FINAL REPORT

For

Physiologically Based Pharmacokinetic Modeling of 1,1,1-Trichloroethane (Project 04-10) ORISE Subcontract 5-10329

Submitted by

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TABLE OF CONTENTS

I. PURPOSE

The U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) Program is preparing a health assessment for 1,1,1-trichloroethane. This health assessment includes a quantitative assessment of the noncancer data for 1,1,1-trichloroethane and a cancer weight-of-evidence determination. The assessment is also piloting the implementation of recommendations provided in the 2002 report, "A Review of the Reference Dose and Reference Concentration Processes," including the development, as supported, of less-than-lifetime reference values. A draft IRIS assessment has undergone internal review. Feedback received, as of winter 2004, suggests that available physiologically based pharmacokinetic (PBPK) models should be further explored. The purpose of this contract is to support EPA in examining the appropriateness of model application to the extrapolations of interest and applying available PBPK models: (1) to compare exposures from the acute human studies on an internal dose basis to provide a better understanding of the differences in response in the different studies and to extrapolate to other acute exposure durations between 1 and 24 hours; (2) for interspecies extrapolation; and (3) for route-to-route extrapolation.

II. BACKGROUND INFORMATION AND SCOPE OF THE REPORT

This final report encompasses the following specific areas:

1. Detailed description of reconstruction of PBPK models published in the literature, including model computer code (CSL files), command files (CMD files), and simulation results.
2. Evaluation of the reconstructed PBPK models, recommendation of the chosen model, and rationale for such a recommendation.
3. Calculation of internal doses based on the final chosen PBPK model under a variety of exposure scenarios relevant to the EPA IRIS health assessment of 1,1,1-trichloroethane and application to duration, interspecies, and route-to-route extrapolations.

These areas are individually discussed in Sections III, IV, V, respectively, below.

III. RECONSTRUCTION OF PBPK MODELS

At the outset, we would like to point out that the PBPK models by Gargas *et al.* (1986a) and Reitz *et al.* (1988) were not "reconstructed" models. Rather, their original codes, along with the data, were kindly provided by Drs. Lisa Sweeney and Richard Reitz, respectively. The Reitz *et al.* code was in SimuSolv format; with some minor revision to conform to Advanced Continuous Simulation Language (ACSL) coding, we were able to perform the PBPK model simulation of all the data published in the Reitz *et al.* (1988) paper. Thus, our final Gargas *et al.* (1986a) and Reitz *et al.* (1988) PBPK models are "reestablished" models. It should also be noted that there were two publications by Reitz *et al.* (1987; 1988) on PBPK modeling of 1,1,1-trichloroethane. While we believe that the same PBPK model was used in these two papers, the values of metabolic parameters (Vmax and Km) were different between the two papers. We used the Reitz *et al.* (1988) parameter values throughout our simulations.

III.1. Methodology in Recreating Selected PBPK Models of 1,1,1-Trichloroethane

To acquire data points from the selected papers, figures of concentration-time courses of 1,1,1-trichloroethane were scanned and electronically saved to computer files in JPEG format. Data points

from the picture files were extracted using digiMatic version 2.2c (FEB Software, Chesterfield, Virginia). In brief, the figure file is opened to the desktop computer, then the digiMatic program is run. The graphical illustration is automatically uploaded to the program. Subsequently, the origin coordinates of the graph and scales of X- and Y-axis of the figure are set corresponding to the uploaded figure. The data point extraction is then performed. An extracted data set is saved in Windows® Notepad format and transformed to a CMD file for modeling.

To recreate the selected PBPK models of 1,1,1-trichloroethane, ACSL version 11.8.4 (Xcellon, West Austin, Texas) was used as a modeling tool. The goodness of the fit between model simulation and original data was assessed by visual inspection.

III.2. Available PBPK Models of 1,1,1-Trichloroethane and Related Information

Fourteen published PBPK models for 1,1,1-trichloroethane in rats or humans are available. They are discussed in chronological order, according to the publication dates, as outlined in the following paragraphs. The model structures and critical parameters (partition coefficients, metabolism rate constant) are briefly summarized in Tables 1 and 2, respectively.

Table 1. Summary of Available Models for 1,1,1-Trichloroethane in Rats and Humans

Model	Structure	Reconstruction
Caperos *et al.* (1982)	Fat, muscle, lung, rapidly perfused tissues; clearance from rapidly perfused tissues	No
Nolan *et al.* (1984)	Fat, muscle, lung, and well perfused tissues; first-order metabolism in well perfused tissues	No
Gargas *et al.* (1986a)	Liver, viscera, muscle/skin, and fat; first-order metabolism in liver	Yes; original code provided by Dr. Lisa Sweeney April 27th, 2006 (Gargas.CSL, Gargas.CMD)
Reitz *et al.* (1987, 1988)	Liver, fat, and slowly and rapidly perfused tissues; saturable metabolism in liver	Original Reitz code modified to run with ACSL TOX 11.8 (Reitz.CSL, Reitz.CMD)
Bogen and Hall (1989)	Liver, fat, skin, and slowly and rapidly perfused tissues; saturable metabolism in liver	No
Dallas *et al. (*1989)	Blood, lung, liver, muscle, fat, and rapidly perfused tissues; first order metabolism in liver	Yes (Dallas.CSL, Dallas.CMD)
Leung (1992)	Fat, liver, and slowly and rapidly perfused tissues; saturable metabolism in liver	Yes
Yoshida (1993)	Fat, liver, and slowly and rapidly perfused tissues; saturable metabolism in liver	Yes
Lapare *et al.* (1995)	Lungs, liver, gastrointestinal tract, fat, muscle and skin, and rapidly and slowly perfused tissues; saturable metabolism in liver	Yes
Loizou *et al.* (1996)	Fat, liver, and rapidly and slowly perfused tissues; first-order metabolism in liver	Yes
DeJongh *et al.* (1998)	Fat, liver, brain, and rapidly and slowly perfused tissues; first-order metabolism in liver	Yes
Tardif and Charest-Tardif (1999)	Liver, fat, and slowly and rapidly perfused tissues; saturable metabolism in liver	Yes (Tardif.CSL, Tardif.CMD)
Poet *et al.* (2000)	Fat, skin, liver, and rapidly and slowly perfused tissues; saturable metabolism in liver	No

Model	Structure	Reconstruction
Dobrev *et al.* (2001, 2002)	Fat, liver, and other tissues lumped into one or two compartments; saturable metabolism in liver	Original code

Table 2. Partition Coefficients and Metabolic Parameters in Available Models for 1,1,1-Trichloroethane in Rats and Humans

Model	Partition Coefficients	Partition Coefficients Reference	Metabolic Parameters	Metabolic Parameters Reference
Caperos *et al.* (1982)	**Human:** Blood:Air = 4.35 Muscle:Blood =1.4 Fat:Blood = 85.75 Rapidly:Blood = 2.1	Droz and Fernandez (1977)	**Human:** 0.025 l/min	Estimated from data Humbert and Fernandez (1977)
Nolan *et al.* (1984)	**Human:** Blood:Air = 1.57 Muscle:Blood =15.78 Fat:Blood = 108.7 Rapidly:Blood = 13.48	Estimated from Nolan *et al.* (1984) data	**Human:** 0.045/hr	Estimated from Nolan *et al.* (1984) data
Gargas *et al.* (1986a)	**Rat:** Blood:Air = 5.76 Muscle:Blood =0.55 Fat:Blood = 45.66 Liver:Blood = 1.49	Determined by a vial equilibration method by the authors	**Rat:** $K_fC = 5.0/hr/kg^{-0.3}$ $K_f = K_fC \times BW^{-0.3}$	Visual optimization against data
Reitz *et al.* (1987, 1988)	**Rat:** Blood:Air = 5.76 Fat:Blood = 45.66 Liver:Blood = 1.49 Slowly:Blood =0.55 Rapidly:Blood = 1.49 **Human:** Blood:Air = 2.53 Fat:Blood = 103.95 Liver:Blood = 3.4 Slowly:Blood =1.25 Rapidly:Blood = 3.4	Experimentally determined by Gargas; obtained through personal communication	**Rat & Human:** $V_{max}C = 0.419$ mg/hr/kg$^{0.7}$ $V_{max} = V_{max}C \times BW^{0.7}$ $K_m = 5.75$ mg/L	Statistical optimization against amount of metabolites; values used in Reitz *et al.* (1988)
Bogen and Hall (1989)	**Rat & Human:** Same as Reitz *et al.* (1987, 1988)	Reitz *et al.* (1987)	**Rat:** $V_{max}C = 0.265$ mg/hr/kg$^{0.7}$ $V_{max} = V_{max}C \times BW^{0.7}$ $K_m = 6.43$ mg/L **Human:** $V_{max}C = 1.06$ mg/hr/kg$^{0.7}$ $V_{max} = V_{max}C \times BW^{0.7}$ $K_m = 6.43$ mg/L	The rat values and human K_m from Reitz *et al.* (1987); the human $V_{max}C$ values adjusted
Dallas *et al.* (1989)	**Rat:** Muscle:Blood =0.55* Fat:Blood = 47.7* Liver:Blood = 1.49* Lung:Blood = 1.49! Blood:Air = 5.76* Rapidly:Blood = 1.49! Lung:Air = 8.6!!	* Gargas *et al.* (1986a, 1989) !: assumed to be the same as Liver:Blood (Dallas *et al.* 1989) !!: = Lung:Blood × Blood:Air (Dallas *et al.* 1989)	**Rat:** $K_f = 0.115$/min	Scaled by $BW^{-0.3}$ from Gargas *et al.* (1986a, 1989)

Model	Partition Coefficients	Partition Coefficients Reference	Metabolic Parameters	Metabolic Parameters Reference
Leung (1992)	**Human:** Same as the human values in Reitz *et al.* (1988)	Reitz *et al.* (1988)	**Human:** Same as Reitz *et al.* (1988)	Reitz *et al.* (1988)
Yoshida (1993)	**Human:** Blood:Air = 2.53 Fat:Blood = 103.95 Liver:Blood = 3.4 Slowly:Blood =1.25 Rapidly:Blood = 3.4	Reitz *et al.* (1987)	**Human:** V_{max} = 6 mg/hr K_m = 6.43 mg/L	Reitz *et al.* (1987)
Lapare *et al.* (1995)	**Human:** Blood:Air = 4.35 Fat:Blood = 57.7 Liver:Blood = 3.68 Slowly:Blood =1.54 Rapidly:Blood = 1.9 Lung:Blood = 1.08 GI:Blood = 3.68	Blood:air partition coefficient from optimization; tissue:air from Fiserova-Bergerova and Diaz (1986)	**Human:** $V_{max}C$ = 0.42 mg/hr/kg$^{0.74}$ $V_{max} = V_{max}C \times BW^{0.74}$ K_m = 5.75 mg/L	Reitz *et al.* (1988)
Loizou *et al.* (1996)	**Rat:** Blood:Air = 5.55 Fat:Blood = 40.5 Liver:Blood = 1.42 Slowly:Blood =0.5 Rapidly:Blood = 1.42	Experimentally measured by Loizou *et al.* (1996)	**Rat:** K_f = 6/hr	From Gargas *et al.* (1986a); however the value is different from the value in Gargas *et al.* (1986a)
DeJongh *et al.* (1998)	**Rat:** Blood:Air = 5.76 Fat:Blood = 45.66 Liver:Blood = 1.49 Slowly:Blood =0.55 Brain:Blood = 2.39 Brain:Brain lipids = 15.64	Gargas *et al.* (1989)	**Rat:** $K_{fc} = 5/hr/kg^{-0.3}$ $K_f = K_{fc} \times BW^{-0.3}$	Gargas *et al.* (1990)
Tardif and Charest-Tardif (1999)	**Rat:** Blood:Air = 5.76 Fat:Blood = 45.66 Liver:Blood = 1.49 Slowly:Blood =0.55 Rapidly:Blood = 1.49 **Human:** Blood:Air = 2.53 Fat:Blood = 103.95 Liver:Blood = 3.4 Slowly:Blood =1.25 Rapidly:Blood = 3.4	Reitz *et al.* (1988)	**Rat & Human:** $V_{max}C$ = 0.42 mg/hr/kg$^{0.7}$ $V_{max} = V_{max}C \times BW^{0.7}$ K_m = 5.75 mg/L	Reitz *et al.* (1988)
Poet *et al.* (2000)	**Rat & Human:** Skin:Blood = 10.8 Others the same as Reitz *et al.* (1988)	Reitz *et al.* (1988); Mattie *et al.* (1994)	**Rat & Human:** Same as Reitz *et al.* (1988)	Reitz *et al.* (1988)
Dobrev *et al.* (2001, 2002)	**Rat:** Blood:Air = 5.8 Fat:Blood = 45.7 Liver:Blood = 1.5 Lumped:Blood =0.6 **Human:** Blood:Air = 2.5 Fat:Blood = 104 Liver:Blood = 3.4 Slowly:Blood =0.6 Rapidly:Blood = 3.4	Reitz *et al.* (1988)	**Rat & Human:** $V_{max}C$ = 0.42 mg/hr/kg$^{0.7}$ K_m = 5.75 mg/L	Reitz *et al.* (1988)

III.3. Reconstruction/Reestablishment of Selected PBPK Models

The first model (Caperos *et al.* 1982) was developed to simulate the alveolar concentrations of 1,1,1-trichloroethane and the urinary excretion of its metabolites in humans, which would lay a foundation for establishing a biologic monitoring method for industrial human exposure. This model simulated various human exposure scenarios: during and after 8-hour inhalation exposure to 213 or 72 ppm; during and after 5-day inhalation exposure to 350 ppm, 7.5 hours per day; and during inhalation exposure with hourly or daily variation in the exposure concentrations. This model was based on an earlier model (Fernandez *et al.*, 1977) for trichloroethylene. It included fat, muscle (representing slowly perfused tissues), lung, and rapidly perfused tissues. The liver was lumped into the rapidly perfused tissues, and the metabolism was represented by the clearance of 1,1,1-trichloroethane from a fixed amount of blood flow per unit time. The model simulated the human data (Humbert and Fernandez, 1977; Stewart *et al.*, 1975) reasonably well. We did not reconstruct this model as we felt that lumping the liver into the well-perfused tissue compartment was not a proper way for handling a chemical like 1,1,1-trichloroethane, which is known to undergo metabolism.

The second model was developed by Nolan *et al.* (1984) for humans. Six male Caucasians 26 to 54 (mean = 43) years of age and weighing between 77 and 106 kg (mean = 85) volunteered in the inhalation study. Separated by three weeks, they were exposed as a group for 6 hours to 350 and 35 ppm of 1,1,1-trichloroethane in a 70 m^3 dynamic chamber (6×5×2.3 m). Venous blood and expired air samples were collected for 1,1,1-trichloroethane analysis using gas chromatography (GC). The Nolan *et al.* model (1984) was similar to the Caperos *et al.* (1982) model. It also included fat, muscle, lung, and well perfused tissues; the liver was lumped into the well perfused tissues and the metabolism occurred in the well perfused tissues in a first order fashion. The partition coefficients and metabolism rate constant were estimated from the data in this study. The model described 1,1,1-trichloroethane concentrations in the expired air and venous blood well. For the same reason given above to the Caperos *et al.* (1982) model, we did not reconstruct this PBPK model.

The third model (Gargas *et al.,* 1986a) was developed using rat data obtained from close-chamber gas uptake studies. This model, based on the styrene model by Ramsey and Andersen (1984), was comprised of four tissue compartments (liver, viscera, muscle/skin, and fat) and a chemical exchange compartment (lung). Male Fischer 344 rats (200–250 g) were exposed to 1,1,1-trichloroethane at initial chamber concentrations of 0.2, 1.0, 10, or 210 ppm. Time-course concentrations of 1,1,1-trichloroethane in the chamber were determined. Tissue and blood:air partition coefficients at 37°C were experimentally measured. The model assumed equilibrium between the concentrations in blood leaving the lung and in alveolar air, controlled by the blood:air partition coefficient, and that the tissue uptake of 1,1,1-trichloroethane was flow-limited. The chemical was eliminated through exhalation and first-order metabolism in the liver. Metabolic parameters used in the model were obtained from optimization against gas uptake data by visual inspection. The model simulated the chamber concentration data from their own gas uptake pharmacokinetic studies in rats very well, but the PBPK model was not further verified with external data. We initially reconstructed this model and later obtained the original code from Dr. Lisa Sweeney (see Appendix I for the code Gargas.CSL and Gargas.CMD). We reproduced the original simulations (Figure 1). Please note that in all the figures, 1,1,1-trichloroethane is abbreviated as TCA.

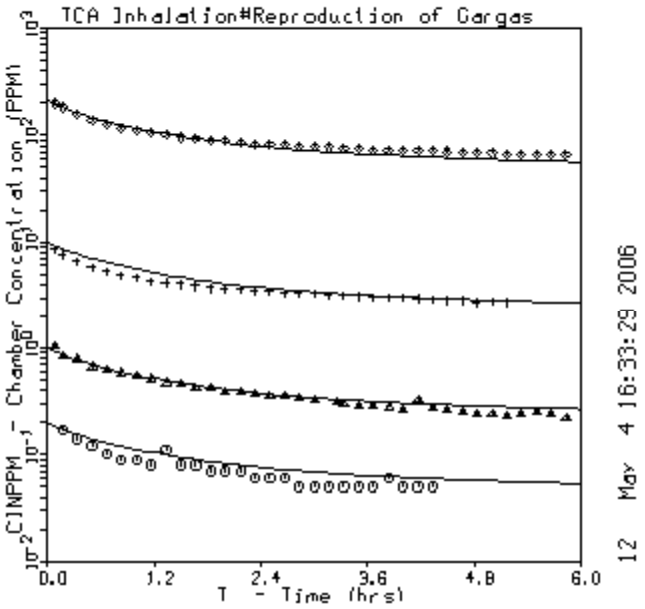


Figure 1. Simulation of 1,1,1-trichloroethane inhalation in rats by the re-established Gargas *et al.* (1986a) model. This figure should be compared with Fig. 4a in the original paper.

The fourth PBPK model was reported by Reitz *et al.* (1988). This model was designed to extrapolate 1,1,1-trichloroethane pharmacokinetics across exposure routes (intravenous, oral, and inhalation) and species (mice, rat, and human). There were three pharmacokinetic experiments in this study (experiments involving single intravenous bolus, single oral gavage, and 1,1,1-trichloroethane in drinking water) in male Fischer 344 rats (240–260 g) for model development. In the first experiment, the rats were intravenously administered a single dose of 8.84, 25.6, or 47.0 mg/kg 1,1,1-trichloroethane dissolved in heparinized rat plasma. Serial blood collections were performed and analyzed for 1,1,1-trichloroethane. In the single oral experiment, the rats were gavaged with 1,1,1-trichloroethane water solution at the dose of 14.2 mg/kg, and 1,1,1-trichloroethane blood concentrations were determined. In the drinking water experiment, ^{14}C-1,1,1-trichloroethane was employed. The animals had free access to drinking water containing ^{14}C-1,1,1-trichloroethane for 8 hours. The animals were maintained in metabolic cages for an additional 48 hours before sacrifice. Urine, feces, liver, kidney, fat, skin, and carcass samples were collected, and radioactivity in the samples was measured.

The four-compartment PBPK model by Reitz *et al.* was also based on the model structure of styrene by Ramsey and Andersen (1984); it consists of liver, fat, and slowly and rapidly perfused compartments. Saturable metabolism of 1,1,1-trichloroethane in the liver was assumed in all species (rat, mouse, and human); the parameters (Vmax and Km) were optimized, using a computerized least-squares optimization procedure, against the amount of metabolites estimated from Schumann *et al.* (1982) in which the formation of metabolites from ^{14}C-1,1,1-trichloroethane was investigated and corrected by a factor derived from the drinking water experiment of Reitz *et al.* (1988). Experimentally determined tissue partition coefficients of mice, rats, and humans were supplied by Michael L. Gargas through the authors' personal communication. In simulating the single gavage data, the gastrointestinal absorption constant was estimated by model fitting. In simulating the drinking water data, a zero-order input of

1,1,1-trichloroethane was assumed. Extrapolation across species, from rats to mice and humans, was achieved by comparing simulations with the corresponding experimental data.

We obtained the original code of this model from Dr. Richard Reitz through personal communication. Written in SimuSolv, the code was modified by us into the format compatible with ACSL TOX 11.8 (see Appendix I for Reitz.CSL and Reitz.CMD). Our modified code produced very similar outputs as Reitz *et al.* (1988) reported (Figures 2–8).

The simulations/predictions of the Reitz *et al.* (1988) model under multiple experimental conditions were compared with the following corresponding data sets:

1. Rat inhalation study: Schumann *et al.* (1982) determined the venous blood concentrations of 1,1,1-trichloroethane in male Fischer 344 rats weighing between 190 to 240 g, during and after 6-hour exposure to 150 or 1500 ppm 1,1,1-trichloroethane in a head-only exposure system. By incorporating corresponding parameters, the Reitz *et al.* (1988) model simulated the postexposure data reasonably well, but the concentrations during exposure were overpredicted by a factor of about 2 (Figure 2).

2. Rat intravenous study: The data were obtained by Reitz *et al.* (1988). The model predicted the shapes of the venous blood concentration profiles but somewhat underpredicted from about 1 hour postexposure (Figure 3).

3. Rat oral gavage study: The data were also collected by Reitz *et al.* (1988). The model simulation did not follow the shape of the time-venous blood concentration curve satisfactorily (Figure 4).

4. Rat drinking water study: The model simulation of the rate of elimination of ^{14}C-1,1,1-trichloroethane in exhaled air of the rats was comparable with the experimental data by Reitz *et al.* (1988) (Figure 5). In addition, the predicted amount metabolized (5.49 μmol, about 2% of ingested 1,1,1-trichloroethane) was also comparable with the experimental measurement in urine and CO_2 (8.19 μmol, about 3% of ingested 1,1,1-trichloroethane).

5. Mouse inhalation study: The B6C3F1 mice (21–35 g) had the same exposure scenario as the rats did in the Schumann *et al.* (1982) study. The venous blood concentrations of 1,1,1-trichloroethane were well predicted by the model (Figure 6).

6. Human volunteer inhalation study: The human inhalation data were collected by Nolan *et al.* (1984) under the above-mentioned conditions. The model overpredicted the venous blood concentrations during exposure by a factor of about 2 and predicted the postexposure concentrations well (Figure 7). The predictions of 1,1,1-trichloroethane concentrations in expired air agreed with the data (Figure 8).

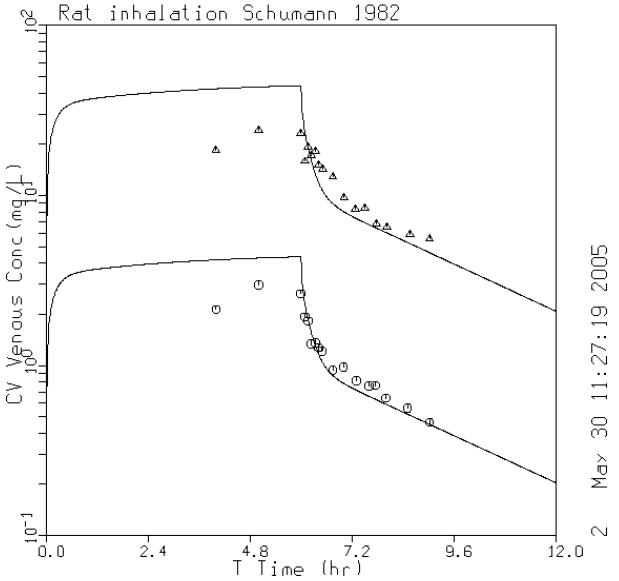


Figure 2. Simulation of 1,1,1-trichloroethane blood concentrations in rats following inhalation, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 1 in the original paper.

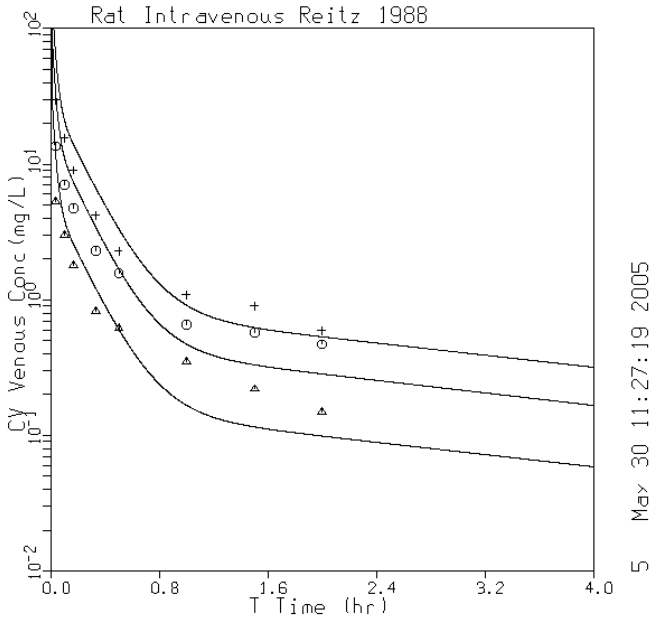


Figure 3. Simulation of 1,1,1-trichloroethane blood concentrations in rats following intravenous administration, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 2 in the original paper.

