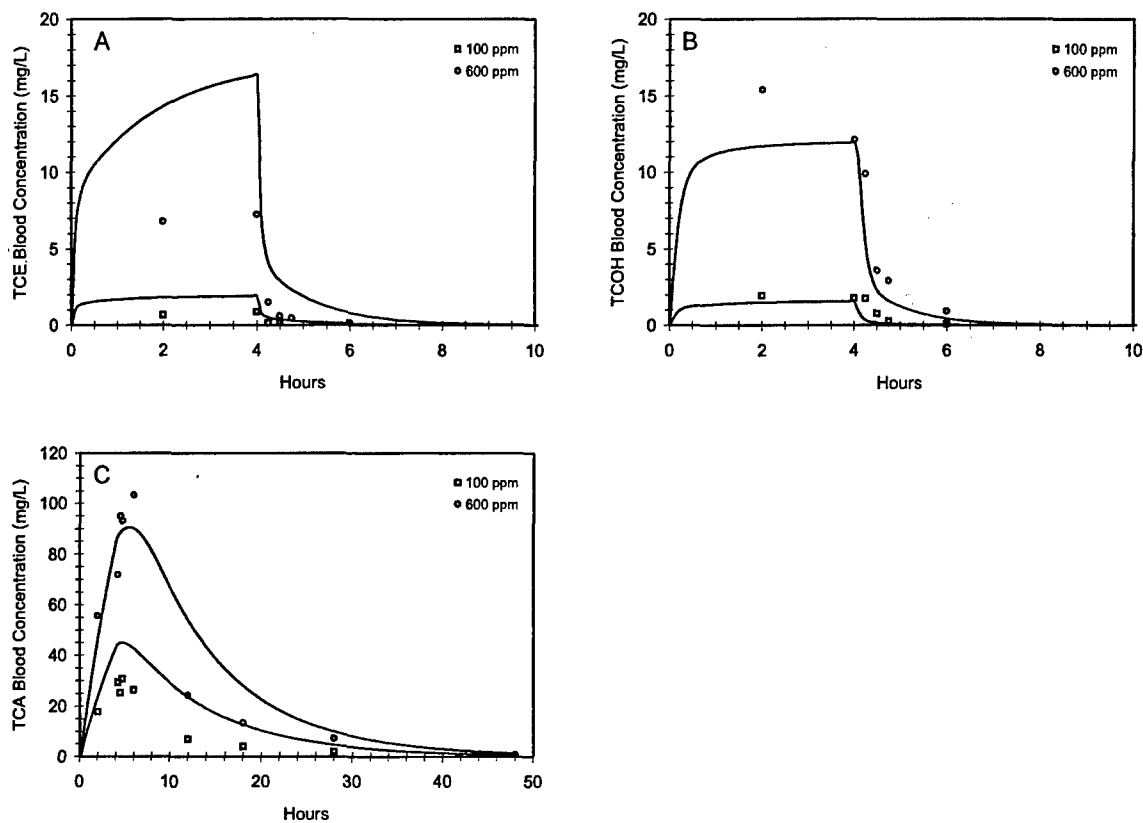
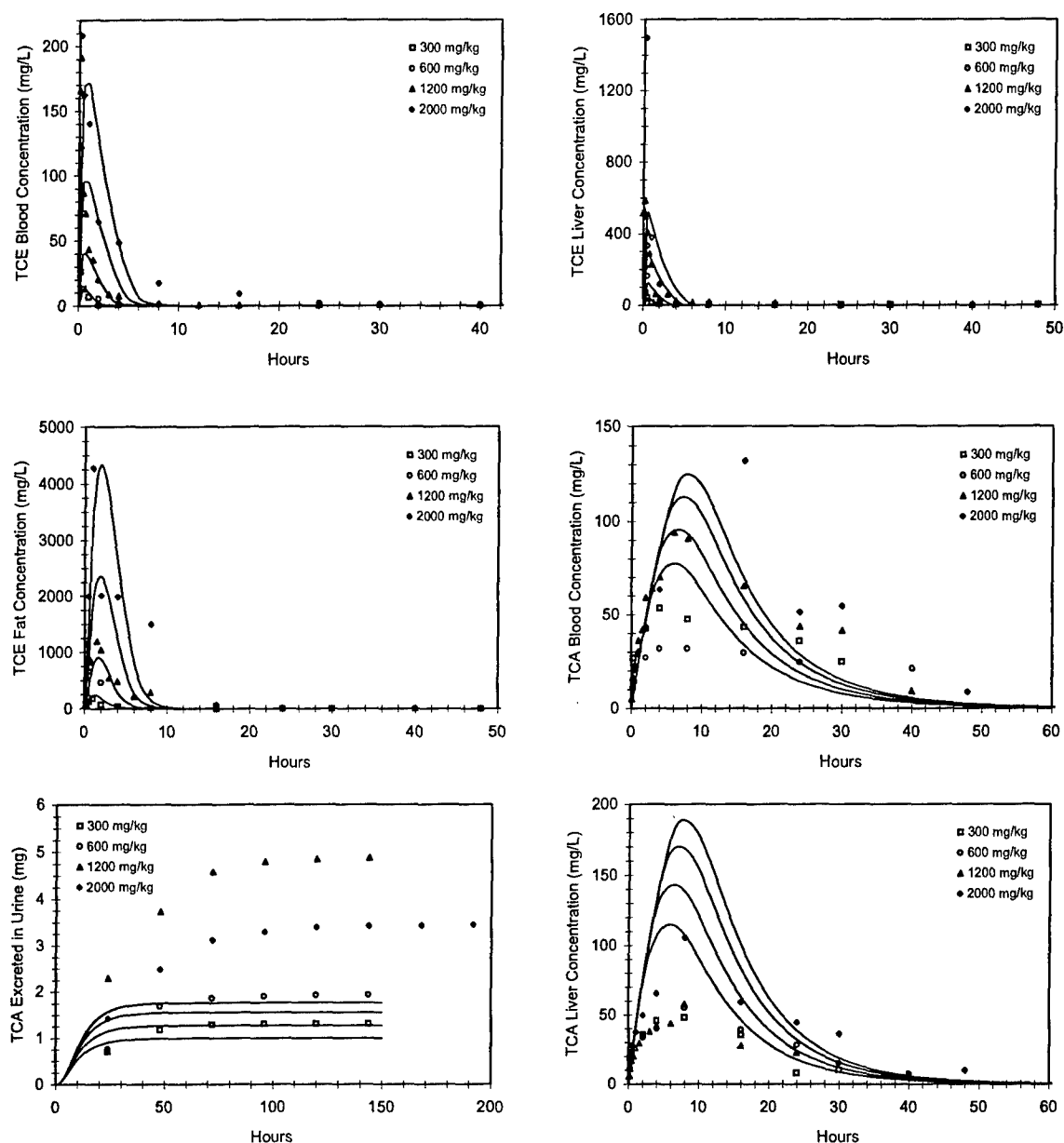


Figure 9. Comparison of predicted and experimental concentrations of TCE in blood, liver, and fat, and TCA in blood, liver, and urine in B6C3F1 mice exposed to 300, 600, 1200, and 2000 mg/kg TCE by gavage in corn oil. Kinetic data are taken from Abbas *et al.*⁸



The parameterization of the model in the rat followed a similar approach to that just presented for the mouse. Figure 10 shows the simulation of the gas uptake data for male rats;²⁸ the resulting estimate of V_{maxC} was $11.2 \text{ mg/hr/kg}^{3/4}$. Estimates of the other kinetic parameters were obtained using data on concentrations of TCE and its metabolites in male rats following oral gavage in corn oil²⁷ and water²⁹ vehicles. The resulting fits of the model to these data sets are shown in Figures 11 and 12. In fitting these two data sets, it was only necessary to use different values for two of the model kinetic parameters. The simulation of the corn oil gavage

data was obtained with $\text{FracTCE}=0.04$ and $\text{VMaxGlucC}=100$, while the aqueous vehicle data was best simulated with $\text{FracTCE}=0.02$ and $\text{VmaxGlucC}=20$. The rest of the model parameters were as shown in Table 1 for both simulations.

Figure 13 shows the predictions of the model for inhalation exposures to TCE in male and female rats.⁵ All of the model parameters in this case were those shown in Table 1 except that for the females the value of VmaxC was increased to $20 \text{ mg/hr/kg}^{3/4}$ and the alveolar ventilation rate was decreased to $15 \text{ L/hr/kg}^{3/4}$.

Figure 10. Comparison of predicted and experimental chamber concentrations of TCE in male F344 rats exposed to TCE in a closed, recirculating chamber. Kinetic data are taken from Andersen *et al.*²⁸

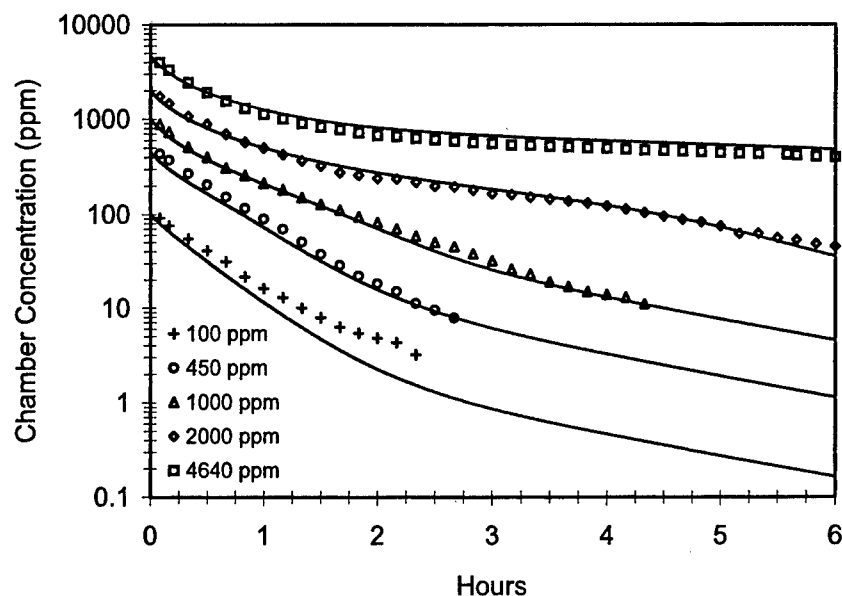


Figure 11. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following corn oil gavage with 1000 mg/kg TCE in rats. Kinetic data are taken from Prout *et al.*²⁷

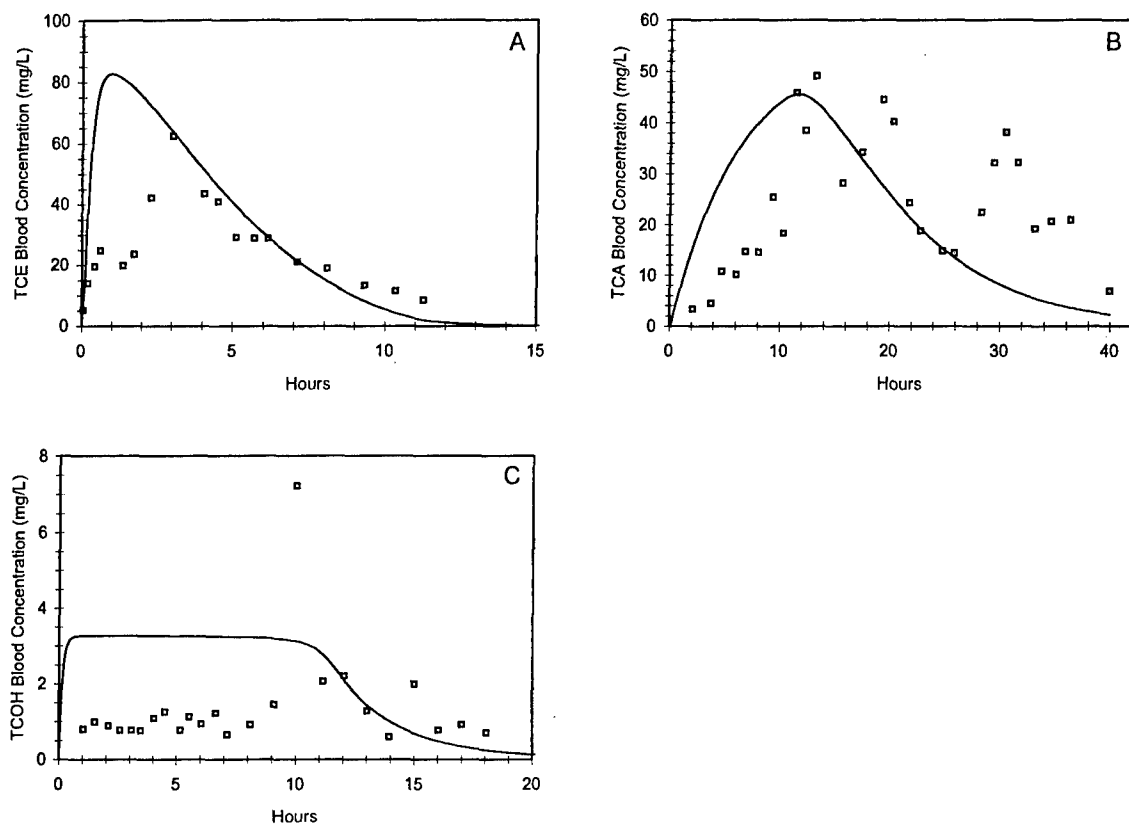


Figure 12. Mean observed and predicted blood concentrations of (A) TCE, (B) TCA and (C) free TCOH following oral doses of 200, 600, and 3000 mg/kg TCE in F-344 rats. Kinetic data are taken from Larson and Bull.²⁹

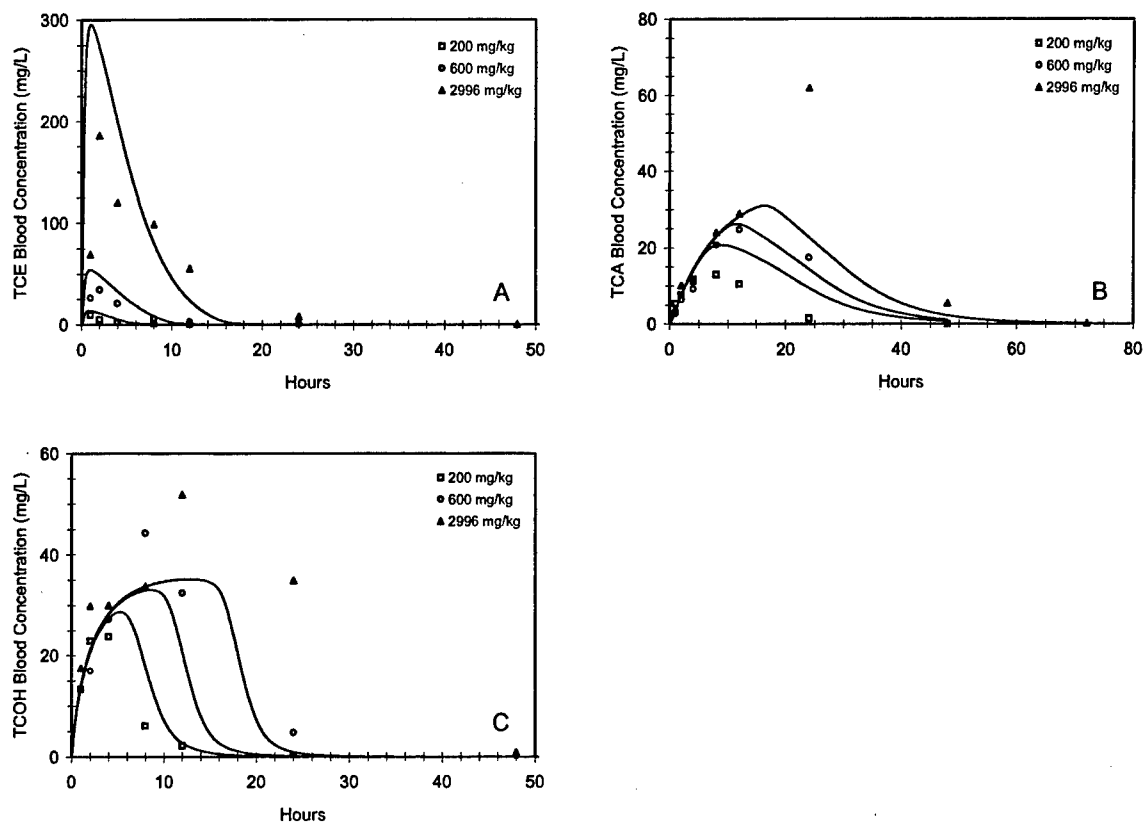
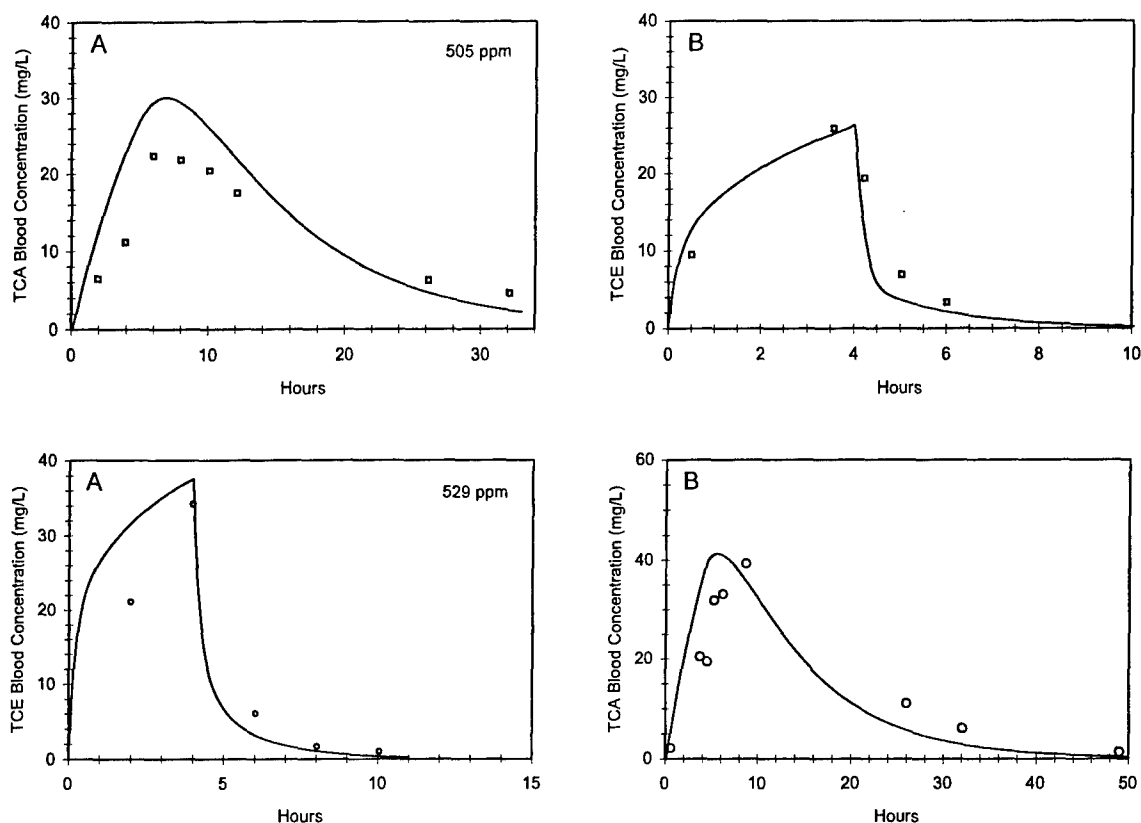


Figure 13. Comparison of predicted and experimental concentrations of TCE in blood and TCA in plasma in F-344 rats exposed to TCE by inhalation. The figures show (A) TCE blood concentrations in male rats exposed for 4 hr to 529 ppm TCE vapors and TCA plasma concentrations in male rats exposed for 4 hr to 505 ppm TCE vapors and (B) TCE blood and TCA plasma concentrations in female rats exposed for 4 hr to 600 ppm TCE vapors. Kinetic data are taken from Fisher *et al.*⁵



Parameterizing the human model is complicated by the fact that inter-individual variation tends to be greater in humans than in in-bred experimental animals. In particular, three of the parameters in the model were found to vary significantly across studies: V_{maxC} , the capacity of the oxidative metabolism of TCE, $V_{maxTCOH}$, the capacity of the oxidative metabolism of TCOH, and $k_{UrnTCAC}$, the rate constant for excretion of TCA. The greatest variation was found for V_{maxC} ; values needed to simulate different experimental subjects ranged from 1.5 to 18 mg/hr/kg^{3/4}. This 10-fold variation is consistent with other observations of the variability in CYP2E1 metabolism in humans. The variation in the value of $k_{UrnTCAC}$ was similar, ranging from 0.05 to 0.6 kg^{1/4}/hr, while that for $V_{maxTCOH}$ was not as great, with values ranging from 12 to 40 mg/hr/kg^{3/4}. The results of fitting several published human studies^{9, 19, 30-32} are shown in Figures 14 – 19. The caption to each figure shows the values of the three parameters discussed above that were used to obtain the simulation displayed.

Figure 14. Mean observed and predicted kinetics of TCE and its metabolites during and after a single 6-hr exposure of human subjects to 100 ppm TCE. The simulation was obtained with $V_{maxC}=12$, $V_{maxTCOH}=25$, $k_{urTCAC}=0.15$, and $V_{BodC}=0.12$. Kinetic data are taken from Muller *et al.*:^{19, 30} (A) TCE blood concentrations (mg/L); (B) TCA plasma concentrations (mg/L); (C) cumulative urinary TCA excretion (mg); (D) total TCOH plasma concentrations (mg/L); (E) cumulative urinary TCOH excretion (mg).

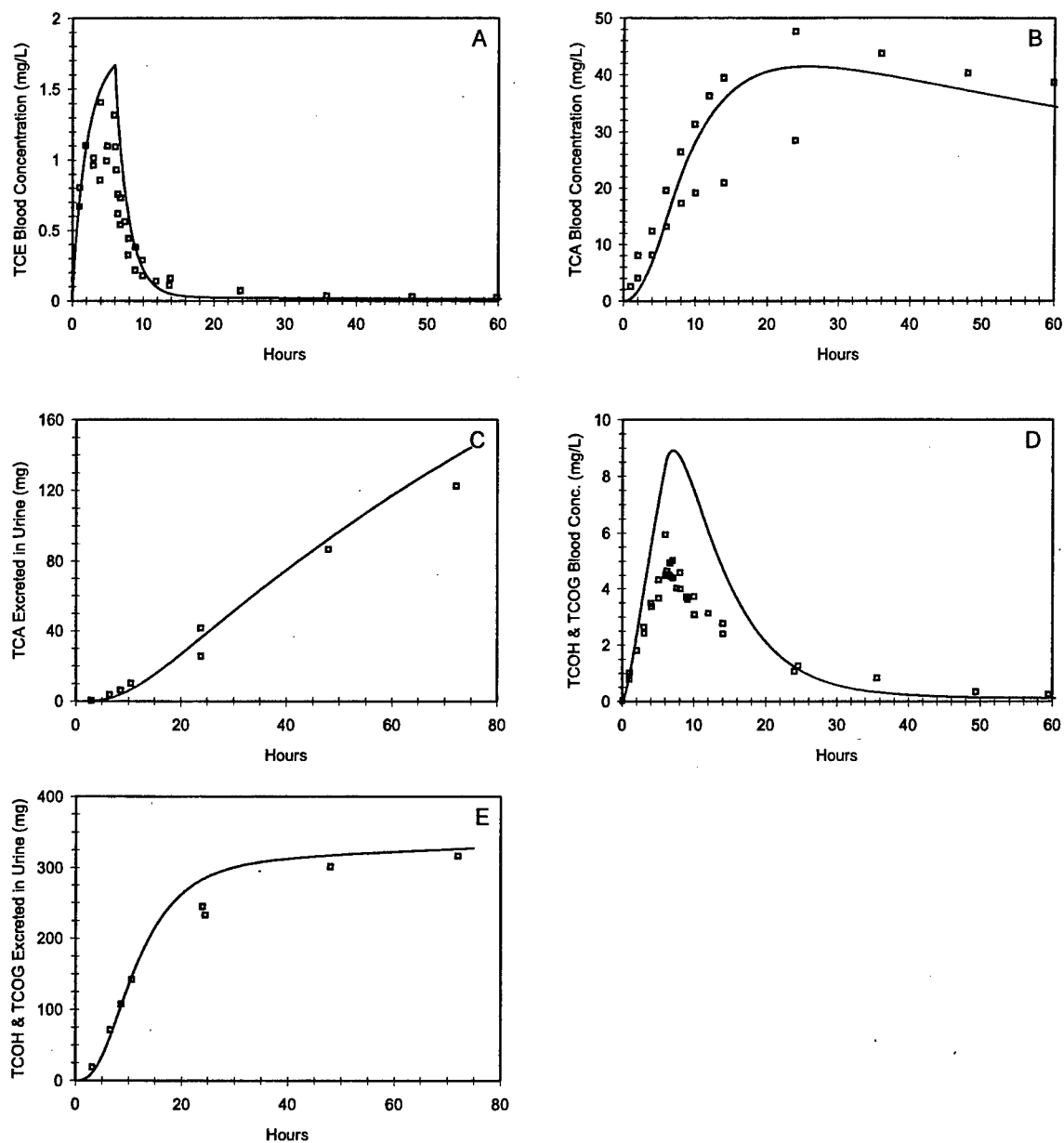


Figure 15. Mean observed and predicted kinetics of TCE and its metabolites during and after 4-hr exposures of human subjects to 70 ppm TCE for 5 days. The simulation was obtained with $V_{maxC}=18$, $V_{maxTCOHC}=12$, $k_{UrTCAC}=0.15$, and $V_{BodC}=0.12$. Kinetic data are taken from Monster *et al.*:³¹ (A) TCE venous blood concentrations (mg/L); (B) TCA plasma concentrations (mg/L); (C) cumulative urinary TCA excretion (mg); (D) cumulative urinary TCOH excretion (mg).