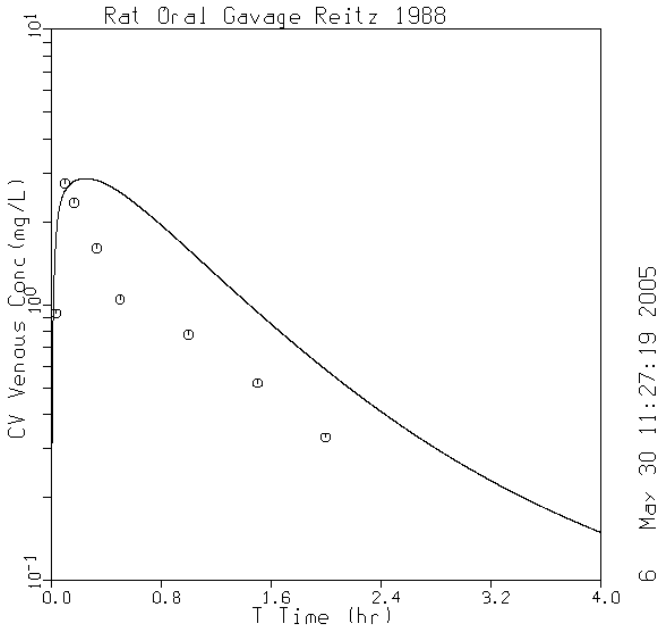


Figure 4. Simulation of 1,1,1-trichloroethane blood concentrations in rats following gavage administration, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 3 in the original paper.

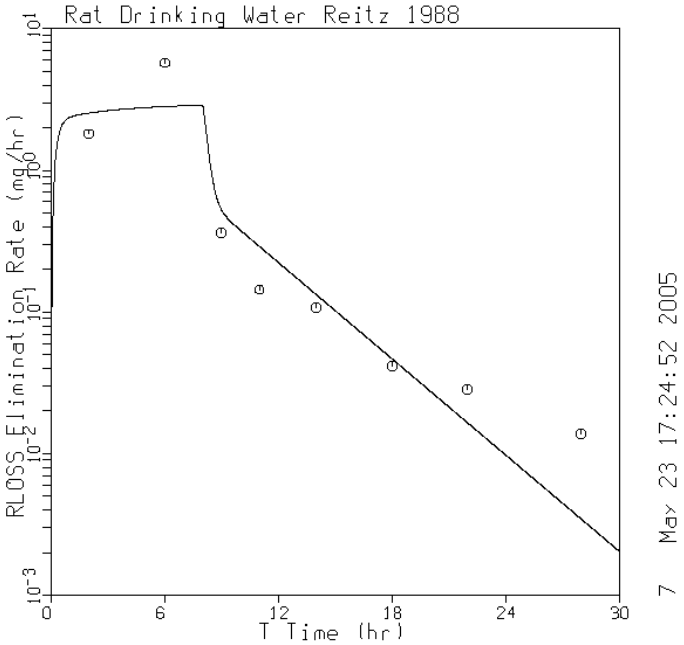


Figure 5. Simulation of 1,1,1-trichloroethane elimination following administration via drinking water, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 4 in the original paper.

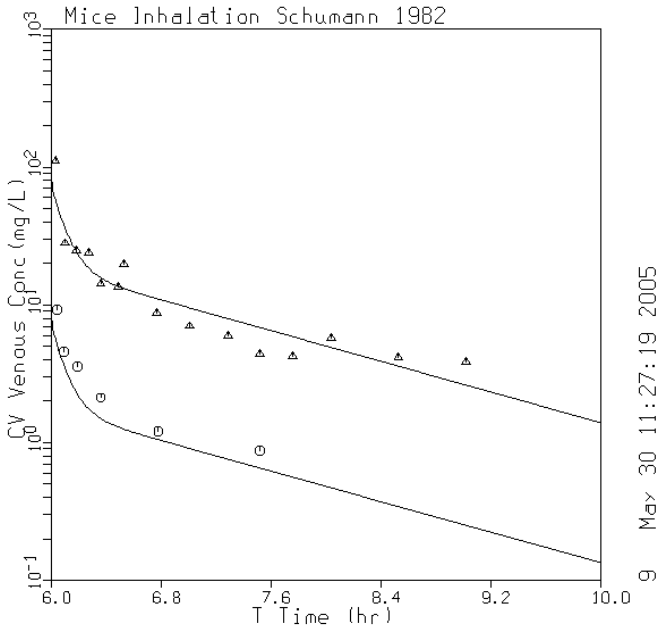


Figure 6. Simulation of 1,1,1-trichloroethane blood concentrations in mice following inhalation, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 5 in the original paper.

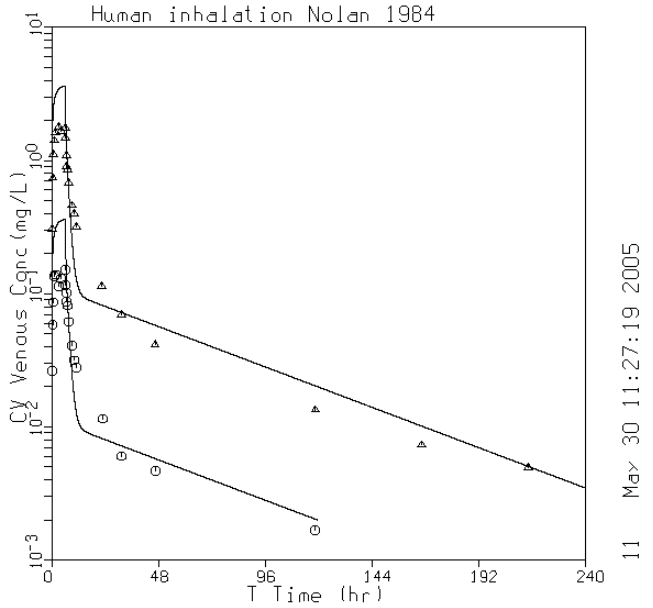


Figure 7. Simulation of 1,1,1-trichloroethane blood concentrations in humans following inhalation, by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 6a in the original paper.

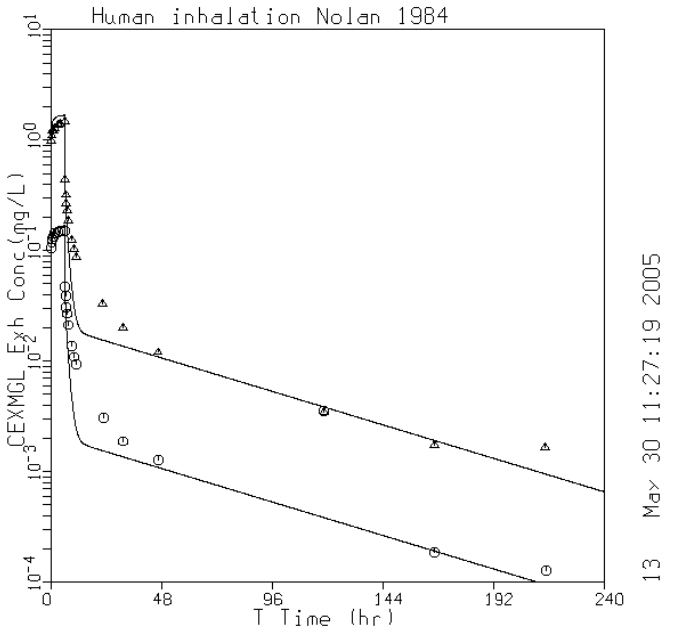


Figure 8. Simulation of 1,1,1-trichloroethane inhalation in humans by our reestablished Reitz *et al.* (1988) original model. This figure should be compared with Fig. 6b in the original paper.

The simulation results in Figures 7 and 8, though matching the results of the original paper very well, show some discrepancies of fitting between model simulation curves and the experimental data sets. This is probably due to the fact that the decay of volatile organics usually follows a tri-exponential behavior rather than a bi-exponential one. Some investigators have tried to use an additional fat compartment to accommodate the more complicated pharmacokinetic behavior. Such a modification of the model was not attempted here.

The fifth model (Bogen and Hall 1989) was a variant of the Reitz *et al.* (1988) model. The model structure included a skin compartment to account for the uptake of 1,1,1-trichloroethane from skin. The physiological and metabolic parameters for rats and mice were taken directly from Reitz *et al.* (1987). The human partition coefficients and Km were also from Reitz *et al.* (1987); the human Vmax was approximately four times greater than the value used by Reitz *et al.* (1987). The human Vmax adjustment, by Bogen and Hall (1989), was made based on the argument that the Reitz *et al.* (1987) model underpredicted metabolite formation in the Nolan *et al.* (1984) study as well as underpredicted urinary metabolite production in the Humbert and Fernandez (1977) study. Furthermore, Bogen and Hall (1989) implied that higher adjustment of Vmax was warranted because urinary metabolites only accounted for about 50% (36.7–68.9%) of the total metabolites of 1,1,1-trichloroethane. There were very little experimental data in this paper, particularly regarding model verification with any experimental data set. As the Bogen and Hall (1989) model is very similar to the Reitz *et al.* (1988) model, we did not reconstruct this model; however, the adjustment of the human Km was taken into consideration in our further analysis.

The sixth model (Dallas *et al.*, 1989) was another variant of the Reitz *et al.* (1988) model. It also describes the disposition of 1,1,1-trichloroethane in rats following inhalation exposure. In addition to

the fat, liver, and rapidly and slowly perfused tissues in the Reitz *et al.* model (1988), this model also includes blood and lung as compartments. Moreover, the metabolism of 1,1,1-trichloroethane in the liver was described as a first-order process. The alveolar ventilation rate was measured in the Dallas *et al.* (1989) study. The other physiological parameters and the metabolism rate constant were from the literature (Gargas *et al.*, 1986a; Ramsey and Andersen, 1984; Gerlowski and Jain, 1983) and scaled to 0.34 kg, the mean body weight of the rats used in their study (Dallas *et al.*, 1989). The partition coefficients were from Gargas *et al.* (1986a, 1989). The lung:blood partition coefficient, not available from Gargas *et al.* (1986a), was assumed the same as the liver:blood partition coefficient; the lung:air partition coefficient was derived by the product of lung:blood coefficient × blood:air coefficient.

In the Dallas *et al.* (1989) study, male Sprague-Dawley rats (12 weeks old, average body weight 340 g) were exposed to 50 or 500 ppm 1,1,1-trichloroethane in nose-only inhalation exposure systems for 2 hours. Concentrations of 1,1,1-trichloroethane in arterial blood and exhaled air were measured during the exposure and up to 4 hours postexposure. In general, the Dallas *et al.* (1989) model simulated the shapes of the time-concentration curves well (Figures 9–12); however, the concentrations were somewhat overpredicted during exposure and underpredicted after exposure. In the paper, the mass balance differential equations were presented; however, we could not successfully reproduce their simulations of arterial blood concentrations (code in Appendix I: Dallas.CSL and Dallas.CMD).

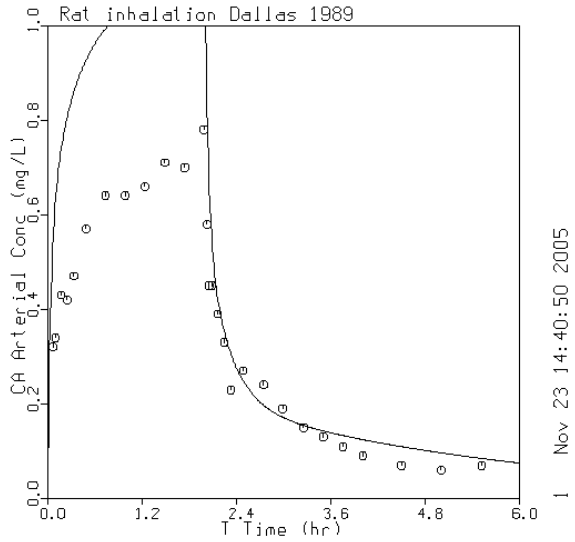


Figure 9. Simulation of 1,1,1-trichloroethane in arterial blood in rats exposed to 50 ppm, by our reconstructed model. Should be compared with the upper panel in Fig. 3 in the Dallas *et al.* (1989) study.

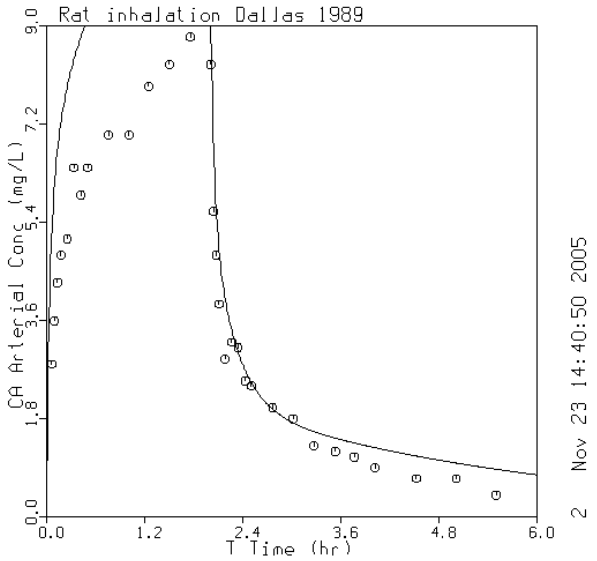


Figure 10. Simulation of 1,1,1-trichloroethane in arterial blood in rats exposed to 500 ppm, by our reconstructed model. Should be compared with the upper panel in Fig. 4 in the Dallas *et al.* (1989) study.

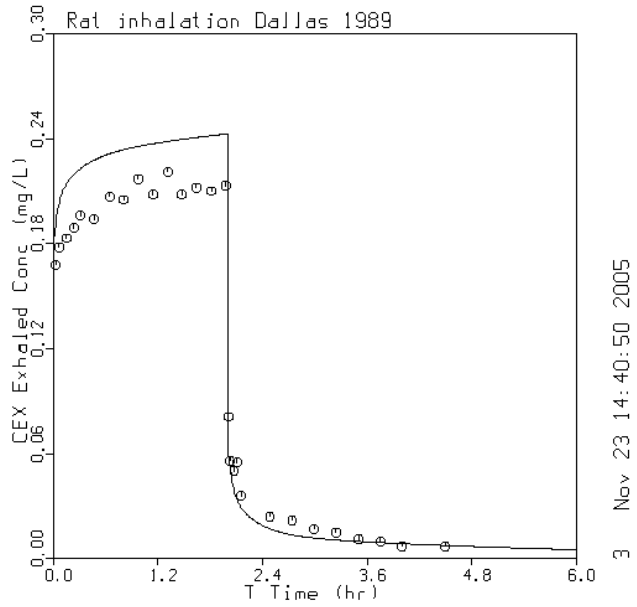


Figure 11. Simulation of 1,1,1-trichloroethane in exhaled air in rats exposed to 50 ppm, by our reconstructed model. Should be compared with the lower panel in Fig. 3 in the Dallas *et al.* (1989) study.

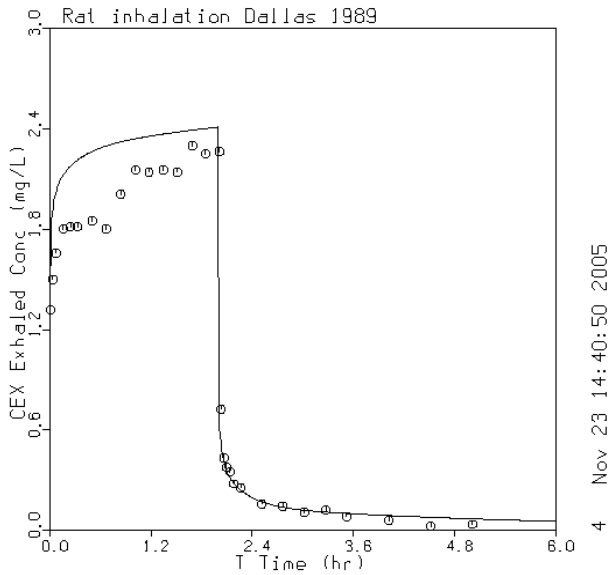


Figure 12. Simulation of 1,1,1-trichloroethane in exhaled air in rats exposed to 500 ppm, by our reconstructed model. Should be compared with the lower panel in Fig. 4 in the Dallas *et al.* (1989) study.

The seventh model (Leung, 1992) was developed to simulate 1,1,1-trichloroethane concentrations in expired air and blood, as well as concentrations of metabolites of 1,1,1-trichloroethane in the urine after human exposure. The exposure regimen was similar to a typical work schedule in which workers were exposed to 350 ppm (occupational exposure limit, OEL) 8 hours/day and 5 days/week; the workers were assumed to perform light-duty exercise (50 watt) during work and be at rest between shifts. The model consisted of four tissue groups (fat, liver, and slowly and rapidly perfused tissues). The chemical distribution was described in a fashion very similar to Gargas *et al.* (1986a) and Reitz *et al.* (1988). Michaelis-Menten metabolism was employed in the liver. The Vmax and Km were scaled allometrically from the rat values (Reitz *et al.*, 1988). The changes in ventilation and blood flow rates due to exercise were incorporated in the model. No comparison was made between model simulations and any data set. As this model has a reasonable structure and it simulates an industrial exposure scenario, we considered it appropriate to reconstruct the model. Our reconstructed model (see Appendix I for Leung.CSL and Leung.CMD) could reproduce the calculated results presented in the Leung (1992) study except that the venous blood concentration at the end of the first shift was slightly underpredicted for unknown reasons (Figure 13). This model adequately simulated the 1,1,1-trichloroethane concentrations in the expired air and venous blood.

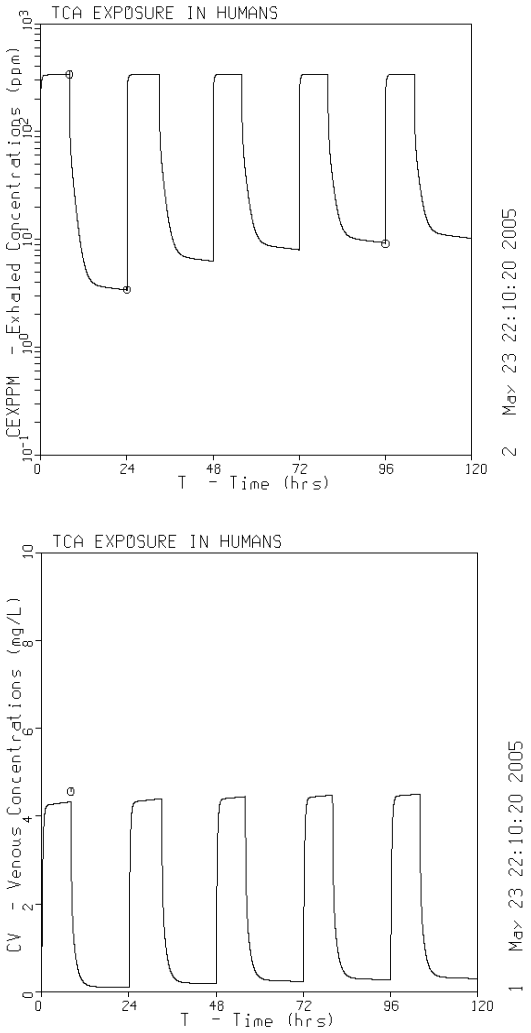


Figure 13. Simulation results of exhaled and venous blood concentrations in humans, by our reconstructed Leung (1992) model, compared with Leung's calculations (the symbols are calculated results by Leung; there were no simulation plots in the original Leung [1992] paper).

Developed by Yoshida (1993), the eighth model was very similar to the Reitz *et al.* (1987; 1988) model. The model was aimed at estimating steady state tissue concentrations of 1,1,1-trichloroethane in the Japanese population after daily exposure through inhalation of ambient air and ingestion of drinking water, milk, meat, fish, and vegetation. The model was comprised of four tissue compartments (liver, fat, and slowly and rapidly perfused tissues). Saturable metabolism of 1,1,1-trichloroethane was assumed, and the partition coefficients and metabolic parameters were adopted from Reitz *et al.* (1987). The model was used to predict human tissue concentrations of 1,1,1-trichloroethane, as described above; however, this model was not verified using human pharmacokinetic data sets from other sources. We also reconstructed this model (see Appendix I for Yoshida.CSL and Yoshida.CMD) and could reproduce the calculated results reported in the paper (Figure 14).

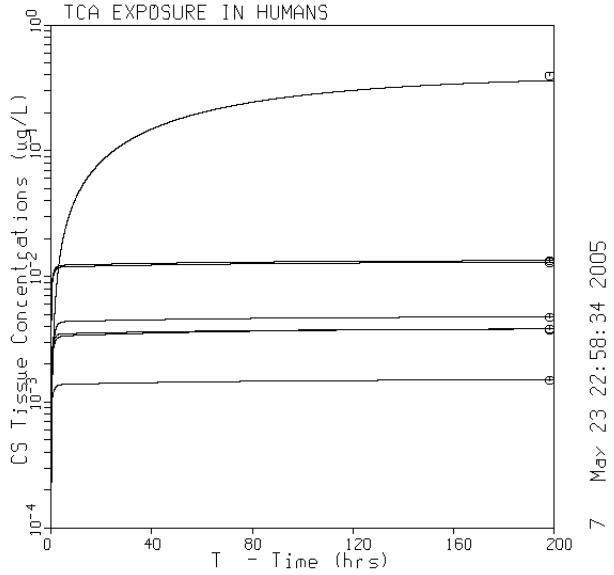


Figure 14. Simulation results of 1,1,1-trichloroethane tissue concentrations in humans, by our reconstructed Yoshida (1993) model, compared with Yoshida's calculations (the symbols are calculated results by Yoshida; there were no simulation plots in the original Yoshida [1993] paper). The seven curves, from top to bottom, are: fat, liver and rapidly perfused (the two curves overlap), slowly perfused, arterial and venous blood (the two curves overlap), and exhaled air.

The ninth model (Lapare *et al.* 1995) was built to describe 1,1,1-trichloroethane pharmacokinetics in human volunteers. Two adult male (age 25–56; weight 55–75 kg) and two adult female (age 26–57; weight 49–63 kg) nonsmoking volunteers were enrolled in the study. They were exposed to 1,1,1-trichloroethane in a dynamic controlled chamber under various sequential regimens. The interval between two consecutive scenarios did not necessarily allow complete elimination of long-lived metabolites; hence, the whole design was similar to industrial exposure conditions. The exposure concentrations ranged from 83.1 to 176.8 ppm. The model included lungs, liver, gastrointestinal tract, fat, muscle and skin, and rapidly and slowly perfused tissues. The effects of workload on blood cardiac output and alveolar ventilation were considered. The metabolism in the liver was considered a saturable process, and the related parameters (Vmax and Km) were from Reitz *et al.* (1988). Excretion of the metabolites in the urine was tracked in their model. While the tissue:air partition coefficients measured using human tissues were adopted from the literature (Fiserova-Bergerova and Diaz, 1986), the blood:air partition coefficient was from model optimization. This model simulated the 1,1,1-trichloroethane concentrations in expired air and venous blood as well as urinary metabolites reasonably well; the predictions were also in good agreement with Nolan *et al.* (1984) data. The Lapare *et al.* (1995) model did not predict the Nolan *et al.* data as well as the Reitz *et al.* (1988) model did. We reconstructed this model (see Appendix I for Lapare.CSL and Lapare.CMD) and could reproduce the simulations of 1,1,1-trichloroethane concentrations in the expired air and venous blood (Figures 15–18).

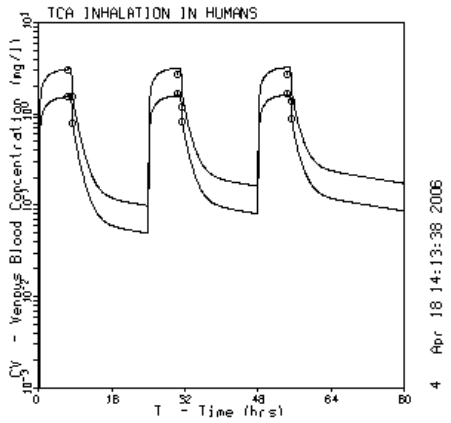


Figure 15. Simulation of venous blood 1,1,1-trichloroethane concentrations following intermittent exposure to 87.5 (lower line) and 175 ppm (upper line) in humans by our reconstructed Lapare *et al.* (1995) model. It should be compared with Fig. 3b in Lapare *et al.* (1995). Note that in the original paper (Lapare *et al.*, 1995) the data and simulations were plotted in an unusual way; hence, this figure looks different from the original one in the Lapare *et al.* (1995) paper although our model reproduced their simulations.