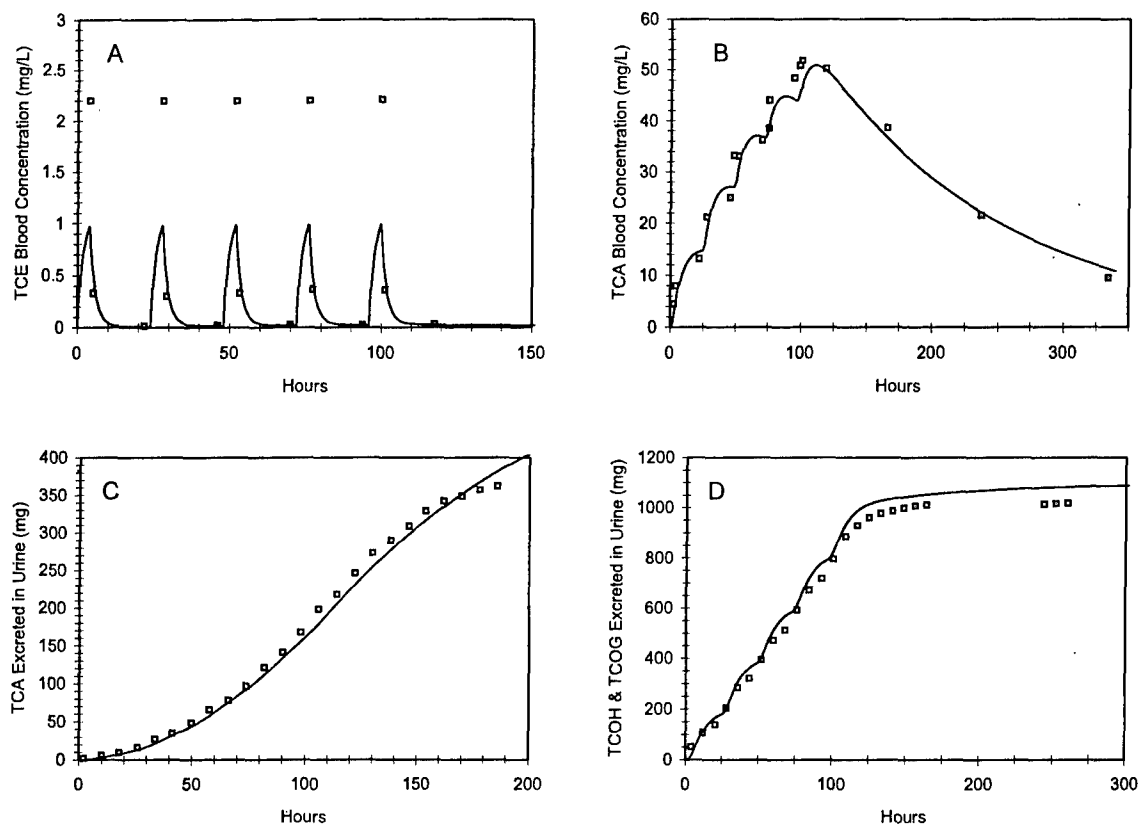


Figure 16. Mean observed and predicted kinetics of TCE and its metabolites during and following interrupted, 7-hr exposures of human subjects to 200 ppm TCE (3 hr of exposure, a one-half hour break, then 4 hr of exposure) for 5 days. The simulation was obtained with $V_{maxC}=5$, $V_{maxTCOHC}=25$, $k_{UrnTCAC}=0.2$, and $V_{BodC}=0.2$. Kinetic data are taken from Stewart *et al.*:³² (A) TCE concentration in exhaled breath (ppm); (B) cumulative urinary TCA excretion (mg); (C) cumulative urinary TCOH excretion (mg).

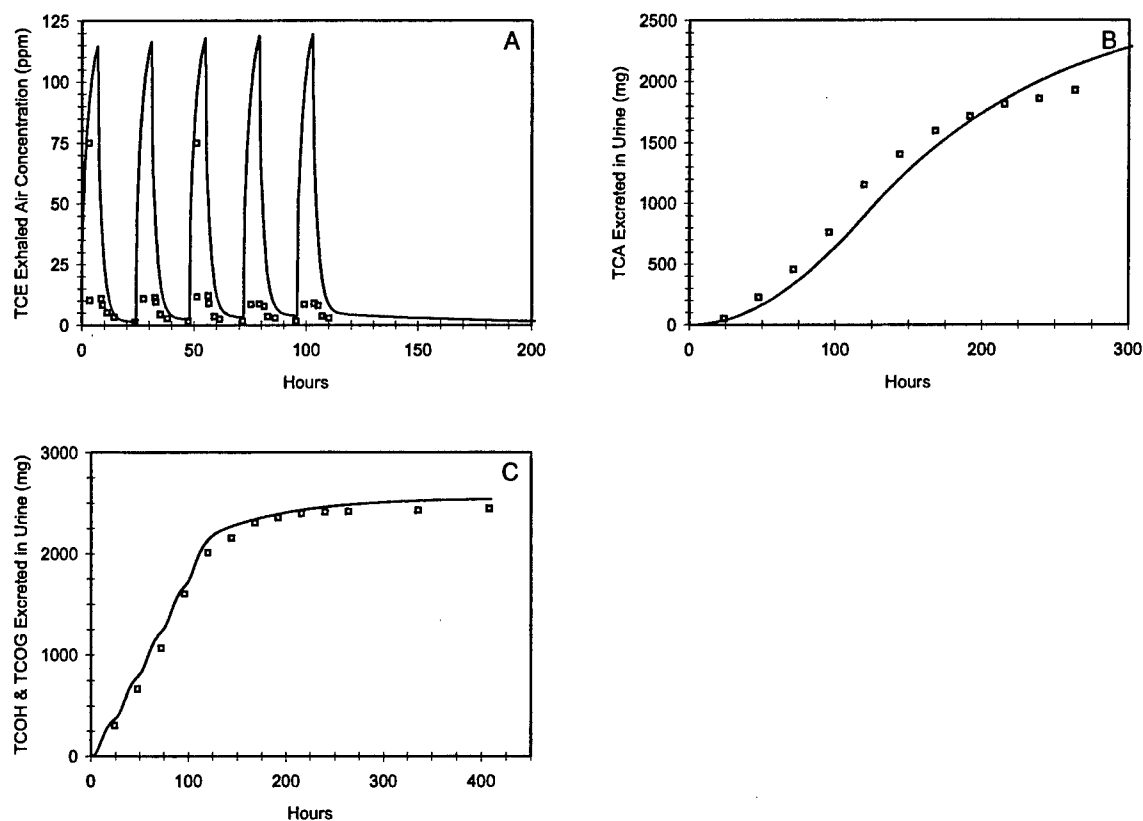


Figure 17. Mean observed and predicted kinetics of TCE and its metabolites during and after 6-hr exposures of human subjects to 50 ppm TCE for 5 days. The simulation was obtained with $V_{maxC}=8$, $V_{maxTCOHC}=30$, $k_{UrTCAC}=0.2$, and $V_{BodC}=0.2$. Kinetic data are taken from Muller *et al.*³⁰ (A) TCA plasma concentrations (mg/L); (B) cumulative urinary TCA excretion (mg); (C) total TCOH plasma concentrations (mg/L); (D) cumulative urinary TCOH excretion (mg).

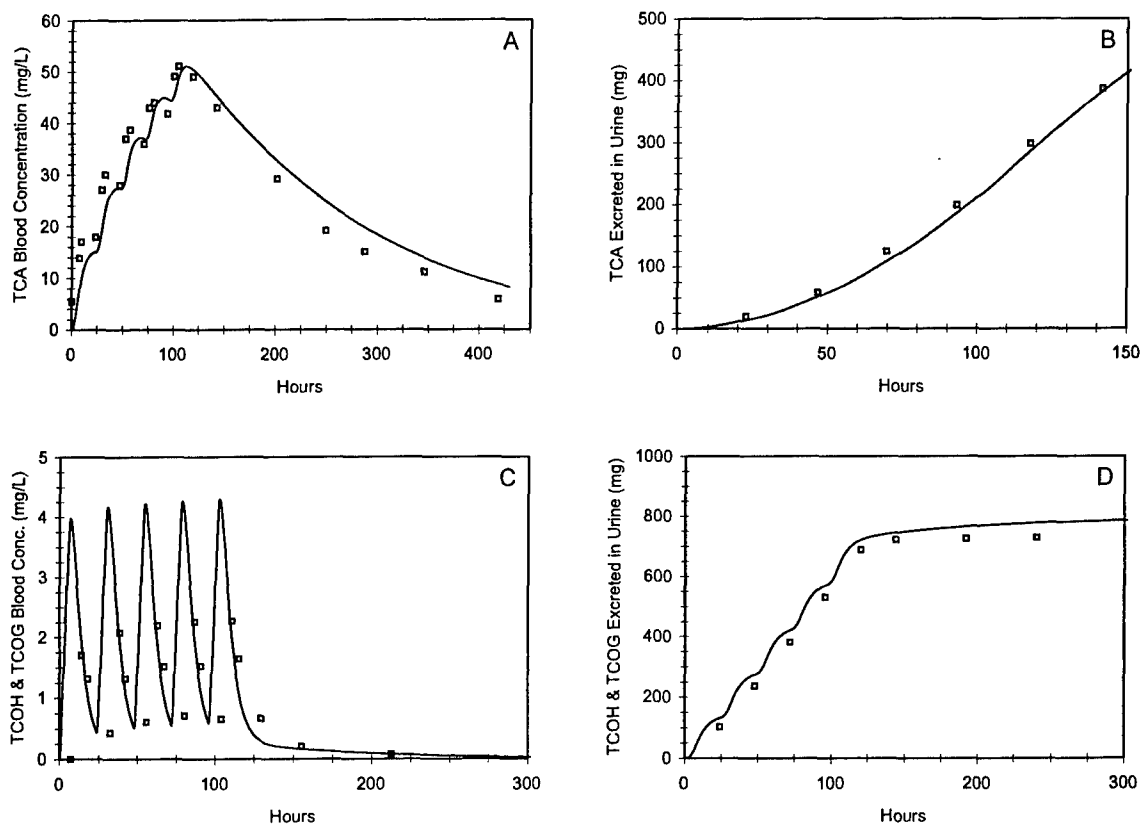


Figure 18. Observed and predicted kinetics of TCE and its metabolites TCA, TCOH, and DCA, as well as urinary excretion of TCA and TCOH, during and after a 4-hr exposure of a male human subject to 100 ppm TCE. The simulation was obtained with $V_{maxC}=3$, $V_{maxTCOHC}=25$, $k_{UrTCAC}=0.2$, and $V_{BodC}=0.2$. Kinetic data are taken from Fisher *et al.*:⁹

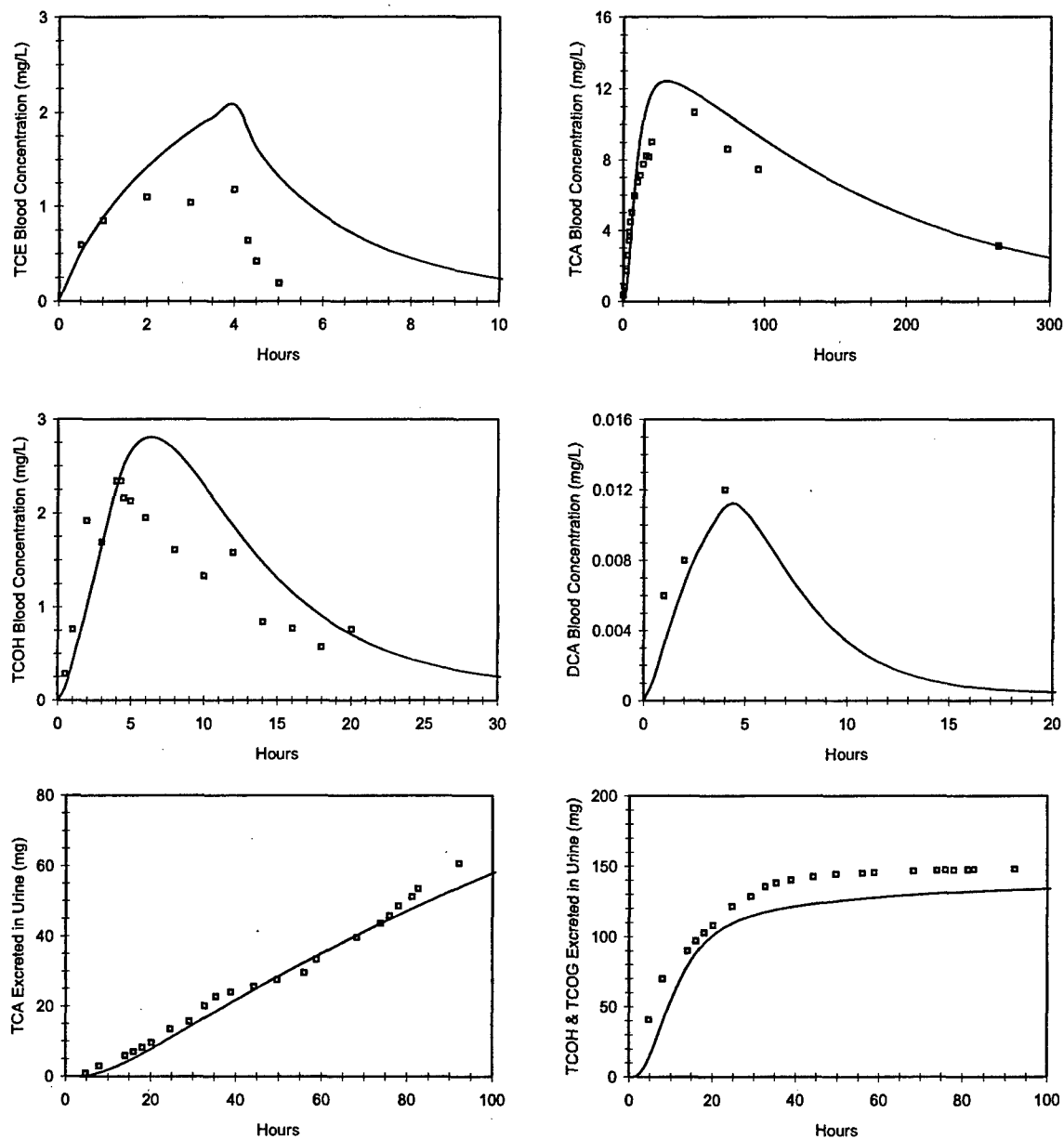
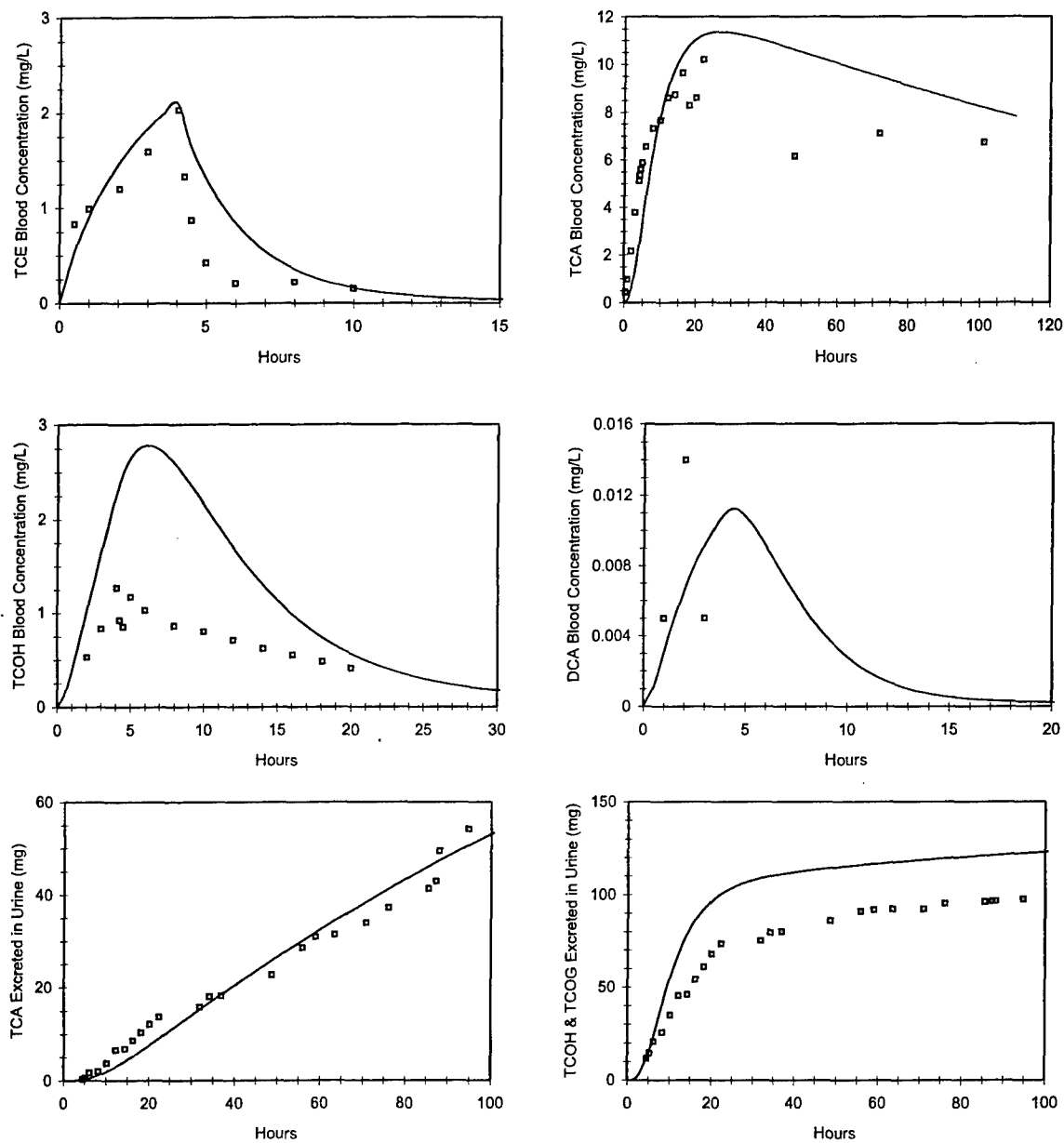


Figure 19. Observed and predicted kinetics of TCE and its metabolites TCA, TCOH, and DCA, as well as urinary excretion of TCA and TCOH, during and after a 4-hr exposure of a female human subject to 100 ppm TCE. The simulation was obtained with $V_{maxC}=3$, $V_{maxTCOH}=35$, $k_{UrTCAC}=0.2$, and $V_{BodC}=0.2$. Kinetic data are taken from Fisher *et al.*:⁹



PBPK Model Validation

The validity of the model for its intended purpose must be evaluated on the basis of the comprehensiveness of its predictive power and the reasonableness of the parameters used to fit the various data sets. The approach for obtaining an initial parameterization of the PBPK model for TCE has already been discussed. This preliminary version of the model is able to reproduce data on TCE and TCA kinetics in the mouse, rat, and human, for both inhalation exposure and oral gavage. In addition, the model is able to describe TCOH kinetics in mice, rats, and humans. No suitable data were available for validation of the model predictions for CHL in the lung, DCVC in the kidney, or DCA in the liver.

It was not possible to obtain complete agreement between the model and each of the studies investigated using a single set of parameters in each species. This failure undoubtedly results from a combination of variation across individuals and animal strains, experimental error, and model error. Nevertheless, given the general agreement of the model with a variety of data on TCE, TCA, and TCOH concentration time-courses in both rodents and humans, there can be relatively high confidence in dose metrics based on the predictions of the PBPK model for these chemicals. Unfortunately, as mentioned earlier, there is a lack of similar data to provide confidence in the model predictions for DCVC in the kidney, CHL in the lung, and DCA in the liver.

DISCUSSION

The harmonized model works reasonably well, considering the variety of data sets it is required to simulate, but it's still in a preliminary state. Final estimates of parameters should be obtained using Markov chain Monte Carlo analysis, similar to previous studies.^{3,4} There are a number of issues associated with the development of a comprehensive PBPK model for TCE. Several issues that are particularly relevant to the application of a PBPK model in a risk assessment for TCE are discussed below.

It no longer appears feasible to model the kidney pathway. Recent data (Larry Lash, personal communication) suggest that direct excretion of DCVC into the urine and metabolism of DCVC in the kidney by flavin mono-oxygenases (FMO) are significant factors in the human. Moreover, metabolism by FMO produces a reactive metabolite different from the thioketene produced by beta-lyase, so it is not possible to assume that the simple description in the current model would be conservative (protective of human health).

Experimental data on CHL in the mouse⁸ indicate that local generation of CHL is the dominant source of the lung concentrations of CHL observed in those studies. In fact, the concentrations of chloral in the lung following oral dosing with TCE were much greater than the concentrations in the blood. Moreover, there is no data with which to parameterize a description of CHL production in the human liver, although local metabolism would be expected to dominate at low environmental exposures. For these reasons, the model does not include CHL in the description of the liver compartment in any species. Nevertheless, the use of the local-metabolism based lung CHL description may still be questionable unless it is possible to resolve uncertainties as to the cross-species scaling of production (i.e., assumptions regarding the relationship between in vitro P450 activity and regional lung metabolic capacity and the relative affinity between the liver and the lung) and clearance (i.e., the question of ADH or related activities in the lung across species).¹

Given the problems with the currently available data,³³⁻³⁵ it is not possible to model the production of DCA from TCE with any confidence. As shown in Figures 6, 18, and 19, an attempt was made to model DCA with a simple one-compartment model, using the empirical volumes of distribution and half-lives.³⁶⁻⁴¹ The production of DCA, which was assumed to represent a constant fraction of the rate of oxidative metabolism, was then estimated from fitting of the limited data in mice and humans on DCA concentrations following exposure to TCE.^{9, 20} However, the resulting predicted time-course for DCA after TCE dosing in the mouse was not consistent with the available data.^{8, 20} Using the DCA half-life measured in naïve animals (0.05 hours),⁴¹ the model predicted that DCA would be cleared much more rapidly than observed in the studies. Better results were obtained when a half-life of 0.3 hours, representative of an animal in which DCA metabolism had been inhibited,⁴¹ was used (Figure 6). However, for the more recent data,⁸ which was collected in such a way as to minimize *ex vivo* conversion of TCA to DCA, the predictions of the model still greatly over-estimated the clearance of DCA as compared to the observed behavior. In fact, the concentrations of DCA measured in this study paralleled those of TCA, suggesting that DCA was being generated from TCA *ex vivo* (rather than from TCE *in vivo*) at a level of about 2%.

Conclusions

The PBPK model described in this paper provides reasonably accurate estimates of dose metrics based on TCE and its major metabolites, TCA and TCOH, in both experimental animals and humans. Tissue dose metrics calculated with the model should therefore be useful in risk assessments for endpoints where the mode of action involves tissue exposure to these chemicals. Other target tissue dose metrics which can be calculated with the model, including CHL in the lung and DCVC in the kidney, are highly uncertain due to a lack of adequate pharmacokinetic data across species. There is currently no adequate data available with which to confidently parameterize a description of DCA. Additional studies could greatly reduce the uncertainty associated with these dose metrics and make their use in risk assessments more viable.

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APPENDIX A. MODEL SOURCE CODE

This code was written as a csl file for acslXtreme, version 1.3.19. The code-based and the graphic versions of the model resulted in identical predictions.

```
PROGRAM TCE_BD.CSL -- Harmonized TCE Cancer Risk Assessment Model

! Model code to correspond to the block diagram version of the model

INITIAL

  LOGICAL CC ! Flag set to .TRUE. for closed chamber runs

  CONSTANT      BW = 70.0          ! Body Wt (kg)

! Flow Rates (L/hr/kg**0.75)
  CONSTANT      QCC = 13.0         ! Cardiac output
  CONSTANT      QPC = 18.0         ! Pulmonary ventilation

! Fractional Blood Flows to Tissues (fraction of cardiac output)
  CONSTANT      QFatC = 0.052      ! Fat
  CONSTANT      QGutC = 0.181      ! Gut
  CONSTANT      QLivC = 0.046      ! Liver
  CONSTANT      QRapC = 0.699      ! Rapidly perfused tissues
  CONSTANT      QSlwC = 0.301      ! Slowly perfused tissues
  CONSTANT      QTBC = 0.025       ! Tracheo-bronchial

! Fractional Tissue Volumes (fraction of BW)
  CONSTANT      VBldC = 0.079      ! Blood
  CONSTANT      VBodC = 0.2         ! Total body
  CONSTANT      VFatBldC = 0.02     ! Fraction of fat that is blood
  CONSTANT      VFatC = 0.214      ! Fat
  CONSTANT      VGutC = 0.017      ! Gut
  CONSTANT      VKidC = 0.004      ! Kidney
  CONSTANT      VLivC = 0.026      ! Liver
  CONSTANT      VRapC = 0.192      ! Rapidly perfused tissues
  CONSTANT      VSlwC = 0.651      ! Slowly perfused tissues
  CONSTANT      VTBC = 0.0008      ! Tracheo-bronchial

! Fractional Volumes of Distribution (fraction of BW)
  CONSTANT      VDDCAC = 0.26      ! DCA
  CONSTANT      VDTCOHC = 0.65     ! TCOH

! Partition Coefficients for TCE
  CONSTANT      PB = 9.2           ! Blood/air
  CONSTANT      PFat = 73.0        ! Fat/blood
  CONSTANT      PGut = 6.8         ! Gut/blood
  CONSTANT      PLiv = 6.8         ! Liver/blood
  CONSTANT      PRap = 6.8         ! Rapidly perfused/blood
  CONSTANT      PSlw = 2.3         ! Slowly perfused/blood
  CONSTANT      PTB = 6.8          ! TB/blood

! Permeation Coefficients for Fat
  CONSTANT      PAFatC1 = 10.0     ! Takeup
  CONSTANT      PAFatC2 = 10.0     ! Release

! Partition Coefficients for TCA
```

```

CONSTANT      PBodTCA = 1.9          ! Body/freeplasma
CONSTANT      PLivTCA = 2.5          ! Liver/freeplasma

! Molecular Weights
CONSTANT      MWTCE = 131.5          ! TCE
CONSTANT      MWDCA = 129.0          ! DCA
CONSTANT      MWDCVC = 216.1         ! DCVC
CONSTANT      MWTCA = 163.5          ! TCA
CONSTANT      MWChlor = 147.5         ! Chloral
CONSTANT      MWTCOH = 149.5         ! TCOH
CONSTANT      MWTCOHgluc = 325.53    ! TCOH-Gluc
CONSTANT      MWNADCVC = 258.8       ! N Acetyl DCVC

! TCE Metabolism Constants
CONSTANT      VMaxC = 12.0            ! Oxidative capacity (mg/hr)
CONSTANT      KM = 1.5                ! Oxidative affinity (mg/L)
CONSTANT      kDCVCC = 0.015          ! Production of DCVC(/hr)
CONSTANT      FracDCA = 0.004         ! Fractional split of TCE to DCA
CONSTANT      FracTCE = 0.08         ! Fractional split of TCE to TCA

! TCE Metabolism Constants for Chloral Kinetics in Clara Cells in Lung
CONSTANT      VMaxClaraC = 0.0045     ! VMax (mouse=3, rat=3, human=0.0045)
CONSTANT      KMClara = 1.5           ! KM
CONSTANT      VMaxClearC = 250.0       ! VMax for chloral clearance
CONSTANT      KMClear = 250.0         ! KM for chloral clearance

! Binding Parameters for TCA
CONSTANT      kDissoc = 174.6          ! Protein/TCA dissociation constant (umole/L)
CONSTANT      NumSites = 2.97         ! Number of binding sites per class protein
CONSTANT      ProtConc = 239.0        ! Protein concentration (umoles/L)

! TCOH Metabolism Constants
CONSTANT      VMaxTCOHC = 25.0         ! VMax for oxidation to TCA
CONSTANT      KMTCOH = 250.0          ! KM for oxidation to TCA
CONSTANT      VMaxGlucC = 5.0          ! VMax for glucuronidation to TCOG
CONSTANT      KMGluc = 25.0           ! KM for glucuronidation to TCOG

! DCVC Kinetics in Kidney (kg**0.25/hr)
CONSTANT      kNATC = 19.0            ! Clearance of DCVC by NAT
CONSTANT      kKidCytoC = 37.0        ! Kidney cytotoxicity from DCVC

! Oral Uptake Constants for TCE (/hr)
CONSTANT      kAS = 0.0               ! Stomach to gut
CONSTANT      kTSD = 10.0             ! Stomach to duodenum
CONSTANT      kAD = 1.0               ! Duodenum to liver
CONSTANT      kTD = 0.0               ! Fecal excretion

! Rate Constants (kg**0.25/hr)
CONSTANT      kBileC = 1.0            ! Biliary excretion of TCOG
CONSTANT      kEHRC = 0.0             ! Enterohepatic recirculation of TCOH
CONSTANT      kClearDCAC = 1.9        ! Clearance of DCA
CONSTANT      kUrnTCAC = 0.2          ! Urinary excretion of TCA
CONSTANT      kUrnTCOGC = 3.0         ! Urinary excretion of TCOG

! Conversion Factor
CONSTANT      FracPlas = 0.58         ! Fraction of blood that is plasma
CONSTANT      TCAPlas = 0.76          ! To convert TCA in plasma to TCA in blood

! Dosing Parameters
CONSTANT      Conc = 0.0              ! Inhalation exposure conc. (ppm)
CONSTANT      IVDose = 0.0            ! IV dose (mg/kg/day)
CONSTANT      TChng = 6.0             ! End of inhalation or IV exposure (hrs)
CONSTANT      PDose = 0.0             ! Oral dose (mg/kg/day)

```

```

CONSTANT      Days = 1.0           ! Days of exposure each week
CONSTANT      TMax = 24.0          ! Maximum length of multiple exposures
CONSTANT      Drink = 0.0          ! Drinking water dose (mg/kg/day)

! Closed Chamber Parameters
CONSTANT      CC = .FALSE.         ! Default to open chamber
CONSTANT      NRats = 0.0          ! Number of animals in the chamber
CONSTANT      kLossC = 0.0         ! Chamber leakage (/hr)
CONSTANT      VChC = 1.0           ! Volume of the chamber without animals

! Simulation Control Parameters
CONSTANT      TStp = 24.0           ! Time to stop simulation (hrs)
CINTERVAL     CINT = 0.01

! Scaled Flow Rates (L/hr)
      QC = QCC * (BW**0.75)
      QP = QPC * (BW**0.75)

! Blood Flows to Tissues (L/hr)
      QFat = QFatC * QC
      QGut = QGutC * QC
      QLiv = QLivC * QC
      QGutLiv = QGut + QLiv
      QRap = (QRapC - QGutC - QLivC - QTBC) * QC
      QSlw = (QSlwC - QFatC) * QC
      QTB = QTBC * QC

! Plasma Flows to Tissues (L/hr)
      QCPlas = FracPlas * QC
      QBodPlas = FracPlas * (QC - (QLivC * QC))
      QLivPlas = FracPlas * (QLivC * QC)

! Tissue Volumes (L)
! (Kidney not included in parent model so not in VRap equation)
      VBld = VBldC * BW
      VBod = (VBodC - VBldC - VLivC) * BW
      VFatBld = (VFatBldC * VFatC) * BW
      VFat = (VFatC * (1.0 - VFatBldC)) * BW
      VGut = VGutC * BW
      VKid = VKidC * BW
      VLiv = VLivC * BW
      VPlas = FracPlas * VBld
      VRap = (VRapC - VGutC - VLivC - VTBC) * BW
      VSlw = (VSlwC - VFatC) * BW
      VTB = VTBC * BW

! Volumes of Distribution
      VDDCA = VDDCAC * BW
      VDTCOH = VDTCOHC * BW

! Permeation Coefficients for Fat
      PAFat1 = PAFatC1 * QFat
      PAFat2 = PAFatC2 * QFat

! Stoichiometry
      StochChlortCE = MWChlor / MWTCE
      StochTCATCE = MWTCA / MWTCE
      StochTCATCOH = MWTCA / MWTCOH
      StochTCOHTCE = MWTCOH / MWTCE
      StochGlucTCOH = MWTCOHGluc / MWTCOH
      StochTCOHGluc = MWTCOH / MWTCOHGluc
      StochTCEGluc = MWTCE / MWTCOHGluc

```

```

StochDCVCTCE = MWDCVC / MWTCE
  StochN = MNADCVC / MWDCVC
  StochDCATCE = MWDCA / MWTCE

! TCE Metabolism Constants
  VMax = VMaxC * (BW**0.75)
  kDCVC = kDCVCC / (BW**0.25)

! TCE Metabolism Constants for Chloral Kinetics in Lung (mg/hr)
  VMaxClara = VMaxClaraC * (BW**0.75)
  VMaxClear = VMaxClearC * (BW**0.75)

! Binding Parameters for TCA
  TotConc = NumSites * ProtConc

! TCOH Metabolism Constants (mg/hr)
  VMaxTCOH = VMaxTCOHC * (BW**0.75)
  VMaxGluc = VMaxGlucC * (BW**0.75)

! DCVC Kinetics in Kidney (/hr)
  kNAT = kNATC / (BW**0.25)
  kKidCyto = kKidCytoC / (BW**0.25)

! Rate Constants (/hr)
  kBile = kBileC / (BW**0.25)
  kEHR = kEHRC / (BW**0.25)
  kUrnTCA = kUrnTCAC / (BW**0.25)
  kUrnTCOG = kUrnTCOGC / (BW**0.25)
  kClearDCA = kClearDCAC / (BW**0.25)

! Initialize doses
  Dose = PDose * BW
  kDrink = (Drink * BW) / 24.0

! Exposure definition
  IF (CC) THEN
    Rats = NRats                ! Closed chamber simulation
    kLoss = kLossC
    VCh = VChC - (Rats * BW)    ! Calculate net chamber volume
  ELSEIF (.NOT.CC) THEN
    Rats = 0.0                  ! Open chamber simulation
    kLoss = 0.0                 ! Turn off chamber losses so conc. is constant
    VCh = 1.0                   ! So that VCh drops out of equations
  ENDIF

! Initialize starting value
  kIV = 0.0
  ConcOn = 1.0
  ACh0 = (Conc * VCh * MWTCE) / 24450.0    ! Initial amount in chamber
  CInh = 0.0
  Total = 0.0
  Day = 0.5
  CVTB = 0.0
  PAUCCBld = 0.0
  PRiskP = 0.0
  FMetInh = 0.0
  FMetINet = 0.0
  FMetOral = 0.0
  PAMetLivlBW = 0.0
  PRiskKid = 0.0
END

```

DYNAMIC

ALGORITHM IALG = 2

DISCRETE Calc

! Calculate weekly dose surrogate
INTERVAL CalcInt = 168.0

AUCCBldDaily = (AUCCBld - PAUCCBld) / 7.0
Cloral = (RiskP - PRiskP) / 7.0
AMetLivlBWDaily = (AMetLivlBW - PAMetLivlBW) / 7.0
RiskKidDaily = (RiskKid - PRiskKid) / 7.0

PAUCCBld = AUCCBld
PRiskP = RiskP
PAMetLivlBW = AMetLivlBW
PRiskKid = RiskKid

END

DISCRETE DoseOn

INTERVAL DoseInt = 24.0 ! Dosing interval (hrs)
SCHEDULE DoseOff .AT. T + TChng

IF ((T .LT. TMax) .AND. (Day .LE. Days)) THEN
kIV = (IVDose * BW) / TChng
ConcOn = 1.0
Total = Total + Dose

ENDIF

Day = Day + 1.0
IF (Day.GT.7.0) Day = 0.5

END

DISCRETE DoseOff

kIV = 0.0
ConcOn = 0.0

END

DERIVATIVE

!*****
!*** TCE Model ***
!*****

! Amount of TCE in inhaled air

RACH = (Rats * ((QP * CALv) - (QP * CInh))) - (kLoss * ACh)
ACh = INTEG(RACH, ACh0)
CInh = (ACh / VCh) * ConcOn
CInhPPM = (CInh * 24450.0) / MWTCE

! Concentration in arterial blood (mg/L)

CART = ((QC * CVen) + (QP * CInh)) / (QC + (QP / PB))
AUCCBld = INTEG(CART, 0.0)

! Concentration in alveolar air (mg/L)

CALv = CART / PB
CALvPPM = CALv * (24450.0 / MWTCE)

```

! Amount exhaled (mg)
  RAExh = QP * CALv
  AExh = INTEG(RAExh, 0.0)

! Concentration in mixed exhaled air (mg/L)
  CMixExh = (0.7 * CALv) + (0.3 * CInh)
  CMixExhPPM = (CMixExh * 24450.0) / MWTCE

! Amount of TCE in the tracheo-bronchial region (mg)
  ResidCVTB = (QTB * (CART - CVTB)) - RAMetLng
  CVTB = IMPLC(ResidCVTB, 0.0)
  ATB = CTB * VTB
  CTB = CVTB * PTB

! Amount metabolized in the tracheo-bronchial region (mg)
  RAMetLng = ((VMaxClara * CVTB) / (KMClara + CVTB))
  AMetLng = INTEG(RAMetLng, 0.0)

! Amount of Chloral in Clara cells (mg)
  ChlFac = (StochChlorTCE / VMaxClear) * RAMetLng
  CChl = (KMClear * ChlFac) / (1.0 - ChlFac)
  RiskP = INTEG(CChl, 0.0)

! Amount of TCE in rapidly perfused tissues (mg)
  RARap = QRap * (CART - CVRap)
  ARap = INTEG(RARap, 0.0)
  CRap = ARap / VRap
  CVRap = CRap / PRap

! Amount of TCE in slowly perfused tissues
  RASlw = QSlw * (CART - CVSlw)
  ASlw = INTEG(RASlw, 0.0)
  CSlw = ASlw / VSlw
  CVSlw = CSlw / PSlw

! Amount of TCE in fat blood (mg)
  RAFatBld = (QFat * (CART - CVFat)) + (PAFat2 * (CFat / PFat)) &
    & - (PAFat1 * CVFat)
  AFatBld = INTEG(RAFatBld, 0.0)
  CVFat = AFatBld / VFatBld

! Amount of TCE in fat tissue (mg)
  RAFat = (PAFat1 * CVFat) - (PAFat2 * (CFat / PFat))
  AFat = INTEG(RAFat, 0.0)
  CFat = AFat / VFat

! Total amount in fat blood and fat tissue (mg)
  ATotFat = AFatBld + AFat

! Amount of TCE in stomach -- for oral dosing only (mg)
  RStom = (kAS * AStom) + (kTSD * AStom)
  AStom = Total - INTEG(RStom, 0.0)
  TotAbsStom = Total - AStom

! Amount of TCE in duodenum -- for oral dosing only (mg)
  RADuod = (kTSD * AStom) - (kAD * ADuod) - (kTD * ADuod)
  ADuod = INTEG(RADuod, 0.0)

```

```

! Amount of TCE excreted in feces (mg)
  RAExc = kTD * ADuod
  AExc = INTEG(RAExc, 0.0)

! Amount of TCE absorbed (mg)
  RAO = (kAS * AStom) + (kAD * ADuod)
  AO = INTEG(RAO, 0.0)

! Amount of TCE in gut compartment (mg)
  RAGut = (QGut * (CArt - CVGut)) + kDrink + RAO
  AGut = INTEG(RAGut, 0.0)
  CGut = AGut / VGut
  CVGut = CGut / PGut

! Amount of TCE in liver (mg)
  RALiv = (QLiv * (CArt - CVLiv)) + (QGut * (CVGut - CVLiv)) - RAMetLiv1 &
    & - RAMetLiv2
  ALiv = INTEG(RALiv, 0.0)
  CLiv = ALiv / VLiv
  CVLiv = CLiv / PLiv
  AUCCLiv = INTEG(CLiv, 0.0)

! Total amount in gut and liver (mg)
  ATotGutLiv = AGut + ALiv

! Amount of TCE metabolized to TCA, DCA and TCOH in liver (mg)
  RAMetLiv1 = (VMax * CVLiv) / (KM + CVLiv)
  AMetLiv1 = INTEG(RAMetLiv1, 0.0)
  AMetLiv1BW = AMetLiv1 / BW

! Amount of TCE metabolized to DCVC in liver (mg)
  RAMetLiv2 = kDCVC * CVLiv * VLiv
  AMetLiv2 = INTEG(RAMetLiv2, 0.0)

! Total amount of TCE metabolized in liver (mg)
  RATotMetLiv = RAMetLiv1 + RAMetLiv2
  ATotMetLiv = AMetLiv1 + AMetLiv2

! Concentration of TCE in mixed venous blood (mg/L)
  CVen = (QFat*CVFat + QGutLiv*CVLiv + QSlw*CVSlw + QRap*CVRap &
    & + QTB*CVTB + kIV) / QC
  CVenMole = CVen / MWTCE

! Mass Balance for TCE
! Total intake from inhalation (mg)
  RInhDose = QP * CInh
  InhDose = INTEG(RInhDose, 0.0)

  TotDose = InhDose + AO + INTEG(kDrink, 0.0)
  TotTissue = ATB + ARap + ASlw + ATotFat + ATotGutLiv
  TotMetab = AMetLng + ATotMetLiv
  TCEDiff = (TotDose + INTEG(kIV, 0.0)) - TotTissue - TotMetab
  MassBalTCE = TCEDiff - AExh
  MassBalAbs = TotAbsStom - (ADuod + AExc + AO)

```

```

!*****
!***          TCA Sub-model          ***
!*****
! Amount of TCA in plasma (mg)
  RAPlasTCA = (QBodPlas*CVBodTCA) + (QLivPlas*CVLivTCA) &
    & - (QCPlas * CPlasTCA) - (kUrnTCA * APlasTCAFree)
  APlasTCA = INTEG(RAPlasTCA, 0.0)
  CPlasTCA = APlasTCA / VPlas

! Concentration of TCA in plasma (umoles/L)
  CPlasTCAMole = (CPlasTCA / MWTCA) * 1000.0

! Concentration of free TCA in plasma in (umoles/L)
  CPlasTCAFreeMole = (0.5*SQRT(((kDissoc+TotConc-CPlasTCAMole)**2.0) &
    & + (4.0*kDissoc*CPlasTCAMole))) &
    & - (0.5*(kDissoc+TotConc-CPlasTCAMole))

! Concentration of free TCA in plasma (mg/L)
  CPlasTCAFree = (CPlasTCAFreeMole * MWTCA) / 1000.0
  APlasTCAFree = CPlasTCAFree * VPlas

! Concentration of bound TCA in plasma (mg/L)
  CPlasTCABnd = CPlasTCA - CPlasTCAFree

! Concentration of total TCA in blood (mg/L)
  CBldTCA = CPlasTCA * TCAPlas

! Amount of TCA in the body (mg)
  RABodTCA = (QBodPlas * (CPlasTCAFree - (CBodTCA / PBodTCA)))
  ABodTCA = INTEG(RABodTCA, 0.0)
  CBodTCA = ABodTCA / VBod
  CVBodTCA = CPlasTCABnd + (CBodTCA / PBodTCA)

! Amount of TCA in the liver (mg)
  RALivTCA = (QLivPlas * (CPlasTCAFree - (CLivTCA / PLivTCA))) &
    & + (FracTCE * StochTCATCE * RAMetLiv1) &
    & + (StochTCATCOH * RAMetTCOHTCA)
  ALivTCA = INTEG(RALivTCA, 0.0)
  CLivTCA = ALivTCA / VLiv
  CVLivTCA = CPlasTCABnd + (CLivTCA / PLivTCA)

! Amount of TCA in urine (mg)
  RAUrnTCA = kUrnTCA * APlasTCAFree
  AUrnTCA = INTEG(RAUrnTCA, 0.0)

! Mass Balance for TCA
  TotTCAIn = (FracTCE*StochTCATCE*AMetLiv1) + (StochTCATCOH*AMetTCOHTCA)
  TotTCATis = APlasTCA + ABodTCA + ALivTCA
  TCADiff = TotTCAIn - TotTCATis
  MassBalTCA = TCADiff - AUrnTCA

!*****
!***          TCOH Sub-model          ***
!*****
! Amount of TCOH (mg)
  RATCOH = (StochTCOHGluc * RAREcircTCOG) &

```

```

      & + ((1.0 - FracDCA - FracTCE) * StochTCOHTCE * RAMetLiv1) &
      & - RAMetTCOHTCA - RAMetTCOHGluc
    ATCOH = INTEG(RATCOH, 0.0)
    CTCOH = ATCOH / VDTCOH
    AUCCTCOH = INTEG(CTCOH, 0.0)
    CTCOHMole = CTCOH / MWTCOH

! Rate of oxidation to TCA (mg/hr)
    RAMetTCOHTCA = (VMaxTCOH * CTCOH) / (KMTCOH + CTCOH)
    AMetTCOHTCA = INTEG(RAMetTCOHTCA, 0.0)

! Amount of glucuronidation to TCOG (mg/hr)
    RAMetTCOHGluc = (VMaxGluc * CTCOH) / (KMGluc + CTCOH)
    AMetTCOHGluc = INTEG(RAMetTCOHGluc, 0.0)

! Mass Balance for TCOH
    TotTCOHIn = ((1.0 - FracDCA - FracTCE) * StochTCOHTCE * AMetLiv1) &
      & + (StochTCOHGluc * ARecircTCOG)
    TotMetabTCOH = AMetTCOHTCA + AMetTCOHGluc
    MassBalTCOH = TotTCOHIn - TotMetabTCOH - ATCOH

!*****
!***          TCOG Sub-model          ***
!*****
! Amount of TCOH-Gluc (mg)
    RATCOG = (StochGlucTCOH * RAMetTCOHGluc) - (kBile * ATCOG) &
      & - (kUrntCOG * ATCOG)
    ATCOG = INTEG(RATCOG, 0.0)
    CTCOG = ATCOG / VDTCOH
    AUCCTCOG = INTEG(CTCOG, 0.0)

! Amount of TCOH-Gluc excreted into bile (mg)
    RABileTCOG = (kBile * ATCOG) - RAREcircTCOG
    ABileTCOG = INTEG(RABileTCOG, 0.0)

! Amount of TCOH-Gluc recirculated (mg)
    RAREcircTCOG = KEHR * ABileTCOG
    ARecircTCOG = INTEG(RAREcircTCOG, 0.0)

! Amount of TCOH-Gluc excreted in urine (mg)
    RAUrntCOG = kUrntCOG * ATCOG
    AUrntCOG = INTEG(RAUrntCOG, 0.0)
    AUrntCOGTCOH = StochTCOHGluc * AUrntCOG
    AUrntCOGTCE = StochTCEGluc * AUrntCOG

! Total amount of TCOH and TCOH-Gluc (mg)
    TotCTCOH = CTCOH + CTCOG

! Total amount of TCA and TCOG in urine (mg)
    AUrntCAMole = AUrntTCA / MWTCOA
    AUrntCOGMole = AUrntTCOG / MWTCOHGluc
    AUrntCTot = AUrntTCA + AUrntCOGTCOH
    AUrntCTotMole = AUrntCAMole + AUrntCOGMole

! Mass Balance for TCOG
    TotTCOGIn = StochGlucTCOH * AMetTCOHGluc
    TotTCOG = ATCOG + ABileTCOG

```

MassBalTCOG = TotTCOGIn - TotTCOG - ARecircTCOG - AUrnTCOG

```

!*****
!***          DCA Sub-model          ***
!*****
! Amount of DCA (mg)
  RADCA = (FracDCA * StochDCATCE * RAMetLiv1) - (kClearDCA * ADCA)
  ADCA = INTEG(RADCA, 0.0)
  CDCA = ADCA / VDDCA

! Amount of DCA eliminated (mg)
  RAElimDCA = kClearDCA * ADCA
  AElimDCA = INTEG(RAElimDCA, 0.0)

! Mass Balance for DCA
  TotDCAIn = FracDCA * StochDCATCE * AMetLiv1
  MassBalDCA = TotDCAIn - ADCA - AElimDCA

!*****
!***          DCVC Sub-model          ***
!*****
! Amount of DCVC in kidney (mg)
  RADCV = (StochDCVCTCE * RAMetLiv2) - ((kNAT + kKidCyto) * ADCVC)
  ADCVC = INTEG(RADCV, 0.0)
  CDCVC = ADCVC / VKid

! Amount of DCVC excreted into urine (mg)
  RAUrDCVC = kNAT * ADCVC
  AUrnDCVC = INTEG(RAUrnDCVC, 0.0)

! Amount of N Acetyl DCVC excreted (mg)
  RAUrNDCVC = StochN * RAUrDCVC
  AUrnNDCVC = INTEG(RAUrnNDCVC, 0.0)
  AUrnNDCVMole = AUrnNDCVC / MWNADCVC

! Kidney toxicity
  RRiskKid = (kKidCyto * ADCVC) / VKid
  RiskKid = INTEG(RRiskKid, 0.0)
  ARiskKid = RiskKid * VKid

! Mass Balance for DCA
  TotDCVCIn = StochDCVCTCE * AMetLiv2
  MassBalDCVC = TotDCVCIn - ADCVC - AUrnDCVC - ARiskKid

!*****
!***          Total Mass Balance          ***
!*****
  TotMassBal = MassBalTCE + MassBalTCA + MassBalTCOH + MassBalTCOG &
    & + MassBalDCA + MassBalDCVC

!*****

```

```

!***                               Dose Metrics                               ***
!*****

! Metabolism rate per default uptake rate or net uptake rate
  IF (CInh. GT. 0.0) THEN
    FMetInh = RATotMetLit . (PO * CInh * 0.4)
    FMetINet = RATotMetLit . (PO * (CInh , CAlt))
  ENDIF

! Metabolism rate per chemical ingestion rate
  IF (Drink .GT. 0.0) FMetNcal = RATotMetLit . ((Drink * AV) . 13.0)

  TERMT(T.GE.TRep+ Rimulation Finished )

END      ! of Deritatile
END      ! of DWhamic
END      ! of Qoeram

```

APPENDIX B: COMMAND FILE

This code was written as a cmd file for acslXtreme, version 1.3.19. This code will not run on newer versions of the software; however, it has been provided to allow a future modeler access to the data sets used in this project.

```
! TCE_CSL.CMD -- command file for
TCE_BD.csl
```

```
PREPARE T, CinhPPM, CalvPPM, CVTB,
CLiv, CFat, CVen, CBldTCA, CLivTCA, &
& AUrnTCA, CTCOH, TotCTCOH,
AUrnTCOGTCOH, AUrnTCTot, &
& AUrnTCTotMole, CDCA, AUrnNDCVC,
AUrnNDCVCMole, MassBaltCE, &
& MassBalAbs, MassBalTCA,
MassBalTCOH, MassBalTCOG, MassBalDCA, &
& MassBalDCVC, TotMassBal, Total
```

```
SET NRWITG=.F., FTSPLT=.T., HVDPRN=.F.,
NCIPRN=10, WESITG=.F.
SET GRDCPL=.F., XINCPL=5, DPNPLT=.F.
```

```
PROCED ResetDoses
SET ZZERR=39*1.0e-8, ZZMERR=39*1.0e-
8
SET Conc=0.0, IVDose=0.0, PDose=0.0,
Drink=0.0
SET CC=.FALSE., NRats=1.0,
kLossC=0.0, VChC=1.0
SET Days=1.0, TMax=24.0
SET TStp=24.0, CINT=0.01
END
```

```
PROCED Human
SET BW=70.0
SET QCC=13.0, QPC=18.0
SET QFatC=0.052, QGutC=0.181,
QLivC=0.046, QRapC=0.699
SET QSlwC=0.301, QTBC=0.025
SET VBldC=0.079, VBodC=0.2,
VFatBldC=0.02, VFatC=0.214
SET VGutC=0.017, VKidC=0.004,
VLivC=0.026, VRapC=0.192
SET VSlwC=0.651, VTBC=0.0008
SET VDDCAC=0.26, VDTCOHC=0.65
SET PB=9.2, PFat=73.0, PGut=6.8,
PLiv=6.8, PRap=6.8, PSlw=2.3, PTB=6.8
SET PAFatC1=10.0, PAFatC2=10.0
SET PBodTCA=1.9, PLivTCA=2.5
SET VMaxC=12.0, KM=1.5, kDCVCC=0.015,
FracDCA=0.004, FractCE=0.08
SET VMaxClaraC=0.0045, KMClara=1.5,
VMaxClearC=250.0, KMClear=250.0
SET kDissoc=174.6, NumSites=2.97,
ProtConc=239.0
```

```
SET VMaxTCOHC=25.0, KMTCOH=250.0,
VMaxGlucC=5.0, KMGluc=25.0
SET kNATC=19.0, kKidCytoC=37.0
SET kAS=0.0, kTSD=10.0, kAD=1.0,
kTD=0.0
SET kBileC=1.0, kEHRC=0.0
SET kClearDCAC=1.9, kUrnTCAC=0.2,
kUrnTCOGC=3.0
SET FracPlas=0.58, TCAPlas=0.76
END
```

```
PROCED Mouse
SET BW=0.035
SET QCC=18.0, QPC=18.0
SET QFatC=0.07, QGutC=0.141,
QLivC=0.02, QRapC=0.713, QSlwC=0.287
SET QTBC=0.005
SET VBldC=0.049, VBodC=0.2,
VFatBldC=0.02, VFatC=0.07, VGutC=0.042
SET VKidC=0.017, VLivC=0.055,
VRapC=0.217, VSlwC=0.619, VTBC=0.0007
SET VDDCAC=0.5, VDTCOHC=0.65
SET PB=14.0, PFat=36.0, PGut=1.8,
PLiv=1.8, PRap=1.8, PSlw=0.75
SET PTB=1.8
SET PAFatC1=10.0, PAFatC2=10.0
SET PBodTCA=0.76, PLivTCA=1.14
SET VMaxC=32.7, KM=0.25,
kDCVCC=0.015, FracDCA=0.04,
FractCE=0.035
SET VMaxClaraC=3.0, KMClara=0.25,
VMaxClearC=250.0, KMClear=250.0
SET kDissoc=46.1, NumSites=0.17,
ProtConc=196.0
SET VMaxTCOHC=1.0, KMTCOH=0.25,
VMaxGlucC=100.0, KMGluc=25.0
SET kNATC=0.5, kKidCytoC=0.4
SET kAS=0.0, kTSD=10.0, kAD=0.6,
kTD=0.0
SET kBileC=1.0, kEHRC=0.0
SET kClearDCAC=1.0, kUrnTCAC=0.3,
kUrnTCOGC=0.5
SET FracPlas=0.58, TCAPlas=0.76
END
```

```
PROCED Rat
SET BW=0.35
SET QCC=15.0, QPC=24.0
SET QFatC=0.07, QGutC=0.162,
QLivC=0.021, QRapC=0.594, QSlwC=0.406
SET QTBC=0.021
```

```

SET VBldC=0.074, VBodC=0.2,
VFatBldC=0.02, VFatC=0.07, VGutC=0.027
SET VKidC=0.007, VlivC=0.034,
VrapC=0.213, VslwC=0.664, VTBC=0.0005
SET VDDCAC=0.5, VDTCHC=0.65
SET PB=18.5, PFat=27.5, PGut=1.3,
PLiv=1.3, PRap=1.3, Pslw=0.5
SET PTB=1.3
SET PAFatC1=10.0, PAFatC2=10.0
SET PBodTCA=0.51, PLivTCA=0.76
SET VMaxC=11.2, KM=0.25,
kDCVCC=0.015, FracDCA=0.04,
FractTCE=0.04
SET VMaxClaraC=0.3, KMClara=0.25,
VMaxClearC=250.0, KMClear=250.0
SET kDissoc=383.6, NumSites=1.49,
ProtConc=190.0
SET VMaxTCOH=0.12, KMTCOH=0.25,
VMaxGlucC=100.0, KMGluc=25.0
SET kNATC=1.1, kKidCytoC=17.0
SET kAS=0.0, kTSD=10.0, kAD=0.3,
kTD=0.0
SET kBileC=1.0, kEHRC=0.0
SET kClearDCAC=1.3, kUrnTCAC=0.3,
kUrnTCOGC=0.5
SET FracPlas=0.58, TCAPlas=0.76
END