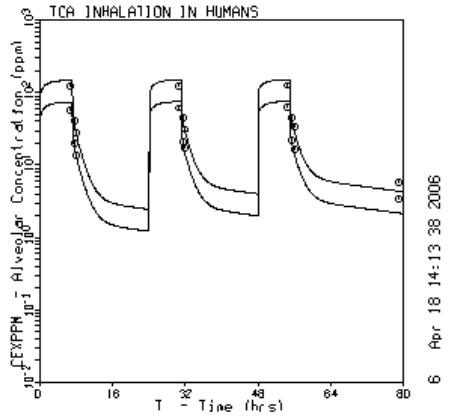


Figure 16. Simulation of 1,1,1-trichloroethane concentrations in expired air following intermittent exposure to 87.5 (lower line) and 175 ppm (upper line) in humans, by our reconstructed Lapare *et al.* (1995) model. It should be compared with Fig. 3a in Lapare *et al.* (1995). Note that in the original paper (Lapare *et al.*, 1995) the data and simulations were plotted in an unusual way; hence, this figure looks different from the original one in the Lapare *et al.* (1995) paper although our model reproduced their simulations.

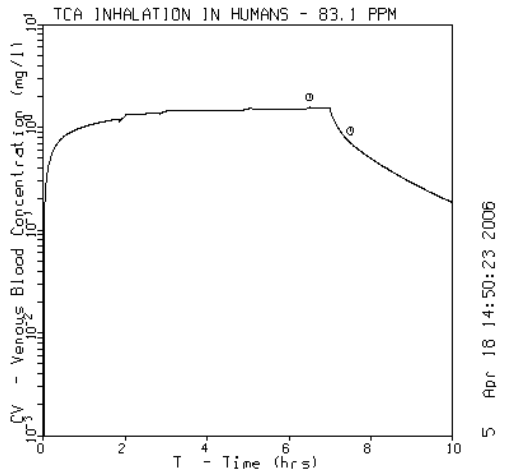


Figure 17. Simulation of venous blood 1,1,1-trichloroethane concentrations following exposure to 83.1 ppm for 7 hrs in humans with intermittent exercise, by our reconstructed Lapare *et al.* (1995) model. The symbols are data in the bottom line of Table 4 in Lapare *et al.* (1995).

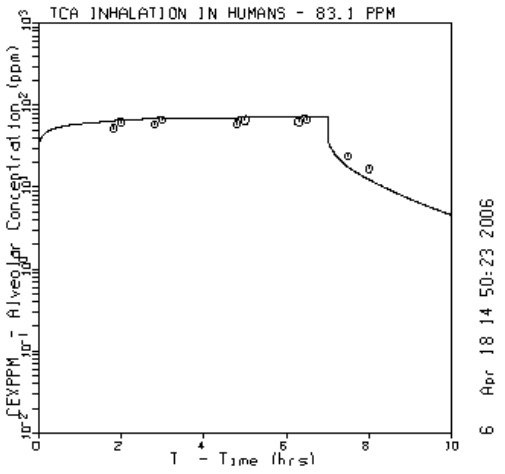


Figure 18. Simulation of expired air 1,1,1-trichloroethane concentrations following exposure to 83.1 ppm for 7 hr in humans with intermittent exercise, by our reconstructed Lapare *et al.* (1995) model. The symbols are data in Table 10 in Lapare *et al.* (1995).

The tenth model (Loizou *et al.*, 1996) described 1,1,1-trichloroethane gas uptake in Wistar albino rats (150–200 g) in a closed chamber system with high exposure concentrations. The rats were placed in a closed chamber for 3 hours with the initial exposure concentrations of 2000, 4000, 8000, 15,000, or 25,000 ppm. Similar to the Gargas *et al.* (1986a), Reitz *et al.* (1988), Leung (1992), and Yoshida (1993) models, this model also had four compartments: fat, liver, and rapidly and slowly perfused tissues. The partition coefficients were experimentally determined by Loizou *et al.* (1996). Although the animals

were exposed to high concentrations, the metabolism in the liver was described as a first-order process. The metabolic rate constant was allometrically scaled from Gargas *et al.* (1986b). The body weight and alveolar ventilation and cardiac output rates were provided as ranges rather than single point values. We used the average value of each range in our reconstruction since this is the most reasonable way of handling such a situation Our reconstruction (see Appendix I for Loizou.CSL and Loizou.CMD) was a result of our interest in the very high concentrations used in this study. In the original paper (Loizou *et al.*, 1996), the 1,1,1-trichloroethane concentrations in the chamber matched the simulation very well. However, we could not successfully reproduce the simulations, except the highest dose, reported by the authors (Figure 19). The reason might be that the combination of the averages of the three parameters does not work for all groups.

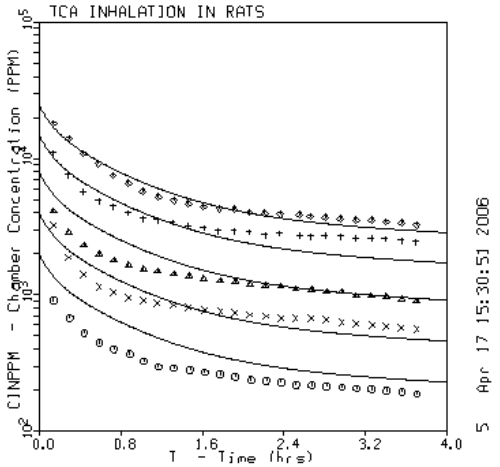


Figure 19. Simulation of 1,1,1-trichloroethane concentrations in a closed chamber by our reconstructed Loizou *et al.* (1996) model. It should be compared with Fig. 4a in Loizou *et al.* (1996).

The eleventh model (DeJongh *et al.*, 1998) was structurally similar to the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models except that it had a brain compartment, divided into water and lipid subcompartments, for exploring the relationship between brain concentration of 1,1,1-trichloroethane and acute lethality in the rat. The partition coefficients were from Gargas *et al.* (1989). The metabolism in the liver was described as a first-order process, and the metabolic rate constant was from Gargas *et al.* (1990). This model predicted the concentrations of 1,1,1-trichloroethane in blood, whole brain, and brain lipid of the rat following short exposure durations (0.25–7 hours) to high concentrations (10,300–38,000 ppm). No comparison between model simulations with experimental data was presented in the paper. We reconstructed this model (see Appendix I for DeJongh.CSL and DeJongh.CMD) and could reproduce the reported calculations in DeJongh *et al.* (1998) as represented in Figure 20. Our model could also reproduce the calculated values following other exposure concentrations in DeJongh *et al.* (1998). These other plots were very similar to Figure 20 and were, therefore, not presented here.

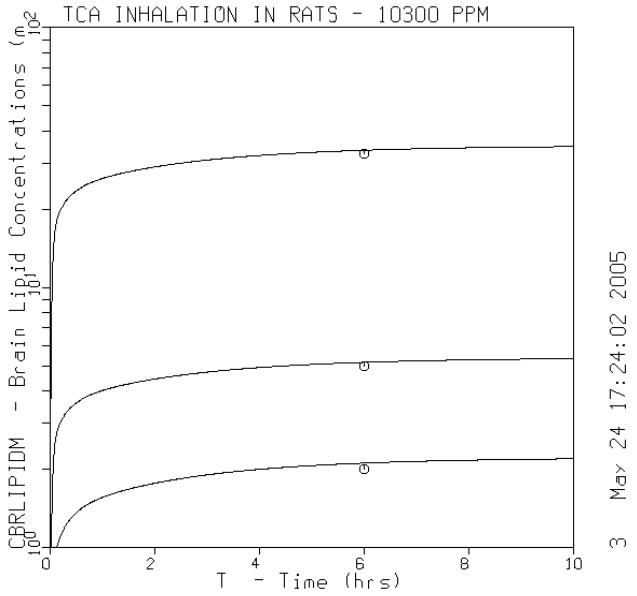


Figure 20. Simulations of 1,1,1-trichloroethane concentrations in venous blood (lower curve), whole brain (middle curve), and brain lipid (upper curve) in rats, by our reconstructed DeJongh *et al.* (1998) model of a 0.35 kg rat following continuous exposure to 10,300 ppm 1,1,1-trichloroethane. The symbols are values calculated by DeJongh *et al.* (1998) from their model prediction instead of real experimental data.

The twelfth model (Tardif and Charest-Tardif 1999) was structurally the same as the Reitz *et al.* (1988) model. This model was established to explore the pharmacokinetic interaction between 1,1,1-trichloroethane and *m*-xylene in the rat and human. While the physiological parameters, primarily volume fractions and blood flow fractions of the compartments were slightly different from those in Reitz *et al.* (1988), the partition coefficients and metabolic parameters were from Reitz *et al.* (1988). This model simulated well the blood concentration in human volunteers during the 4 hrs exposure to 400 ppm of 1,1,1-trichloroethane, but the simulation of the blood concentration in the rat was not plotted with data. We reconstructed this model (see Appendix I for Tardif.CSL and Tardif.CMD) and could reproduce the simulations (Figures 21 and 22).

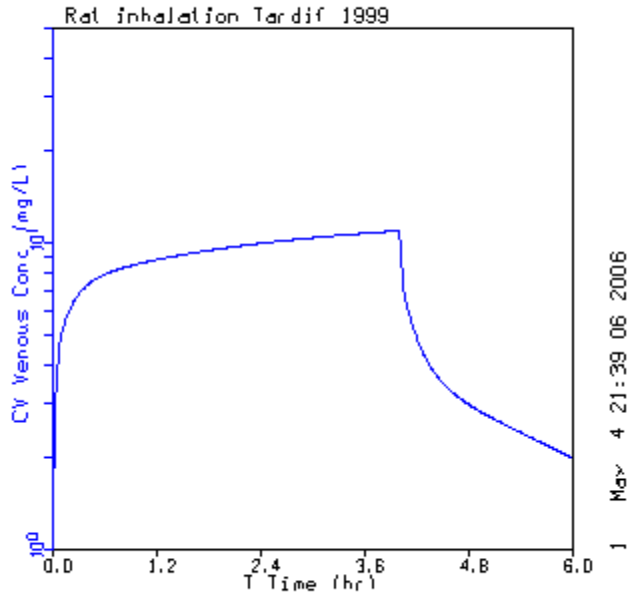


Figure 21. Simulation of venous blood 1,1,1-trichloroethane concentration in the rat exposed to 400 ppm of 1,1,1-trichloroethane for 4 hrs by our reconstructed Tardif and Charest-Tardif (1999) model. This graph should be compared with the left side of Fig. 2 in Tardif and Charest-Tardif (1999).

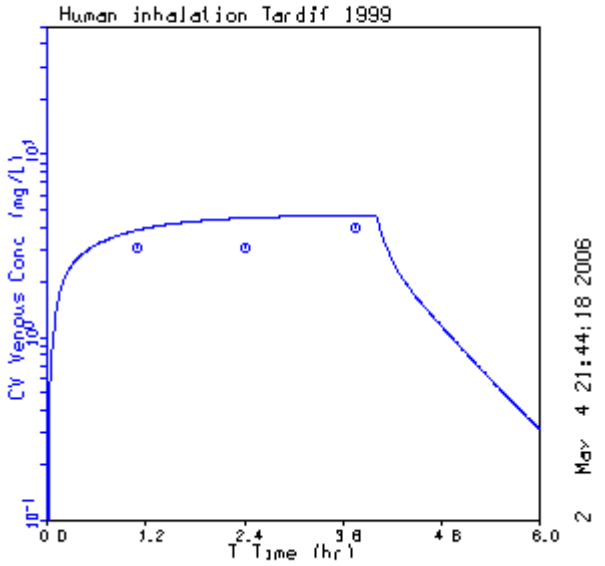


Figure 22. Simulation of venous blood concentration in the human volunteers exposed to 400 ppm of 1,1,1-trichloroethane for 4 hrs by our reconstructed Tardif and Charest-Tardif (1999) model. This graph should be compared with the left side of Fig. 1 in Tardif and Charest-Tardif (1999).

The thirteenth model (Poet *et al.* 2000), similar to the Bogen and Hall (1989) model, was a modification of Reitz *et al.* (1988) by including a skin compartment. Except for skin permeability, the other parameters were from experimentation and the literature (Brown *et al.*, 1997; Jepson and McDougal, 1997; Mattie *et al.*, 1994; Reitz *et al.*, 1988). Comparing the experimental and model simulated 1,1,1-trichloroethane concentrations in appropriate samples, the Poet *et al.* model (2000) determined the skin permeability of 1,1,1-trichloroethane in rats and humans. As dermal exposure to 1,1,1-trichloroethane is not of concern in this project, we did not reconstruct the Poet *et al.* (2000) model.

The fourteenth model (Dobrev *et al.,* 2001, 2002) was developed for a ternary mixture of volatile organic chemicals in the rat and human. We decided not to pursue this model further for the following reasons: (1) The model structures and parameters were very similar to the existing models of Gargas *et al. (*1986a) and Reitz *et al.* (1988), and only minimal modifications were made; (2) The main purpose of the Dobrev *et al.* (2001, 2002) studies was to explore the interactions and related mechanisms among trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane.

Among the reconstructed models, the Dallas *et al.* (1989), Leung (1992), Yoshida (1993), and DeJongh *et al.* (1998) models were excluded from further consideration because they are simply variants of the earlier models (Gargas *et al.*, 1986a; Reitz *et al.*, 1988) and their predictions were not compared with any experimental data. The Tardif and Charest-Tardif (1999) model was also excluded because its parameters and structures were very similar to those of Reitz *et al.* (1988), and its performance was only tested under one concentration level. The Lapare *et al.* (1995) model has a somewhat unnecessarily complex structure; for instance, lung, GI tract, and muscle/skin are separate tissue compartments for no apparent advantages. Furthermore, there is a direct shunt from arterial to venous blood without detailed explanation. Thus, we excluded this model based on the law of parsimony. The Loizou *et al.* (1996) model was also rejected because our reconstructed model could not reproduce the simulation reported in the original paper by Loizou *et al.* (1996). Therefore, our initial model selection narrowed down to the two PBPK models by Gargas *et al.* (1986a) and Reitz *et al.* (1988). These two models were then further evaluated against the same eleven data sets as described in the next section.

IV. EVALUATION OF THE RECONSTRUCTED PBPK MODELS

IV.1. Selection of Data Sets for Further PBPK Model Evaluation and Rationale for Selection

We selected eleven data sets for the further evaluation of the two final PBPK models (Gargas *et al.* [1986a] and Reitz *et al.* [1988]); seven of these are from experiments conducted in rats and the other four are from human experiments. These data sets are summarized in Table 3 and explained below.

Table 3. Data Sets Selected for Testing Gargas *et al.* (1986a) and Reitz *et al.* (1988) Models

Reference	Species	Exposure conditions	Remarks
Schumann *et al.* (1982)	Rat	Inhalation of ^{14}C-1,1,1-trichloroethane at 150 and 1,500 ppm; Radioactivities in chamber, expired air, and organs determined.	Used in Reitz *et al.* (1988) model development.
Gargas *et al.* (1986a)	Rat	Inhalation in a closed chamber system; Initial concentrations of 0.2, 1.0, 10, and 210 ppm; Chamber concentration determined.	Used in Gargas *et al.* (1986a) model development.

Reference	Species	Exposure conditions	Remarks
Reitz *et al*. (1988)	Rat	Single intravenous dose of 8.84, 25.6, and 47.0 mg/kg; Single oral gavage of 14.2 mg ^{14}C-1,1,1-trichloroethane/kg; Drinking water for 8 hrs at a level equivalent to 14.5 mg/kg/hour; Venous blood and expire air concentrations determined.	Used in Reitz *et al.* (1988) model development.
Loizou *et al.* (1996)	Rat	Inhalation in a closed chamber system for 3 hours; Initial concentrations of 2,000, 4,000, 8,000, 15,000, and 25,000 ppm; Chamber concentration determined.	-
You and Dallas (1998)	Rat	Inhalation in a dynamic chamber up to 2 hrs; Constant levels of 3,500 and 5,000 ppm; Blood concentrations measured.	-
Warren *et al.* (1998)	Rat	Inhalation in a dynamic chamber up to 100 min; Constant levels of 1,000, 2,000, 3,500 and 5,000 ppm; Blood concentrations measured.	-
Bruckner (personal communication)	Rat	Single oral gavage at 6 mg/kg; Concentrations in venous blood and internal organs determined	-
Savolainen *et al.* (1981)	Human	Nine male human volunteers; Inhalation exposure in a chamber at rest to 200 or 400 ppm (8.2 or 16.4 μmol/l) for 4 hrs; Venous blood concentration determined.	-
Nolan *et al*. (1984)	Human	Six male human volunteers; Inhalation of 35 and 350 ppm for 6 hrs in a dynamic chamber; Concentrations in expired air and venous blood determined.	Used in Reitz *et al.* (1988) model development.
Mackay *et al.* (1987)	Human	Twelve male human volunteers; Inhalation of 0, 175, and 350 ppm for 3.5 hrs; Concentration in venous blood determined.	Neurobehavioral tests conducted immediately after blood sampling.
Lapare *et al*. (1995)	Human	Two male and two female healthy volunteers; Four different exposure scenarios, varying in concentration, duration, and workload; Concentrations in exhaled air and venous blood measured.	-

IV.1.1. Selection of Data Sets from Experiments Conducted in Rats

The following seven data sets of 1,1,1-trichloroethane pharmacokinetics in rats were selected: Schumann *et al.* (1982), Gargas *et al.* (1986a), Reitz *et al*. (1988), Loizou *et al.* (1996), You and Dallas (1998), Warren *et al.* (1998) and Bruckner (unpublished data; personal communication). Criteria for selection were as follows: (1) essential experimental information, such as strain, age, body weight, and dosing conditions are available; (2) the analytical method used for 1,1,1-trichlorethane measurements in the samples is a sensitive and reliable one; (3) preference is given to studies that used multiple exposure levels; (4) the chemical was administered to the rats by inhalation, intravenous, or oral administration; and (5) the data set provides sufficient data points of the concentration-time courses of the chemical in exposure chambers, blood, and/or organs.

Schumann *et al*. (1982) performed their study in male Fischer 344 rats (body weight: 190–240 g). The rats were exposed to ^{14}C-1,1,1-trichloroethane by inhalation at 150 and 1500 ppm. Radioactivities in chamber, expired air, and organs were determined. The data set was subsequently used in 1,1,1-trichloroethane PBPK model development by Reitz *et al.* (1988).

Gargas *et al*. (1986a) conducted their study in male Fischer 344 rats (body weight: 200–250 g) in a closed-chamber system. The animals were exposed by inhalation to initial 1,1,1-trichloroethane concentration of 0.2, 1.0, 10, and 210 ppm. Concentration of the chemical in the chamber was determined by GC. Partition coefficients were also experimentally determined. A PBPK model of 1,1,1-trichloroethane was constructed and verified by the experimental data. The model showed appropriate fittings at all four different dosing levels. The model and its parameters were extensively used in the subsequent development of PBPK models of the chemical by other researchers.

Reitz *et al.* (1988) performed their experiment in male Fischer 344 rats (body weight: 240-260 g). Rats were exposed to 1,1,1-trichloroethane by single dose intravenous administration (8.84, 25.6, and 47.0 mg/kg), single oral gavage (14.2 mg/kg), or drinking water. In the drinking water study, rats were exposed to a solution of ^{14}C-1,1,1-trichloroethane in drinking water (0.8–1.0 mg/ml; 2.70×10^5 dpm/ml) for one 8-hour period. Average water consumption was 8.1 ± 3.8 mL, corresponding to an average dose of 116 mg/kg or 14.5 mg/kg/hour. Subsequently, concentrations of the chemicals in exhaled air, venous blood, fat, and liver were determined by GC analyses or radioactivity measurements. A PBPK model was constructed and verified using their own data and data sets from other sources. Route-to-route extrapolations in rats and interspecies extrapolations (rats-to-mice and rats-to-humans) of the chemical were demonstrated.

Loizou *et al.* (1996) studied 1,1,1-trichloroethane uptake in Wistar albino rats (150–200 g) in a closed chamber system. The rats were placed in a closed chamber for 3 hours with the initial exposure concentrations of 2,000, 4,000, 8,000, 15,000, or 25,000 ppm. The chamber 1,1,1-trichloroethane time-course concentrations were measured by GC.

You and Dallas (1998) exposed male adult Sprague-Dawley rats (275-325 g) to 3500 or 5000 ppm 1,1,1-trichloroethane in a dynamic chamber up to 120 min. Upon sacrifice, blood was collected by cardiac puncture. Meanwhile, the brains were collected and dissected into seven regions. The concentrations of 1,1,1-trichloroethane in blood and brain regions were determined by GC.

Similar to the You and Dallas (1998) study, the Warren *et al.* (1998) study involved male adult Sprague-Dawley rats (275-350 g) exposed to 1,000, 2,000, 3,500, and 5,000 ppm of 1,1,1-trichloroethane up to 100 min in a dynamic chamber. Venous blood concentration of 1,1,1-trichloroethane was determined at a series of time points.

Bruckner (unpublished data; personal communication) conducted experiments in male Sprague-Dawley rats, 306–360 g. Because this information came late, we used 350 g/rat in our PBPK model simulations. 1,1,1-Trichloroethane was administered by single oral gavage (6 mg/kg). Chemical analysis of venous blood and internal organs was performed using GC (Bruckner, personal communication).

IV.1.2. Selection of Data Sets from Experiments Conducted in Humans

Four human data sets were selected from the studies conducted by Savolainen *et al.* (1981), Nolan *et al*. (1984), Mackay *et al*. (1987) and Lapare *et al*. (1995). Criteria for selection were similar to those given above for the rat studies except that the human study was conducted under an appropriate ethical

standards with written informed consent from the participants, and the study reveals findings of toxicological significance, such as impairment of psychomotor performance from exposure to 1,1,1-trichloroethane as reported by Mackay *et al*. (1987).

Savolainen *et al.* (1981) exposed nine healthy male student volunteers (20–25 years old, body weight 57–82 kg) to 1,1,1-trichloroethane in a 15 m^3 dynamic chamber at the concentrations of 200 and 400 ppm (8.2 and 16.4 μmol/L). The exposure was 4 hours per day, once a week, with a 6-day interval between succeeding exposures over 6 consecutive weeks. Venous blood concentrations of 1,1,1-trichloroethane were determined before and during each exposure; psychophysiological indices were measured before, during, and after each exposure. See Section V.2.1. for more information.

Nolan *et al*. (1984) conducted their experiment in six male human volunteers (age: 26–54 years, body weight: 77–106 kg). The volunteers were exposed to 35 and 350 ppm of 1,1,1-trichloroethane in ambient atmosphere. Concentrations of the chemical in expired air and in venous blood were determined by GC. The results were used as the human data set to verify the 1,1,1-trichloroethane PBPK model by Reitz *et al*. (1988).

Mackay *et al.* (1987) conducted their experiments in 12 male human volunteers (no age and body weight reported). The volunteers were exposed to 0, 175, and 350 ppm of 1,1,1-trichloroethane in atmospheric air for 3.5 hours. Concentrations of the chemical in venous blood were determined using GC. In addition, certain neurobehavioral tests were conducted immediately after blood sampling, and correlations between these neurobehavioral changes and 1,1,1-trichloroethane exposure at different time periods were reported.

Lapare *et al*. (1995) conducted their experiments in two male and two female healthy volunteers (ages: 25–57 years, body weights: 49–75 kg). The volunteers were assigned into four different scenarios in order to establish exposure concentration, duration of exposure, variation of exposure concentration, and influence of workload on pharmacokinetics of 1,1,1-trichloroethane. Concentrations of 1,1,1-trichloroethane in exhaled air and venous blood were measured by GC.

IV.2. Further Evaluation of Gargas *et al.* (1986a) and Reitz *et al.* (1988) PBPK Models Using Common Data Sets

The difference between the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models is that Gargas *et al.* only focused on rat inhalation data. Furthermore, the metabolism of 1,1,1-trichloroethane in the liver is first order (K_fC = 5.0/hr, $K_f = K_fC/BW^{0.3}$) in the Gargas *et al.* study, while it is saturable metabolism (VmaxC = 0.419 mg/hour/kg, $Vmax = VmaxC \times BW^{0.7}$, Km = 5.75 mg/L) in the Reitz *et al.* (1988) study. Since the Gargas *et al.* (1986a) study did not extrapolate to a human PBPK model, physiological parameters and human partition coefficients in Reitz *et al.* (1988) were used to test the performance of the Gargas *et al.* (1986a) model against human data sets unless stated otherwise.

IV.2.1. Evaluations Against Savolainen *et al.* (1981) Human Data

The performance of the Gargas *et al.* (1986a) and Reitz *et al.* (1988) model in simulating the Savolainen *et al.* (1981) human data are shown in Figure 23. While both models performed well, the Reitz *et al.* (1988) model caught the trends of the blood concentrations slightly better.

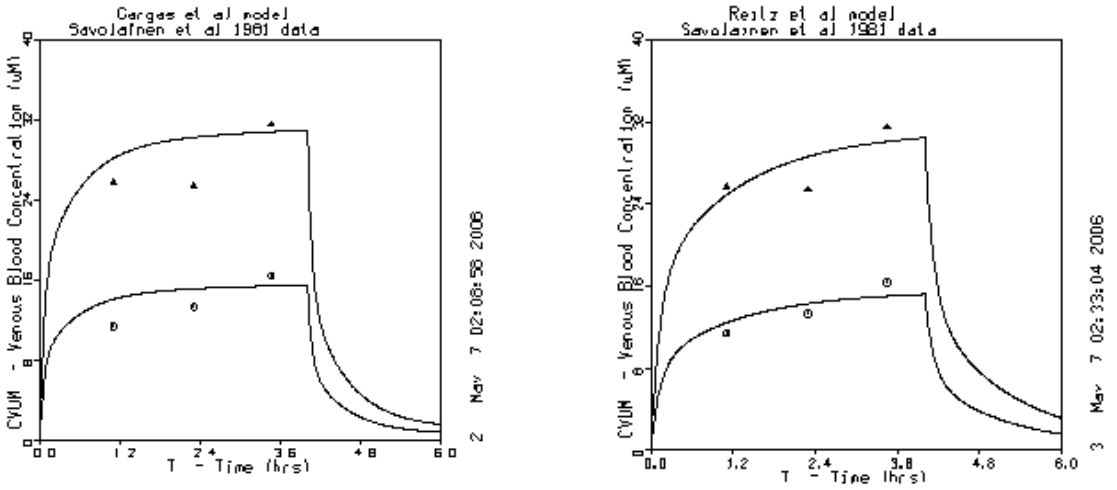


Figure 23. Simulations of venous blood 1,1,1-trichloroethane concentrations in the human volunteers in the Savolainen *et al.* (1981) study. The upper and lower lines represent 400 and 200 ppm of exposure levels.

IV.2.2. Evaluations Against Nolan *et al.* (1984) Human Data

As shown in Figure 24, simulations of 1,1,1-trichloroethane concentrations in venous blood and expired air using the reestablished Gargas *et al.* (1986a) model resulted in very similar findings to the simulations by the Reitz *et al.* (1988) model. This similarity suggests that, for the Nolan *et al.* (1984) data set, the two models performed similarly. It further suggests that, at the exposure concentration of 350 ppm, the assumptions of first order and saturable metabolism in human liver do not seem to affect the simulation outcomes. This result is further supported as presented below.

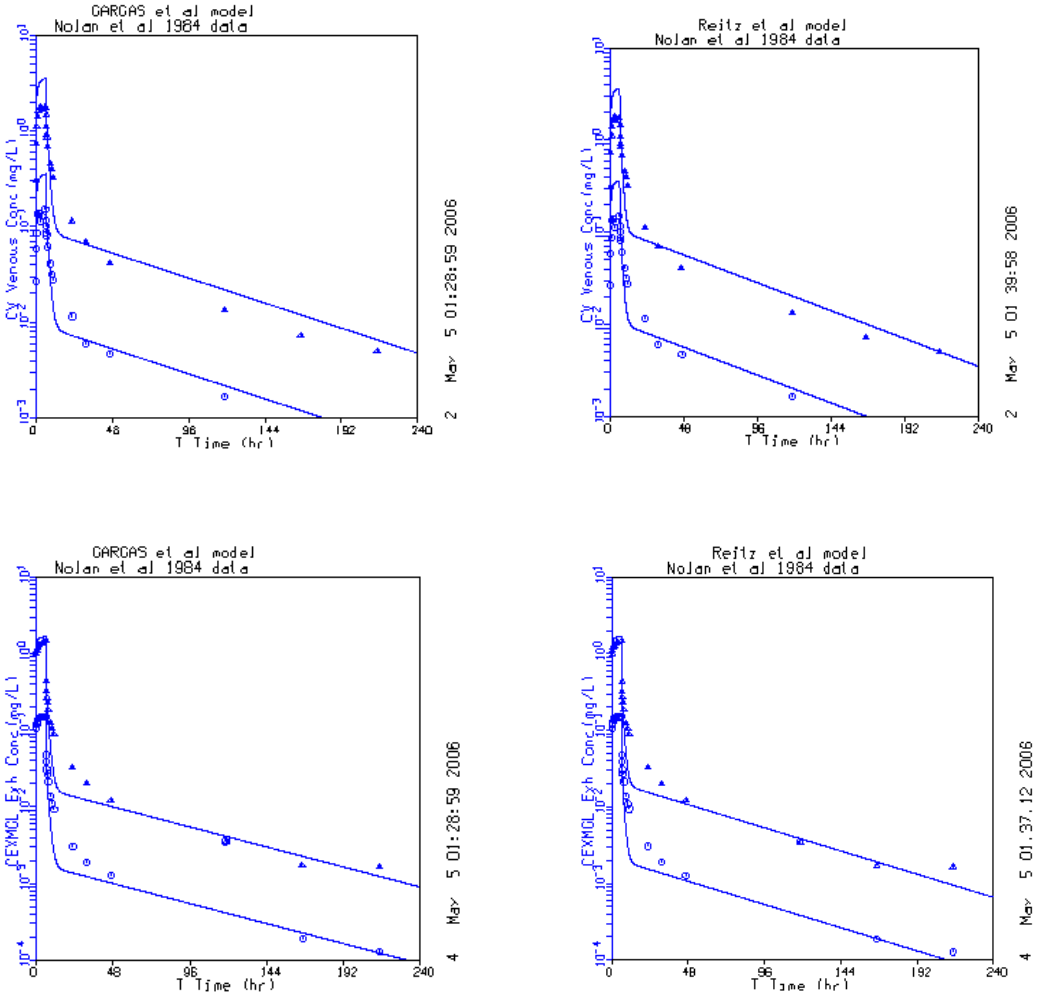


Figure 24. Simulations of the 1,1,1-trichloroethane concentrations in the venous blood and expired air of the human volunteers in the Nolan *et al.* (1984) study.

IV.2.3. Evaluations Against Lapare *et al.* (1995) Human Data

When the Gargas *et al.* (1986a) model was used to simulate Lapare *et al.* (1995) data, the human partition coefficients and physiological parameters were from Reitz *et al.* (1988) because Gargas *et al.* did not simulate 1,1,1-trichloroethane in humans. The cardiac output, alveolar ventilation, and the blood flow fractions to all compartments during exercise for both Gargas *et al.* (1986a) and Reitz *et al.* (1988) model were from Lapare *et al.* (1995) as Reitz *et al.* (1988) did not simulate the scenario of exercise. The simulations of 1,1,1-trichloroethane concentrations in venous blood and expired air following different exposure scenarios are shown in Figures 25 through 28. Note that the discrepancy between these simulations and the original ones in Lapare *et al.* is mainly due to the lower blood:air partition coefficient used by Reitz *et al.* (1988).

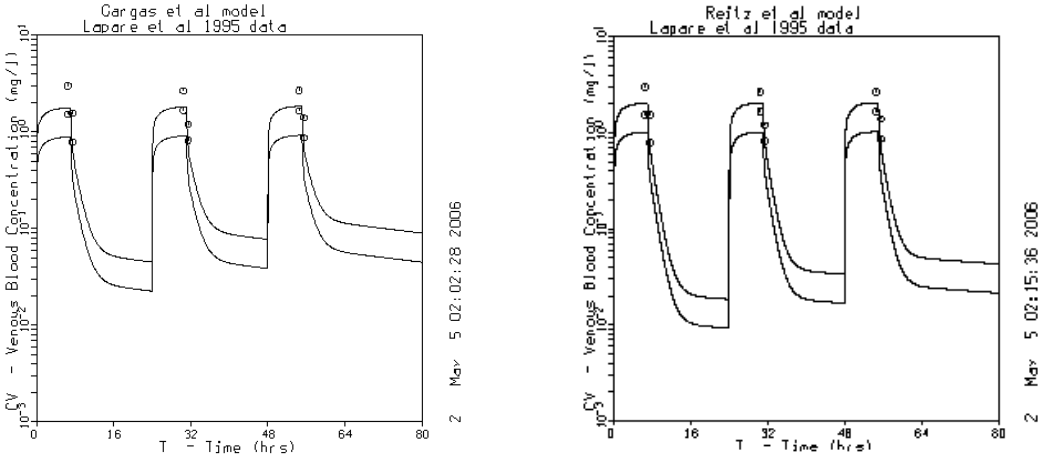


Figure 25. Simulations of 1,1,1-trichloroethane concentrations in venous blood following intermittent exposure to 87.5 (lower line) and 175 ppm (upper line) in humans using the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

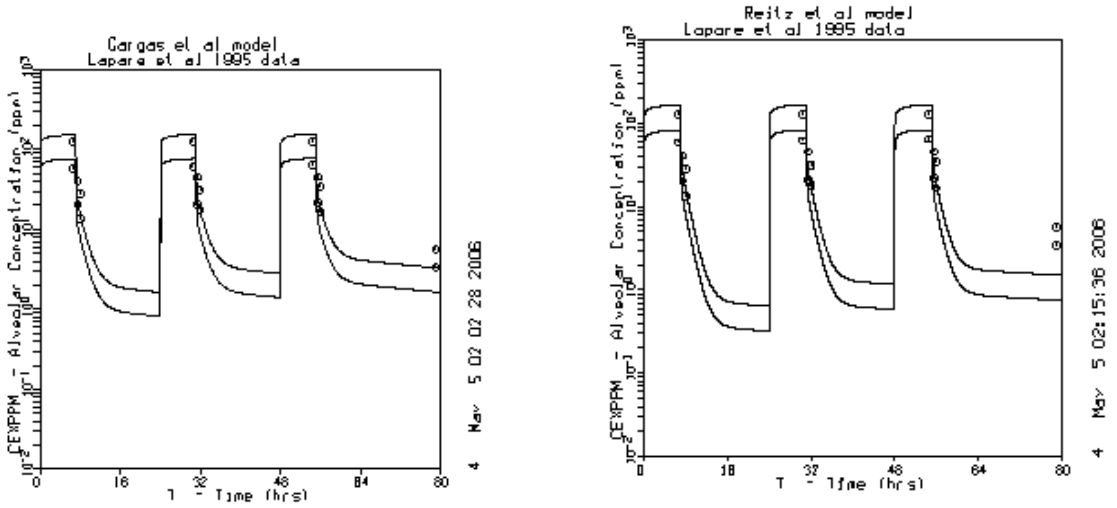


Figure 26. Simulations of 1,1,1-trichloroethane concentrations in expired air following intermittent exposure to 87.5 (lower line) and 175 ppm (upper line) in humans using the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

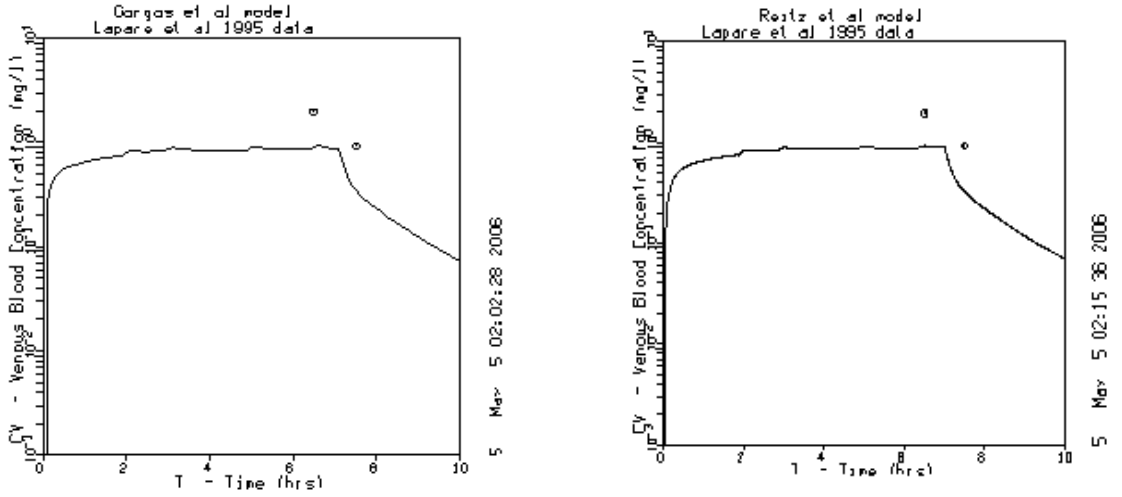


Figure 27. Simulations of venous blood 1,1,1-trichloroethane concentrations following exposure to 83.1 ppm for 7 hrs in humans with intermittent exercise using the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

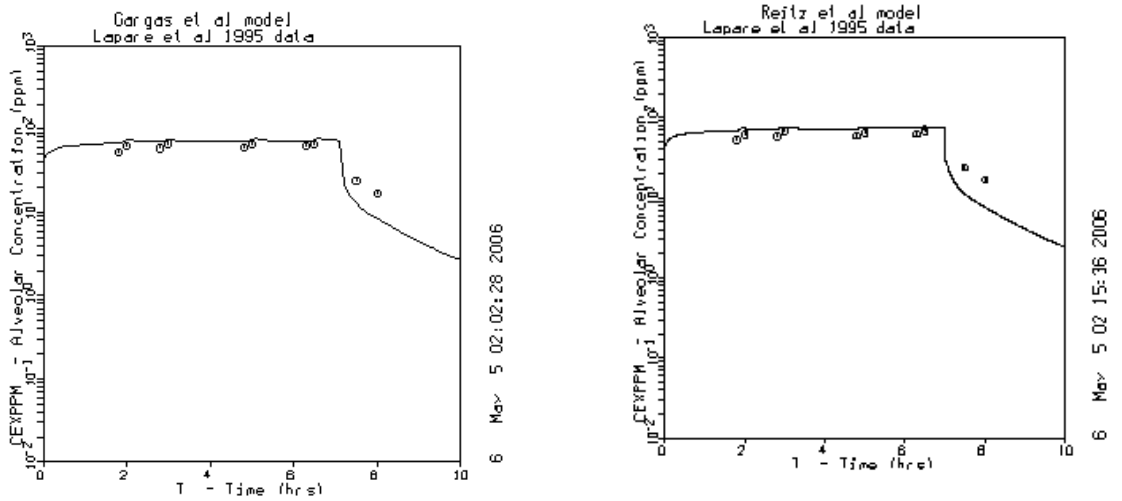


Figure 28. Simulations of 1,1,1-trichloroethane concentrations in expired air following exposure to 83.1 ppm for 7 hrs in humans with intermittent exercise using the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

Both the Gargas *et al.* (1986a) model and the Reitz *et al.* (1988) model appeared to be overestimating the Nolan *et al.* (1984) venous blood concentration data while under-estimating Lapare *et al.* (1995) venous blood concentration data. On the other hand, no such discrepancies were observed for exhaled 1,1,1-trichloroethane concentrations when both model simulations were used with human experimental data from Nolan *et al.* (1984) and Lapare *et al.* (1995), respectively. As exhaled 1,1,1-trichloroethane concentration is dependent on the blood:air partition coefficient, it is not reasonable to assume that the earlier over- and underestimations of venous blood concentration from the two PBPK models were the

result of the choice of this parameter. The reason for the apparent discrepancies in the prediction of venous blood concentrations is unknown; however, it is possible that some of the difference might be attributable to human variability between the two studies.

Based on the above evaluation, our conclusion is that the two PBPK models by Gargas *et al.* (1986a) and Reitz *et al.* (1988) performed similarly against the Lapare *et al.* (1995) human data.

IV.2.4. Evaluations Against Mackay *et al.* (1987) Human Data

It should be noted that Mackay *et al.* (1987) did not provide information on the body weights of the human volunteers in their experiments. We therefore assumed that the average body weight for the individuals tested is 70 kg. The simulations by the two models are shown in Figure 29.

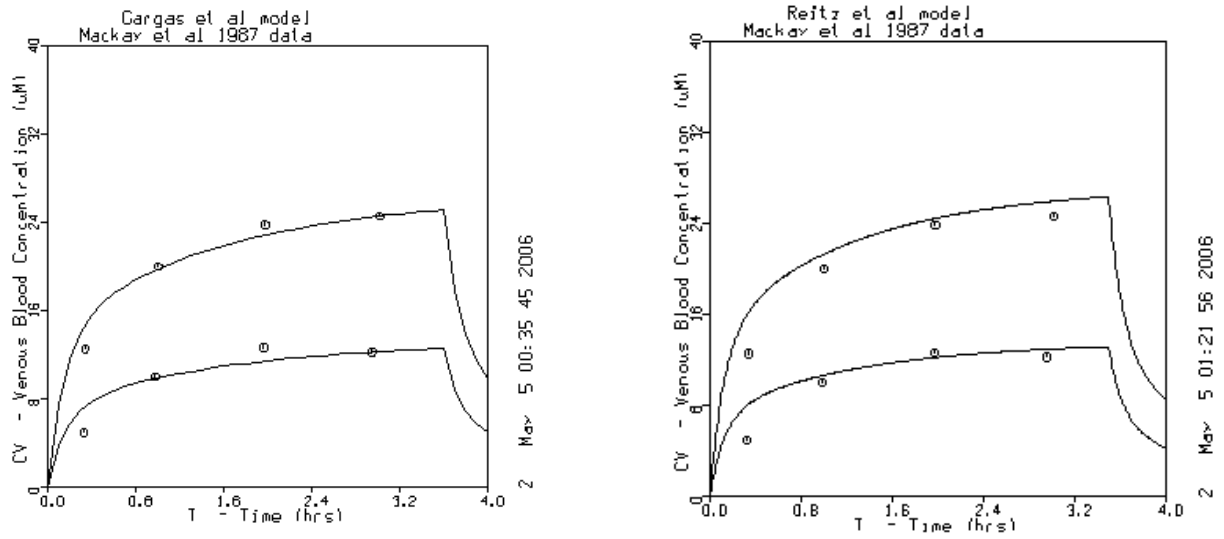


Figure 29. Simulations of the venous blood concentration of 1,1,1-trichloroethane in the Mackay *et al.* (1987) human study by the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

There does not seem to be much difference between the simulations of the Gargas *et al.* (1986a) and Reitz *et al.* (1988) PBPK models in comparison with the Mackay *et al.* (1987) data.

IV.2.5. Evaluations Against Schumann *et al.* (1982) Rat Data

Figure 30 shows the simulations of Schumann *et al.* (1982) data by the two models (Gargas *et al.* 1986a, Reitz *et al.* 1988) The two models performed similarly against the Schumann *et al.* (1982) data.

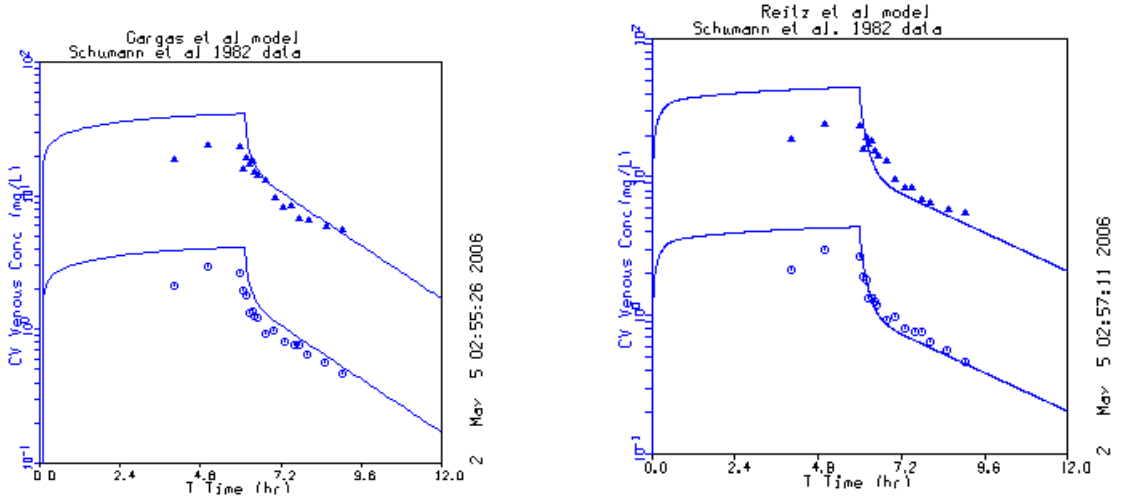


Figure 30. Simulations of the venous blood concentrations of 1,1,1-trichloroethane following inhalation exposure to 150 (lower line) and 1500 (upper line) ppm in the Schumann *et al.* (1982) rat study by the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

IV.2.6. Evaluations Against Gargas *et al.* (1986a) Rat Data

Simulations of the Gargas *et al.* (1986a) data by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) model are shown in Figure 31. The simulations of Reitz *et al.* (1988) model were not as well-fitted to the experimental data as those of Gargas *et al.* (1986a) model.

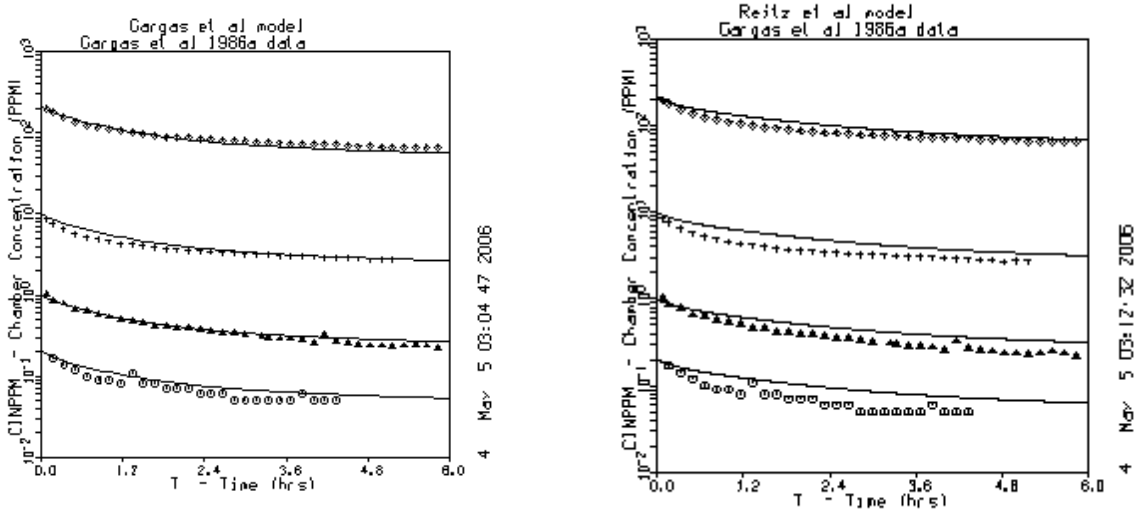


Figure 31. Simulations of the chamber concentrations of 1,1,1-trichloroethane in the Loizou *et al.* (1996) study, where the initial chamber concentrations were 0.2, 1, 10, and 210 ppm, by the Gargas *et al.* (1986a) (left plot) and Reitz *et al.* (1988) (right plot) models.

IV.2.7. Evaluations Against Reitz *et al.* (1988) Rat Data

The simulations of our reestablished Reitz *et al.* (1988) PBPK model were shown in Figures 2–8 in Section III. Since the Reitz *et al.* (1988) data consist of results from intravenous, oral gavage, and drinking water studies, the Reitz *et al.* (1988) PBPK model was able to carry out route-to-route extrapolations. However, the Gargas *et al.* (1986a) PBPK model, being focused on inhalation studies, cannot simulate the Reitz *et al.* (1988) data without further modification of the present model code.

IV.2.8. Evaluations Against Loizou *et al.* (1996) Rat Data

The simulations of the chamber 1,1,1-trichloroethane concentrations in the Loizou *et al.* (1996) closed chamber rat inhalation study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models are shown in Figure 32. The Gargas *et al.* model performed somewhat better than the Reitz *et al.* model did. The higher predictions by the Reitz *et al.* model may be due to the lower metabolism designated by the saturable process in this model (roughly 8-10-fold lower than that calculated by the Gargas *et al.* model)

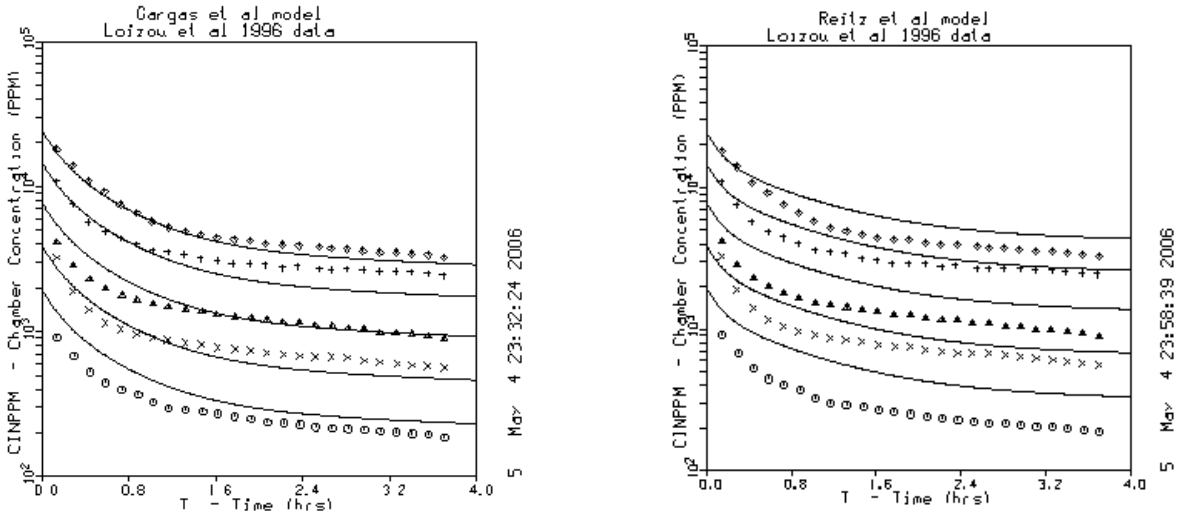


Figure 32. Simulations of the chamber 1,1,1-trichloroethane concentrations in the Loizou *et al.* (1996) rat study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models. The lines, from the bottom to the top, represent initial concentrations of 2,000, 4,000, 8,000, 15,000, and 25,000 ppm.