```

```

PROCED FisherMM
! Data from Fisher et al. (1991)
! From procedures FG3A and FG5A in
TCENew.cmd
! 110 ppm TCE 4 hr -- Male Mouse
Mouse
ResetDoses
SET Conc=110.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=24.0
START /NC
PLOT /DATA=fishermm1 CVen
PLOT /DATA=fishermm2 CBldTCA
display t cven cbltca
END

```

```

DATA FisherMM1 (T, CVen)
2.026 1.516
3.845 1.514
4.168 0.382
4.359 0.383
END

```

```

DATA FisherMM2 (T, CBldTCA)
1.976 18.519
3.869 47.996
4.23 49.273
4.267 38.833
5.065 69.449
5.994 53.35
8.015 40.811
20.974 7.224

```

END

```

PROCED FisherFMPParam
SET kUrnTCAC=0.6
END

```

```

PROCED FisherFM
! Data from Fisher et al. (1991)
! From procedures FG4C and FG6C in
TCENew.cmd
! 368 ppm TCE 4 hr -- Female Mouse
Mouse
ResetDoses
FisherFMPParam
SET Conc=368.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=30.0
START /NC
PLOT /DATA=fisherfml CVen
PLOT /DATA=fisherfm2 CBldTCA
END

```

```

DATA FisherFM1 (T, CVen)
2.013 5.964
3.831 6.427
4.32 1.076
4.688 0.839
5.012 0.226
END

```

```

DATA FisherFM2 (T, CBldTCA)
1.872 60.384
3.852 60.746
4.198 63.009
5.09 60.083
6.922 35.596
9.978 24.862
29.979 0.326
END

```

```

PROCED Fisher ! TCE in blood
! Data from Abbas R and Fisher JW.
1997. A physiologically based
! pharmacokinetic model for
trichloroethylene and its metabolites,
! chloral hydrate, trichloroacetate,
dichloroacetate, trichloroethanol,
! and trichloroethanol glucuronide in
B6C3F1 mice. Toxicology and
! Applied Pharmacology 147:15-30.
!
! Sixteen male B6C3F1 mice (0.025-0.03
kg) (4 per dose group) were
! exposed by gavage to 300, 600, 1200,
or 2000 mg/kg TCE in corn oil
! Abbas and Fisher. 1997. Mice -
Gavage
!
! From procedure Fisher in TCENew.cmd
Mouse
ResetDoses

```

SET QPC=20.0, QCC=20.0
 SET PDose=300.0, Days=1.0, TMax=48.0,
 TStp=250.0
 START /NC

SET NRWITG=.T., PDose=600.0,
 QPC=15.0, QCC=15.0
 START /NC

SET PDose=1200.0, QPC=12.0, QCC=12.0
 START /NC

SET PDose=2000.0, QPC=6.0, QCC=6.0
 START /NC

PLOT CVen/run=1, CVen/run=2,
 CVen/run=3, CVen/run=4, /DATA=fisher1
 CVen

PLOT TotCTCOH/run=1, TotCTCOH/run=2,
 TotCTCOH/run=3, TotCTCOH/run=4,
 /DATA=fisher2 TotCTCOH

PLOT CBldTCA/run=1, CBldTCA/run=2,
 CBldTCA/run=3, CBldTCA/run=4,
 /DATA=fisher3 CBldTCA

PLOT CDCA/run=1, CDCA/run=2,
 CDCA/run=3, CDCA/run=4, /DATA=fisher4
 CDCA

PLOT AUrnTCOGTCOH/run=1,
 AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
 AUrnTCOGTCOH/run=4, /DATA=fisher5
 AUrnTCOGTCOH

PLOT AUrnTCA/run=1, AUrnTCA/run=2,
 AUrnTCA/run=3, AUrnTCA/run=4,
 /DATA=fisher6 AUrnTCA
 SET NRWITG=.F.
 END

DATA Fisher1 (T, CVen)

0.0	27.163
0.25	12.748
0.75	6.792
2.0	0.671
4.0	0.602
0.25	83.918
0.5	70.013
2.0	5.485
4.0	1.850
8.0	0.908
0.0	165.900
0.25	194.010
0.35	125.004
0.5	84.095
0.75	68.477
1.0	42.323
1.5	36.486
2.0	19.839
3.0	8.744
4.0	7.510
8.0	1.607
12.0	0.708
16.0	0.454
0.5	215.549

0.75	171.258
1.5	147.229
2.0	68.737
4.0	50.630
8.0	17.752
16.0	9.572
24.0	1.179

END

DATA Fisher2 (T, TotCTCOH)

0.25	14.951
0.5	19.507
1.0	38.154
2.0	9.823
4.0	4.857
8.0	2.260
16.0	1.493
0.0	18.211
0.25	26.209
2.0	23.683
4.0	8.231
8.0	2.157
12.0	1.006
0.25	19.170
0.35	28.340
0.5	31.025
1.0	36.238
1.5	28.637
2.0	42.998
3.0	22.019
4.0	24.938
6.0	4.559
12.0	4.293
0.25	21.512
0.5	33.544
1.0	42.775
2.0	37.136
4.0	29.707
16.0	4.323

END

DATA Fisher3 (T, CBldTCA)

0.0	21.153
0.25	28.602
2.0	44.260
4.0	55.510
8.0	49.842
16.0	45.073
24.0	37.740
30.0	26.349
0.0	11.742
0.25	15.416
2.0	29.059
4.0	34.313
8.0	34.148
16.0	31.568
24.0	26.453
40.0	22.201
0.0	5.114
0.1	11.547
0.25	16.582
0.5	22.928
0.75	28.620

1.0	35.192	48.0	9.000
1.5	41.618	72.0	9.522
2.0	59.699	96.0	9.646
3.0	62.719	120.0	9.738
4.0	68.996	144.0	9.807
6.0	93.311	24.0	8.248
8.0	89.934	48.0	11.220
16.0	65.678	72.0	12.043
24.0	43.161	96.0	12.257
30.0	40.748	120.0	12.460
40.0	9.223	144.0	12.478
0.25	11.747	24.0	15.291
0.5	21.259	48.0	21.270
1.0	31.250	72.0	23.935
2.0	45.460	96.0	24.801
4.0	66.279	120.0	25.488
16.0	136.826	144.0	26.000
24.0	52.348	168.0	26.047
30.0	57.359	192.0	26.075
48.0	9.197		

END

DATA Fisher4 (T, CDCA)

0.25	0.040	24.0	0.711
2.0	0.181	48.0	1.173
4.0	0.195	72.0	1.281
8.0	0.108	96.0	1.292
16.0	0.060	120.0	1.284
24.0	0.051	144.0	1.283
0.25	0.047	24.0	0.688
2.0	0.166	48.0	1.663
4.0	0.467	72.0	1.839
8.0	0.897	96.0	1.876
16.0	0.127	120.0	1.861
24.0	0.087	144.0	1.871
0.0	0.074	24.0	2.306
0.5	0.214	48.0	3.677
1.0	0.149	72.0	4.449
1.5	0.184	96.0	4.698
2.0	0.232	120.0	4.661
3.0	0.409	144.0	4.720
4.0	0.378	24.0	1.283
6.0	0.455	48.0	2.430
8.0	0.920	72.0	2.937
16.0	0.589	96.0	3.128
24.0	0.501	120.0	3.299
30.0	0.406	144.0	3.345
40.0	0.177	168.0	3.369
0.5	0.099	192.0	3.313
4.0	2.046		
8.0	2.861		
24.0	1.869		
40.0	0.186		

END

DATA Fisher5 (T, AUrnTCOGTCOH)

24.0	1.935
48.0	3.537
72.0	3.732
96.0	3.792
120.0	3.806
144.0	3.819
24.0	6.844

PROCED GargasMMParam

SET VFatC=0.05

END

PROCED GargasMM

! Data from Abbas and Fisher (1997)

! Data from MICE_gasuptake_gargas.dat

! Male Mice Closed Chamber

Mouse

ResetDoses

GargasMMParam

SET BW=0.03, QPC=30.0

```

SET Conc=1020.0, CC=.TRUE.,
NRats=14.0, kLossC=0.02, VChC=9.1
SET TChng=6.0, Days=1.0, TMax=24.0,
TStp=6.0
START /NC
SET NRWITG=.T.
SET BW=0.026, Conc=1800.0, NRats=15.0
START /NC
SET BW=0.03, Conc=3800.0, NRats=14.0
START /NC
SET BW=0.028, Conc=5600.0, NRats=15.0
START /NC
SET BW=0.026, Conc=10000.0,
NRats=15.0
START /NC
PLOT CInhPPM/run=1, CInhPPM/run=2,
CInhPPM/run=3, CInhPPM/run=4,
CInhPPM/run=5, /DATA=gargasmm CInhPPM
SET NRWITG=.F.
END

```

DATA GargasMM (T, CInhPPM)

0.083	821.0
0.167	620.0
0.33	377.0
0.5	226.0
0.667	154.0
0.83	98.0
1.0	63.6
1.167	41.8
1.33	28.0
1.5	18.5
1.67	13.0
1.83	8.99
2.0	6.79
2.167	5.27
2.33	4.5
0.167	1336.0
0.25	1108.0
0.33	940.0
0.5	719.0
0.67	600.0
0.83	492.0
1.0	400.0
1.167	310.0
1.33	246.0
1.5	186.0
1.67	131.0
1.83	92.9
2.0	63.7
2.167	41.4
2.33	27.4
2.5	17.4
2.67	12.1
2.83	8.65
0.167	2516.0
0.33	1846.0
0.5	1540.0
0.67	1351.0
0.83	1226.0
1.0	1128.0
1.167	1047.0
1.33	977.0

1.5	916.0
1.67	853.0
1.83	799.0
2.0	749.0
2.167	696.0
2.33	650.0
2.5	603.0
2.67	552.0
2.83	493.0
3.0	456.0
3.167	403.0
3.33	359.0
3.5	308.0
3.67	264.0
3.83	216.0
4.0	162.0
4.167	122.0
4.33	89.2
4.5	67.1
4.67	50.9
4.83	34.3
5.0	23.3
5.167	16.6
0.083	5143.0
0.167	4386.0
0.33	3255.0
0.5	2608.0
0.67	2209.0
0.83	1939.0
1.0	1786.0
1.167	1618.0
1.33	1513.0
1.5	1432.0
1.67	1360.0
1.83	1291.0
2.0	1232.0
2.167	1182.0
2.33	1128.0
2.5	1084.0
2.67	1046.0
2.75	1026.0
2.92	988.0
3.08	950.0
3.25	914.0
3.42	880.0
3.58	849.0
3.75	819.0
3.92	789.0
4.08	760.0
4.25	732.0
4.42	703.0
4.58	675.0
4.75	652.0
4.92	612.0
5.08	586.0
5.25	555.0
0.083	8218.0
0.167	7215.0
0.33	5804.0
0.5	5170.0
0.67	4752.0
0.83	4435.0
1.0	4101.0

1.167	3830.0	0.5	245.0
1.33	3623.0	0.667	179.0
1.5	3446.0	0.83	136.0
1.67	3305.0	1.0	108.0
1.83	3180.0	1.167	82.4
2.0	3114.0	1.333	63.7
2.167	3055.0	1.5	48.9
2.33	2948.0	1.67	40.5
2.5	2856.0	1.83	32.6
2.67	2790.0	2.0	27.4
2.83	2709.0	2.167	20.7
3.0	2637.0	2.333	16.2
END		2.5	13.8
		2.67	11.7
		0.083	965.0
PROCED GargasFMParam		0.167	803.0
SET VFatC=0.10, VMaxC=23.2		0.333	580.0
END		0.5	467.0
		0.667	391.0
PROCED GargasFM		0.83	314.0
! Data from Abbas and Fisher (1997)		1.0	270.0
! Data from female_rat_mice_fisher.dat		1.167	235.0
! TCE - female B6C3F1 mice		1.333	198.0
! Female Mice Closed Chamber		1.5	160.0
Mouse		1.667	140.0
ResetDoses		1.83	119.0
GargasFMParam		2.0	101.0
SET BW=0.024, QPC=30.0		2.167	86.2
SET Conc=300.0, CC=.TRUE.,		2.333	70.3
NRats=14.0, kLossC=0.02, VChC=9.1		2.5	59.1
SET TChng=7.0, Days=1.0, TMax=24.0,		2.667	50.8
TStp=7.0		2.83	41.8
START /NC		3.0	34.6
SET NRWITG=.T.		3.167	28.7
SET BW=0.021, Conc=700.0		3.333	22.6
START /NC		3.5	19.4
SET BW=0.022, Conc=1100.0		3.667	16.1
START /NC		3.83	13.5
SET BW=0.022, Conc=3700.0		0.083	3611.0
START /NC		0.167	2854.0
SET BW=0.022, Conc=7000.0		0.333	2269.0
START /NC		0.5	1848.0
PLOT CInhPPM/run=1, CInhPPM/run=2,		0.667	1569.0
CInhPPM/run=3, CInhPPM/run=4,		0.83	1276.0
CInhPPM/run=5, /DATA=gargasfm CInhPPM		1.0	1244.0
SET NRWITG=.F.		1.167	1147.0
END		1.333	1080.0
		1.5	982.0
DATA GargasFM (T, CInhPPM)		1.667	940.0
0.083	214.0	1.83	935.0
0.5	99.0	2.0	897.0
0.667	70.3	2.167	869.0
0.83	52.3	2.333	840.0
1.0	38.1	2.5	816.0
1.167	28.5	2.667	792.0
1.333	22.2	3.0	742.0
1.500	16.9	3.167	719.0
1.67	12.3	3.333	699.0
1.83	9.4	3.5	676.0
2.0	7.1	3.667	656.0
0.083	624.0	3.83	621.0
0.167	502.0	4.0	602.0
0.333	357.0	4.167	578.0

4.333	553.0
4.5	530.0
4.667	505.0
4.83	480.0
5.0	451.0
5.167	429.0
5.333	402.0
5.5	374.0
5.667	350.0
6.0	297.0
0.083	6401.0
0.167	5475.0
0.333	4161.0
0.5	3303.0
0.667	2868.0
0.83	2702.0
1.0	2467.0
1.167	2290.0
1.333	2203.0
1.5	2122.0
1.667	2048.0
1.83	2004.0
2.0	1984.0
2.167	1951.0
2.333	1913.0
2.5	1885.0
2.667	1801.0
2.83	1776.0
3.0	1771.0
3.167	1753.0
3.333	1736.0
3.5	1711.0
3.667	1689.0
3.83	1667.0
4.0	1647.0
4.167	1622.0
4.333	1599.0
4.5	1574.0
5.0	1556.0
5.167	1531.0
5.333	1446.0
5.5	1418.0
5.667	1389.0
5.83	1369.0
6.0	1320.0

END

```

PROCED Greenberg  ! TCE in blood
! Data from Greenberg MS, Burton GA,
and Fisher JW. 1999.
! Physiologically based
pharmacokinetic modeling of inhaled
! trichloroethylene and its oxidative
metabolites in B6C3F mice.
! Toxicology and Applied Pharmacology
154:264-278.
!
! Male B6C3F1 mice (0.028-0.032 kg)
were exposed by inhalation to
! 100 or 600 ppm for up to 4 hours
! Greenberg et al. 1999. Mice -
Inhalation

```

```

!
! From procedure Greenberg in
TCENew.cmd
  Mouse
  ResetDoses
  SET ZZERR=39*1.0e-9, ZZMERR=39*1.0e-
9
  SET Conc=100.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=48.0,
TStp=48.0
  START /NC

  SET NRWITG=.T., Conc=600.0
  SET ZZERR=39*1.0e-8, ZZMERR=39*1.0e-
8
  START /NC
  PLOT CVen/run=1, CVen/run=2,
/ DATA=greenberg1 CVen
  PLOT CTCOH/run=1, CTCOH/run=2,
/ DATA=greenberg2 CTCOH
  PLOT CBldTCA/run=1, CBldTCA/run=2,
/ DATA=greenberg3 CBldTCA
  SET NRWITG=.F.
END

```

DATA Greenberg1 (T, CVen)

2.0	0.672
4.0	0.879
4.25	0.139
4.5	0.151
2.0	6.791
4.0	7.238
4.25	1.507
4.5	0.594
4.75	0.461
6.0	0.169

END

DATA Greenberg2 (T, CTCOH)

2.0	1.948
4.0	1.793
4.25	1.749
4.5	0.795
4.75	0.301
6.0	0.090
2.0	15.386
4.0	12.114
4.25	9.880
4.5	3.610
4.75	2.944
6.0	0.952

END

DATA Greenberg3 (T, CBldTCA)

2.0	17.771
4.25	29.296
4.5	25.167
4.75	30.500
6.0	26.292
12.0	6.945
18.0	3.922
28.0	1.965

```

2.0      55.636
4.25     71.795
4.5       94.831
4.75     93.010
6.0     103.233
12.0     24.451
18.0     13.390
28.0      7.196
48.0      0.790
END

```

```

PROCED ProutMParam
  SET VMaxC=50.0, VMaxTCOHC=2.0,
  kAD=0.3
END

PROCED ProutM
! Data from Prout et al. (1985)
! From procedures P3M, P5M, and P6M in
TCENew.cmd
! Mouse - 1000 mg/kg tce in oil
  Mouse
  ResetDoses
  SET ZZXERR=39*1.0e-7, ZZMERR=39*1.0e-
7
  ProutMParam
  SET BW=0.028, PDose=1000.0, Days=1.0,
TMax=1.0, TStp=45.0
  START /NC
  PLOT /DATA=proutm1 CVen
  PLOT /DATA=proutm2 CTCOH
  PLOT /DATA=proutm3 CBldTCA
END

```

```

DATA ProutM1 (T, CVen)
0.09      9.81
0.415     17.719
0.753     13.021
1.028      7.965
1.638     10.105
2.035      6.004
2.717      5.831
3.097      1.154
3.571      1.329
4.161      1.679
4.714      2.17
5.302      2.485
5.766      2.554
6.285      3.529
6.766      3.864
7.233      1.735
END

```

```

DATA ProutM2 (T, CTCOH)
0.296      9.477
0.588     21.574
0.776     29.357
1.012     27.676
1.507     30.546
2.08      27.443
2.677     20.031

```

```

3.487      9.369
4.071     10.662
4.578     14.157
5.136      2.601
5.443      7.302
5.925      6.516
6.641      5.316
7.067      2.516
7.563      1.166
8.025      0.51

```

END

```

DATA ProutM3 (T, CBldTCA)
0.804     38.161
1.381     108.001
1.778     68.642
2.936     146.642
3.552     122.081
4.49      157.897
5.009     134.087
5.536     150.322
5.864     101.92
7.315     120.738
7.822     162.399
8.048     197.051
8.707     209.215
9.52      201.666
10.12     189.58
11.122    188.781
12.916    170.32
14.151    259.614
15.243    240.369
15.993    216.341
16.121    179.322
17.06     116.241
18.557     59.745
19.617    123.052
20.712    196.42
21.953    169.549
22.4       145.33
24.632    237.856
25.757    223.972
27.457    157.147
28.877    150.795
30.272    266.082
31.375    283.333
32.672     70.593
33.491     56.951
34.341     29.533
35.625     28.261
36.534     38.283
38.911     28.988
41.193     19.915
44.214      7.202

```

END

```

PROCED TemplinMParam
  SET VMaxC=60.0, VMaxTCOHC=0.5,
  kAD=1.0
END

```

```

PROCED TemplinM

```

! Data from Templin et al. (1993)
! From procedures T1TCE, T1TCA, T1TCOH,
and T1DCA in TCENew.cmd
! Also from data block TCE500 in
MouseB.cmd

! Mouse - 499.32 mg/kg TCE in 2% tween
Mouse
ResetDoses
SET ZZXERR=39*1.0e-7, ZYMERR=39*1.0e-

7
TemplinMParam
SET BW=0.02, PDose=500.0, Days=1.0,
TMax=1.0, TStp=36.0

START /NC
PLOT /DATA=templinm1 CVen
PLOT /DATA=templinm2 CBldTCA
PLOT /DATA=templinm3 CTCOH
PLOT /DATA=templinm4 CDCA

END

DATA TemplinM1 (T, CVen)

0.267	27.871
0.489	24.25
0.756	21.428
0.976	11.727
1.479	3.827
1.964	1.709

END

DATA TemplinM2 (T, CBldTCA)

0.236	10.865
0.531	18.549
0.756	24.867
1.03	42.942
1.501	46.140
2.024	43.821
2.999	57.877
3.977	64.961
5.996	40.28
9.002	38.183
12.023	31.739
17.858	10.926
23.894	9.015
35.888	1.990

END

DATA TemplinM3 (T, CTCOH)

0.255	17.84
0.756	35.8
0.996	40.0
1.491	30.0
1.977	8.36
2.949	0.72

END

DATA TemplinM4 (T, CDCA)

0.229	0.787932
0.499	4.658448
0.756	4.728237
0.971	5.141037
1.469	5.768106
2.949	2.965452
5.965	1.68732

8.98 0.785094
END

PROCED MouseM

! Data from Abbas and Fisher (1997)
! From procedures Mouse300M, Mouse600M,
Mouse1200M, Mouse2000M

! TCE300, TCE600, TCE1200 and TCE2000
in MouseB.cmd

! Data also in TCA CTCV CTCL.xls
! Mice data--April 1996, TCE oral
gavage dosing in mice
! 300, 600, 1200, or 2000 mg/kg corn
oil gavage

! Male

! Mouse

ResetDoses
SET PDose=300.0, Days=1.0, TMax=24.0,
TStp=150.0

START /NC
PLOT /DATA=mouse300m1 CVen
PLOT /DATA=mouse300m2 CLiv
PLOT /DATA=mouse300m3 CFat
PLOT /DATA=mouse300m4 CLivTCA
PLOT /DATA=mouse300m5 CBldTCA
PLOT /DATA=mouse300m6 AUrnTCA

SET NRWITG=.T., PDose=600.0
SET ZZXERR=39*1.0e-10,
ZYMERR=39*1.0e-10

START /NC
PLOT /DATA=mouse600m1 CVen
PLOT /DATA=mouse600m2 CLiv
PLOT /DATA=mouse600m3 CFat
PLOT /DATA=mouse600m4 CLivTCA
PLOT /DATA=mouse600m5 CBldTCA
PLOT /DATA=mouse600m6 AUrnTCA

SET PDose=1200.0
START /NC
PLOT /DATA=mouse1200m1 CVen
PLOT /DATA=mouse1200m2 CLiv
PLOT /DATA=mouse1200m3 CFat
PLOT /DATA=mouse1200m4 CLivTCA
PLOT /DATA=mouse1200m5 CBldTCA
PLOT /DATA=mouse1200m6 AUrnTCA

SET PDose=2000.0, TStp=200.0
SET ZZXERR=39*1.0e-8, ZYMERR=39*1.0e-

8

START /NC
PLOT /DATA=mouse2000m1 CVen
PLOT /DATA=mouse2000m2 CLiv
PLOT /DATA=mouse2000m3 CFat
PLOT /DATA=mouse2000m4 CLivTCA
PLOT /DATA=mouse2000m5 CBldTCA
PLOT /DATA=mouse2000m6 AUrnTCA

END

DATA Mouse300M1 (T, CVen)

0.25	26.11
0.5	12.99

1.0	6.67
2.0	0.68
4.0	0.61

END

DATA Mouse300M2 (T, CLiv)

0.25	70.0
0.5	42.1
1.0	16.98
2.0	8.08
4.0	4.17
8.0	1.89
16.0	0.945
24.0	4.18
30.0	3.39
48.0	1.33

END

DATA Mouse300M3 (T, CFat)

0.25	60.13
0.5	125.4
1.0	189.9
2.0	72.58
4.0	40.32
8.0	18.12
16.0	31.3
24.0	0.65
30.0	0.778
48.0	0.32

END

DATA Mouse300M4 (T, CLivTCA)

0.25	18.9
2.0	35.8
4.0	45.6
8.0	48.0
16.0	35.3
24.0	8.16
30.0	10.4

END

DATA Mouse300M5 (T, CBldTCA)

0.25	26.7
0.5	20.4
2.0	42.6
4.0	53.4
8.0	47.6
16.0	43.2
24.0	35.9
30.0	25.0

END

DATA Mouse300M6 (T, AUrnTCA)

24.0	0.707
48.0	1.176
72.0	1.292
96.0	1.304
120.0	1.307
144.0	1.308

END

DATA Mouse600M1 (T, CVen)

0.25	81.9
------	------

0.5	71.3
2.0	5.71
4.0	1.94
8.0	0.965
24.0	1.72
30.0	0.72
40.0	0.71

END

DATA Mouse600M2 (T, CLiv)