IV.2.9. Evaluations Against You and Dallas (1998) Rat Data

The simulations of the blood 1,1,1-trichloroethane concentrations in the You and Dallas (1998) study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models are shown in Figure 33. Both models overpredicted the blood concentrations; the Gargas *et al.* (1986a) model performed slightly better than the Reitz *et al.* (1988) model.

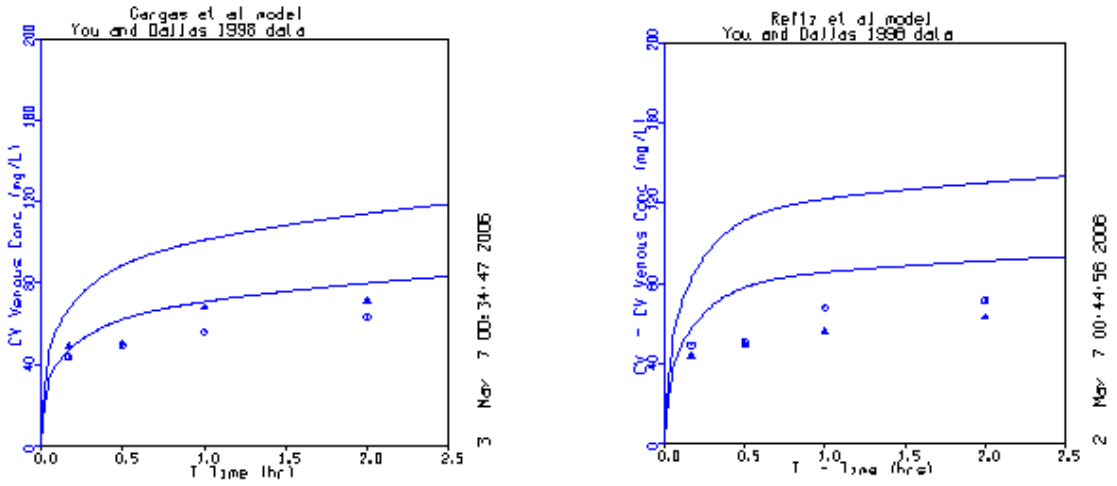


Figure 33. Simulations of the blood 1,1,1-trichloroethane concentrations in the You and Dallas (1998) rat study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models. The upper and lower lines represent 5,000 and 3,500 ppm, respectively.

IV.2.10. Evaluations Against Warren *et al.* (1998) Rat Data

The simulations of the blood 1,1,1-trichloroethane concentrations in the Warren *et al.* (1998) study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models are shown in Figure 34. Both models similarly overpredicted the blood concentrations.

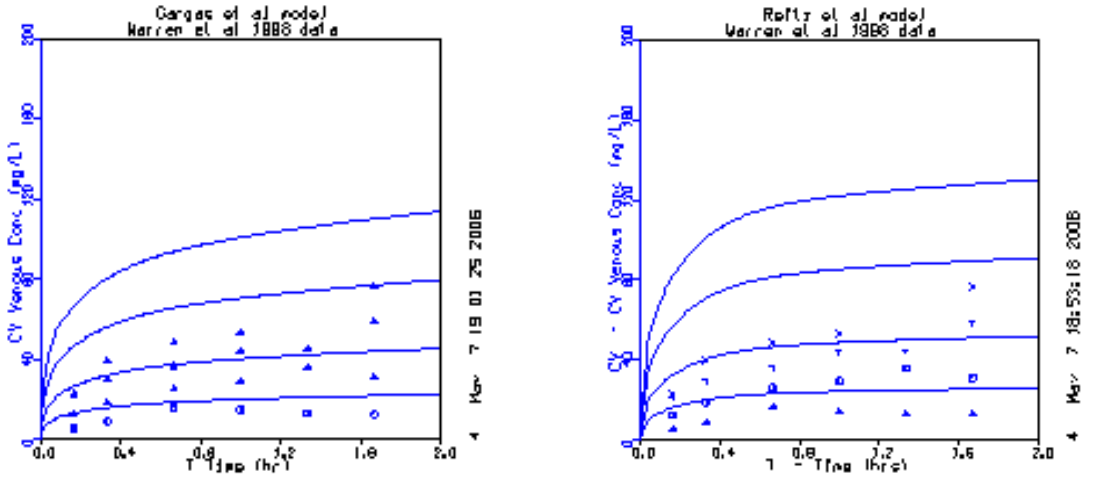


Figure 34. Simulations of the venous blood 1,1,1-trichloroethane concentrations in the Warren *et al.* (1998) rat study by the Gargas *et al.* (1986a) and Reitz *et al.* (1988) models. The lines, from the bottom to the top, represent 1,000, 2,000, 3,500, and 5,000 ppm, respectively.

IV.2.11. Evaluations Against Bruckner Rat Data (unpublished data; personal communication)

As indicated earlier, we made the assumption that the average body weight of the rats used in this study is 350 g. This assumption is based on an earlier publication from Dr. Bruckner's laboratory (Dallas *et al.*, 1989).

Figures 35 through 38 are simulations of the Bruckner data by our reestablished Reitz *et al*. (1988) model. Since the Bruckner data consist of results from oral gavage studies, the Gargas *et al.* (1986a) PBPK model, being focused on inhalation studies, cannot simulate the Bruckner data without further modification of the present model code. Although the simulations of our reestablished Reitz *et al.* model follow the general trend of the pharmacokinetic data, they do not fit the different phases of pharmacokinetic behavior in these data sets, particularly the absorption phase of the data. In the original publication of Reitz *et al*. (1988), the PBPK model simulation of the oral gavage results did not match the experimental data very well either; this was reproduced in Figure 4 (Section III) with our reestablished Reitz *et al*. (1988) PBPK model. In all these simulations, we did not change any parameter values of the Reitz *et al*. (1988) PBPK model. Two issues should be noted here: (1) in Figures 35-38, the absorption rate constant (Ka) was set at 1.25 hr^{-1} in the PBPK model simulations, (2) in the Reitz *et al*. (1988) study, the vehicle for oral gavage was water while, in the Bruckner study, an aqueous 5% Emulphor was used. A higher absorption rate should be anticipated in the latter case.

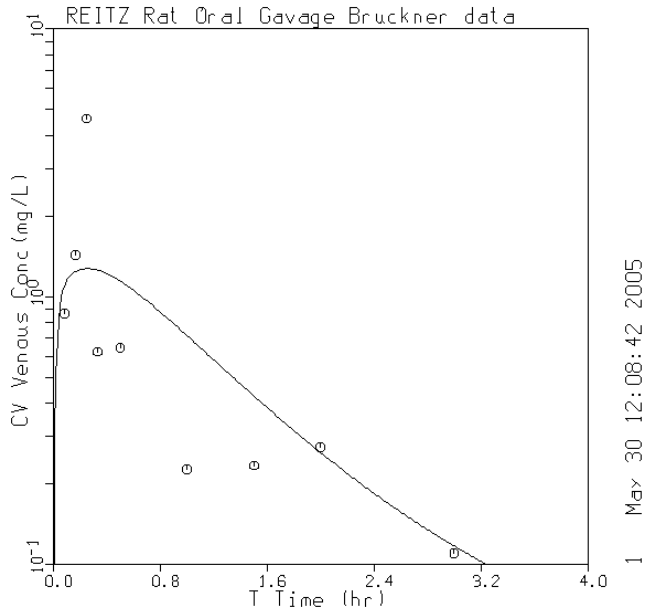


Figure 35. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model.

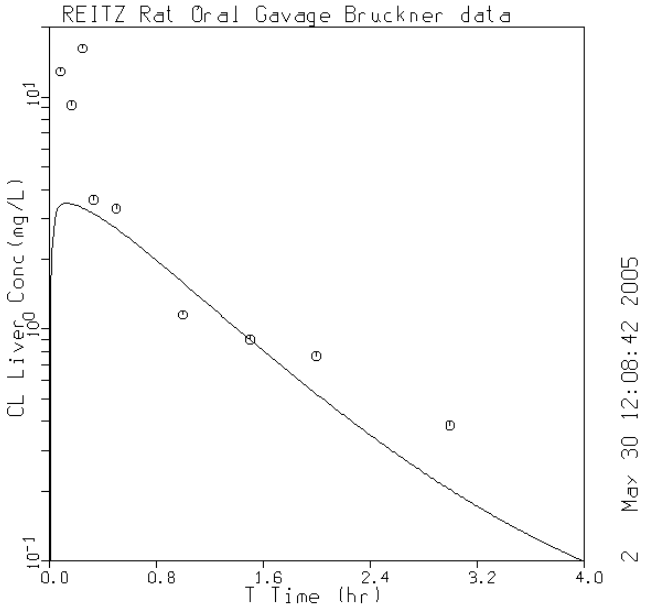


Figure 36. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model.

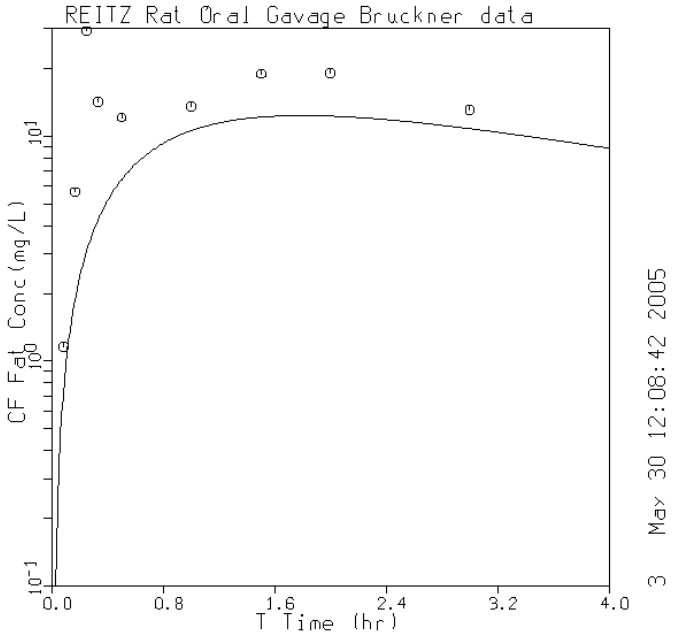


Figure 37. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model.

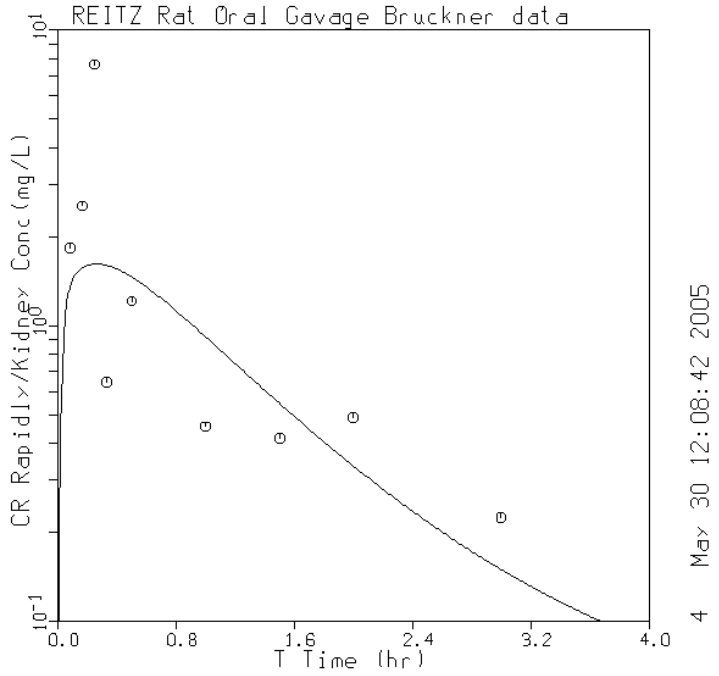


Figure 38. Simulation of the 1,1,1-trichloroethane concentration in the rapidly perfused compartment (represented by kidney) in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model.

Our initial conclusion was that the Reitz *et al*. (1988) PBPK model, in its present form, has limitations in route-to-route extrapolation to oral dosing. Since absorption from the GI tract is a very complex process, considerable effort would be required, including possible additional experimental work, to improve the capability of the Reitz *et al*. (1988) PBPK model for oral route extrapolation. However, some insights into the ability to use the model for route-to-route extrapolation could be gained with additional PBPK modeling of Bruckner data, particularly the early time points, by varying the absorption rate constant. A series of plots of such simulations when Ka was varied between 1.25 and 10 hr^{-1} are provided below; the simulation results were worse with Ka<1.25 hr^{-1}.

Figures 39-41 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 1.25 hr^{-1}

The three plots were, respectively, time-course venous blood concentration, liver concentration, and fat concentration. In these plots, we focused on the early time points (0 to 1 hour).

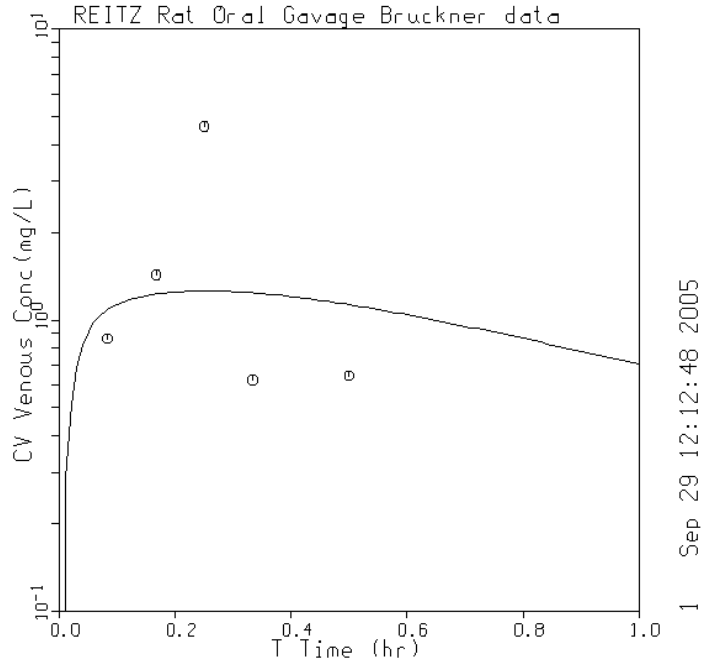


Figure 39. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 1.25/hr.

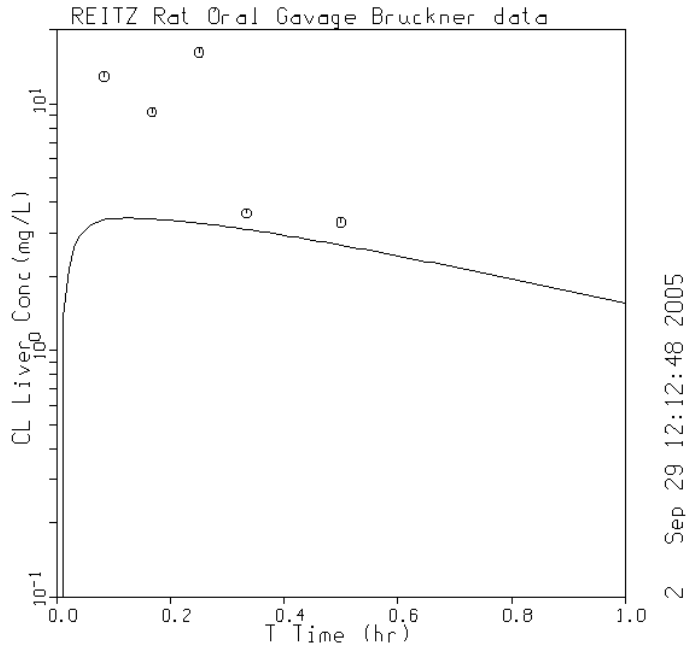


Figure 40. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 1.25/hr.

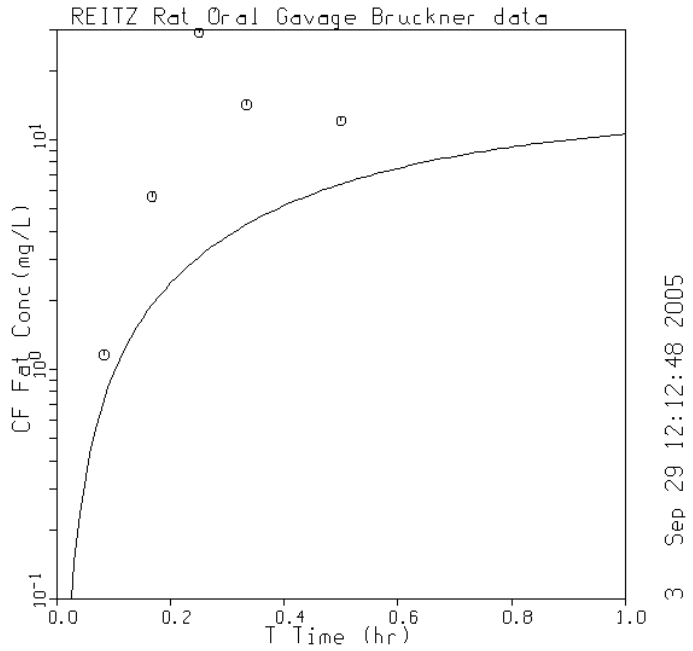


Figure 41. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 1.25/hr.

Figures 42-44 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 2 hr^{-1}

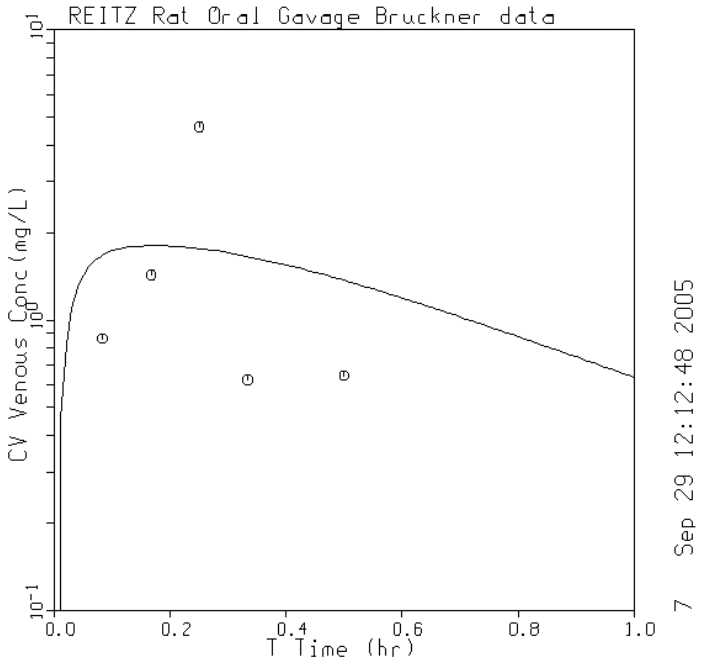


Figure 42. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 2/hr.

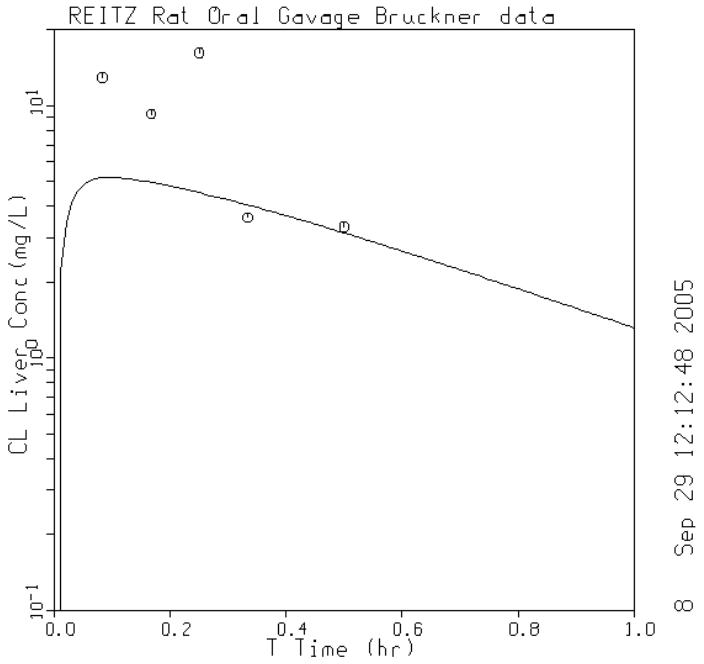


Figure 43. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 2/hr.

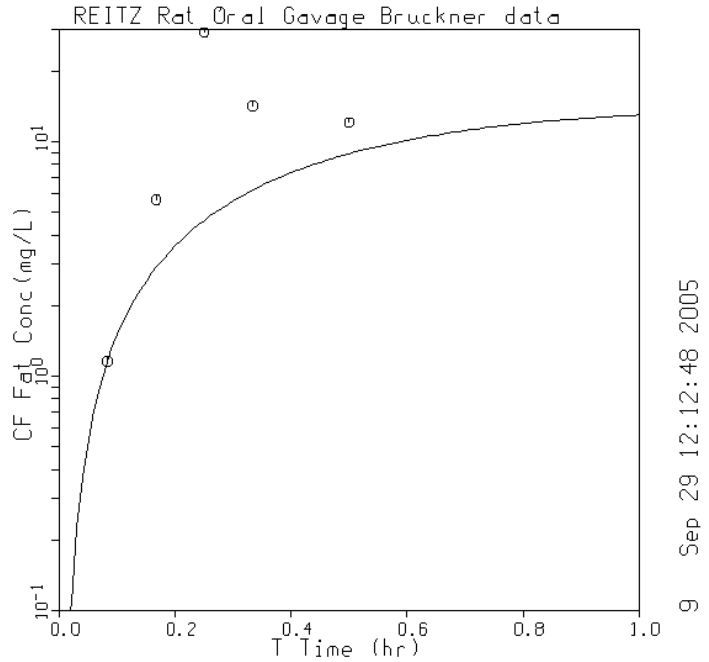


Figure 44. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 2/hr.

Figures 45-47 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 3 hr^{-1}

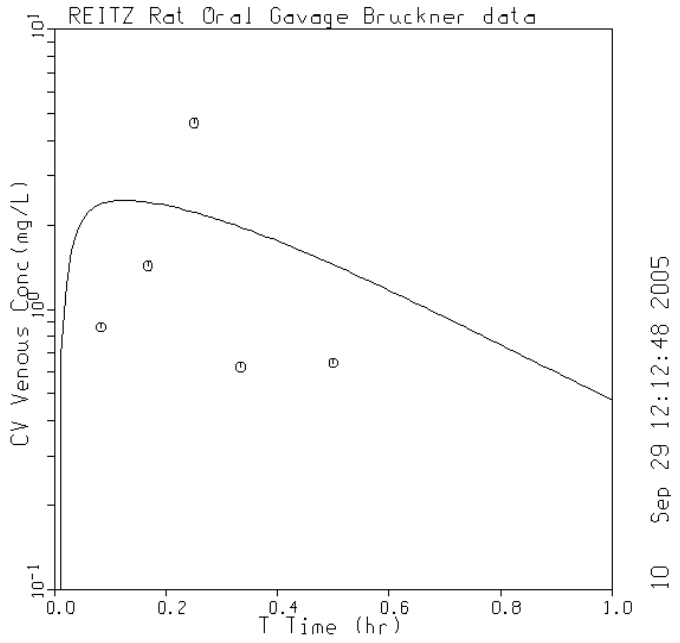


Figure 45. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 3/hr.

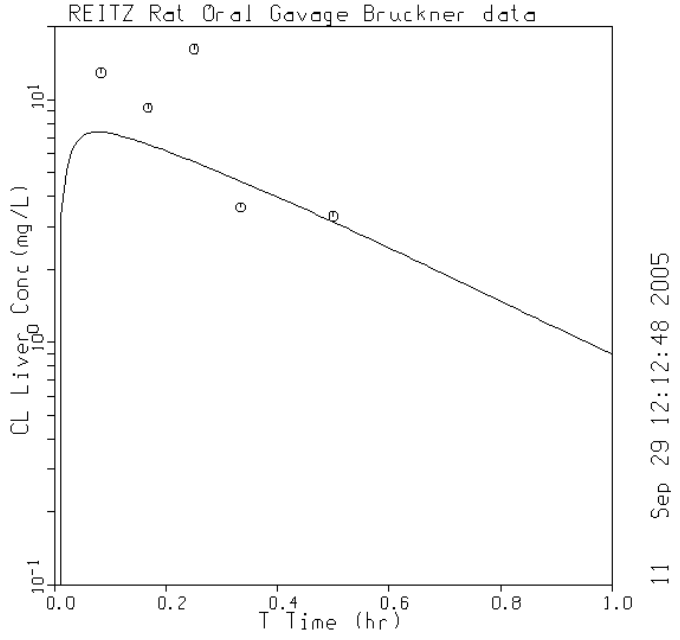


Figure 46. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 3/hr.

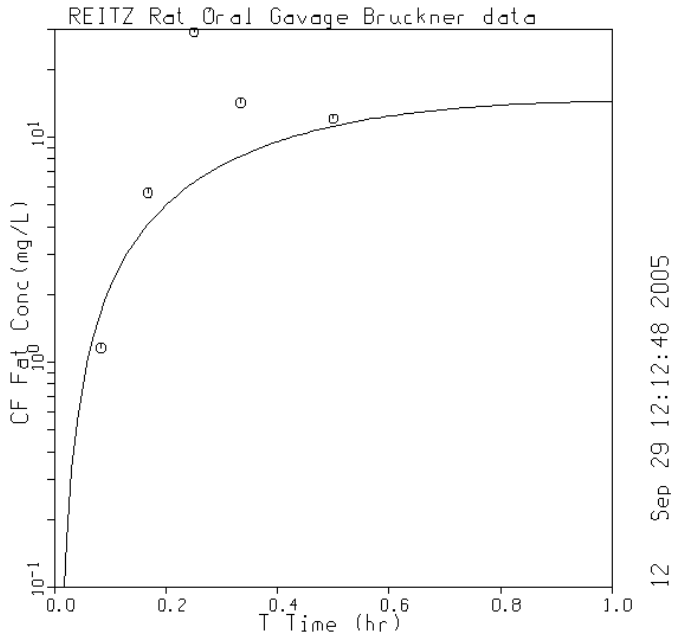


Figure 47. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 3/hr.

Figures 48-50 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 5 hr^{-1}

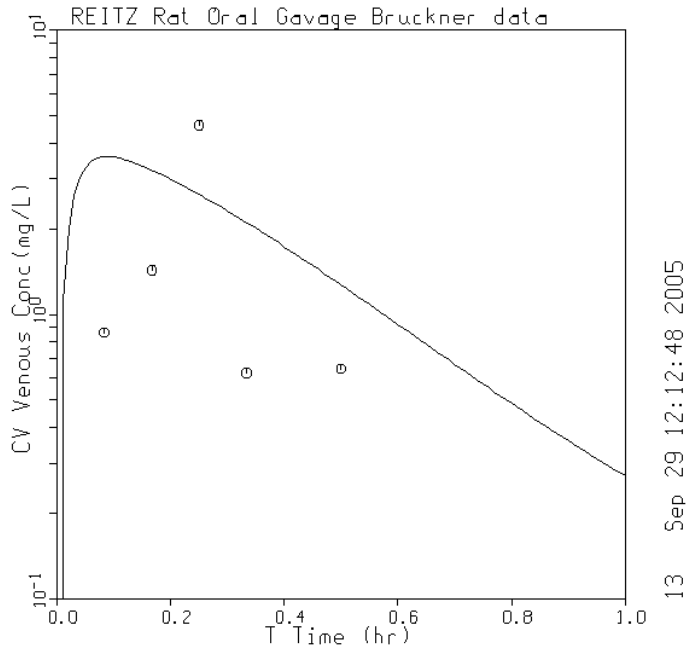


Figure 48. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

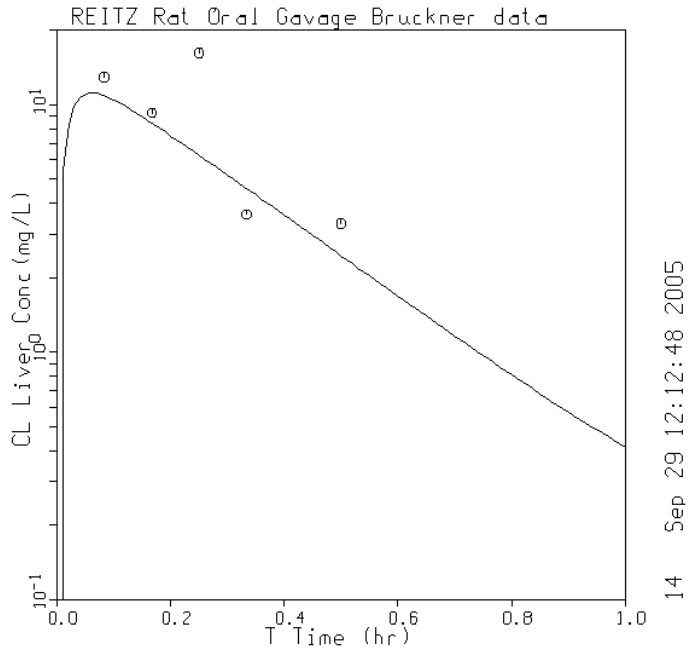


Figure 49. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

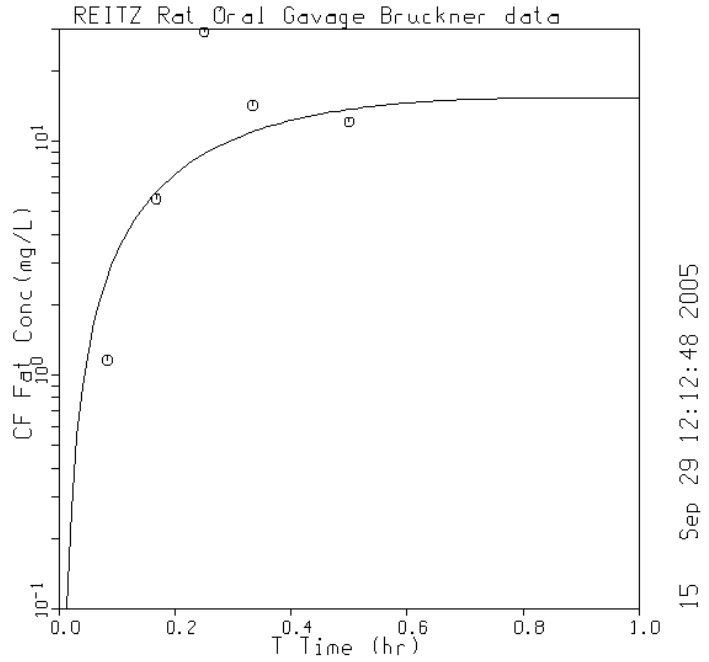


Figure 50. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

Figures 51-53 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 7.5 hr^{-1}

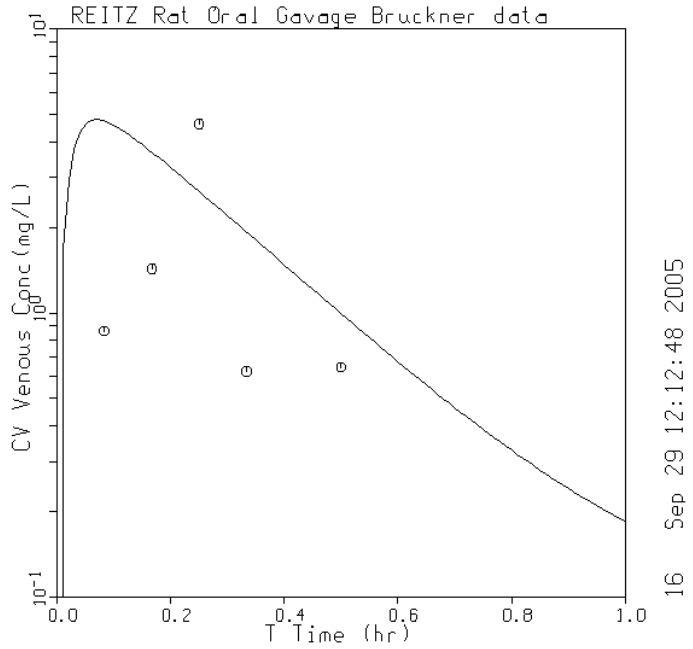


Figure 51. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

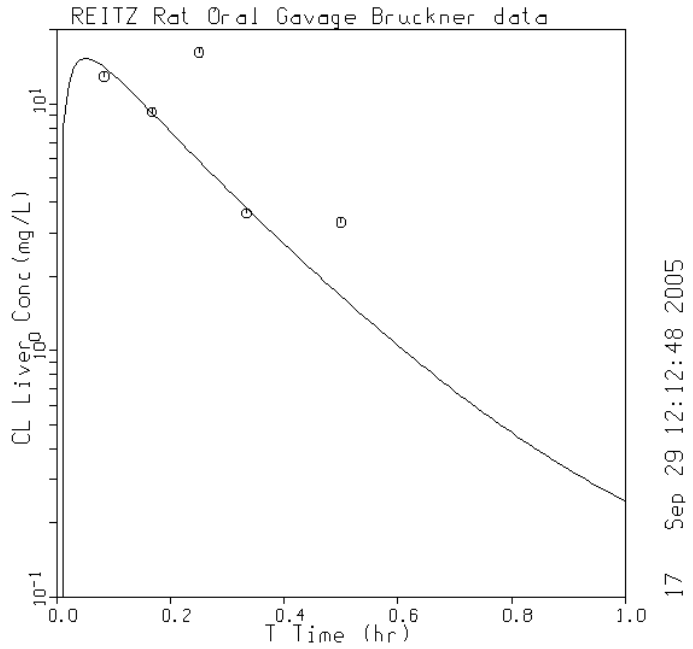


Figure 52. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

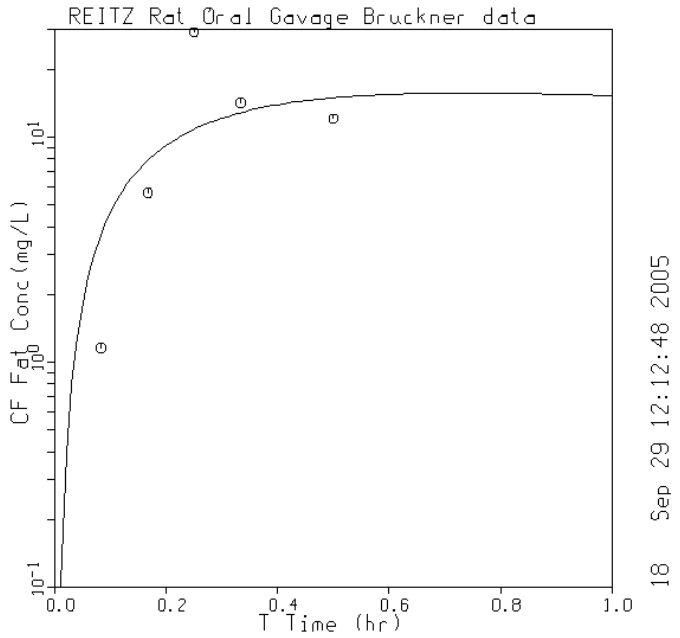


Figure 53. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

Figures 54-56 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 10 hr^{-1}

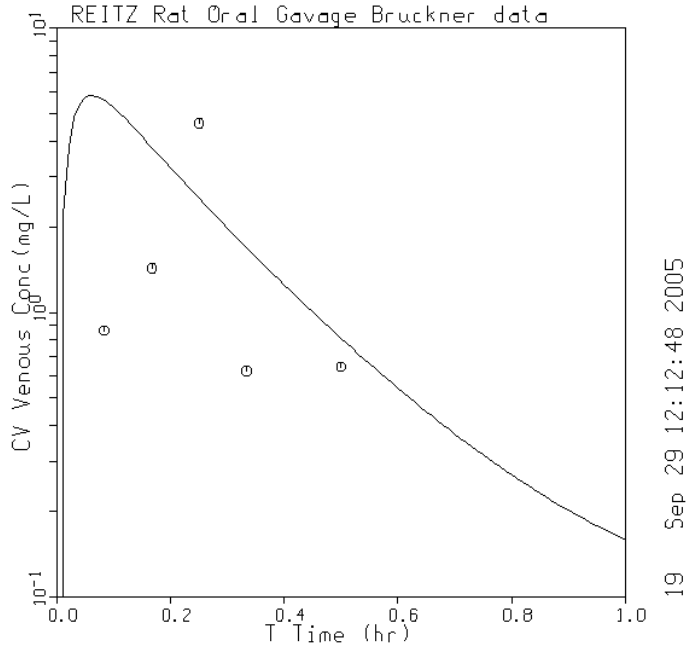


Figure 54. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 10/hr.

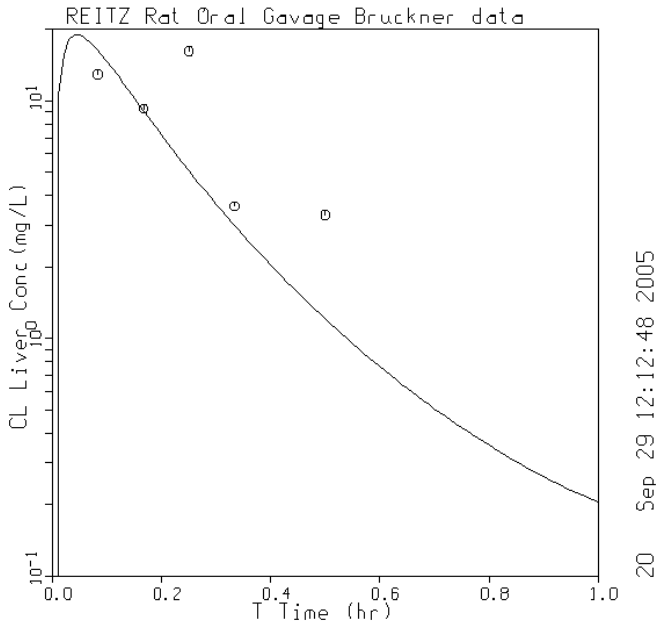


Figure 55. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 10/hr.

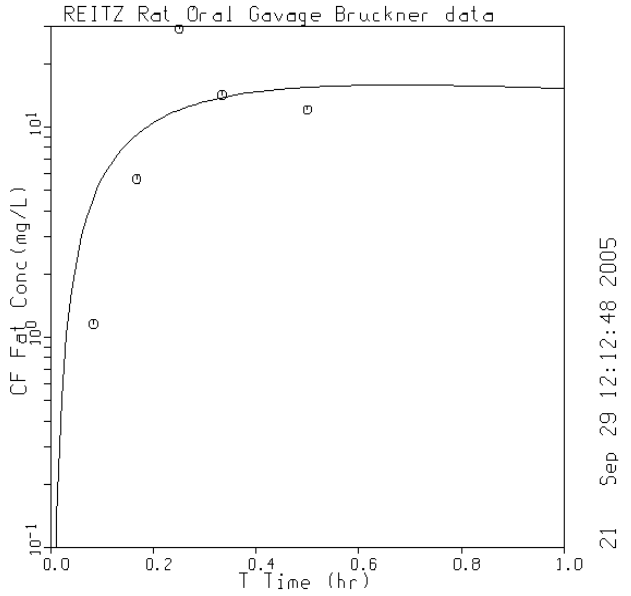


Figure 56. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 10/hr.

Since the two higher values of absorption rate constants (*i.e.,* Ka = 5 and 7.5) appeared to have given better fits for the earlier time points (*i.e.*, 0–1 hour) of the Bruckner data, full time-scale (4 hours) simulation plots with exactly the same X- and Y-axes are provided for comparison with the original simulations when Ka = 1.25 hr^{-1} (pages 34–36). Thus, figures 57-59 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 5 hr^{-1}
Full scale of 4 hours; these plots should be compared with original simulations on pp. 34-36.

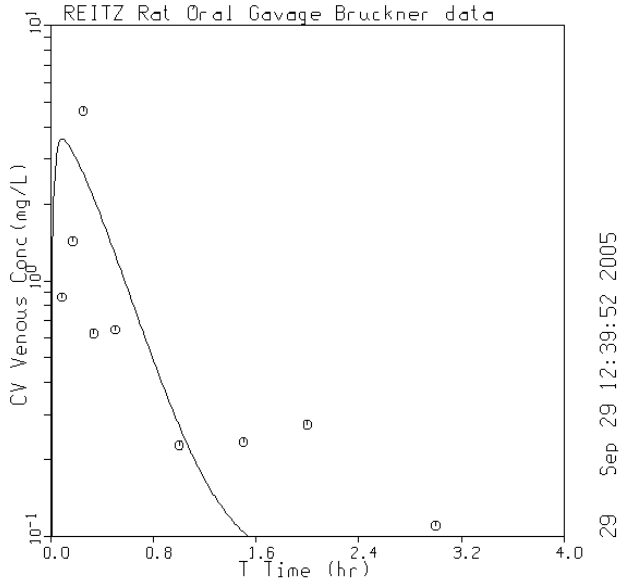


Figure 57. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

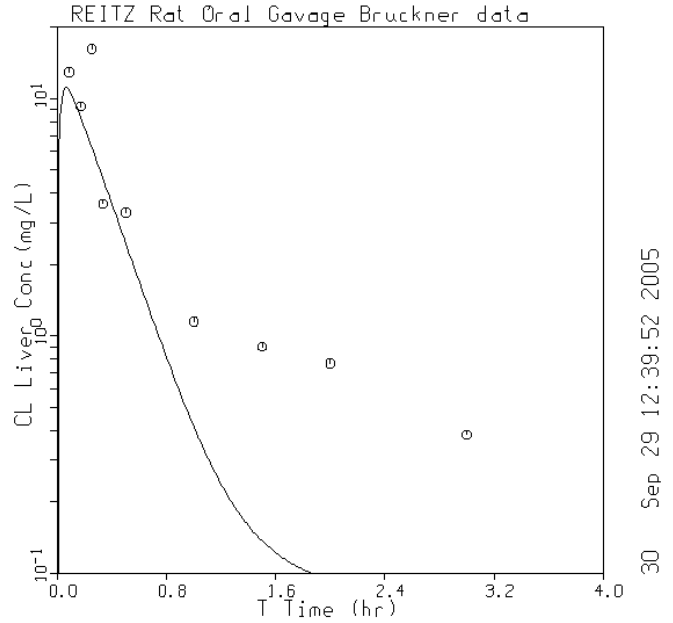


Figure 58. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

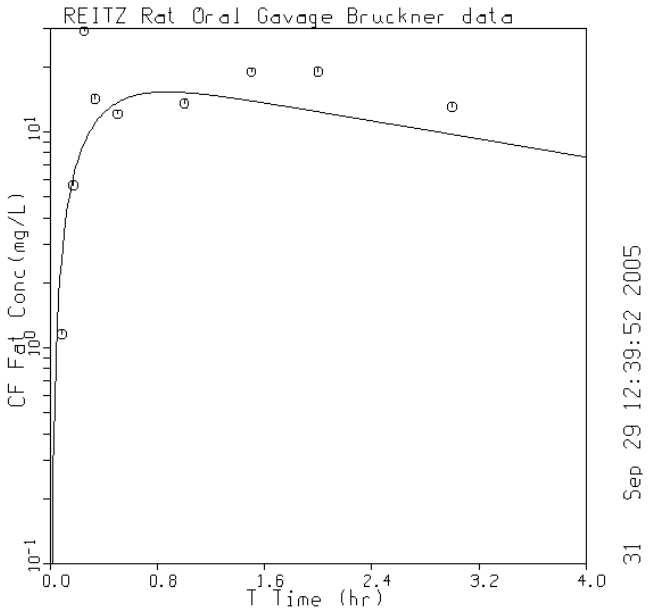


Figure 59. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 5/hr.

Likewise, figures 60-62 were from PBPK modeling under the following conditions:

Bruckner data
Ka = 7.5 hr^{-1}
Full scale of 4 hours; these plots should be compared with original simulations on pp. 34-36.

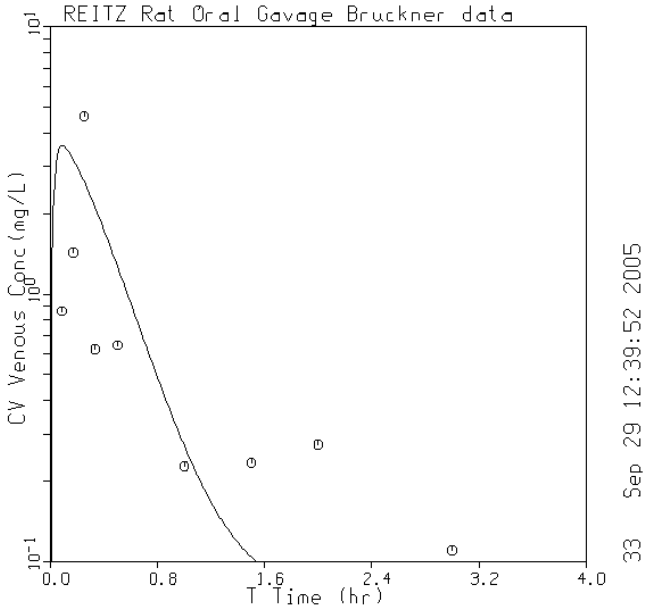


Figure 60. Simulation of the venous blood 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

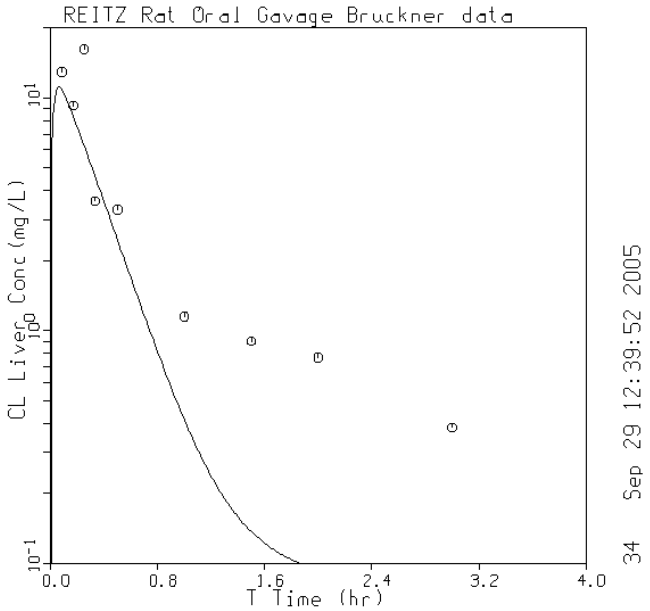


Figure 61. Simulation of the liver 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

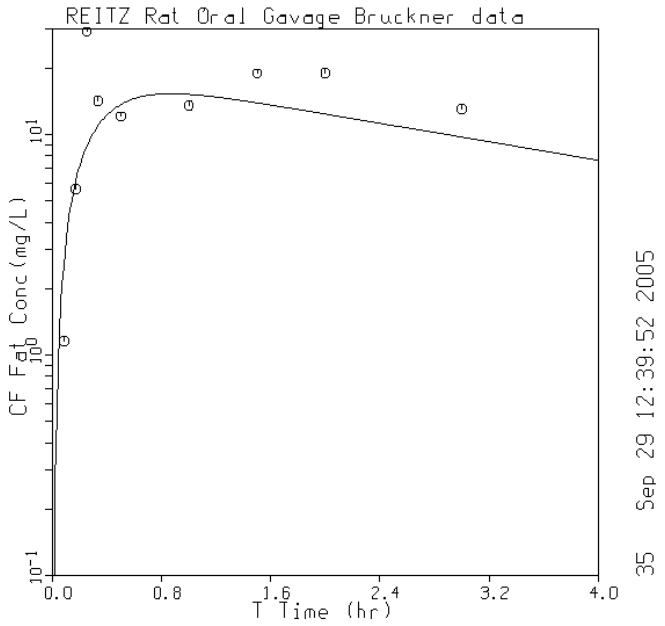


Figure 62. Simulation of the fat 1,1,1-trichloroethane concentration in the Bruckner (unpublished data; personal communication) rat oral gavage study by the Reitz *et al.* (1988) model with Ka = 7.5/hr.

Our conclusion of PBPK model simulation against Bruckner experimental results is that the data, especially venous blood and liver concentrations, cannot be fitted well whatever the value of Ka is. However, an increase in Ka somewhat improves the description of the concentrations in the fat. When Ka was set to values of 5 or 7.5, the simulations of fat concentrations were more consistent with the experimental data.

IV.3. Overall Conclusions on the Evaluation of the Gargas *et al.* (1986a) and Reitz *et al.* (1988) PBPK Models

Given the fact that both models performed similarly on inhalation data sets, we selected the Reitz *et al.* (1988) PBPK model over the Gargas *et al.* (1986a) PBPK model based on its higher versatility for other routes of exposure. However, it is noteworthy that the Reitz *et al*. (1988) PBPK model generally overpredicts venous blood concentration of 1,1,1-trichloroethane when the exposure level is at the magnitude of 10^3 ppm or higher. In addition, it has limitations in route-to-route extrapolation to oral dosing.

V. CALCULATION OF INTERNAL DOSES BASED ON PBPK MODELING

The objective of this project is to provide support to the EPA in conducting PBPK modeling for 1,1,1-trichloroethane to refine the derivation of reference dose (RfD) and reference concentration (RfC) values for this chemical. This section summarizes the Reitz *et al.* (1988) PBPK model (Section V.1) and its applications to the derivation of acute inhalation RfC and acute oral RfD values (Sections V.2 and V.3), and interspecies and route-to-route extrapolation in deriving chronic inhalation RfC and oral RfD values based on laboratory animal data (Section V.4).