0.25	213.5
0.5	163.8
2.0	19.43
4.0	10.63
8.0	0.71
24.0	0.34
30.0	0.26
40.0	0.30

END

DATA Mouse600M3 (T, CFat)

0.25	278.50
0.5	659.0
2.0	468.91
4.0	46.76
8.0	9.48
24.0	0.13
30.0	0.15
40.0	0.12

END

DATA Mouse600M4 (T, CLivTCA)

0.25	11.2
0.5	22.9
2.0	33.5
4.0	39.9
8.0	54.99
16.0	39.06
24.0	28.2
30.0	15.3
40.0	7.6

END

DATA Mouse600M5 (T, CBldTCA)

0.25	11.18
0.5	14.26
2.0	26.98
4.0	31.73
8.0	31.87
16.0	29.48
24.0	24.81
40.0	21.1

END

DATA Mouse600M6 (T, AUrnTCA)

24.0	0.762
48.0	1.683
72.0	1.867
96.0	1.904
120.0	1.927
144.0	1.941

END

DATA Mouse1200M1 (T, CVen)

0.083	165.87
0.17	191.31
0.25	123.52
0.5	86.9
0.75	70.9
1.0	43.08
1.5	35.17
2.0	20.36
3.0	8.97
4.0	7.50
8.0	1.64
12.0	0.72
16.0	0.47
24.0	0.52
30.0	0.43
40.0	0.45

END

DATA Mouse1200M2 (T, CLiv)

0.083	522.6
0.17	585.3
0.25	499.4
0.5	408.0
0.75	289.8
1.0	228.8
1.5	63.04
2.0	38.97
3.0	59.74
4.0	26.5
6.0	15.37
8.0	14.97
16.0	12.86
24.0	1.79
30.0	1.27
40.0	1.42

END

DATA Mouse1200M4 (T, CFat)

0.083	61.53
0.17	156.7
0.25	567.2
0.5	826.0
0.75	865.3
1.5	1199.9
2.0	1050.5
3.0	550.2
4.0	485.0
6.0	219.2
8.0	293.7
16.0	4.400
24.0	1.446
30.0	1.121
40.0	1.507

END

DATA Mouse1200M4 (T, CLivTCA)

0.083	5.69
0.17	6.2
0.25	11.09
0.5	16.95
0.75	20.09
1.0	26.02

1.5	29.44
2.0	35.65
3.0	37.76
4.0	42.07
6.0	43.92
8.0	57.83
16.0	27.71
24.0	22.67
40.0	6.34

END

DATA Mouse1200M5(T, CBldTCA)

0.083	5.01
0.17	11.2
0.25	16.5
0.5	23.1
0.75	29.2
1.0	36.1
1.5	41.8
2.0	59.1
3.0	64.0
4.0	70.2
6.0	94.1
8.0	90.8
16.0	65.2
24.0	43.86
30.0	41.48
40.0	9.15

END

DATA Mouse1200M6(T, AUrnTCA)

24.0	2.294
48.0	3.731
72.0	4.579
96.0	4.796
120.0	4.848
144.0	4.878

END

DATA Mouse2000M1 (T, CVen)

0.25	208.3
0.5	162.01
1.0	140.1
2.0	64.8
4.0	48.6
8.0	17.48
16.0	9.4
24.0	1.15
40.0	0.78

END

DATA Mouse2000M2 (T, CLiv)

0.25	1498.0
0.5	335.0
1.0	379.7
2.0	116.2
16.0	9.2
24.0	2.0
30.0	1.2
40.0	0.3

END

DATA Mouse2000M3 (T, CFat)

0.25	1152.0
0.5	1993.0
1.0	4279.0
2.0	2015.0
4.0	1991.0
8.0	1503.0
16.0	75.5
24.0	7.4

END

DATA Mouse2000M4 (T, CLivTCA)

0.25	15.18
0.5	27.58
1.0	37.49
2.0	49.46
4.0	65.32
8.0	105.65
16.0	59.0
24.0	44.6
30.0	36.35
48.0	9.98

END

DATA Mouse2000M5 (T, CBldTCA)

0.25	11.22
0.5	20.57
1.0	30.34
2.0	43.51
4.0	63.43
16.0	131.85
24.0	51.38
30.0	54.57
48.0	8.74

END

DATA Mouse2000M6 (T, AUrnTCA)

24.0	1.423
48.0	2.486
72.0	3.122
96.0	3.294
120.0	3.395
144.0	3.426
168.0	3.438
192.0	3.450

END

PROCED BernRParam

SET KM=12.0

END

PROCED BernR

! Data from Bernauer et al. (1996) --

Rats

! From procedure BernR in TCENew.cmd

! Rats -- 40, 80, 160 ppm TCE for 6

hours

Rat

ResetDoses

BernRParam

SET BW=0.275

SET Conc=40.0, CC=.FALSE., TChng=6.0,
Days=1.0, TMax=6.0, TStp=50.0

START /NC

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

SET NRWITG=.T., Conc=80.0

START /NC

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

SET Conc=160.0

START /NC

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

PLOT AUrnTCTotMole/run=1,
AUrnTCTotMole/run=2,
AUrnTCTotMole/run=3, /DATA=bernr1
AUrnTCTotMole

PLOT AUrnNDCVCMole/run=1,
AUrnNDCVCMole/run=2,
AUrnNDCVCMole/run=3, /DATA=bernr2
AUrnNDCVCMole

PLOT AUrnTCA/run=1, AUrnTCA/run=2,
AUrnTCA/run=3, /DATA=bernr3 AUrnTCA
PLOT AUrnTCOGTCOH/run=1,
AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
/DATA=bernr4 AUrnTCOGTCOH

PLOT AUrnNDCVC/run=1,
AUrnNDCVC/run=2, AUrnNDCVC/run=3,
/DATA=bernr5 AUrnNDCVC
SET NRWITG=.F.

END

DATA BernR1 (T, AUrnTCTotMole)

48.0	0.0069
48.0	0.0130
48.0	0.0333

END

DATA BernR2 (T, AUrnNDCVCMole)

48.0	0.000007
48.0	0.000010
48.0	0.000013

END

DATA BernR3 (T, AUrnTCA)

12.0	0.061
24.0	0.061
36.0	0.061
48.0	0.061
12.0	0.131
24.0	0.210
36.0	0.256
48.0	0.281
12.0	0.563
24.0	0.858
36.0	0.995
48.0	1.063

END

DATA BernR4 (T, AUrnTCOGTCOH)

12.0	1.166
------	-------

24.0	1.234
36.0	1.309
48.0	1.345
12.0	2.338
24.0	2.827
36.0	3.100
48.0	3.294
12.0	3.850
24.0	4.320
36.0	4.666
48.0	4.937

END

DATA BernR5 (T, AUrnNDCVC)

12.0	5.41e-5
24.0	1.42e-4
36.0	1.95e-4
48.0	2.71e-4
12.0	1.23e-4
24.0	2.63e-4
36.0	4.05e-4
48.0	5.71e-4
12.0	2.13e-4
24.0	6.72e-4
36.0	1.24e-3
48.0	1.59e-3

END

PROCED FisherMR

! Data from Fisher et al. (1991)
! From procedures FG2B and FG2D in
TCENew.cmd

! 505 ppm TCE 4 hr -- Male Rat

Rat

ResetDoses

SET Conc=505.0, CC=.FALSE.,

TChng=4.0, Days=1.0, TMax=24.0,

TStp=33.0

START /NC

PLOT /DATA=fishermr1 CBldTCA

SET Conc=529.0, TStp=11.0

START /NC

PLOT /DATA=fishermr2 CVen

END

DATA FisherMR1 (T, CBldTCA)

1.97	6.445
3.915	11.179
5.986	22.381
7.982	21.866
10.099	20.455
12.099	17.526
26.216	6.232
32.139	4.561

END

DATA FisherMR2 (T, CVen)

1.976	21.091
3.981	34.209
6.031	6.027
8.031	1.662

10.054	0.986
--------	-------

END

PROCED FisherFRParam

SET QPC=15.0, VMaxC=20.0

END

PROCED FisherFR

! Data from Fisher et al. (1991)

! From procedures FG2A and FG2C in

TCENew.cmd

! 600 ppm TCE 4 hr -- Female Rat

Rat

ResetDoses

FisherFRParam

SET Conc=600.0, CC=.FALSE.,

TChng=4.0, Days=1.0, TMax=24.0,

TStp=50.0

START /NC

PLOT /DATA=fisherfr1 CVen

PLOT /DATA=fisherfr2 CBldTCA

END

DATA FisherFR1 (T, CVen)

0.498	9.448
3.556	25.889
4.215	19.272
5.033	6.865
6.009	3.341

END

DATA FisherFR2 (T, CBldTCA)

0.622	2.137
3.677	20.408
4.44	19.485
5.196	31.914
6.175	33.11
8.661	39.233
25.972	11.036
32.033	6.03
49.023	1.362

END

PROCED GargasR

! Data from Andersen et al. (1987)

! Data from CC.dat from Mike Gargas

! Rat Closed Chamber

Rat

ResetDoses

SET BW=0.256

SET Conc=100.0, CC=.TRUE., NRats=3.0,

kLossC=0.01, VChC=9.1

SET TChng=6.0, Days=1.0, TMax=24.0,

TStp=6.0

START /NC

SET NRWITG=.T.

SET BW=0.249, Conc=450.0

START /NC

SET BW=0.274, Conc=1000.0

START /NC

SET BW=0.269, Conc=2000.0

START /NC		3.500	19.00
SET BW=0.272, Conc=4640.0		3.667	17.00
START /NC		3.833	15.00
PLOT CInhPPM/run=1, CInhPPM/run=2,		4.000	14.00
CInhPPM/run=3, CInhPPM/run=4,		4.167	13.00
CInhPPM/run=5, /DATA=gargasr CInhPPM		4.333	11.00
SET NRWITG=.F.		0.083	1741.00
END		0.167	1460.00
		0.333	1076.00
DATA GargasR (T, CInhPPM)		0.500	887.00
0.083 92.30		0.667	697.00
0.167 76.10		0.833	580.00
0.333 54.90		1.000	501.00
0.500 41.00		1.167	427.00
0.667 31.30		1.333	369.00
0.833 21.70		1.500	324.00
1.000 16.30		1.667	276.00
1.167 13.00		1.833	259.00
1.333 10.00		2.000	240.00
1.500 7.90		2.167	236.00
1.667 6.30		2.333	218.00
1.833 5.40		2.500	198.00
2.000 4.80		2.667	195.00
2.167 4.30		2.833	181.00
2.333 3.20		3.000	165.00
0.083 435.00		3.167	162.00
0.167 375.00		3.333	152.00
0.333 270.00		3.500	145.00
0.500 206.00		3.667	138.00
0.667 153.00		3.833	132.00
0.833 116.00		4.000	122.00
1.000 89.20		4.167	113.00
1.167 69.10		4.333	104.00
1.333 50.30		4.500	95.10
1.500 37.40		4.667	88.10
1.667 28.50		4.833	82.30
1.833 22.00		5.000	74.10
2.000 18.20		5.167	62.10
2.167 15.00		5.333	61.90
2.333 11.20		5.500	55.40
2.500 9.52		5.667	52.90
2.667 7.82		5.833	48.30
0.083 884.00		6.000	45.00
0.167 738.00		0.083	3986.00
0.333 519.00		0.167	3333.00
0.500 406.00		0.333	2443.00
0.667 312.00		0.500	1904.00
0.833 259.00		0.667	1553.00
1.000 215.00		0.833	1298.00
1.167 184.00		1.000	1128.00
1.333 152.00		1.167	1004.00
1.500 128.00		1.333	902.00
1.667 111.00		1.500	825.00
1.833 94.00		1.667	775.00
2.000 82.00		1.833	724.00
2.167 70.00		2.000	675.00
2.333 58.00		2.167	661.00
2.500 50.00		2.333	631.00
2.667 45.00		2.500	612.00
2.833 38.00		2.667	591.00
3.000 32.00		2.833	570.00
3.167 26.00		3.000	556.00
3.333 23.00		3.167	538.00

3.333	535.00
3.500	522.00
3.667	512.00
3.833	500.00
4.000	498.00
4.167	486.00
4.333	474.00
4.500	472.00
4.667	465.00
4.833	455.00
5.000	445.00
5.167	439.00
5.333	436.00
5.583	428.00
5.667	418.00
5.833	409.00
6.000	403.00

END

```

PROCED LarsonRParam
  SET FracTCE=0.02, VMaxGlucC=20.0
END

PROCED LarsonR
! Data from Larson and Bull (1992)
! From procedures LarTCE1-LarTCE3,
LarTCA1-LarTCA3, and LarTOH1-LarTOH3
! in TCENew.cmd
! Rat - 200 mg/kg TCE in 1% tween
  Rat
  ResetDoses
  LarsonRParam
  SET PDose=200.0, Days=1.0, TMax=24.0,
TStp=48.0
  START /NC
  PLOT /DATA=larsonr1a CVen
  PLOT /DATA=larsonr1b CBldTCA
  PLOT /DATA=larsonr1c CTCOH

! Rat - 600 mg/kg TCE in 1% tween
  SET PDose=600.0
  START /NC
  PLOT /DATA=larsonr2a CVen
  PLOT /DATA=larsonr2b CBldTCA
  PLOT /DATA=larsonr2c CTCOH

! Rat - 2996 mg/kg TCE in 1% tween
  SET PDose=2996.0, TStp=73.0
  SET ZZERR=39*1.0e-7, ZMERR=39*1.0e-
7
  START /NC
  PLOT /DATA=larsonr3a CVen
  PLOT /DATA=larsonr3b CBldTCA
  PLOT /DATA=larsonr3c CTCOH
END

```

DATA LarsonR1a (T, CVen)	
1.0	9.745938
2.0	5.031306
4.0	2.116854
8.0	1.069596
12.0	0.36135

END

DATA LarsonR1b (T, CBldTCA)	
1.0	5.36769
2.0	7.650388
4.0	11.841598
8.0	12.996836
12.0	10.447796
24.0	1.516352
48.0	0.047386

END

DATA LarsonR1c (T, CTCOH)	
1.0	13.27261
2.0	22.883965
4.0	23.739105
8.0	6.07269
12.0	2.17373
24.0	0.399165

END

DATA LarsonR2a (T, CVen)	
1.0	26.530974
2.0	34.693542
4.0	20.953044
8.0	6.132438
12.0	2.934162
24.0	0.674082

END

DATA LarsonR2b (T, CBldTCA)	
1.0	2.828454
2.0	6.370966
4.0	9.233734
8.0	20.766506
12.0	24.740394
24.0	17.43478
48.0	0.042484

END

DATA LarsonR2c (T, CTCOH)	
1.0	13.47294
2.0	16.94134
4.0	27.195545
8.0	44.252
12.0	32.46542
24.0	4.75111
48.0	0.145015

END

DATA LarsonR3a (T, CVen)	
1.0	69.226776
2.0	185.690538
4.0	120.072006
8.0	98.804916
12.0	55.408752
24.0	7.852464
48.0	0.237834

END

DATA LarsonR3b (T, CBldTCA)	
1.0	4.058856
2.0	10.104656

```

4.0 11.207606
8.0 23.965878
12.0 28.884218
24.0 61.918796
48.0 5.496776
72.0 0.165034
END

```

```

DATA LarsonR3c (T, CTCOH)
1.0 17.48851
2.0 29.883555
4.0 29.961295
8.0 33.76906
12.0 51.827165
24.0 34.89928
48.0 0.86411
END

```

```

PROCED ProutR
! Data from Prout et al. (1985)
! From procedures P3R, P5R, and P6R in
TCENew.cmd
! Rat - 1000 mg/kg TCE in corn oil
Rat
ResetDoses
SET BW=0.19, PDose=1000.0, Days=1.0,
TMax=1.0, TStp=40.0
START /NC
PLOT /DATA=proutr1 CVen
PLOT /DATA=proutr2 CTCOH
PLOT /DATA=proutr3 CBldTCA
END

```

```

DATA ProutR1 (T, CVen)
0.058 5.227
0.201 14.055
0.431 19.529
0.616 24.837
1.358 19.794
1.742 23.578
2.301 42.371
3.015 62.47
4.06 43.553
4.507 40.977
5.121 29.243
5.707 28.869
6.148 28.964
7.105 21.193
8.092 18.967
9.33 13.418
10.354 11.543
11.279 8.631
END

```

```

DATA ProutR2 (T, CTCOH)
1.042 0.802
1.531 0.989
2.105 0.889
2.597 0.778
3.091 0.773
3.48 0.767
4.06 1.092

```

```

4.513 1.256
5.182 0.774
5.55 1.126
6.068 0.933
6.663 1.229
7.149 0.655
8.118 0.918
9.113 1.455
10.001 7.222
11.14 2.062
12.033 2.214
13.026 1.278
13.955 0.592
14.975 1.994
16.041 0.772
17.016 0.92
18.071 0.71

```

END

```

DATA ProutR3 (T, CBldTCA)
2.153 3.391
3.815 4.492
4.723 10.821
6.058 10.155
6.918 14.629
8.071 14.598
9.365 25.456
10.354 18.378
11.496 45.88
12.31 38.522
13.248 49.159
15.695 28.235
17.43 34.252
19.366 44.523
20.272 40.253
21.761 24.383
22.843 18.858
24.838 14.865
25.888 14.386
28.323 22.531
29.447 32.197
30.457 38.11
31.603 32.229
33.151 19.265
34.613 20.718
36.365 20.975
39.99 6.918

```

END

```

PROCED TemplinRParam
SET FractTCE=0.01, VMaxTCOHC=0.06,
VMaxGlucC=150.0, kEHRC=0.3, kAD=0.6
END

```

```

PROCED TemplinR
! Data from Templin et al. (1995)
! From procedures TT, TC, and TS in
TCENew.cmd
! Rat - 100 mg/kg TCE in 2% tween
Rat
ResetDoses

```

```

TemplinRParam
SET BW=0.2, PDose=100.0, Days=1.0,
TMax=24.0, TStp=48.0
START /NC
PLOT /DATA=templinr1 CVen
PLOT /DATA=templinr2 CBldTCA
PLOT /DATA=templinr3 CTCOH
END

```

```

DATA TemplinR1 (T, CVen)

```

0.252	5.627367
0.494	8.889005
0.736	10.184595
0.993	6.760255
1.49	2.313853
1.972	1.55759
2.475	0.922502

```

END

```

```

DATA TemplinR2 (T, CBldTCA)

```

0.252	0.951757
0.494	1.410765
0.728	1.923237
0.984	1.645322
1.958	4.274023
2.475	3.862448
2.984	4.968566
3.987	6.032467
4.97	6.719023
5.97	6.954884
8.979	7.540054
11.98	7.226116
23.963	4.362369
47.986	1.516552

```

END

```

```

DATA TemplinR3 (T, CTCOH)

```

0.233	0.8934
0.482	1.5903
0.728	1.97115
0.961	2.0589
1.463	2.0523
1.962	2.7261
2.455	3.28275
2.958	2.7078
3.972	2.52705
5.017	2.24115
5.984	2.06565
8.964	1.02

```

END

```

```

PROCED BernH

```

```

! Data from Bernauer et al. (1996) --
Human

```

```

! From procedure BernH in TCENew.cmd
! Human -- 40, 80, 160 ppm TCE for 6
hours

```

```

Human

```

```

ResetDoses

```

```

SET Conc=40.0, CC=.FALSE., TChng=6.0,
Days=1.0, TMax=6.0, TStp=54.0

```

```

START /NC

```

```

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

```

```

SET NRWITG=.T., Conc=80.0

```

```

START /NC

```

```

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

```

```

SET Conc=160.0

```

```

START /NC

```

```

D AUrnTCTotMole, AUrnNDCVCMole,
AUrnNDCVC

```

```

PLOT AUrnTCTotMole/run=1,
AUrnTCTotMole/run=2,
AUrnTCTotMole/run=3, /DATA=bernh1
AUrnTCTotMole

```

```

PLOT AUrnNDCVCMole/run=1,
AUrnNDCVCMole/run=2,
AUrnNDCVCMole/run=3, /DATA=bernh2
AUrnNDCVCMole

```

```

PLOT AUrnTCA/run=1, AUrnTCA/run=2,
AUrnTCA/run=3, /DATA=bernh3 AUrnTCA

```

```

PLOT AUrnTCOGTCOH/run=1,
AUrnTCOGTCOH/run=2, AUrnTCOGTCOH/run=3,
/DATA=bernh4 AUrnTCOGTCOH

```

```

PLOT AUrnNDCVC/run=1,
AUrnNDCVC/run=2, AUrnNDCVC/run=3,
/DATA=bernh5 AUrnNDCVC

```

```

SET NRWITG=.F.

```

```

END

```

```

DATA BernH1 (T, AUrnTCTotMole)

```

54.0	0.823
54.0	1.775
54.0	3.080

```

END

```

```

DATA BernH2 (T, AUrnNDCVCMole)

```

54.0	0.00025
54.0	0.00037
54.0	0.00043

```

END

```

```

DATA BernH3 (T, AUrnTCA)

```

6.0	0.84
11.0	1.56
16.0	3.37
23.0	6.19
30.0	9.73
35.0	11.49
40.0	13.20
47.0	15.14
54.0	16.46
6.0	2.06
11.0	4.27
16.0	6.52
23.0	10.49
30.0	17.08
35.0	21.57
40.0	26.87
47.0	31.84

54.0	37.96
6.0	2.29
11.0	5.71
16.0	10.74
23.0	18.57
30.0	28.08
35.0	34.58
40.0	41.75
47.0	49.31
54.0	57.51

END

DATA BernH4 (T, AUrnTCOGTCOH)

6.0	12.65
11.0	28.58
16.0	43.41
23.0	53.72
30.0	65.12
35.0	73.70
40.0	81.61
47.0	88.40
54.0	93.21
6.0	37.44
11.0	79.43
16.0	112.69
23.0	145.30
30.0	173.21
35.0	188.35
40.0	201.73
47.0	217.09
54.0	230.08
6.0	52.50
11.0	113.78
16.0	168.73
23.0	222.17
30.0	243.14
35.0	263.43
40.0	280.17
47.0	294.98
54.0	311.45

END

DATA BernH5 (T, AUrnNDCVC)

6.0	0.0015
11.0	0.0028
16.0	0.0049
23.0	0.0068
30.0	0.0124
35.0	0.0144
40.0	0.0163
47.0	0.0180
54.0	0.0193
6.0	0.0035
11.0	0.0055
16.0	0.0113
23.0	0.0152
30.0	0.0262
35.0	0.0306
40.0	0.0347
47.0	0.0384
54.0	0.0416
6.0	0.0051
11.0	0.0118

16.0	0.0225
23.0	0.0301
30.0	0.0368
35.0	0.0382
40.0	0.0447
47.0	0.0531
54.0	0.0577

END

PROCED MonsterParam

SET VBodC=0.12, VMaxc=18.0,
VMaxTCOHC=12.0, kUrnTCAC=0.15
END

PROCED Monster

! Data from Monster et al. (1979)
! From procedures AF3A-AF3F and AF5A-
AF5D in TCENew.cmd
! 70 ppm TCE -- Human

Human

ResetDoses

MonsterParam

SET Conc=70.0, CC=.FALSE., TChng=4.0,
Days=5.0, TMax=150.0, TStp=340.0

START /NC

PLOT /DATA=monster1 CVen

PLOT /DATA=monster2 CBldTCA

PLOT /DATA=monster3 AUrnTCA

PLOT /DATA=monster4 CalvPPM

PLOT /DATA=monster5 TotCTCOH

PLOT /DATA=monster6 AUrnTCOGTCOH

END

DATA Monster1 (T, CVen)

4.0	2.2
5.4	0.33
22.0	0.014
28.0	2.2
29.4	0.3
46.0	0.02
52.0	2.2
53.4	0.33
70.0	0.027
76.0	2.2
77.4	0.365
94.0	0.027
100.0	2.209
101.4	0.361
118.0	0.03

END

DATA Monster2 (T, CBldTCA)

2.807	4.484
3.899	7.958
22.0	13.177
27.956	21.134
45.658	24.953
48.779	33.159
52.451	33.057
69.989	36.207
75.3	38.465
75.772	43.948

94.43	48.398
98.451	50.838
100.291	51.825
118.458	50.265
165.324	38.583
237.579	21.545
334.247	9.462

END

DATA Monster3 (T, AUrnTCA)

2.277	1.607
10.14	5.542
17.883	9.98
26.19	16.14
33.796	27.248
41.501	35.067
49.78	48.356
57.61	65.827
66.042	77.979
74.02	96.759
81.924	121.256
90.081	141.155
98.153	167.439
106.014	198.695
114.175	218.116
122.134	246.406
129.989	273.143
138.0	289.619
146.006	308.377
153.675	328.452
161.622	342.279
169.804	348.791
177.792	357.064
185.706	362.083

END

DATA Monster4 (T, CALvPPM)

1.041	8.909
1.959	8.914
2.942	13.337
3.969	14.060
4.949	18.097
5.968	13.956
6.368	5.407
7.007	2.765
7.032	4.025
8.016	2.589
9.026	1.549
9.991	0.770
11.987	0.388
13.978	0.393
24.586	0.199
35.520	0.103
48.493	0.065
59.576	0.061
0.030	1.280
1.009	6.968
2.018	8.344
2.970	10.207
3.989	11.057
4.966	13.605
5.924	11.602
6.077	6.861

6.269	5.581
6.434	3.635
6.919	2.997
7.426	2.488
7.895	2.396
8.892	1.532
9.913	1.342
13.902	0.681
23.996	0.420

END

DATA Monster5 (T, TotCTCOH)

0.984	0.775
2.034	1.807
3.006	2.638
4.009	3.490
5.044	4.332
6.007	5.941
6.216	4.647
6.646	4.943
7.010	5.030
8.018	4.589
9.008	3.715
9.997	3.719
12.005	3.129
14.007	2.771
24.546	1.265
35.566	0.829
49.399	0.336
59.480	0.245
0.025	0.024
1.003	1.010
3.025	2.419
4.058	3.367
5.082	3.675
6.051	4.477
6.396	4.525
6.523	4.477
6.798	4.444
7.040	4.401
7.597	4.031
8.101	4.006
9.099	3.623
10.090	3.082
14.034	2.399
23.999	1.069

END

DATA Monster6 (T, AUrnTCOGTCOH)

3.912	51.482
11.904	106.747
20.184	138.360
27.984	202.971
36.072	284.271
44.064	320.665
52.128	393.523
60.312	471.060
68.232	512.698
76.368	591.433
84.552	671.339
92.736	717.257
100.704	795.718

```

108.696      884.483
116.472      928.646
124.656      959.874
132.672      976.041
140.760      986.787
148.344      998.355
156.192      1006.748
163.992      1012.067
243.912      1014.424
251.976      1016.263
259.968      1017.808
END

```

```

PROCED Monster2
! Data from Monster et al. (1979)
! From procedure Monster in HumanB.cmd
! Male
  Human
  ResetDoses
  SET BW=69.7
  SET Conc=70.0, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=220.0
  START /NC
  PLOT /DATA=mon70a CBldTCA
  PLOT /DATA=mon70b AUrnTCOGTCOH
  PLOT /DATA=mon70c AUrnTCA
  PLOT /DATA=mon70d CTCOH

```

```

  SET Conc=140.0
  START /NC
  PLOT /DATA=mon140a CBldTCA
  PLOT /DATA=mon140b AUrnTCOGTCOH
  PLOT /DATA=mon140c AUrnTCA
  PLOT /DATA=mon140d CTCOH
END

```

```

DATA Mon70a (T, CBldTCA)
  4.0  3.5
  6.0  5.1
 24.0  8.19
 48.0  8.97
 72.0  8.58
144.0  5.07
216.0  2.73
END

```

```

DATA Mon70b (T, AUrnTCOGTCOH)
  6.0  35.3
 14.0  86.4
 22.0 113.4
 30.0 133.7
 38.0 143.5
 46.0 149.2
 54.0 153.4
 62.0 158.1
 70.0 160.7
END

```

```

DATA Mon70c (T, AUrnTCA)
 22.0  7.0
 46.0 18.7
 70.0 26.5

```

```

END
DATA Mon70d (T, CTCOH)
  4.0  4.4
  6.0  4.1
 24.0  0.91
END

```

```

DATA Mon140a (T, CBldTCA)
  4.0  3.8
  6.0  6.0
 24.0 11.3
 48.0 12.8
 72.0 11.3
144.0  7.55
216.0  4.5
END

```

```

DATA Mon140b (T, AUrnTCOGTCOH)
  6.0  55.1
 14.0 153.9
 22.0 206.8
 30.0 243.3
 38.0 265.3
 46.0 276.4
 54.0 284.0
 62.0 290.0
END

```

```

DATA Mon140c (T, AUrnTCA)
 22.0  7.6
 46.0 24.1
 70.0 42.3
END

```

```

DATA Mon140d (T, CTCOH)
  4.0  6.4
  6.0  7.2
 24.0  2.5
 48.0  0.6
END

```

```

PROCED MullerSingleParam
  SET VBodC=0.12, kUrnTCAC=0.15
END

```

```

PROCED MullerSingle
! Data from Muller et al. (1974, 1975)
! From procedures AF7A-AF7D in
TCENew.cmd
! 100 ppm TCE -- Human
  Human
  ResetDoses
  MullerSingleParam
  SET Conc=100.0, CC=.FALSE.,
TChng=6.0, Days=1.0, TMax=24.0,
TStp=75.0
  START /NC
  PLOT /DATA=mullersingle1 CVen
  PLOT /DATA=mullersingle2 CBldTCA
  PLOT /DATA=mullersingle3 AUrnTCA
  PLOT /DATA=mullersingle4 TotCTCOH

```

PLOT /DATA=mullersingle5 AUrnTCOGTCOH
PLOT /DATA=mullersingle6 CALvPPM
END

DATA MullerSingle1 (T, CVen)

0.965	0.67
1.879	1.105
2.9	0.961
3.876	0.859
4.8	0.994
5.992	1.093
6.396	0.756
6.736	0.539
7.851	0.323
8.86	0.217
9.915	0.179
11.853	0.14
13.741	0.11
23.769	0.072
35.864	0.034
47.915	0.031
59.823	0.023
1.021	0.804
2.954	1.014
3.944	1.407
4.921	1.1
5.898	1.318
6.195	0.93
6.369	0.617
6.749	0.732
7.362	0.561
7.887	0.441
8.891	0.381
9.897	0.289
13.864	0.16
23.731	0.073

END

DATA MullerSingle2 (T, CBldTCA)

0.974	2.553
2.032	8.048
3.965	12.369
5.913	19.65
7.946	26.426
9.915	31.304
11.92	36.274
13.897	39.523
13.902	39.419
23.873	47.577
35.93	43.756
48.006	40.306
59.891	38.657
1.996	4.038
4.0	8.087
6.011	13.162
8.011	17.286
10.006	19.154
13.985	20.938
23.887	28.444

END

DATA MullerSingle3 (T, AUrnTCA)

23.826	41.585
--------	--------

47.946	86.675
72.156	122.458
2.970	0.484
6.457	3.771
8.533	6.289
10.468	10.26
23.859	25.593

END

DATA MullerSingle4 (T, TotCTCOH)

0.984	0.775
2.032	1.807
3.006	2.638
4.009	3.490
5.044	4.332
6.007	5.941
6.216	4.647
6.646	4.943
7.008	5.030
8.017	4.589
9.008	3.715
9.994	3.719
12.005	3.129
14.007	2.771
24.546	1.265
35.566	0.829
49.399	0.336
59.480	0.245
0.027	0.024
1.006	1.010
3.025	2.419
4.058	3.367
5.082	3.675
6.051	4.477
6.396	4.525
6.523	4.477
6.798	4.444
7.040	4.401
7.597	4.031
8.101	4.006
9.099	3.623
10.090	3.082
14.034	2.399
23.997	1.069

END

DATA MullerSingle5 (T, AUrnTCOGTCOH)

24.0	245.244
48.0	301.207
72.0	316.49
3.158	18.6
6.573	71.2
8.634	107.2
10.627	142.3
24.47	233.1

END

DATA MullerSingle6 (T, CALvPPM)

1.041	8.909
1.959	8.914
2.942	13.337
3.965	14.060
4.949	18.097

```

5.968 13.956
6.368 5.407
7.008 2.765
7.032 4.025
8.017 2.589
9.026 1.549
9.994 0.770
11.987 0.388
13.978 0.393
24.586 0.199
35.520 0.103
48.493 0.065
59.576 0.061
0.027 1.280
1.006 6.968
2.018 8.344
2.970 10.207
3.989 11.057
4.966 13.605
5.924 11.602
6.077 6.861
6.269 5.581
6.434 3.635
6.919 2.997
7.426 2.488
7.895 2.396
8.891 1.532
9.913 1.342
13.902 0.681
23.997 0.420
END

PROCED MullerMultiParam
  SET VMaxC=8.0, VMaxTCOHC=30.0
END

PROCED MullerMulti
! Data from Muller et al. (1974, 1975)
! From procedures AF7A-AF7D in
TCENew.cmd
! 50 ppm TCE -- Human
Human
ResetDoses
MullerMultiParam
  SET Conc=50.0, CC=.FALSE., TChng=6.0,
Days=5.0, TMax=150.0, TStp=430.0
  START /NC
  PLOT /DATA=mullermulti1 CBldTCA
  PLOT /DATA=mullermulti2 AUrnTCA
  PLOT /DATA=mullermulti3 TotCTCOH
  PLOT /DATA=mullermulti4 AUrnTCOGTCOH
END

DATA MullerMulti1 (T, CBldTCA)
0.338 5.501
7.905 13.882
9.745 17.048
23.744 17.932
29.249 27.023
32.948 29.95
46.87 27.981
52.887 36.986

```

```

57.38 38.724
71.086 35.964
76.223 42.944
80.282 43.978
94.18 41.804
100.307 49.053
104.611 51.055
118.7 49.005
142.839 42.958
201.431 29.181
249.517 19.104
287.758 15.022
345.641 11.051
419.058 5.815
END

DATA MullerMulti2 (T, AUrnTCA)
22.913 19.094
46.855 57.6
69.715 124.243
93.319 198.682
117.8 297.932
141.622 386.56
END

DATA MullerMulti3 (T, TotCTCOH)
13.800 1.703
18.312 1.318
32.520 0.428
38.616 2.079
42.480 1.318
56.088 0.606
62.880 2.197
67.176 1.513
80.424 0.710
86.736 2.257
90.720 1.519
104.184 0.649
110.784 2.270
115.080 1.640
129.672 0.665
155.304 0.202
212.664 0.075
END

DATA MullerMulti4 (T, AUrnTCOGTCOH)
24.0 102.573
48.0 236.288
72.0 380.370
96.0 529.931
120.0 687.668
144.0 721.680
192.0 725.865
240.0 728.355
END

PROCED Muller72
! Data from Muller et al. (1972)
! From procedure Muller72 in HumanB.cmd
! Male
Human
ResetDoses

```

SET Conc=50.0, CC=.FALSE., TChng=6.0,
Days=1.0, TMax=24.0, TStp=25.0

START /NC

PLOT /DATA=muller72a CBldTCA

PLOT /DATA=muller72b CTCOH

PLOT /DATA=muller72c AUrnTCOGTCOH

PLOT /DATA=muller72d AUrnTCA

END

! CBldTCA, TCA data divided by 2,
plasma to whole blood conversion

DATA Muller72a (T, CBldTCA)

7.0 2.9

13.0 7.1

17.0 8.9

END

DATA Muller72b (T, CTCOH)

16.0 1.7

20.0 1.3

END

DATA Muller72c (T, AUrnTCOGTCOH)

24.0 100.8

END

DATA Muller72d (T, AUrnTCA)

24.0 18.4

END

PROCED Muller74

! Data from Muller et al. (1974)

! From procedure Muller74 in HumanB.cmd

! Male

Human

ResetDoses

SET Conc=100.0, CC=.FALSE.,
TChng=6.0, Days=1.0, TMax=24.0,
TStp=75.0

START /NC

PLOT /DATA=muller74a CVen

PLOT /DATA=muller74b CTCOH

PLOT /DATA=muller74c CBldTCA

PLOT /DATA=muller74d CALvPPM

PLOT /DATA=muller74e AUrnTCOGTCOH

PLOT /DATA=muller74f AUrnTCA

END

! TCA data divided by 2 to account for
plasma

DATA Muller74a (T, CVen)

0.97 0.67

1.92 1.05

3.0 0.93

3.97 0.83

5.00 1.02

5.95 1.02

6.38 0.72

6.53 0.52

7.98 0.31

8.99 0.21

10.0 0.18

END

DATA Muller74b (T, CTCOH)

0.97 0.76

1.92 1.74

3.0 2.51

3.97 3.43

5.00 4.18

5.95 5.75

6.38 5.02

6.53 4.47

7.98 4.42

8.99 3.54

10.0 3.59

12.0 3.03

14.0 2.61

24.5 1.24

35.59 0.8

48.5 0.33

END

DATA Muller74c (T, CBldTCA)

0.97 1.2

1.92 3.8

3.97 5.9

5.95 9.4

7.98 13.1

10.0 14.3

12.0 16.7

14.0 19.1

24.5 23.3

35.59 21.8

48.5 19.7

59.5 18.7

END

DATA Muller74d (T, CALvPPM)

0.97 9.0

1.92 9.0

3.0 13.44

3.97 14.27

5.00 18.34

5.95 14.06

6.38 5.37

6.53 3.94

7.98 2.52

8.99 1.5

10.0 0.76

12.0 0.37

END

DATA Muller74e (T, AUrnTCOGTCOH)

24.5 244.8

48.5 300.8

72.0 315.9

END

DATA Muller74f (T, AUrnTCA)

24.5 43.2

48.5 88.1

72.0 133.5

END

```

PROCED StewartParam
  SET VMaxC=5.0
END

PROCED Stewart
! Data from Stewart et al. (1970)
! From procedures AF6A, AF6B, and AF6C
in TCENew.cmd
! 200 ppm TCE -- Human
  Human
  ResetDoses
  SET ZZERR=39*1.0e-7, ZMERR=39*1.0e-
7
  StewartParam
  SET Conc=200.0, CC=.FALSE.,
TChng=7.0, Days=5.0, TMax=150.0, ...
  TStp=410.0
  START /NC
  PLOT /DATA=stewart1 CalvPPM
  PLOT /DATA=stewart2 AUrnTCA
  PLOT /DATA=stewart3 AUrnTCOGTCOH
END

DATA Stewart1 (T, CalvPPM)
  3.399 10.264
  3.135 75.053
  8.505 10.84
  9.198 8.306
  11.141 5.108
  14.287 3.315
  23.69 1.207
  27.506 10.935
  32.604 11.376
  32.965 9.629
  34.996 4.435
  38.121 2.753
  47.419 1.602
  51.096 75.077
  51.43 11.628
  56.358 12.144
  56.589 8.984
  59.26 3.528
  61.543 2.448
  71.645 1.616
  75.282 8.477
  79.185 8.686
  81.269 7.745
  82.919 3.548
  86.226 2.931
  95.579 1.648
  99.343 8.523
  103.74 8.834
  105.49 8.082
  107.159 3.686
  110.124 2.926
END

DATA Stewart2 (T, AUrnTCA)
  23.928 51.208
  47.574 225.786
  71.475 455.927
  95.852 761.268

```

```

119.615 1154.375
143.872 1402.376
168.119 1594.802
191.701 1713.81
215.25 1813.51
239.152 1858.527
263.597 1927.884
END

DATA Stewart3 (T, AUrnTCOGTCOH)
  24.0 308.0
  48.0 667.0
  72.0 1066.0
  96.0 1604.0
  120.0 2009.0
  144.0 2154.0
  168.0 2303.0
  192.0 2355.0
  216.0 2395.0
  240.0 2410.0
  264.0 2414.0
  336.0 2428.0
  408.0 2442.0
END

PROCED Triebig
! Data from Triebig et al. (1976)
! From procedure Triebig in HumanB.cmd
! Male
  Human
  ResetDoses
  SET Conc=136.0, CC=.FALSE.,
TChng=6.0, Days=1.0, TMax=24.0,
TStp=25.0
  START /NC
  PLOT /DATA=triebig1 CVen
  PLOT /DATA=triebig2 CTCOH
  PLOT /DATA=triebig3 CBldTCA
  PLOT /DATA=triebig4 CalvPPM
END

DATA Triebig1 (T, CVen)
  6.0 1.3
END

DATA Triebig2 (T, CTCOH)
  6.0 6.2
  24.0 3.8
END

DATA Triebig3 (T, CBldTCA)
  6.0 12.1
  24.0 32.8
END

DATA Triebig4 (T, CalvPPM)
  6.0 31.9
  24.0 4.6
END

PROCED M60

```

```

! Data from Fisher et al. (1998)
! Data from procedure M60 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3
  Human
  ResetDoses
  SET BW=71.1, VFatC=0.14
  SET Conc=55.2, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0
  START /NC
  PLOT /DATA=m60a CVen
  PLOT /DATA=m60b CTCOH
  PLOT /DATA=m60c CBldTCA
  PLOT /DATA=m60d AUrnTCA
  PLOT /DATA=m60e AUrnTCOGTCOH

```

END

DATA M60a (T, CVen)

0.58	1.89
0.98	1.36
2.02	2.68
3.02	2.67
4.02	2.79
4.25	2.42
4.44	1.52
5.02	0.82
5.83	0.37
8.0	0.29

END

DATA M60b (T, CTCOH)

0.58	0.63
0.98	1.07
2.02	1.57
3.02	1.90
4.02	1.94
4.25	2.02
4.44	2.26
5.02	1.02
5.83	0.96
8.0	1.65
10.0	1.38
12.0	1.26
14.17	1.13
16.02	1.03
18.02	1.05
20.0	0.90

END

DATA M60c (T, CBldTCA)

0.58	0.43
0.98	0.55
2.02	1.07
3.02	1.57
4.02	1.96
4.25	2.01
4.44	2.19
5.02	2.28
5.83	2.52
8.0	2.92
10.0	3.20
12.0	3.56
14.17	4.19

16.02	3.90
18.02	4.95
20.0	5.04
22.0	5.08
44.83	5.51
68.72	9.45
93.12	4.27

END

DATA M60d (T, AUrnTCA)

0.5	0.002
3.12	0.082
4.63	0.184
5.45	0.249
6.45	0.307
8.13	0.539
10.17	0.852
12.15	1.35
14.27	1.78
16.13	2.12
18.15	2.48
20.2	2.89
22.22	3.48
24.22	4.28
32.85	5.35
34.22	5.66
39.85	6.72
44.25	7.42
47.25	8.14
52.13	8.93
58.59	10.17
67.75	11.19
72.37	12.56
77.15	13.78
82.92	14.44
91.83	15.63

END

DATA M60e (T, AUrnTCOGTCOH)

0.5	0.0
3.12	8.24
4.63	11.60
5.45	13.64
6.45	15.64
8.13	19.73
10.17	23.26
12.15	28.95
14.27	28.95
16.13	29.79
18.15	32.07
20.2	34.21
22.22	38.49
24.22	43.06
32.85	47.48
34.22	48.60
39.85	52.15
44.25	53.88
47.25	55.21
52.13	57.21
58.59	59.15
67.75	60.89
72.37	61.46
77.15	61.84

82.92 62.20
91.83 62.56
END

PROCED M50_1
! Data from Fisher et al. (1998)
! Data from procedure M50_1 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3
Human
ResetDoses
SET BW=52.3, VFatC=0.1
SET Conc=53.1, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
START /NC
PLOT /DATA=m50_1a CVen
PLOT /DATA=m50_1b CTCOH
PLOT /DATA=m50_1c CBldTCA
PLOT /DATA=m50_1d AUrnTCA
PLOT /DATA=m50_1e AUrnTCOGTCOH
END

DATA M50_1a (T, CVen)
0.5 0.67
1.0 1.37
2.03 1.96
3.0 1.92
4.02 2.08
4.25 1.13
4.5 0.76
5.02 0.42
6.02 0.30
8.08 0.21
10.0 0.15
END

DATA M50_1b (T, CTCOH)
1.0 0.43
2.03 1.20
3.0 1.26
4.02 1.69
4.25 1.66
4.5 1.60
5.02 1.58
6.02 1.51
8.08 1.44
10.0 1.52
12.0 1.14
14.0 1.05
16.0 1.04
18.0 1.06
20.0 0.45
22.0 0.75
END

DATA M50_1c (T, CBldTCA)
1.0 0.29
2.03 0.77
3.0 1.33
4.02 1.84
4.25 1.93
4.5 2.07

5.02 2.27
6.02 2.94
8.08 3.58
10.0 3.72
12.0 3.98
14.0 4.40
16.0 4.58
18.0 4.86
20.0 5.73
22.0 4.22
44.78 5.00
68.72 4.72
100.4 4.47
END

DATA M50_1d (T, AUrnTCA)
5.25 1.00
5.97 1.53
8.0 3.34
10.17 6.01
12.17 7.60
14.17 13.02
16.17 14.83
18.17 16.67
20.17 18.69
22.17 21.30
25.0 21.95
29.83 26.24
37.83 31.79
44.83 40.44
45.67 40.86
49.67 42.64
53.33 42.94
61.23 43.80
62.83 44.54
79.1 48.73
END

DATA M50_1e (T, AUrnTCOGTCOH)
5.25 5.26
5.97 8.23
8.0 13.05
10.17 16.30
12.17 19.05
14.17 24.62
16.17 26.97
18.17 29.06
20.17 30.62
22.17 32.53
25.0 33.35
29.83 35.43
37.83 37.99
44.83 38.21
45.67 39.06
49.67 39.63
53.33 39.70
61.23 39.90
62.83 40.23
79.1 40.67
END

PROCED M50_2

```

! Data from Fisher et al. (1998)
! Data from procedure M50_2 (in Bld50_M
and Urin50_M) in HumanB.cmd
! Male 50 ppm exposure, n=3

```

```

Human
ResetDoses
SET BW=69.3, VFatC=0.27
SET Conc=49.3, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0
START /NC
PLOT /DATA=m50_2a CVen
PLOT /DATA=m50_2b CTCOH
PLOT /DATA=m50_2c CBldTCA
PLOT /DATA=m50_2d AUrnTCA
PLOT /DATA=m50_2e AUrnTCOGTCOH
END

```

```
DATA M50_2a (T, CVen)
```

0.5	0.61
1.0	0.74
2.0	1.11
3.0	1.01
4.0	1.05
4.25	0.81
4.5	0.46

```
END
```

```
DATA M50_2b (T, CTCOH)
```

0.5	0.44
1.0	0.55
2.0	0.83
3.0	1.08
4.0	1.35
4.25	1.26
4.5	1.34
5.0	1.11
6.0	1.01
8.0	0.9
10.0	0.76
14.0	0.66
16.0	0.63
18.0	0.56
20.0	0.51

```
END
```

```
DATA M50_2c (T, CBldTCA)
```

0.5	0.29
1.0	0.65
2.0	1.47
3.0	2.27
4.0	2.91
4.25	2.99
4.5	3.12
5.0	3.49
6.0	3.66
8.0	4.29
10.0	4.69
12.0	5.11
14.0	5.17
16.0	5.26
18.0	5.66
20.0	5.18
22.0	5.69

49.08	6.67
71.72	6.49
97.47	6.01

```
END
```

```
DATA M50_2d (T, AUrnTCA)
```

4.55	0.041
5.08	0.062
6.06	0.15
8.08	0.26
10.06	0.41
12.08	0.53
14.08	0.65
16.08	0.80
18.08	0.92
20.08	1.05
22.17	1.18
31.33	1.46
49.0	2.20
64.33	3.61
77.0	4.36
86.25	5.03

```
END
```

```
DATA M50_2e (T, AUrnTCOGTCOH)
```

4.55	8.45
5.08	15.20
6.06	21.60
8.08	28.09
10.06	35.67
12.08	39.98
14.08	43.78
16.08	47.68
18.08	50.54
20.08	53.03
22.17	55.30
31.33	60.62
49.0	69.80
64.33	73.15
77.0	74.82
86.25	76.02

```
END
```

```
PROCED F50_1
```

```

! Data from Fisher et al. (1998)
! Data from procedure F50_1 (in Bld50_F
and Urin50_F) in HumanB.cmd
! Female 50 ppm exposure, n=2

```

```

Human
ResetDoses
SET BW=62.3, VFatC=0.24
SET Conc=53.0, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=110.0
START /NC
PLOT /DATA=f50_1a CVen
PLOT /DATA=f50_1b CTCOH
PLOT /DATA=f50_1c CBldTCA
PLOT /DATA=f50_1d AUrnTCA
PLOT /DATA=f50_1e AUrnTCOGTCOH
END

```

```
DATA F50_1a (T, CVen)
```

0.5	0.93
1.0	1.33
2.0	1.65
3.0	1.85
4.0	1.45
4.27	0.94
4.55	0.63
5.10	0.32
6.0	0.18

END

DATA F50_1b (T, CTCOH)

1.0	0.33
2.0	0.63
3.0	0.79
4.0	0.98
4.27	0.83
4.55	0.83
5.10	0.90
6.0	0.89
8.0	0.76
10.0	0.66
12.0	0.67
14.0	0.54
16.05	0.48
18.0	0.47
22.0	0.35

END

DATA F50_1c (T, CBldTCA)

1.0	0.38
2.0	1.23
3.0	1.96
4.0	2.80
4.27	2.81
4.55	3.23
5.10	3.34
6.0	3.72
8.0	4.88
10.0	4.93
12.0	5.28
14.0	5.18
16.05	5.37
18.0	6.03
20.02	4.87
22.0	6.66
44.92	6.66
68.86	5.27
100.44	2.27

END

DATA F50_1d (T, AUrnTCA)

5.25	1.35
5.97	4.49
8.0	7.17
10.17	9.38
12.17	10.36
14.17	11.91
16.17	13.46
18.17	14.70
20.17	15.64
22.17	16.49
25.0	22.11

29.83	23.27
37.83	26.03
44.83	27.35
49.67	33.94
53.33	35.83
61.23	42.58
62.83	43.36
67.92	50.68
75.75	52.36
79.63	53.79
96.67	54.16
96.92	55.93

END

DATA F50_1e (T, AUrnTCOGTCOH)

5.25	4.42
5.97	6.71
8.0	12.00
10.17	15.40
12.17	16.73
14.17	20.35
16.17	23.49
18.17	25.44
20.17	25.44
22.17	26.96
25.0	30.55
29.83	32.71
37.83	34.38
44.83	34.88
49.67	37.25
53.33	38.53
61.23	41.16
62.83	41.38
67.92	43.01
75.75	43.29
79.63	43.53
96.67	43.66
96.92	43.85

END

PROCED F60_1

! Data from Fisher et al. (1998)
! Data from procedure F60_1 (in Bld50_F
and Urin50_F) in HumanB.cmd

! Female 50 ppm exposure, n=2

Human

ResetDoses

SET BW=66.5, VFatC=0.32

SET Conc=55.1, CC=.FALSE., TChng=4.0,
Days=1.0, TMax=24.0, TStp=100.0

START /NC

PLOT /DATA=f60_1a CVen

PLOT /DATA=f60_1b CTCOH

PLOT /DATA=f60_1c CBldTCA

PLOT /DATA=f60_1d AUrnTCA

PLOT /DATA=f60_1e AUrnTCOGTCOH

END

DATA F60_1a (T, CVen)

0.58	1.00
1.02	1.29
2.0	1.38

3.0	1.70
4.0	1.72
4.25	1.08
4.47	1.17
5.0	0.55
6.0	0.39
8.03	0.22

END

DATA F60_1b (T, CTCOH)

0.58	0.32
1.02	0.49
2.0	0.85
3.0	0.97
4.0	1.20
4.25	1.14
4.47	1.18
5.0	1.13
9.98	0.70
12.0	0.60
14.02	0.52
16.0	0.55
18.03	0.54
20.0	0.45
22.0	0.35

END

DATA F60_1c (T, CBldTCA)

0.58	0.16
1.02	0.46
2.0	1.15
3.0	1.53
4.0	1.90
4.25	2.10
4.47	2.18
5.0	2.13
6.0	2.56
8.03	3.32
9.98	2.83
12.0	2.98
14.02	3.42
16.0	3.44
18.03	3.31
20.0	4.15
22.0	4.07
44.33	3.70
68.32	3.31
93.38	1.02

END

DATA F60_1d (T, AUrnTCA)

4.58	0.64
5.26	0.76
6.12	0.85
8.12	1.83
10.18	2.57
12.18	3.36
14.32	3.94
16.18	5.12
18.16	6.03
20.25	6.67
22.53	7.30
23.25	7.60

25.25	7.96
27.58	8.60
29.5	8.89
30.92	9.21
32.92	9.86
35.0	9.66
39.83	11.19
42.0	11.85
43.08	12.35
44.72	12.73
46.5	13.49
49.83	14.31
52.00	15.73
53.59	16.12
54.53	16.34
56.83	16.93
58.5	17.24
59.25	17.85
63.83	18.13
68.28	18.53
70.67	19.18
72.78	19.42
74.75	20.00
76.92	20.58
80.33	20.79
81.50	20.93
82.42	21.82
83.5	21.37
90.25	21.56
91.42	21.69
92.33	21.87

END

DATA F60_1e (T, AUrnTCOGTCOH)