V.1. PBPK Model for Internal Dose Calculation

V.1.1. Basics of the Reitz *et al.* Model

The PBPK model structure for our reestablished Reitz *et al*. (1988) model is graphically illustrated in Figure 63.

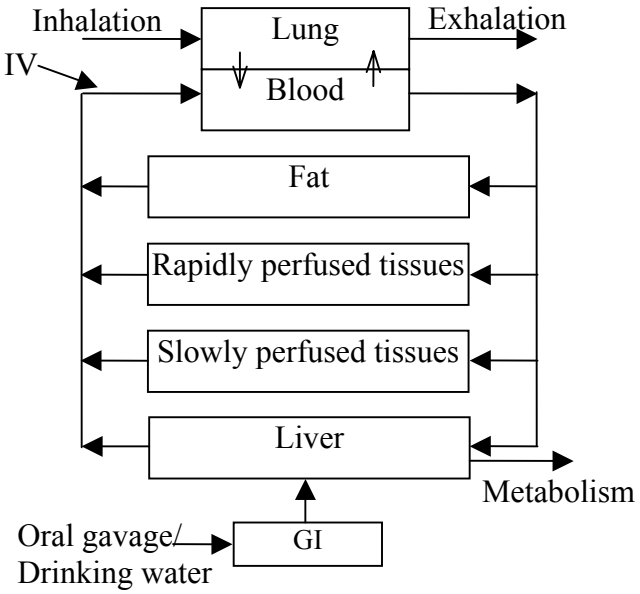


Figure 63. Structure of the Reitz *et al.* (1988) PBPK model for 1,1,1-trichloroethane.

Some model limitations are as follows: (1) a brain compartment was not included in the model because of lack of experimental kinetic data on the brain and evidence from acute inhalation studies in laboratory animals that the blood concentration reflects well the brain concentration (Warren *et al.*, 1998, 2000); (2) the GI absorption is too complicated a pharmacokinetic phenomenon to be described by one single absorption rate constant (Ka); however, it was outside of the scope of this project to attempt more complicated model structures such as sub-compartmentalization for the GI tract; and (3) even though the decay of volatile organics usually follows a tri-exponential behavior, no attempt was made to split fat into sub-compartments to accommodate such more complicated pharmacokinetic behavior. Because tests of neurobehavioral performance were generally conducted during the exposure phase, refinement of the decay (postexposure) phase was not considered necessary.

V.1.2. Physiological Parameters

Since a thorough compilation (Brown *et al.* 1997) of physiological parameters in rats and humans was published after the Reitz *et al.* (1988) model, it is necessary to assess the plausibility of the physiological parameters used by Reitz *et al.* (1988). A comparison of the values of the volume fractions, blood flow fractions, cardiac output rate constant, and pulmonary ventilation rate used by Reitz *et al.* (1988) and reported by Brown *et al.* (1997) is listed in Table 4. The Reitz *et al.* (1988) parameter values generally agreed with those in Brown *et al.* (1997).

Table 4. Comparison of Physiological Parameters in Reitz *et al.* (1988) Model to Values Reported by Brown *et al.* (1997)

Species	Parameters	Reitz *et al.* (1988)	Brown *et al.* (1997)
Rat	*Volume fractions*		
	Liver (VLC)	0.04	0.0366 ± 0.65
	Fat (VFC)	0.07	0.035 × (BW in grams) + 0.205
	Rapidly perfused (VRC)	0.05	0.91 – VLC – VFC – VSC
	Slowly perfused (VSC)	0.75	Muscle 0.4043±0.0717, Skin 0.1903±0.0262
	Blood flow fractions		
	Liver (QLC)	0.24	0.174 (13.1-22.1)
	Fat (QFC)	0.05	0.07
	Rapidly perfused (QRC)	0.53	1 – QLC –QFC – QSC
	Slowly perfused (QSC)	0.18	Muscle 0.278, Skin 0.058
	Cardiac output rate constant (QCC) ($L/hr/kg^{0.74}$)	15	14.1 with the scaling factor = 0.75
	Pulmonary ventilation (QP) (L/hr)	Constant = 15 with a body weight scaling factor = 0.74	1.89-8.256 per 100 g body weight
Human	*Volume fractions*		
	Liver (VLC)	0.031	0.026
	Fat (VFC)	0.231	0.213 in males and 0.327 in females
	Rapidly perfused (VRC)	0.037	0.91 – VLC – VFC – VSC
	Slowly perfused (VSC)	0.611	Muscle 0.40, Skin 0.0371
	Blood flow fractions		
	Liver (QLC)	0.24	0.227 (0.11-0.342)
	Fat (QFC)	0.09	0.052 (0.037-0.118)
	Rapidly perfused (QRC)	0.49	1 – QLC –QFC – QSC
	Slowly perfused (QSC)	0.18	Muscle 0.191 (0.057-0.422) Skin 0.058 (0.033-0.086)
	Cardiac output rate constant (QCC) ($L/hr/kg^{0.74}$)	15	14.1 with the scaling factor = 0.75
	Pulmonary ventilation (QP) (L/hr)	Constant = 15 with a body weight scaling factor = 0.74	Reference man 316.8-685.8, Reference woman 262.8-506.4

V.1.3. Sensitivity Analysis

Sensitivity analysis is a valuable means for measuring the relative importance of parameters in a model influencing an output of interest. The theory of sensitivity analysis in PBPK modeling has been discussed by Clewell *et al.* (1994). The sensitivity of an output, R, to a parameter, x, is measured by a lognormalized sensitivity coefficient (LSC):

$$LSC = \frac{\frac{\partial R}{R}}{\frac{\partial x}{x}} = \frac{\partial \ln R}{\partial \ln x}.$$

The LSC is generally in the range of -1 to 1. The higher the LSC is, the more sensitive of an output to a parameter. In this report, we analyzed parameter sensitivity in two groups of scenarios: (1) during acute (10 hrs) continuous inhalation exposure, the sensitivity of the venous blood concentration of 1,1,1-trichloroethane to physiological and metabolism parameters and partition coefficients. Two inhalation levels, 150 and 5000 ppm, were applied to explore the effect, if any, of exposure level on the sensitivity; (2) during chronic (6 months) continuous inhalation or infusion exposure, the sensitivity of the concentrations in venous blood and liver to model parameters. The analysis was performed using the forward difference method at the default delta value (0.0001) in acslXtreme 2.0.1.6 (Xcellon, West Austin, Texas).

V.1.3.1. Acute Inhalation Exposure

Figures 64-67 demonstrate the sensitivity of venous blood 1,1,1-trichloroethane concentration to physiological parameters (Figures 64 and 65), partition coefficients (Figure 66), and metabolism parameters (Figure 67) during continuous inhalation of 150 ppm 1,1,1-trichloroethane for 10 hrs calculated from the rat PBPK model. The only sensitive parameter was the blood:air partition coefficient (PB). The metabolism parameters, Km and VmaxC, were among the most insensitive ones, implying that metabolism is a minor elimination pathway for 1,1,1-trichloroethane. When the inhalation level was as high as 5000 ppm, the sensitivity of the venous blood concentration to the parameters remained almost unchanged, except the LSCs of Km and $V_{max}C$ reduced to near zero.

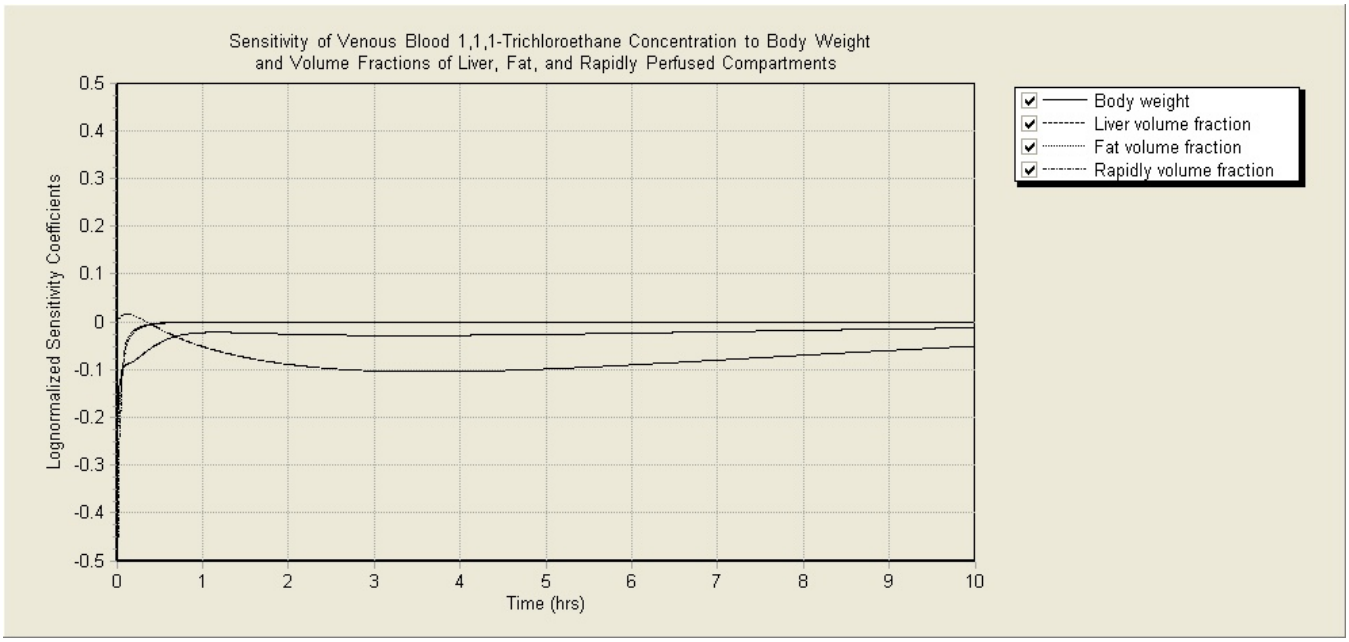


Figure 64. Sensitivity of venous blood 1,1,1-trichloroethane concentration to body weight and volume fractions of liver, fat, and rapidly perfused compartments during continuous inhalation exposure to 150 ppm 1,1,1-trichloroethane. At one hour, the four curves, from top to bottom, are: VFC and VRC (the two curves overlap), BW, and VLC.

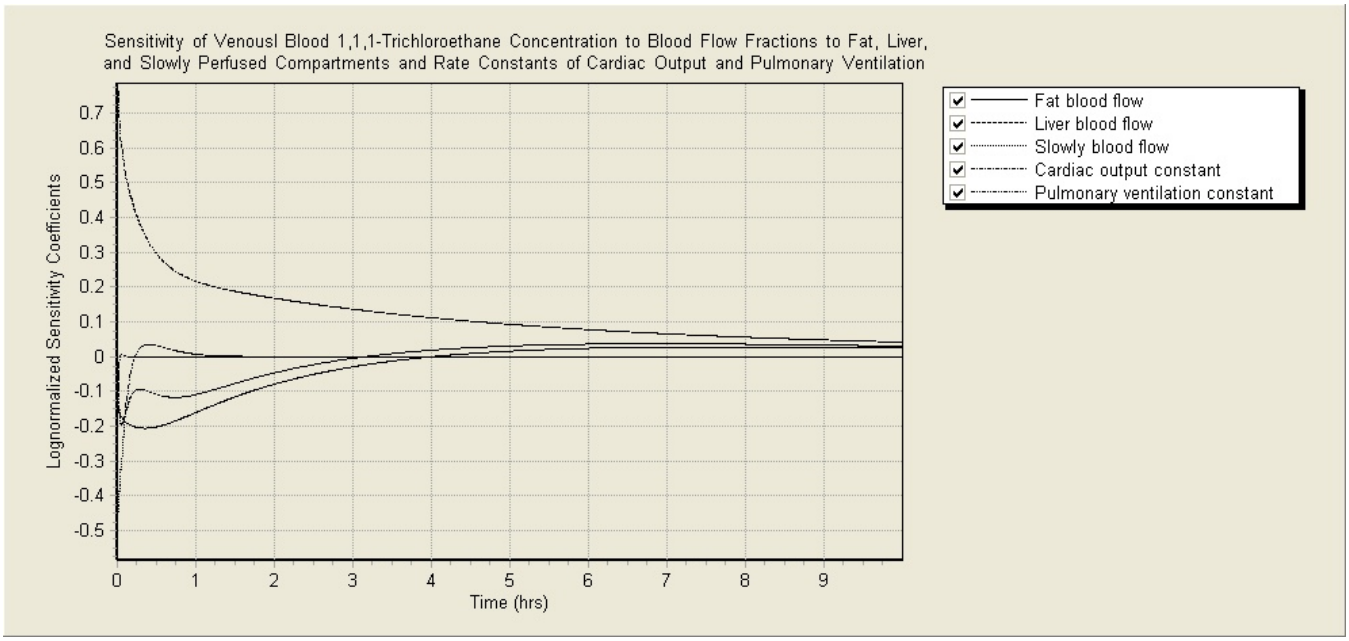


Figure 65. Sensitivity of venous blood 1,1,1-trichloroethane concentration to blood flow fractions to fat, liver (the top line), and slowly perfused compartments and rate constants of cardiac output and pulmonary ventilation during continuous inhalation exposure to 150 ppm 1,1,1-trichloroethane. At one hour, the five curves, from top to bottom, are: QP, QSC, QLC, QCC, and QFC.

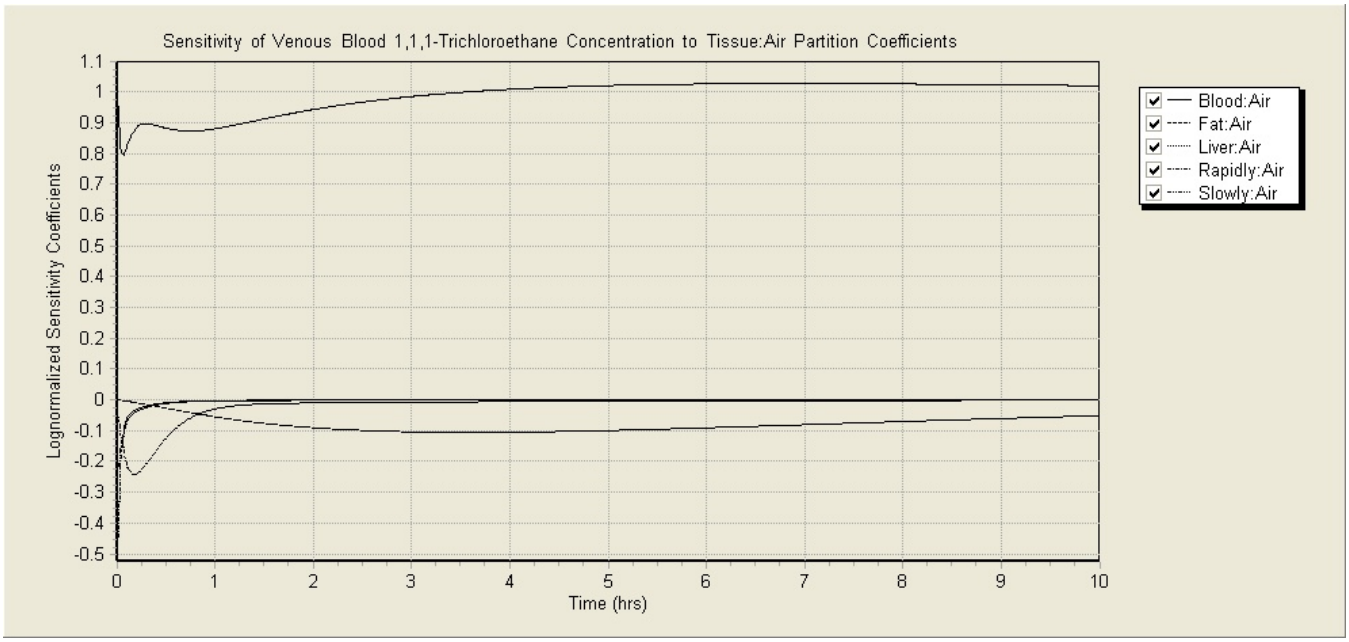


Figure 66. Sensitivity of venous blood 1,1,1-trichloroethane concentration to tissue:air partition coefficients during continuous inhalation exposure to 150 ppm 1,1,1-trichloroethane. The top line represents blood:air partition coefficient. At one hour, the five curves, from top to bottom, are: PB, PL and PR (the two curves overlap), PS, and PF.

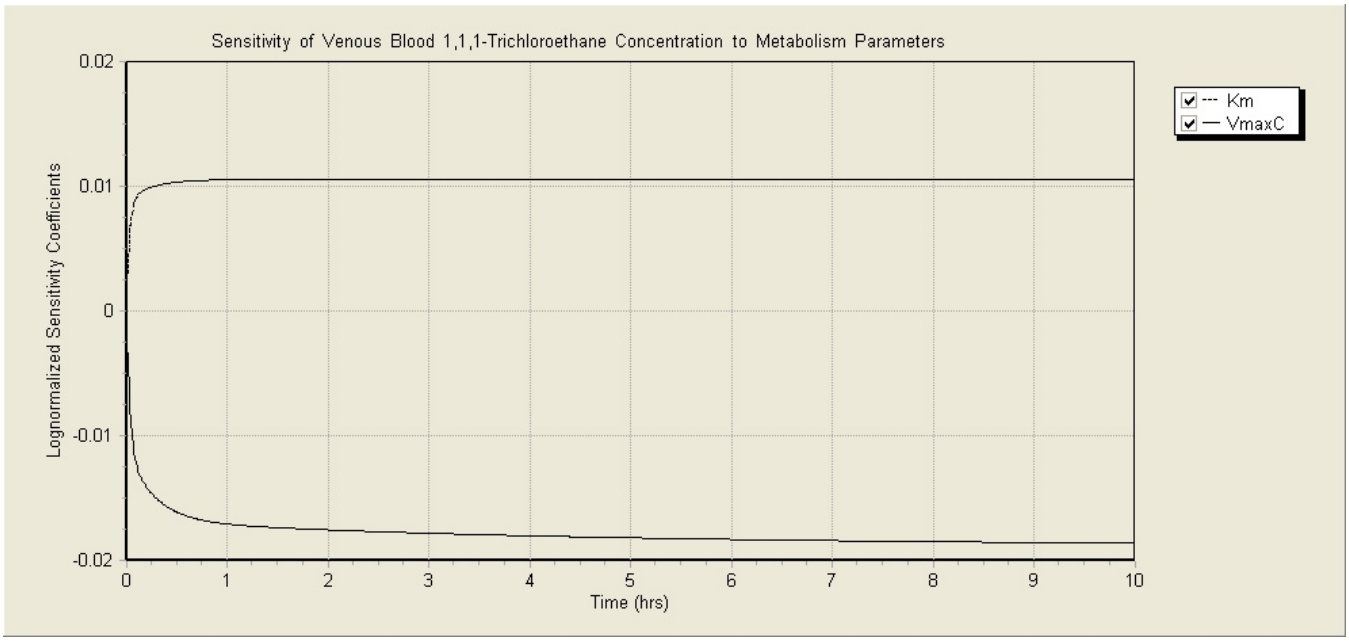


Figure 67. Sensitivity of venous blood 1,1,1-trichloroethane concentration to metabolism parameters, Km (the upper line) and VmaxC (the lower line), during continuous inhalation exposure to 150 ppm 1,1,1-trichloroethane.

V.1.3.2. Chronic Exposure

Chronic infusion exposure: Figures 68-71 demonstrate the sensitivity of venous blood 1,1,1-trichloroethane concentration to physiological parameters (Figures 68 and 69), partition coefficients (Figure 70), and metabolism parameters (Figure 71) during chronic continuous infusion of 1,1,1-trichloroethane for 6 months calculated from the human PBPK model. The sensitive parameters included body weight (BW), rate constants of cardiac output (QCC) and pulmonary ventilation (QPC), and blood:air partition coefficient (PB). The sensitivity of liver 1,1,1-trichloroethane concentration to the parameters was generally similar to that of venous blood concentration except that (1) the influence of PB became negative (Figure 73), (2) the sensitivity of QCC overran that of QPC (Figure 72), and (3) the blood flow fraction of the liver (QLC) became as sensitive as QCC (Figure 72).

Chronic inhalation exposure: During chronic inhalation in humans, the only sensitive parameter to the venous blood 1,1,1-trichloroethane concentration was PB (LSC ~ 1.0), same as in the scenario of acute inhalation. To the liver concentration, the only sensitive parameter was liver:air partition coefficient (PLA, LSC ~ 1.0).

These results suggested that, during the extrapolation of rat inhalation to human inhalation, PB and PLA would be the only parameters that should be assessed carefully. However, extrapolation from rat inhalation to human infusion requires careful assessment of more parameters such as QCC, QPC, and QLC. Therefore, in the latter extrapolation, higher uncertainty would be expected.

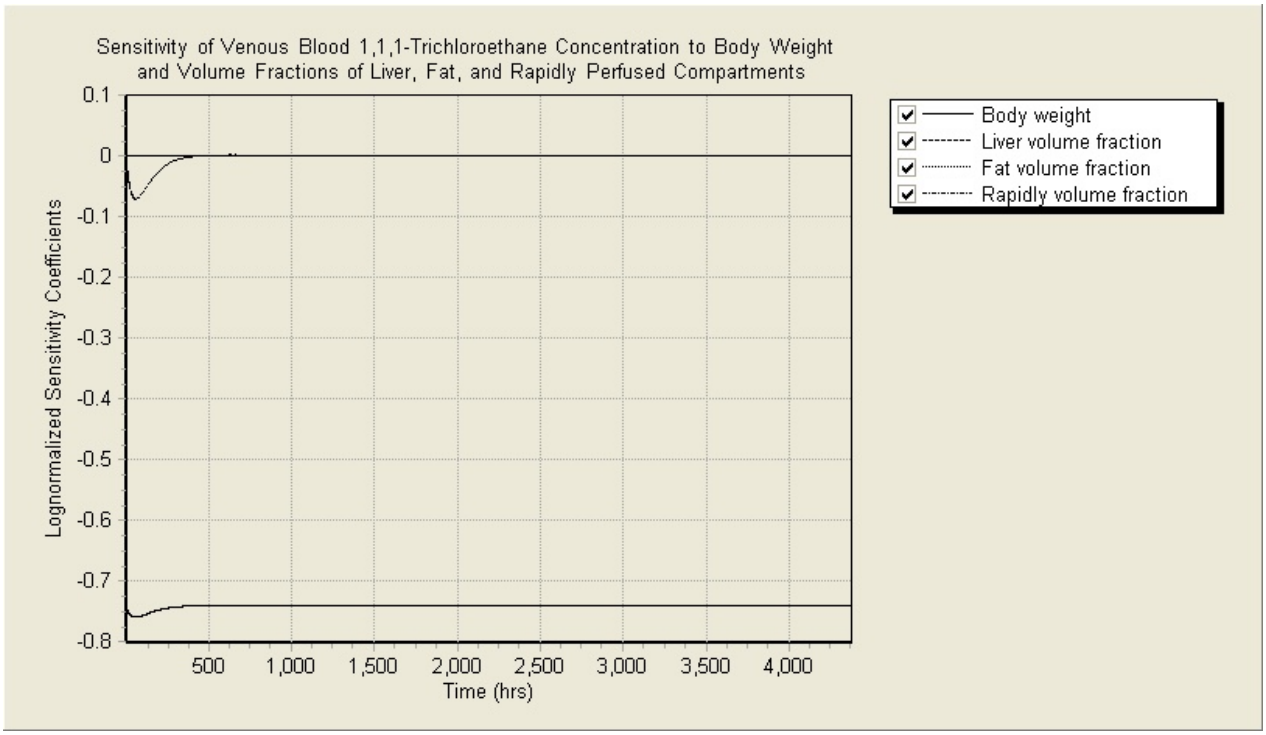


Figure 68. Sensitivity of venous blood 1,1,1-trichloroethane concentration to body weight (the bottom line) and volume fractions of liver, fat, and rapidly perfused compartments during chronic continuous infusion of 1,1,1-trichloroethane.