4.58	20.08
5.26	22.91
6.12	24.87
8.12	28.94
10.18	36.46
12.18	39.14
14.32	42.64
16.18	45.16
18.16	53.64
20.25	56.34
22.53	57.08
23.25	57.64
25.25	58.45
27.58	60.33
29.5	61.44
30.92	62.83
32.92	67.36
35.0	68.30
39.83	69.92
42.0	70.88
43.08	71.09
44.72	71.59
46.5	71.99
49.83	72.60
52.00	73.60
53.59	73.93
54.53	74.27
56.83	74.26
58.5	74.56

59.25	74.71
63.83	74.77
68.28	75.16
70.67	75.34
72.78	75.52
74.75	75.75
76.92	75.81
80.33	76.05
81.50	76.06
82.42	76.12
83.5	76.15
90.25	76.30
91.42	76.34
92.33	76.39

END

```

PROCED M100_1
! Data from Fisher et al. (1998)
! Data from procedure M100_1 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
Human
ResetDoses
SET BW=71.4, VFatC=0.17
SET Conc=105.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=m100_1a CVen
PLOT /DATA=m100_1b CTCOH
PLOT /DATA=m100_1c CBldTCA
PLOT /DATA=m100_1d AUrnTCA
PLOT /DATA=m100_1e AUrnTCOGTCOH
END

```

DATA M100_1a (T, CVen)

0.52	1.98
1.0	2.69
2.0	3.38
3.0	3.76
4.0	3.95
4.25	3.26
4.5	2.54
5.0	1.12
6.0	0.72
8.0	0.52
10.0	0.31
12.0	0.28
14.0	0.23
16.0	0.17
18.0	0.15

END

DATA M100_1b (T, CTCOH)

1.0	0.39
2.0	1.30
3.0	2.18
4.0	2.83
4.25	2.94
4.5	3.21
5.0	2.78
6.0	2.84

8.0	2.52
10.0	2.03
12.0	1.56
14.0	1.56
16.0	1.31
18.0	1.21
20.03	1.15

END

DATA M100_1c (T, CBldTCA)

0.52	0.15
1.0	0.50
2.0	1.07
3.0	2.11
4.0	3.12
4.25	2.87
4.5	3.39
5.0	4.00
6.0	4.09
8.0	4.76
10.0	5.52
12.0	6.16
14.0	6.48
16.0	8.12
18.0	7.18
20.03	8.56
22.02	8.14
45.83	9.30
69.74	7.37
93.75	6.97

END

DATA M100_1d (T, AUrnTCA)

4.5	1.47
6.1	2.82
8.0	5.02
10.1	7.10
11.4	8.87
12.1	10.22
14.1	12.67
16.0	15.33
18.0	16.85
20.23	22.83
21.97	25.23
26.0	30.03
31.5	33.10
34.25	39.59
35.5	42.21
36.75	48.47
44.75	52.39
52.0	55.28
54.5	58.64
56.5	59.80
59.5	62.40
60.5	65.00
68.5	79.17
70.25	83.51
73.00	88.15
79.5	99.19
81.5	100.11
84.67	100.62

END

DATA M100_1e (T, AUrnTCOGTCOH)

4.5	13.94
6.1	23.22
8.0	30.95
10.1	37.58
11.4	43.49
12.1	46.17
14.1	50.32
16.0	56.69
18.0	61.37
20.23	65.35
21.97	68.94
26.0	74.63
31.5	79.76
34.25	82.89
35.5	84.29
36.75	86.91
44.75	90.23
52.0	91.80
54.5	93.75
56.5	94.88
59.5	96.10
60.5	96.99
68.5	99.59
70.25	100.64
73.00	102.16
79.5	104.07
81.5	104.74
84.67	104.94

END

PROCED M100_2

! Data from Fisher et al. (1998)
! Data from procedure M100_2 (in Bld_M
and Urine_M) in HumanB.cmd
! Male 100 ppm exposure
Human
ResetDoses
SET BW=82.3, VFatC=0.14
SET Conc=105.5, CC=FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=m100_2a CVen
PLOT /DATA=m100_2b CTCOH
PLOT /DATA=m100_2c CBldTCA
PLOT /DATA=m100_2d CDCA
PLOT /DATA=m100_2e AUrnTCA
PLOT /DATA=m100_2f AUrnTCOGTCOH
END

DATA M100_2a (T, CVen)

0.52	1.69
1.0	2.50
2.02	3.50
3.02	4.24
4.02	4.75
4.27	3.76
4.52	2.20
5.02	0.96
6.42	0.53
8.0	0.26

10.0	0.17
12.0	0.17

END

DATA M100_2b (T, CTCOH)

1.0	0.37
2.02	1.41
3.02	2.40
4.02	3.59
4.27	4.16
4.52	3.73
5.02	3.65
6.42	3.63
8.0	2.60
10.0	2.82
12.0	1.84
14.0	1.55
16.0	1.59
18.0	1.06
20.0	1.23
22.03	0.75

END

DATA M100_2c (T, CBldTCA)

0.52	0.24
1.0	0.60
2.02	1.24
3.02	2.71
4.27	4.23
4.52	3.86
5.02	3.92
6.42	4.54
8.0	5.71
10.0	6.21
14.0	7.96
16.0	9.08
18.0	8.30
20.0	8.43
22.03	8.95
69.72	5.51
93.61	3.55

END

DATA M100_2d (T, CDCA)

0.52	0.004
1.0	0.004
2.02	0.004
3.02	0.004
4.27	0.005
8.0	0.007

END

DATA M100_2e (T, AUrnTCA)

4.38	1.74
6.0	2.77
8.0	3.94
10.0	5.52
12.0	7.66
14.0	9.62
16.0	11.69
18.0	13.57
20.0	20.39
22.0	26.25

24.42	30.32
31.0	40.91
35.42	50.70
44.90	65.02
49.75	65.02
53.75	78.15
54.76	79.79
59.42	83.82
68.9	93.09
70.83	98.82
72.0	100.66
74.58	112.13
77.0	117.83
83.92	118.82
86.0	119.30
92.67	120.02

END

DATA M100_2f (T, AUrnTCOGTCOH)

6.0	8.69
8.0	18.39
10.0	27.48
12.0	37.49
14.0	44.58
16.0	51.78
18.0	56.11
20.0	60.47
22.0	64.77
24.42	66.98
31.0	75.49
35.42	79.43
44.90	82.13
49.75	85.29
53.75	88.15
54.76	88.66
59.42	89.44
68.9	90.60
70.83	91.71
72.0	91.84
74.58	92.37
77.0	93.07
83.92	93.79
86.0	94.17
92.67	94.55

END

PROCED M100_3

! Data from Fisher et al. (1998)
! Data from procedure M100_3 (in Bld_M
and Urine_M) in HumanB.cmd

! Male 100 ppm exposure

Human

ResetDoses

SET BW=82.7, VFatC=0.14

SET Conc=102.6, CC=.FALSE.,

TChng=4.0, Days=1.0, TMax=24.0,

TStp=100.0

START /NC

PLOT /DATA=m100_3a CVen

PLOT /DATA=m100_3b CTCOH

PLOT /DATA=m100_3c CBldTCA

PLOT /DATA=m100_3d AUrnTCA

PLOT /DATA=m100_3e AUrnTCOGTCOH
END

DATA M100_3a (T, CVen)

0.5	1.93
1.07	2.34
2.0	2.84
3.0	3.40
3.98	3.41
4.25	2.20
4.5	1.66
5.0	0.89
6.0	0.38

END

DATA M100_3b (T, CTCOH)

0.5	0.45
1.07	0.77
2.0	1.51
3.0	2.41
3.98	3.3
4.25	3.64
4.5	3.67
5.0	3.48
6.0	3.05
8.0	2.52
10.02	2.38
12.0	2.16
14.0	1.73
16.02	1.48
18.07	1.12
20.0	1.01
22.0	0.85

END

DATA M100_3c (T, CBldTCA)

0.5	0.23
1.07	0.49
2.0	1.07
3.0	1.89
3.98	2.87
4.25	3.69
4.5	3.87
5.0	3.59
6.0	4.18
8.0	4.71
10.02	5.46
12.0	5.67
14.0	5.97
16.02	6.05
18.07	6.22
20.0	7.54
22.0	7.26
46.85	8.43
71.47	3.86
95.50	3.55

END

DATA M100_3d (T, AUrnTCA)

3.03	0.488
4.75	0.961
6.7	2.09
8.25	2.96

10.17	5.56		
12.08	7.17		
14.19	8.37		
15.58	9.09		
17.6	9.70		
18.23	10.13		
19.58	10.99		
20.05	11.24		
21.33	11.88		
22.17	12.36		
23.2	13.03		
35.42	14.18		
40.67	16.14		
46.67	18.07		
47.17	19.06		
52.33	20.35		
55.25	23.68		
68.17	24.71		
69.75	27.02		
END			
DATA M100_3e (T, AUrnTCOGTCOH)			
3.03	32.70		
4.75	60.26		
6.7	97.98		
8.25	130.67		
10.17	182.90		
12.08	204.64		
14.19	224.53		
15.58	233.79		
17.6	240.99		
18.23	245.36		
19.58	253.46		
20.05	255.90		
21.33	261.17		
22.17	265.40		
23.2	269.76		
35.42	271.64		
40.67	276.15		
46.67	277.54		
47.17	277.83		
52.33	278.12		
55.25	278.81		
68.17	278.88		
69.75	279.07		
END			
PROCED M100_4			
! Data from Fisher et al. (1998)			
! Data from procedure M100_4 (in Bld_M			
and Urine_M) in HumanB.cmd			
! Male 100 ppm exposure			
Human			
ResetDoses			
SET BW=71.1, VFatC=0.14			
SET Conc=101.5, CC=FALSE.,			
TChng=4.0, Days=1.0, TMax=24.0,			
TStp=100.0			
START /NC			
PLOT /DATA=m100_4a CVen			
PLOT /DATA=m100_4b CTCOH			
PLOT /DATA=m100_4c CBldTCA			
PLOT /DATA=m100_4d AUrnTCA			
PLOT /DATA=m100_4e AUrnTCOGTCOH			
END			
DATA M100_4a (T, CVen)			
0.5	3.10		
1.0	3.76		
2.0	3.46		
3.0	3.83		
4.02	3.78		
4.25	2.90		
4.5	2.11		
5.0	1.09		
END			
DATA M100_4b (T, CTCOH)			
0.5	0.56		
1.0	1.12		
2.0	1.75		
3.0	2.55		
4.02	3.48		
4.25	3.73		
4.5	3.52		
5.0	3.78		
6.0	3.79		
8.0	3.30		
10.0	2.96		
12.05	2.71		
14.0	2.38		
16.0	2.04		
18.0	1.89		
20.0	1.57		
22.05	1.40		
END			
DATA M100_4c (T, CBldTCA)			
0.5	0.3		
1.0	0.75		
2.0	1.42		
3.0	2.34		
4.02	3.01		
4.25	2.58		
4.5	3.10		
5.0	3.26		
6.0	4.21		
8.0	4.99		
10.0	5.46		
12.05	5.74		
14.0	6.69		
16.0	6.85		
18.0	7.14		
20.0	9.85		
22.05	9.32		
50.52	8.87		
74.03	8.08		
98.58	3.82		
END			
DATA M100_4d (T, AUrnTCA)			
4.35	0.98		
5.03	1.21		
6.07	1.42		
8.07	2.05		

10.04	3.12		0.5	0.76
12.07	3.60		1.0	0.86
14.06	4.09		2.0	1.15
16.03	4.57		3.0	1.15
18.02	4.86		4.0	1.23
20.04	5.28		4.25	0.77
22.13	5.98		4.53	0.46
25.5	8.14		5.0	0.34
36.5	8.94		6.0	0.21
44.1	10.97		8.0	0.15
47.0	11.58			
54.0	13.48			
61.45	15.33			
69.3	17.47			
85.0	21.65			
93.55	21.65			
END			END	
DATA M100_4e (T, AUrnTCOGTCOH)			DATA M100_5b (T, CTCOH)	
4.35	28.92		1.0	0.52
5.03	31.85		2.0	1.35
6.07	40.01		3.0	1.87
8.07	56.31		4.0	2.50
10.04	68.48		4.25	2.59
12.07	78.80		4.53	2.58
14.06	89.82		5.0	2.25
16.03	98.66		6.0	2.15
18.02	105.25		8.0	1.98
20.04	112.29		10.0	1.56
22.13	122.73		12.0	1.02
25.5	141.62		14.0	1.26
36.5	150.29		16.03	0.89
44.1	162.32		18.0	0.79
47.0	165.74		20.0	0.73
54.0	173.84		22.0	0.70
61.45	178.30			
69.3	182.24			
85.0	185.01			
93.55	186.89			
END			END	
PROCED M100_5			DATA M100_5c (T, CBldTCA)	
! Data from Fisher et al. (1998)			0.5	0.11
! Data from procedure M100_5 (in Bld_M,			1.0	0.36
Exh_M and Urine_M) in HumanB.cmd			2.0	1.07
! Male 100 ppm exposure			3.0	1.55
Human			4.0	2.31
ResetDoses			4.25	2.03
SET BW=73.2, VFatC=0.18			4.53	2.16
SET Conc=102.0, CC=.FALSE.,			5.0	2.35
TChng=4.0, Days=1.0, TMax=24.0,			6.0	2.53
TStp=110.0			8.0	3.61
START /NC			10.0	3.93
PLOT /DATA=m100_5a CVen			12.0	4.57
PLOT /DATA=m100_5b CTCOH			14.0	4.50
PLOT /DATA=m100_5c CBldTCA			16.03	5.02
PLOT /DATA=m100_5d CALvPPM			18.0	5.10
PLOT /DATA=m100_5e AUrnTCA			20.0	5.07
PLOT /DATA=m100_5f AUrnTCOGTCOH			22.0	5.91
END			51.0	6.38
DATA M100_5a (T, CVen)			78.08	5.33
			100.83	4.01
			END	
			DATA M100_5d (T, CALvPPM)	
			4.0	12.386
			4.25	3.305
			4.53	2.478
			5.0	1.567
			6.0	0.577
			8.0	0.317
			10.0	0.286
			END	

DATA M100_5e (T, AUrnTCA)

4.67	1.36
5.05	1.66
6.3	2.70
8.05	4.22
10.07	6.04
12.07	8.04
14.07	10.37
16.15	13.33
18.08	16.55
20.05	20.04
22.15	23.89
25.33	30.02
31.92	35.07
35.33	38.42
43.58	43.06
51.08	46.65
53.25	48.88
56.92	54.83
58.33	57.31
59.67	59.49
63.75	62.36
67.42	66.44
73.08	70.15
78.0	73.57
80.58	75.42
82.75	77.73
84.25	78.87
84.92	80.37
87.58	83.60
91.83	86.81

END

DATA M100_5f (T, AUrnTCOGTCOH)

4.67	16.05
5.05	18.22
6.3	25.28
8.05	34.46
10.07	43.49
12.07	49.91
14.07	55.78
16.15	59.33
18.08	65.07
20.05	68.36
22.15	71.48
25.33	76.10
31.92	81.25
35.33	83.82
43.58	86.11
51.08	87.66
53.25	88.38
56.92	89.39
58.33	89.71
59.67	89.92
63.75	89.92
67.42	90.38
73.08	91.07
78.0	91.55
80.58	91.79
82.75	91.94
84.25	92.03
84.92	92.22

87.58 92.37

91.83 92.55

END

PROCED M100_6

! Data from Fisher et al. (1998)

! Data from procedure M100_6 (in Bld_M,
Exh_M and Urine_M) in HumanB.cmd

! Male 100 ppm exposure

Human

ResetDoses

SET BW=52.3, VFatC=0.06

SET Conc=97.8, CC=.FALSE., TChng=4.0,

Days=1.0, TMax=24.0, TStp=110.0

START /NC

PLOT /DATA=m100_6a CVen

PLOT /DATA=m100_6b CTCOH

PLOT /DATA=m100_6c CBldTCA

PLOT /DATA=m100_6d CALvPPM

PLOT /DATA=m100_6e AUrnTCA

PLOT /DATA=m100_6f AUrnTCOGTCOH

END

DATA M100_6a (T, CVen)

0.5	0.64
1.0	0.94
2.02	1.35
3.0	1.62
4.02	1.56
4.25	1.16
4.5	0.77
5.0	0.37
6.0	0.23
8.0	0.19
10.03	0.17

END

DATA M100_6b (T, CTCOH)

1.0	0.47
2.02	1.10
3.0	1.58
4.02	2.10
4.25	2.21
4.5	2.20
5.0	2.15
6.0	1.94
8.0	1.88
10.03	1.61
12.02	1.39
14.03	1.26
16.0	1.06
18.0	0.95
19.97	0.88
22.07	0.77

END

DATA M100_6c (T, CBldTCA)

0.5	0.21
1.0	0.49
2.02	1.10
3.0	1.67
4.02	2.52

4.25	2.44
4.5	2.71
5.0	3.18
6.0	3.46
8.0	4.26
10.03	4.93
12.02	5.43
14.03	5.85
16.0	6.02
18.0	6.18
19.97	6.35
22.07	6.52
48.0	12.88
71.83	6.25
101.08	5.07

END

DATA M100_6d (T, CALvPPM)

4.02	24.679
4.25	6.422
4.5	4.394
5.0	2.691
6.0	1.388
8.0	1.198
10.03	0.592
12.02	0.470
14.03	0.369
16.0	0.351

END

DATA M100_6e (T, AUrnTCA)

4.55	0.32
5.12	0.41
6.08	1.04
8.13	1.32
10.13	2.51
12.1	4.77
14.1	7.29
16.1	10.23
18.12	11.50
20.08	13.03
22.3	14.26
30.42	17.65
35.67	18.58
51.83	18.58
56.67	18.58
61.5	18.95
70.17	20.95
72.67	22.77
76.92	25.76
82.67	30.01
85.75	30.70
93.67	34.88

END

DATA M100_6f (T, AUrnTCOGTCOH)

4.55	11.60
5.12	13.64
6.08	18.54
8.13	25.00
10.13	33.99
12.1	42.10
14.1	50.19

16.1	60.58
18.12	64.73
20.08	70.85
22.3	77.69
30.42	79.75
35.67	80.14
51.83	80.23
56.67	80.32
61.5	80.66
70.17	81.44
72.67	82.38
76.92	82.74
82.67	83.28
85.75	83.35
93.67	83.79

END

PROCED M100_7Param

SET VMaxC=3.0

END

PROCED M100_7

! Data from Fisher et al. (1998)

! Data from procedure M100_7 (in Bld_M,

Exh_M and Urine_M) in HumanB.cmd

! Male 100 ppm exposure

Human

ResetDoses

M100_7Param

SET BW=60.9, VFatC=0.10

SET Conc=101.1, CC=.FALSE.,

TChng=4.0, Days=1.0, TMax=24.0,

TStp=300.0

START /NC

PLOT /DATA=m100_7a CVen

PLOT /DATA=m100_7b CTCOH

PLOT /DATA=m100_7c CBldTCA

PLOT /DATA=m100_7d CALvPPM

PLOT /DATA=m100_7e CDCA

PLOT /DATA=m100_7f AUrnTCA

PLOT /DATA=m100_7g AUrnTCOGTCOH

END

DATA M100_7a (T, CVen)

0.5	0.59
1.0	0.85
2.0	1.1
3.0	1.04
4.0	1.18
4.3	0.64
4.5	0.42
5.0	0.19

END

DATA M100_7b (T, CTCOH)

0.5	0.28
1.0	0.76
2.0	1.92
3.0	1.69
4.0	2.34
4.3	2.34
4.5	2.16

5.0	2.13	18.1	8.28
6.0	1.95	20.25	9.63
8.0	1.61	24.67	13.46
10.0	1.33	29.17	15.73
12.0	1.58	32.67	20.11
14.0	0.84	35.33	22.71
16.0	0.77	38.83	24.07
18.0	0.57	44.25	25.60
20.03	0.76	49.67	27.51
END		55.92	29.60
DATA M100_7c (T, CBldTCA)		58.75	33.36
0.5	0.36	68.25	39.61
1.0	0.84	73.83	43.70
2.0	1.73	75.92	45.78
3.0	2.60	77.92	48.52
4.0	3.42	81.17	51.21
4.3	3.90	82.58	53.54
4.5	3.67	92.17	60.72
5.0	4.47	END	
6.0	5.00	DATA M100_7g (T, AUrnTCOGTCOH)	
8.0	5.95	4.75	40.71
10.0	6.74	7.95	69.81
12.0	7.12	14.08	89.76
14.0	7.75	16.08	96.80
16.0	8.22	18.1	102.69
18.0	8.17	20.25	107.93
20.03	9.01	24.67	121.30
49.75	10.66	29.17	128.51
73.8	8.6	32.67	135.51
95.24	7.46	35.33	138.05
264.0	3.13	38.83	140.20
END		44.25	142.48
DATA M100_7d (T, CALvPPM)		49.67	144.47
4.0	21.575	55.92	144.96
4.03	14.272	58.75	145.55
4.05	10.770	68.25	146.67
4.08	7.056	73.83	147.09
4.167	5.876	75.92	147.25
4.3	5.773	77.92	147.38
4.5	5.010	81.17	147.50
5.0	2.498	82.58	147.62
6.0	1.713	92.17	147.98
8.0	1.263	END	
10.0	1.029	PROCED M100_8	
12.0	0.936	! Data from Fisher et al. (1998)	
14.0	0.809	! Data from procedure M100_8 (in Bld_M	
16.0	0.738	and Urine_M) in HumanB.cmd	
18.0	0.683	! Male 100 ppm exposure	
END		Human	
DATA M100_7e (T, CDCA)		ResetDoses	
1.0	0.006	SET BW=70.9, VFatC=0.18	
2.0	0.008	SET Conc=103.4, CC=.FALSE.,	
4.0	0.012	TChng=4.0, Days=1.0, TMax=24.0,	
END		TStp=300.0	
DATA M100_7f (T, AUrnTCA)		START /NC	
4.75	0.93	PLOT /DATA=m100_8a CVen	
7.95	3.02	PLOT /DATA=m100_8b CTCOH	
14.08	5.95	PLOT /DATA=m100_8c CBldTCA	
16.08	7.07	PLOT /DATA=m100_8d CDCA	
		PLOT /DATA=m100_8e AUrnTCA	

PLOT /DATA=m100_8f AUrnTCOGTCOH
END

DATA M100_8a (T, CVen)

0.5	2.69
1.0	2.98
2.0	3.51
3.0	3.58
4.0	2.88
4.25	1.96
4.5	1.53
5.75	0.81
6.0	0.52
8.0	0.32
10.0	0.27
12.0	0.24
14.0	0.22
16.0	0.22
18.0	0.20
20.0	0.16
22.0	0.16

END

DATA M100_8b (T, CTCOH)

0.5	0.47
1.0	0.68
2.0	1.51
3.0	3.58
4.0	2.72
4.25	2.87
4.5	2.77
5.75	2.63
6.0	2.30
8.0	1.90
10.0	1.59
12.0	1.28
14.0	1.23
16.0	1.06
18.0	0.98
20.0	0.72
22.0	0.71

END

DATA M100_8c (T, CBldTCA)

0.5	0.43
1.0	1.00
2.0	2.15
3.0	3.40
4.0	4.94
4.25	5.42
4.5	5.67
5.75	5.83
6.0	5.99
8.0	7.23
10.0	7.96
12.0	8.14
14.0	8.39
16.0	8.36
18.0	8.83
20.0	8.96
22.0	9.51
44.98	10.75
68.9	9.21

93.08	7.94
264.0	1.94

END

DATA M100_8d (T, CDCA)

2.0	0.004
3.0	0.010
4.0	0.008
4.25	0.005
4.5	0.005
5.75	0.004
8.0	0.005
16.0	0.005

END

DATA M100_8e (T, AUrnTCA)

4.58	40.02
5.03	40.67
6.03	57.48
8.05	76.60
10.03	99.19
12.03	115.98
14.07	126.00
16.05	136.55
18.03	143.51
20.02	150.54
22.08	163.57
45.42	196.37
47.42	197.62
48.92	198.48
50.42	199.33
53.92	201.12
57.33	201.12
59.17	201.73
60.92	202.15
63.92	202.88
67.92	203.60
74.58	204.11
80.25	204.47
82.42	204.92
84.33	205.07
85.58	205.15
86.92	205.30

END

DATA M100_8f (T, AUrnTCOGTCOH)

4.58	0.935
5.03	1.34
6.03	4.10
8.05	6.10
10.03	9.74
12.03	13.29
14.07	16.29
16.05	20.29
18.03	22.87
20.02	24.83
22.08	29.98
45.42	56.81
47.42	61.82
48.92	64.84
50.42	67.02
53.92	74.27
57.33	76.87

59.17	78.68
60.92	61.05
63.92	88.53
67.92	90.31
74.58	92.43
80.25	95.17
82.42	97.12
84.33	100.02
85.58	100.76
86.92	103.23

END

```

PROCED F100_1
! Data from Fisher et al. (1998)
! Data from procedure F100_1 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
Human
ResetDoses
SET BW=57.5, VFatC=0.21
SET Conc=102.5, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=f100_1a CVen
PLOT /DATA=f100_1b CTCOH
PLOT /DATA=f100_1c CBldTCA
PLOT /DATA=f100_1d AUrnTCA
PLOT /DATA=f100_1e AUrnTCOGTCOH

```

END

DATA F100_1a (T, CVen)

0.5	1.11
1.0	1.36
2.0	2.11
3.0	1.92
4.0	2.30
4.25	1.56
4.50	1.26
5.0	0.73
6.0	0.42

END

DATA F100_1b (T, CTCOH)

0.5	0.22
1.0	0.46
2.0	1.18
3.0	2.18
4.0	3.03
4.25	3.29
4.50	3.67
5.0	3.13
6.0	2.57
8.0	2.46
10.0	1.93
12.0	1.57
14.0	1.30
16.05	1.08
18.0	0.89
20.02	0.56
22.02	0.65
46.17	0.3

END

DATA F100_1c (T, CBldTCA)

0.5	0.21
1.0	0.39
2.0	1.05
3.0	1.86
4.0	3.46
4.25	3.78
4.50	3.91
5.0	4.22
6.0	4.67
8.0	5.71
10.0	6.29
12.0	7.76
14.0	7.78
16.05	8.11
18.0	8.79
20.02	9.05
22.02	9.34
46.17	9.58
69.83	7.93
94.67	6.69

END

DATA F100_1d (T, AUrnTCA)

4.62	0.51
5.08	0.65
6.86	1.26
8.33	1.85
10.25	2.92
12.13	3.91
14.08	4.92
16.15	5.91
18.0	5.91
20.05	7.12
22.17	9.55
30.67	15.22
33.67	17.85
35.42	19.66
40.67	24.08
46.67	26.68
47.17	27.91
52.33	30.49
55.25	35.74
68.17	35.75
69.75	36.78
73.92	37.71
76.0	41.25
78.17	45.21
80.33	46.43
81.5	47.22
82.25	47.91
92.58	49.66
93.67	50.98
94.17	51.67

END

DATA F100_1e (T, AUrnTCOGTCOH)

4.62	44.83
5.08	52.08
6.86	77.84
8.33	89.76

10.25	108.58
12.13	122.65
14.08	133.38
16.15	140.85
18.0	147.19
20.05	151.76
22.17	155.86
30.67	169.38
33.67	174.67
35.42	175.78
40.67	179.31
46.67	179.77
47.17	179.97
52.33	180.44
55.25	181.52
68.17	184.09
69.75	184.16
73.92	184.26
76.0	184.70
78.17	185.20
80.33	185.35
81.5	185.42
82.25	185.51
92.58	185.81
93.67	185.91
94.17	185.95

END

```

PROCED F100_2
! Data from Fisher et al. (1998)
! Data from procedure F100_2 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
Human
ResetDoses
SET BW=66.6, VFatC=0.32
SET Conc=101.4, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=f100_2a CVen
PLOT /DATA=f100_2b CTCOH
PLOT /DATA=f100_2c CBldTCA
PLOT /DATA=f100_2d AUrnTCA
PLOT /DATA=f100_2e AUrnTCOGTCOH

```

END

DATA F100_2a (T, CVen)

0.5	1.18
1.0	2.17
2.0	2.30
3.0	2.41
4.0	2.65
4.23	1.84
4.5	1.17
5.0	0.62
6.0	0.38

END

DATA F100_2b (T, CTCOH)

1.0	0.74
2.0	1.38

3.0	1.93
4.0	2.41
4.23	2.40
4.5	2.33
5.0	2.17
6.0	1.94
8.05	1.81
10.0	1.38
12.0	1.17
14.02	1.25
16.0	1.01
18.0	0.88
20.0	0.74
22.02	0.70

END

DATA F100_2c (T, CBldTCA)

2.0	0.91
3.0	1.75
4.0	2.65
4.23	2.54
4.5	2.65
5.0	2.73
6.0	3.26
8.05	3.58
10.0	4.50
12.0	4.02
14.02	4.17
16.0	4.45
18.0	4.90
20.0	5.26
22.02	5.94
46.70	6.68
70.25	5.20
93.72	3.60

END

DATA F100_2d (T, AUrnTCA)

4.37	0.31
5.03	0.39
6.1	0.64
8.1	1.21
10.07	1.66
12.03	2.16
14.1	2.96
16.05	3.66
18.05	4.37
20.06	5.44
22.15	6.66
24.32	7.63
27.05	8.16
28.3	8.71
30.1	10.30
32.45	10.92
34.2	11.77
36.1	12.45
43.2	13.71
45.4	14.04
48.0	15.07
51.4	15.98
54.05	16.51
56.4	17.0
58.2	17.60

```

59.55 19.57
67.55 19.76
70.20 20.25
72.20 21.31
75.0 22.08
77.55 22.65
81.55 24.79
84.1 30.86
89.1 31.05
91.35 31.06
END

DATA F100_2e (T, AUrnTCOGTCOH)
  4.37 35.78
  5.03 44.40
  6.1 54.40
  8.1 72.58
 10.07 90.61
 12.03 104.44
 14.1 116.90
 16.05 127.49
 18.05 127.49
 20.06 136.49
 22.15 144.45
 24.32 147.89
 27.05 150.61
 28.3 154.52
 30.1 157.72
 32.45 160.74
 34.2 163.47
 36.1 165.86
 43.2 167.54
 45.4 168.21
 48.0 169.24
 51.4 170.26
 54.05 171.66
 56.4 172.85
 58.2 173.70
 59.55 175.02
 67.55 175.31
 70.20 175.67
 72.20 176.21
 75.0 176.60
 77.55 177.07
 81.55 178.04
 84.1 178.43
 89.1 178.65
 91.35 178.94
END

PROCED F100_3
! Data from Fisher et al. (1998)
! Data from procedure F100_3 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human
  ResetDoses
  SET BW=55.5, VFatC=0.23
  SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
  START /NC

PLOT /DATA=f100_3a CVen
PLOT /DATA=f100_3b CTCOH
PLOT /DATA=f100_3c CBldTCA
PLOT /DATA=f100_3d AUrnTCA
PLOT /DATA=f100_3e AUrnTCOGTCOH
END

DATA F100_3a (T, CVen)
  0.58 0.81
  1.0 0.88
  2.0 1.09
  3.0 1.03
  4.0 1.13
  4.17 0.59
  4.5 0.47
  5.0 0.30
  6.0 0.18
  8.02 0.15
END

DATA F100_3b (T, CTCOH)
  0.58 0.33
  1.0 0.57
  2.0 1.01
  3.0 1.25
  4.0 1.79
  4.17 1.64
  4.5 1.54
  5.0 1.43
  6.0 1.27
  8.02 0.95
 10.02 1.01
 12.02 0.90
 14.03 0.88
 16.0 0.74
 18.0 0.69
 20.0 0.63
 22.0 0.61
END

DATA F100_3c (T, CBldTCA)
  0.58 0.40
  1.0 0.97
  2.0 1.72
  3.0 2.64
  4.0 3.41
  4.17 3.62
  4.5 3.86
  5.0 4.39
  6.0 4.80
  8.02 5.73
 10.02 6.79
 12.02 7.55
 14.03 7.68
 16.0 7.98
 18.0 9.27
 20.0 8.91
 22.0 9.12
 46.08 11.31
 75.67 10.49
 94.25 8.47
END

```

```

DATA F100_3d (T, AUrnTCA)
  4.58  0.44
  6.03  0.71
  8.12  1.31
 10.08  2.28
 12.1   3.48
 14.1   4.64
 16.05  5.64
 18.1   6.76
 20.05  7.66
 21.92  8.89
 26.17 10.64
 33.25 13.81
 37.92 14.11
 44.92 15.44
 49.0   16.00
 54.92 23.2
 58.42 22.4
 61.42 24.1
 66.42 29.1
 70.67 32.6
 74.75 36.2
 80.42 36.8
 82.42 37.5
 84.92 37.79
 93.42 45.72
END

DATA F100_3e (T, AUrnTCOGTCOH)
  4.58 12.63
  6.03 17.83
  8.12 26.05
 10.08 30.40
 12.1  36.72
 14.1  41.26
 16.05 44.27
 18.1  47.94
 20.05 50.31
 21.92 53.17
 26.17 57.90
 33.25 65.27
 37.92 65.80
 44.92 69.74
 49.0  69.74
 54.92 72.07
 58.42 73.58
 61.42 75.39
 66.42 76.98
 70.67 79.89
 74.75 80.98
 80.42 82.20
 82.42 82.57
 84.92 82.74
 93.42 83.41
END

PROCED F100_4
! Data from Fisher et al. (1998)
! Data from procedure F100_4 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
  Human

ResetDoses
SET BW=61.8, VFatC=0.33
SET Conc=102.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=f100_4a CVen
PLOT /DATA=f100_4b CTCOH
PLOT /DATA=f100_4c CBldTCA
PLOT /DATA=f100_4d AUrnTCA
PLOT /DATA=f100_4e AUrnTCOGTCOH
END

DATA F100_4a (T, CVen)
  0.55  0.55
  1.0   0.81
  2.12  1.30
  3.05  1.37
  4.0   1.43
  4.25  0.81
  4.50  0.54
  5.0   0.35
  6.0   0.18
END

DATA F100_4b (T, CTCOH)
  1.0   0.39
  2.12  1.2
  3.05  1.59
  4.0   1.93
  4.25  1.97
  4.50  1.75
  5.0   1.63
  6.0   1.32
  8.05  1.10
 10.08  0.91
 14.03  0.83
 18.02  0.69
 22.02  0.54
END

DATA F100_4c (T, CBldTCA)
  0.55  0.47
  1.0   1.05
  2.12  2.73
  3.05  3.85
  4.0   4.82
  4.25  5.02
  4.50  5.29
  5.0   5.37
  6.0   6.01
  8.05  7.60
 10.08  6.77
 14.03  8.65
 18.02  9.49
 22.02 10.64
 46.08  9.58
 75.67  8.55
 94.25  7.82
END

DATA F100_4d (T, AUrnTCA)
  2.33  0.29

```

4.57	1.62
5.12	2.09
6.12	4.01
8.12	5.81
10.33	8.27
12.08	10.21
14.12	13.06
16.0	16.29
18.08	19.09
20.0	21.96
21.92	24.17
25.08	27.09
29.25	29.05
32.58	35.13
35.83	45.84
38.33	56.12
41.0	65.21
45.0	75.98
48.83	81.05
50.33	83.74
53.67	87.89
56.33	91.72
59.33	97.13
66.83	100.34
73.25	102.88
80.58	106.50
83.5	110.02
86.0	113.61
93.0	117.51

END

DATA F100_4e (T, AUrnTCOGTCOH)

2.33	4.52
4.57	8.37
5.12	12.49
6.12	19.46
8.12	29.26
10.33	35.93
12.08	40.21
14.12	44.90
16.0	48.15
18.08	51.04
20.0	55.72
21.92	58.76
25.08	60.75
29.25	62.24
32.58	72.07
35.83	76.15
38.33	79.24
41.0	81.48
45.0	83.84
48.83	86.37
50.33	87.44
53.67	88.84
56.33	90.90
59.33	92.91
66.83	94.07
73.25	94.96
80.58	96.17
83.5	96.82
86.0	97.41
93.0	98.54

END

PROCED F100_5

! Data from Fisher et al. (1998)
! Data from procedure F100_5 (in Bld_F,
Exh_F and Urine_F) in HumanB.cmd

! Female 100 ppm exposure

Human

ResetDoses

SET BW=67.3, VFatC=0.35

SET Conc=102.0, CC=.FALSE.,

TChng=4.0, Days=1.0, TMax=24.0,

TStp=100.0

START /NC

PLOT /DATA=f100_5a CVen

PLOT /DATA=f100_5b CTCOH

PLOT /DATA=f100_5c CBldTCA

PLOT /DATA=f100_5d CALvPPM

PLOT /DATA=f100_5e AUrnTCA

PLOT /DATA=f100_5f AUrnTCOGTCOH

END

DATA F100_5a (T, CVen)

0.5	0.74
1.0	1.0
2.0	1.27
3.0	1.45
4.0	1.19
4.25	0.81
4.55	0.66
5.0	0.46
6.02	0.25
8.02	0.19

END

DATA F100_5b (T, CTCOH)

1.0	0.41
2.0	0.78
3.0	1.04
4.0	1.18
4.25	1.17
4.55	1.18
5.0	1.18
8.02	0.84
10.0	0.72
12.0	0.82
14.0	0.56
18.02	0.49
20.0	0.41

END

DATA F100_5c (T, CBldTCA)

0.5	0.25
1.0	0.76
2.0	1.48
3.0	2.21
4.0	2.79
4.25	2.78
4.55	3.12
5.0	3.23
6.02	3.52
8.02	4.76
10.0	4.95

12.0	5.29
14.0	5.33
18.02	6.46
20.0	6.91
22.0	7.10
46.58	6.63
70.5	5.28

END

DATA F100_5d (T, CALvPPM)

4.25	4.243
4.55	2.798
5.0	1.849
6.02	1.467
8.02	0.681
10.0	0.452
12.0	0.409
14.0	0.356

END

DATA F100_5e (T, AUrnTCA)

4.67	0.69
5.0	0.80
6.3	1.64
8.08	3.16
10.08	4.95
12.07	7.19
14.08	9.89
16.12	13.14
18.11	17.46
20.1	21.67
22.12	26.40
22.67	29.05
26.5	35.18
29.67	41.73
34.17	49.36
35.67	50.76
40.67	56.47
43.67	60.68
47.17	69.00
49.67	73.32
53.42	76.81
56.17	79.16
58.0	81.70
59.67	83.84
60.17	84.56
61.67	86.11
67.67	91.59
72.67	95.63
76.67	100.35
82.67	110.14
84.17	111.45
85.67	112.62
91.67	115.92

END

DATA F100_5f (T, AUrnTCOGTCOH)

4.67	9.98
5.0	9.98
6.3	12.41
8.08	16.09
10.08	18.99
12.07	20.96

14.08	23.08
16.12	24.46
18.11	26.22
20.1	27.92
22.12	29.05
22.67	29.64
26.5	32.31
29.67	34.40
34.17	36.58
35.67	37.14
40.67	38.80
43.67	39.86
47.17	40.61
49.67	41.58
53.42	42.31
56.17	42.94
58.0	43.30
59.67	43.53
60.17	43.60
61.67	43.78
67.67	44.79
72.67	45.19
76.67	45.69
82.67	46.42
84.17	46.54
85.67	46.60
91.67	47.13

END

PROCED F100_6Param

SET VMaxC=3.0

END

PROCED F100_6

! Data from Fisher et al. (1998)

! Data from procedure F100_6 (in Bld_F, Exh_F and Urine_F) in HumanB.cmd

! Female 100 ppm exposure

Human

ResetDoses

F100_6Param

SET BW=62.3, VFatC=0.24

SET Conc=97.7, CC=.FALSE., TChng=4.0, Days=1.0, TMax=24.0, TStp=110.0

START /NC

PLOT /DATA=f100_6a CVen

PLOT /DATA=f100_6b CTCOH

PLOT /DATA=f100_6c CBldTCA

PLOT /DATA=f100_6d CALvPPM

PLOT /DATA=f100_6e CDCA

PLOT /DATA=f100_6f AUrnTCA

PLOT /DATA=f100_6g AUrnTCOGTCOH

END

DATA F100_6a (T, CVen)

0.5	0.83
1.0	0.99
2.03	1.20
3.0	1.59
4.03	2.03
4.25	1.33
4.5	0.87

5.0	0.42
6.0	0.21
8.0	0.22
10.0	0.15

END

DATA F100_6b (T, CTCOH)

2.03	0.53
3.0	0.83
4.03	1.27
4.25	0.92
4.5	0.85
5.0	1.17
6.0	1.03
8.0	0.86
10.0	0.80
12.0	0.71
14.03	0.62
16.03	0.55
18.07	0.48
20.0	0.41

END

DATA F100_6c (T, CB1dTCA)

0.5	0.44
1.0	0.97
2.03	2.16
3.0	3.79
4.03	5.12
4.25	5.35
4.5	5.60
5.0	5.88
6.0	6.55
8.0	7.30
10.0	7.66
12.0	8.61
14.03	8.73
16.03	9.65
18.07	8.29
20.0	8.60
22.0	10.2
47.95	6.15
71.98	7.11
101.22	6.73

END

DATA F100_6d (T, CALvPPM)

4.03	22.398
4.25	7.317
4.5	5.917
5.0	2.903
6.0	1.382
8.0	0.982
10.0	0.691
12.0	0.524
14.03	0.428

END

DATA F100_6e (T, CDCA)

1.0	0.005
2.03	0.014
3.0	0.005

END

DATA F100_6f (T, AUrnTCA)

4.55	0.30
5.12	0.56
6.08	1.75
8.19	1.97
10.19	3.75
12.17	6.58
14.33	6.81
16.23	8.64
18.19	10.30
20.13	12.13
22.38	13.64
31.92	15.77
34.25	18.03
36.92	18.16
48.67	22.69
55.83	28.52
59.0	30.85
63.5	31.36
70.8	33.88
76.0	37.20
85.5	41.32
87.25	42.86
88.08	49.42
94.75	54.14

END

DATA F100_6g (T, AUrnTCOGTCOH)

4.55	11.67
5.12	14.56
6.08	20.78
8.19	25.55
10.19	34.83
12.17	45.33
14.33	45.98
16.23	54.21
18.19	60.91
20.13	68.01
22.38	73.35
31.92	75.14
34.25	79.52
36.92	79.97
48.67	85.95
55.83	90.84
59.0	91.82
63.5	92.13
70.8	92.13
76.0	95.09
85.5	96.05
87.25	96.34
88.08	96.45
94.75	97.45

END

PROCED F100_7

! Data from Fisher et al. (1998)
! Data from procedure F100_7 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
Human
ResetDoses

```

SET BW=63.2, VFatC=0.26
SET Conc=101.0, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=100.0
START /NC
PLOT /DATA=f100_7a CVen
PLOT /DATA=f100_7b CTCOH
PLOT /DATA=f100_7c CBldTCA
PLOT /DATA=f100_7d AUrnTCA
PLOT /DATA=f100_7e AUrnTCOGTCOH
END

```

```

DATA F100_7a (T, CVen)
0.52 0.53
1.0 1.0
2.0 0.97
3.0 1.31
4.0 1.48
4.28 0.84
4.5 0.58
5.0 0.39
END

```

```

DATA F100_7b (T, CTCOH)
0.52 0.35
1.0 0.58
2.0 0.86
3.0 1.60
4.0 2.03
4.28 2.04
4.5 1.93
5.0 1.95
6.05 1.79
8.0 1.29
10.0 1.14
12.0 1.03
END

```

```

DATA F100_7c (T, CBldTCA)
0.52 0.39
1.0 1.08
2.0 1.90
3.0 3.83
4.0 4.48
4.28 4.65
4.5 4.80
5.0 4.73
6.05 6.02
8.0 6.02
10.0 7.12
12.0 7.13
46.75 9.10
73.97 6.92
95.42 6.14
END

```

```

DATA F100_7d (T, AUrnTCA)
4.67 2.51
5.17 3.07
6.25 6.21
8.08 9.97
10.13 13.01
12.08 16.35

```

```

14.12 20.65
16.02 23.23
18.02 26.31
20.17 26.31
25.27 34.28
25.75 34.84
30.0 42.19
34.5 51.62
37.92 61.19
45.08 75.52
49.33 81.43
56.92 92.21
60.42 104.12
68.33 116.32
72.58 121.17
80.5 131.94
84.33 134.71
86.17 136.09
93.5 142.30
END

```

```

DATA F100_7e (T, AUrnTCOGTCOH)
4.67 37.76
5.17 42.18
6.25 48.68
8.08 60.91
10.13 72.32
12.08 81.05
14.12 86.76
16.02 94.78
18.02 100.92
20.17 105.91
25.27 115.12
25.75 116.22
30.0 125.29
34.5 131.36
37.92 135.91
45.08 143.62
49.33 146.34
56.92 149.70
60.42 151.17
68.33 153.38
72.58 154.28
80.5 155.70
84.33 155.93
86.17 156.09
93.5 156.70
END

```

```

PROCED F100_8
! Data from Fisher et al. (1998)
! Data from procedure F100_8 (in Bld_F
and Urine_F) in HumanB.cmd
! Female 100 ppm exposure
Human
ResetDoses
SET BW=48.6, VFatC=0.23
SET Conc=103.3, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
START /NC
PLOT /DATA=f100_8a CVen

```

```

PLOT /DATA=f100_8b CTCOH
PLOT /DATA=f100_8c CBldTCA
PLOT /DATA=f100_8d CDCA
PLOT /DATA=f100_8e AUrnTCA
PLOT /DATA=f100_8f AUrnTCOGTCOH
END

```

DATA F100_8a (T, CVen)

0.5	1.32
1.0	1.68
2.0	1.86
3.0	2.37
4.0	2.66
4.25	2.10
4.5	1.23
5.0	0.83
6.0	0.42
8.05	0.33
10.03	0.30

END

DATA F100_8b (T, CTCOH)

0.5	0.47
1.0	0.68
2.0	1.51
3.0	2.15
4.0	2.72
4.25	2.87
4.5	2.77
5.0	2.63
6.0	2.30
8.05	1.90
10.03	1.59
12.05	1.28
14.02	1.23
16.0	1.10
18.0	0.98
20.0	0.72
22.0	0.71

END

DATA F100_8c (T, CBldTCA)

0.5	0.27
1.0	0.70
2.0	1.48
3.0	2.80
4.0	3.92
4.25	3.86
4.5	3.98
5.0	4.55
6.0	4.80
8.05	5.96
10.03	6.09
12.05	6.41
14.02	7.01
16.0	7.23
18.0	7.57
20.0	7.68
22.0	8.46
45.03	8.75
69.03	7.73
93.13	5.72
264.0	0.53

END

DATA F100_8d (T, CDCA)

0.5	0.008
1.0	0.008
2.0	0.007
3.0	0.007
4.0	0.006
4.25	0.009
4.5	0.013
5.0	0.012
6.0	0.011
8.05	0.005
12.05	0.005
16.0	0.004
18.0	0.004
22.0	0.005
45.03	0.006
69.03	0.004

END

DATA F100_8e (T, AUrnTCA)

4.58	2.34
5.05	2.92
6.05	5.27
8.08	8.33
10.07	12.15
12.08	17.02
14.31	21.46
16.05	26.02
18.05	28.88
20.03	32.60
22.08	37.96
43.33	80.45
45.58	85.25
47.58	87.93
49.17	91.55
53.58	99.63
61.33	110.21
67.33	114.43
70.58	118.52
74.58	123.23
77.25	128.78
83.25	133.51
84.25	134.95
85.17	136.29
90.5	143.83

END

DATA F100_8f (T, AUrnTCOGTCOH)

4.58	15.54
5.05	18.22
6.05	24.58
8.08	33.76
10.07	41.25
12.08	47.80
14.31	54.36
16.05	59.99
18.05	63.23
20.03	68.23
22.08	73.90
43.33	110.18
45.58	112.61

47.58	113.70
49.17	115.14
53.58	118.20
61.33	122.07
67.33	124.30
70.58	125.29
74.58	126.29
77.25	127.48
83.25	128.07
84.25	128.31
85.17	128.49
90.5	129.56

END

```

PROCED MaleHiM
! Data from Fisher et al. (1998)
! M file created Tue 18 Nov 2003
! Malehi.m
! Last Modified: 22 Jan 2004
! Modified by: Deborah Keys
! 100ppm 4 hr inhalation blood:
fish,mahle,abbas

! Male
Human
ResetDoses
SET BW=60.9, VFatC=0.10
SET Conc=101.1, CC=.FALSE.,
TChng=4.0, Days=1.0, TMax=24.0,
TStp=300.0
START /NC
PLOT /DATA=male100_7a CTCOH
PLOT /DATA=male100_7b CBldTCA
PLOT /DATA=male100_7c AUrnTCA
PLOT /DATA=male100_7d AUrnTCOGTCOH
END

```

DATA Male100_7a (T, CTCOH)

0.5	0.28
1.0	0.76
2.0	1.92
3.0	1.69
4.0	2.34
4.3	2.34
4.5	2.16
5.0	2.13
6.0	1.95
8.0	1.61
10.0	1.33
12.0	1.58
14.0	0.84
16.0	0.77
18.0	0.57
20.03	0.76

END

DATA Male100_7b (T, CBldTCA)

0.5	0.36
1.0	0.84
2.0	1.73
3.0	2.6
4.0	3.42

4.3	3.9
4.5	3.67
5.0	4.47
6.0	5.0
8.0	5.95
10.0	6.74
12.0	7.12
14.0	7.75
16.0	8.22
18.0	8.17
20.03	9.01
49.75	10.66
73.8	8.6
95.24	7.46
264.0	3.13

END

DATA Male100_7c (T, AUrnTCA)

4.75	0.93
7.95	3.02
14.08	5.95
16.08	7.07
18.1	8.28
20.25	9.63
24.67	13.46
29.17	15.73
32.67	20.11
35.33	22.71
38.83	24.07
44.25	25.6
49.67	27.51
55.92	29.6
58.75	33.36
68.25	39.61
73.83	43.7
75.92	45.78
77.92	48.52
81.17	51.21
82.58	53.54
92.17	60.72

END

DATA Male100_7d (T, AUrnTCOGTCOH)

4.75	40.71
7.95	69.81
14.08	89.76
16.08	96.8
18.1	102.69
20.25	107.93
24.67	121.3
29.17	128.51
32.67	135.51
35.33	138.05
38.83	140.2
44.25	142.48
49.67	144.47
55.92	144.96
58.75	145.55
68.25	146.67
73.83	147.09
75.92	147.25
77.92	147.38
81.17	147.5

82.58 147.62
92.17 147.98
END

```
PROCED MaleLoM
! Data from Fisher et al. (1998)
! M file created Tue 18 Nov 2003
! MaleLo.m
! Last Modified: 22 Jan 2004
! Modified by: Deborah Keys
! 100ppm 4 hr inhalation blood:
fish,mahle,abbas

! Male
  Human
  ResetDoses
  SET BW=82.7, VFatC=0.14
  SET Conc=102.6, CC=.FALSE.,
  TChng=4.0, Days=1.0, TMax=24.0,
  TStp=100.0
  START /NC
  PLOT /DATA=male100_3a CTCOH
  PLOT /DATA=male100_3b CBldTCA
  PLOT /DATA=male100_3c AUrnTCA
  PLOT /DATA=male100_3d AUrnTCOGTCOH
END
```

```
DATA Male100_3a (T, CTCOH)
  0.5 0.45
  1.07 0.77
  2.0 1.51
  3.0 2.41
  3.98 3.3
  4.25 3.64
  4.5 3.67
  5.0 3.48
  6.0 3.05
  8.0 2.52
  10.02 2.38
  12.0 2.16
  14.0 1.73
  16.02 1.48
  18.07 1.12
  20.0 1.01
  22.0 0.85
```

END

```
DATA Male100_3b (T, CBldTCA)
  0.5 0.23
  1.07 0.49
  2.0 1.07
  3.0 1.89
  3.98 2.87
  4.25 3.69
  4.5 3.87
  5.0 3.59
  6.0 4.18
  8.0 4.71
  10.02 5.46
  12.0 5.67
  14.0 5.97
  16.02 6.05
```

18.07 6.22
20.0 7.54
22.0 7.26
46.85 8.43
71.47 3.86
95.5 3.55

END

DATA Male100_3c (T, AUrnTCA)

3.03 0.488
4.75 0.961
6.7 2.09
8.25 2.96
10.17 5.56
12.08 7.17
14.19 8.37
15.58 9.09
17.6 9.7
18.23 10.13
19.58 10.99
20.05 11.24
21.33 11.88
22.17 12.36
23.2 13.03
35.42 14.18
40.67 16.14
46.67 18.07
47.17 19.06
52.33 20.35
55.25 23.68
68.17 24.71
69.75 27.02

END

DATA Male100_3d (T, AUrnTCOGTCOH)

3.03 32.7
4.75 60.26
6.7 97.98
8.25 130.67
10.17 182.9
12.08 204.64
14.19 224.53
15.58 233.79
17.6 240.99
18.23 245.36
19.58 253.46
20.05 255.9
21.33 261.17
22.17 265.4
23.2 269.76
35.42 271.64
40.67 276.15
46.67 277.54
47.17 277.83
52.33 278.12
55.25 278.81
68.17 278.88
69.75 279.07

END

SET CMD=5