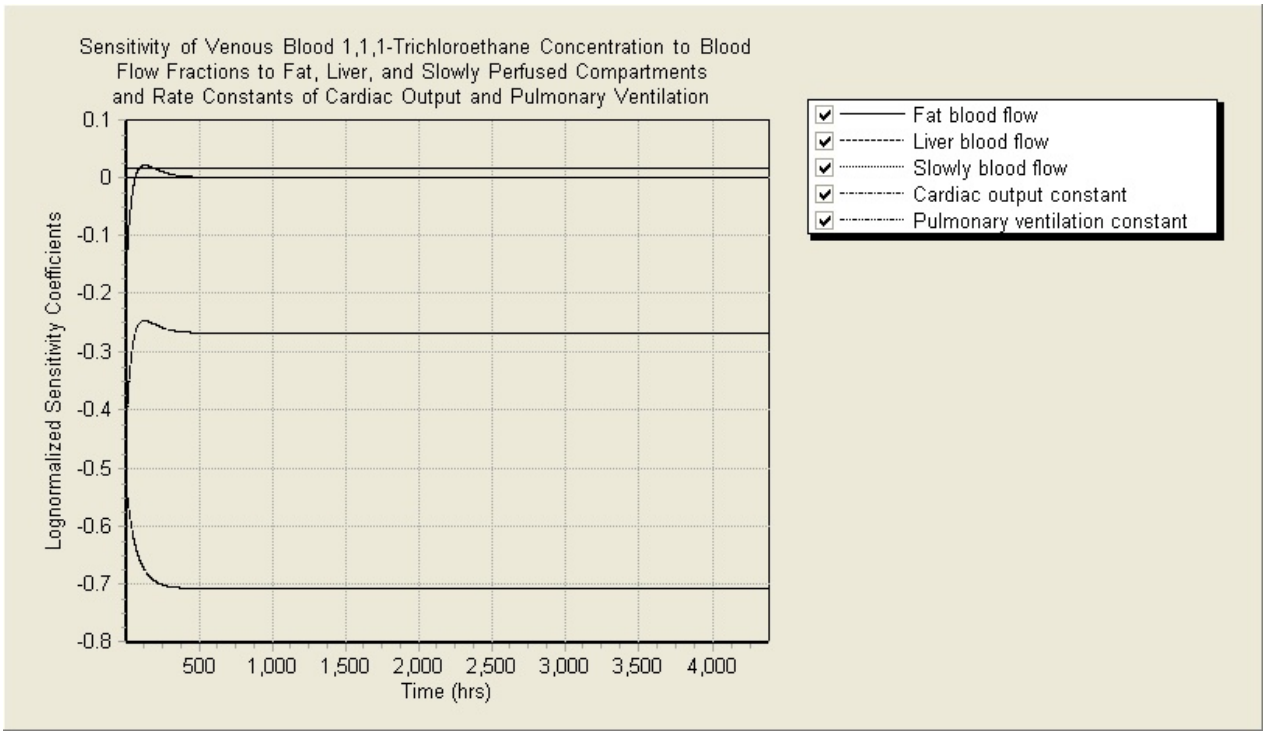


Figure 69. Sensitivity of venous blood 1,1,1-trichloroethane concentration to blood flow fractions to fat, liver, and slowly perfused compartments and rate constants of cardiac output (the second line from the bottom) and pulmonary ventilation (the bottom line) during chronic continuous infusion of 1,1,1-trichloroethane.

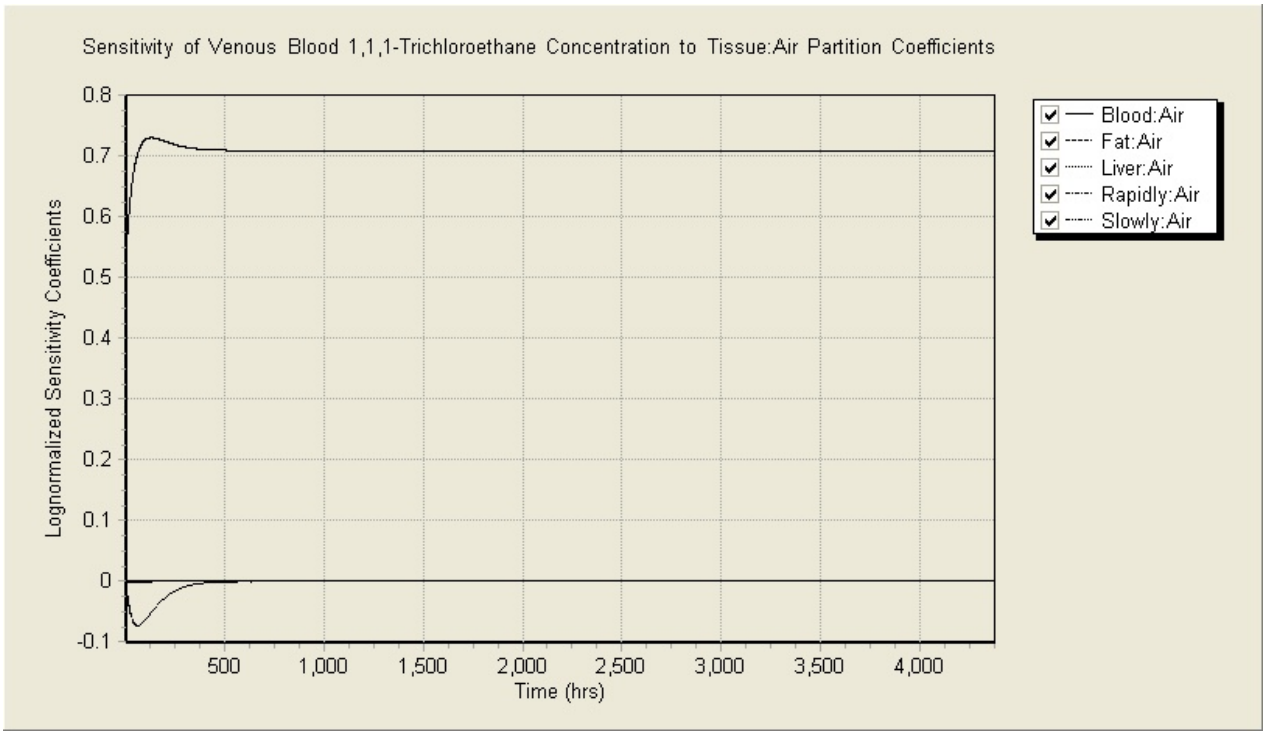


Figure 70. Sensitivity of venous blood 1,1,1-trichloroethane concentration to tissue:air partition coefficients during chronic continuous infusion of 1,1,1-trichloroethane. The top line represents blood:air partition coefficient.

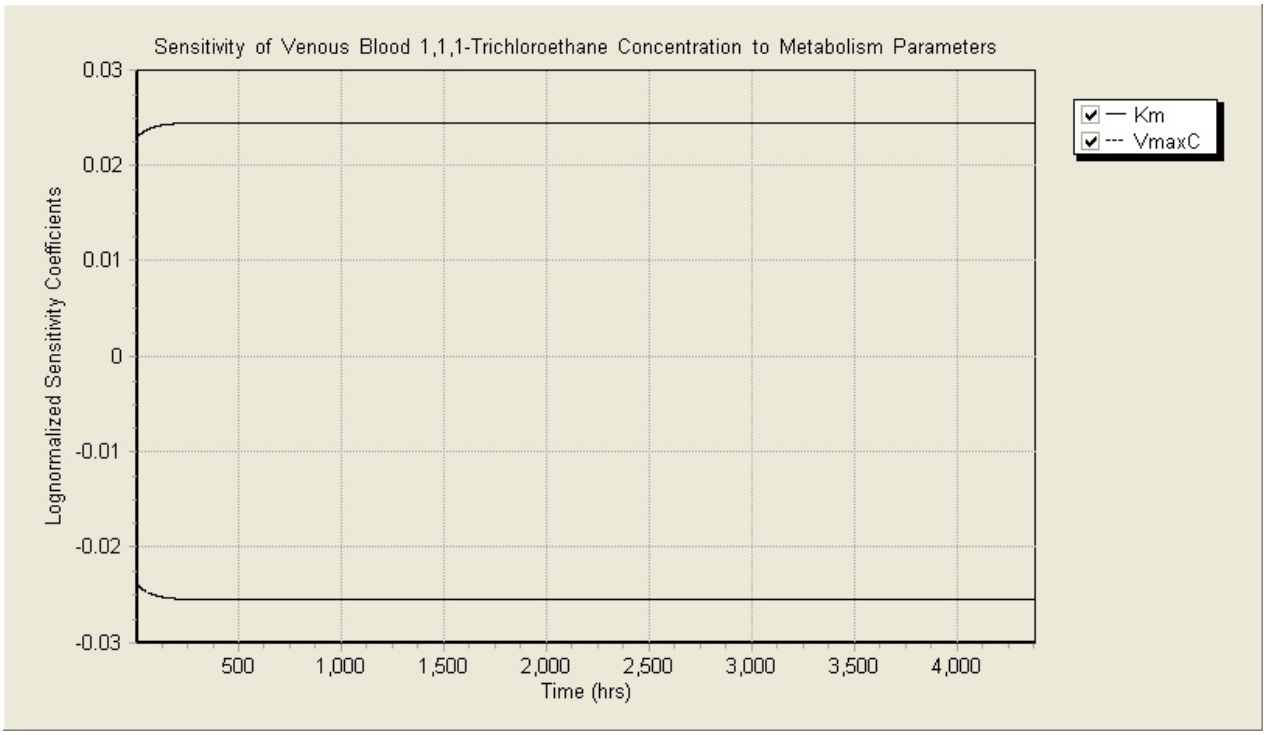


Figure 71. Sensitivity of venous blood 1,1,1-trichloroethane concentration to metabolism parameters Km (the upper line) and VmaxC (the lower line) during chronic continuous infusion of 1,1,1-trichloroethane.

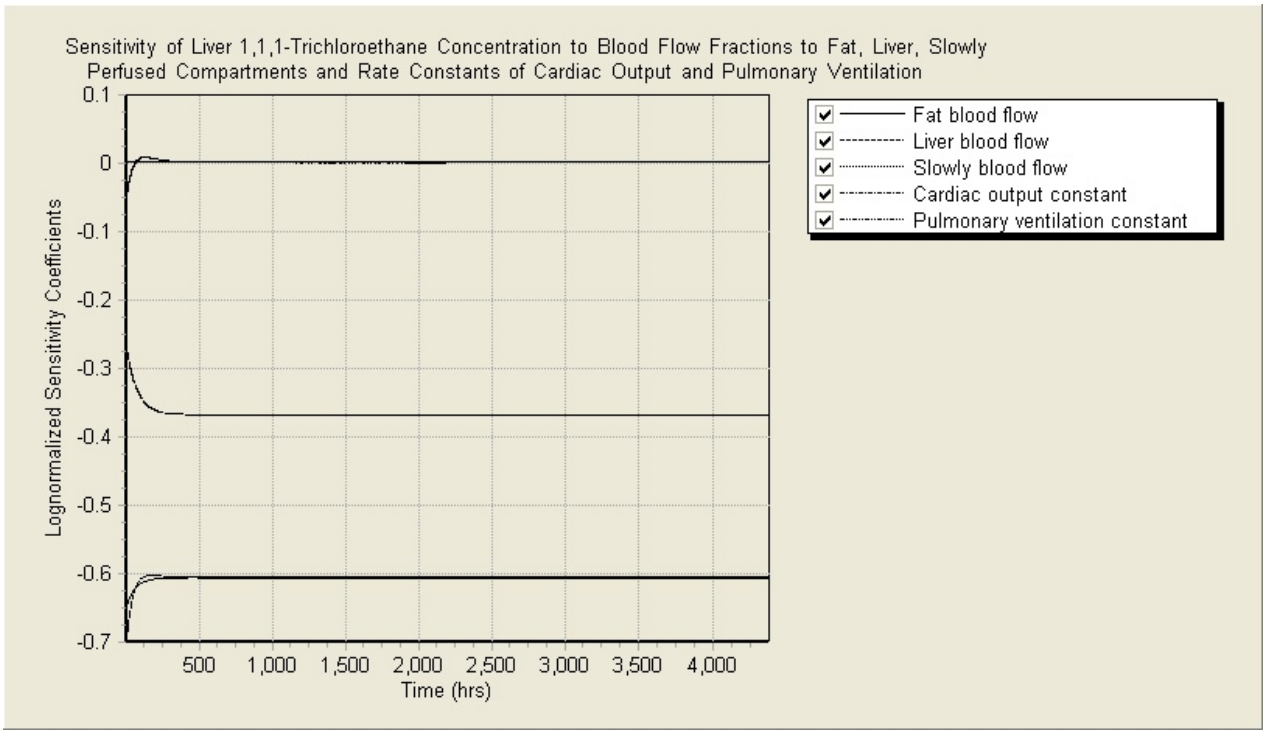


Figure 72. Sensitivity of liver 1,1,1-trichloroethane concentration to blood flow fractions to fat, liver, and slowly perfused compartments and rate constants of cardiac output and pulmonary ventilation during chronic continuous infusion of 1,1,1-trichloroethane. The middle line represents pulmonary ventilation rate constant, and the two bottom lines represent the liver blood flow fraction and cardiac output rate constant.

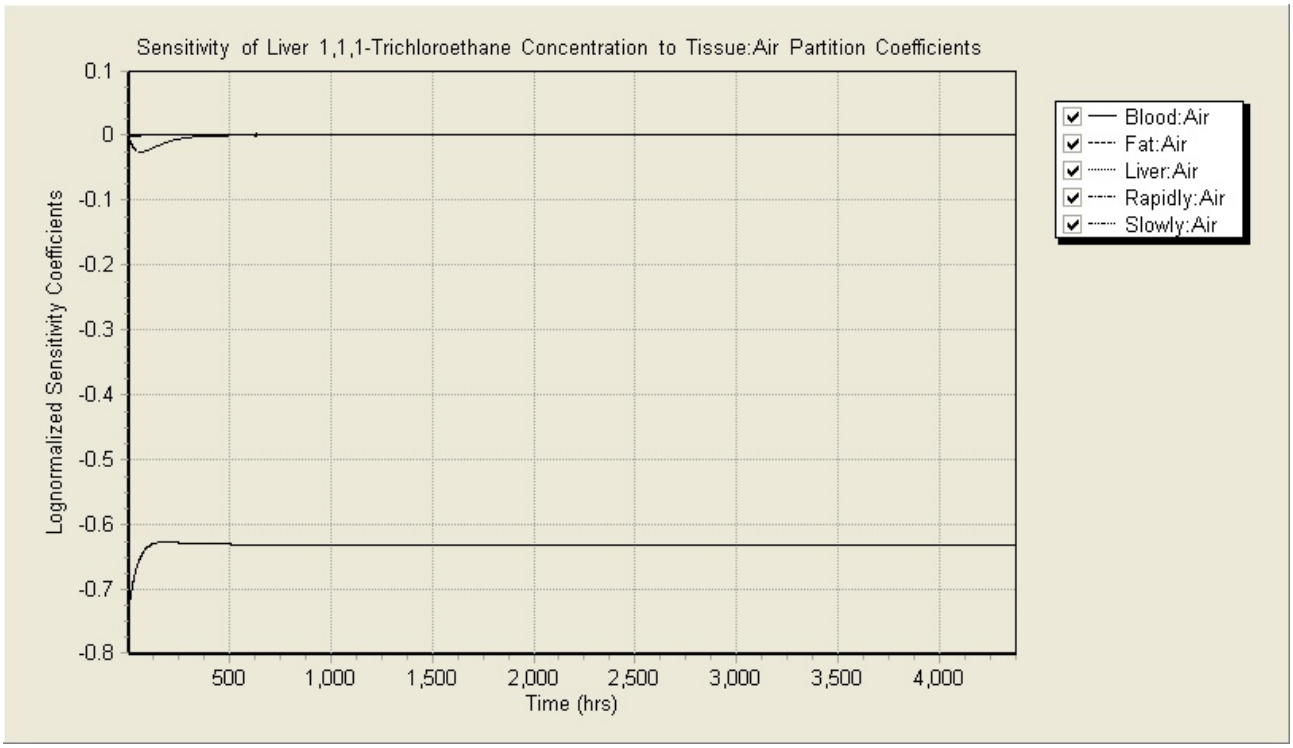


Figure 73. Sensitivity of liver 1,1,1-trichloroethane concentration to tissue:air partition coefficients during chronic continuous infusion of 1,1,1-trichloroethane. The bottom line represents blood:air partition coefficient.

The Reitz *et al.* (1988) model was then extrapolated to a human PBPK model by incorporating the appropriate human parameters into the model. Table 5 below provides a summary for parameters used in simulating all the human studies.

Table 5. Parameters Used in the 1,1,1-Trichloroethane PBPK Models for Various Human Exposure Scenarios

Parameter	Value	Reference	Remark
Body weight (BW, kg)	Default = 70[a] given values[b] averages[c]	-	[a]Assumed value if no BW value revealed in the related papers [b]BW given in the related papers [c]Averages of study subjects
Liver volume fraction (VLC)	0.031	Reitz *et al.*, 1988	-
Fat volume fraction (VFC)	0.231[d] measured[e]	[d]Reitz *et al.*, 1988 [e]Wallace *et al.*, 1997	-
Rapidly perfused volume fraction (VRC)	0.037	Reitz *et al.*, 1988	-
Slowly perfused volume fraction (VSC)	0.611	Reitz *et al.*, 1988	-
Alveolar ventilation rate constant (QPC, L/hr/kg)	15[f] 65.31[g]	[f] Reitz *et al.*, 1988 [g]Lapare *et al.*, 1995	[f]QP=348 from in Reitz *et al.*, 1988 [f]At rest [g]At exercise
Alveolar ventilation rate (QP, L/hr)	$QPC \times BW^{0.74}$	Reitz *et al.*, 1988	-
Cardiac output rate constant	15[f]	[f]Reitz *et al.*, 1988	[f]QC=348 from in Reitz *et al.*, 1988

Parameter	Value	Reference	Remark
(QCC, L/hr/kg)	31.89[g]	[g]Lapare *et al.*, 1995	[f]At rest [g]At exercise
Cardiac output rate (QC, L/hr)	$QCC \times BW^{0.74}$	Reitz *et al.*, 1988	-
Liver blood flow fraction	0.24[f]	[f]Reitz *et al.*, 1988	[f]At rest
(QLC)	0.133[g,h]	[g]Lapare *et al.*, 1995	[g]At exercise [h](= hepatic arterial blood + venous blood from stomach and intestines in Lapare *et al.* 1995)
Fat blood flow fraction (QFC)	0.09[i]	Reitz *et al.*, 1988	[i]Assumed the same at rest and at exercise
Slowly blood flow fraction	0.18[f]	[f]Reitz *et al.*, 1988	[f]At rest
(QSC)	0.354[g,j]	[g]Lapare *et al.*, 1995	[g]At exercise [j](= muscle + skin + poorly perfused in Lapare *et al.* 1995)
Rapidly blood flow fraction	0.49[f]	[f]Reitz *et al.*, 1988	[g]At exercise
(QRC)	0.423[g,k]		[k](= 1 – QLC – QFC – QSC)
Partition coefficient			
Blood:Air (PB)	2.53	Reitz *et al.*, 1988	-
Liver:Blood (PL)	3.4	Reitz *et al.*, 1988	-
Fat:Blood (PF)	103.95	Reitz *et al.*, 1988	-
Slowly:Blood (PS)	1.25	Reitz *et al.*, 1988	-
Rapidly:Blood (PR)	3.4	Reitz *et al.*, 1988	-
Saturable Metabolism			
Capacity constant (VmaxC, mg/hr/kg)	0.419	Reitz *et al.*, 1988	-
Capacity (Vmax, mg/hr)	$VmaxC \times BW^{0.7}$	Reitz *et al.*, 1988	-
Affinity (Km, mg/L)	5.75	Reitz *et al.*, 1988	-
Gastrointestinal absorption rate constant (Ka, hr^{-1})	1.25	Reitz *et al.*, 1988	Use the value from rats

V.2. Analysis of Human Intentional Dosing Data to Support Derivation of an Acute Inhalation RfC

V.2.1. Human Studies and PBPK Model Simulations

Relevant human studies of 1,1,1-trichloroethane are summarized in Appendix II. The Reitz *et al.* (1988) PBPK model was used to simulate measured values (concentrations of 1,1,1-trichloroethane in venous blood or exhaled air) from five human intentional dosing studies. PBPK modeling results are presented below for four human studies; model simulation results of the Mackay *et al.* (1987) human study are presented earlier in Section IV.2.3. The parameters for simulations of all five human studies are presented in Table 3 in the previous section (Section V.1.).

Savolainen *et al.* (1981, 1982a) studies: These two papers were from the same study with the latter (Savolainen *et al.*, 1982a) as an abbreviated presentation of the former (Savolainen *et al.*,1981). Nine health male student volunteers (20–25 years old, body weight 57–82 kg) were exposed to 1,1,1-trichloroethane in a 15 m^3 dynamic chamber at the concentrations of 200 and 400 ppm (8.2 and 16.4 μmol/L). The study was conducted according to the ethical standards adopted under the Declaration of Helsinki. The exposure was 4 hours per day, once a week, with a 6-day interval between succeeding exposures over 6 consecutive weeks. Venous blood concentrations of 1,1,1-trichloroethane were determined before and during each exposure; psychophysiological indices were measured before,

during, and after each exposure. The psychophysiological indices included body sway, simple reaction time and tapping speed of the dominant hand, critical flicker fusion threshold, gaze deviation nystagmus, and subjective feelings and symptoms. The overall results suggest that the study did not reveal any marked impairment by short-term exposure to 1,1,1-trichloroethane on psychophysiological functions. The low concentration exposure slightly shortened the cumulative reaction time; whereas, in the high concentration case, the time was initially slightly shortened (1 hour after exposure started) and then prolonged (3 hours after exposure started). The reaction time can be digitized from Figure 1 of the original paper. By inputting the proper body weight (mean 69.5 kg), the Reitz *et al.* (1988) model could predict the venous blood concentration well (Figure 23).

In another Savolainen *et al.* paper (1982b), the same volunteers had the same exposure patterns and the ratio of body sway with the eyes closed to the sway with the eyes open was reported.

Laine *et al.* (1996) study: Nine male student volunteers (21–24 years old, 67–78 kg) were involved. The study was conducted according to the ethical standards adopted under the Declaration of Helsinki. Subjects were exposed to clean air and 1,1,1-trichloroethane in a 15 m^3 dynamic chamber on 3 separate days. The exposures were split into a morning and an afternoon session, lasting 3 hours and 40 minutes, respectively, with 40 min of break in between. The subjects always exercised at 100 watt for 10 minutes at the beginning of both sessions. The two 1,1,1-trichloroethane exposure scenarios were (1) constant concentration of 200 ppm, and (2) a baseline concentration of 135 ppm with a transient peak concentration of 400 ppm for 20 minutes each at the beginning of the morning and afternoon sessions. Physiological or psychophysiological indices measured included EEG, visual evoked potentials, body sway, venous blood concentrations of 1,1,1-trichloroethane, and symptom questionnaire. Overall, no deleterious effects of exposure were noted. In our PBPK modeling, the cardiac output and ventilation rate constants during exercises were from Lapare *et al.* (1995). The simulated model results vs. experimental venous blood concentration of 1,1,1-trichloroethane following exposure with constant (lower line and circles) and fluctuated concentrations (higher line and triangles) are presented in Figure 74. There was exercise in both exposure scenarios that lasted from 0–0.167 hours and 3.667–3.834 hours. The model underestimated the venous blood concentrations (Figure 74).

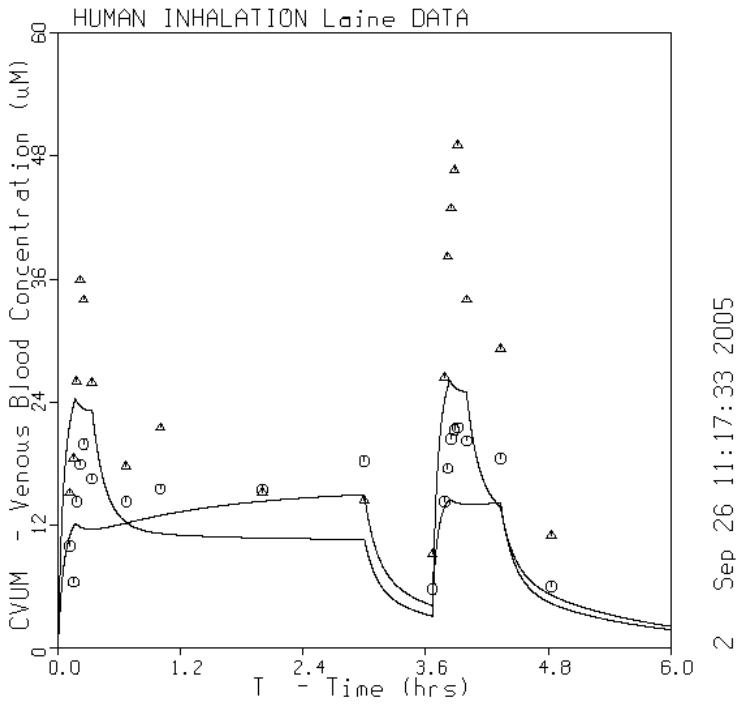


Figure 74. Simulation of the venous blood concentration of 1,1,1-trichloroethane in the Laine *et al.* (1996) human study by the Reitz *et al.* (1988) model.

Muttray *et al.* (2000) study: Twelve male student subjects (mean age 27.0 ± 1.9 years) were exposed for 4 hours to 20 and 200 ppm 1,1,1-trichloroethane in an exposure chamber using a cross-over design. A one week interval was imposed between two sessions. EEGs were recorded before and at the end of exposure. A questionnaire of the Swedish Performance Evaluation System was administered before, during, and after exposure. This study was conducted according to the ethical standards adopted under the Declaration of Helsinki (1989 Hong Kong version). The overall conclusion was that changes in EEG and the increased score for tiredness indicated a slight sedative effect of 200 ppm 1,1,1-trichloroethane. Only one data point was provided for venous blood concentration of 1,1,1-trichloroethane after 3.7 hours of exposure at 200 ppm; blood concentration was below detection limit at 3.7 hours under 20 ppm exposure conditions. As shown in Figure 75, the model simulation is lower than the data.

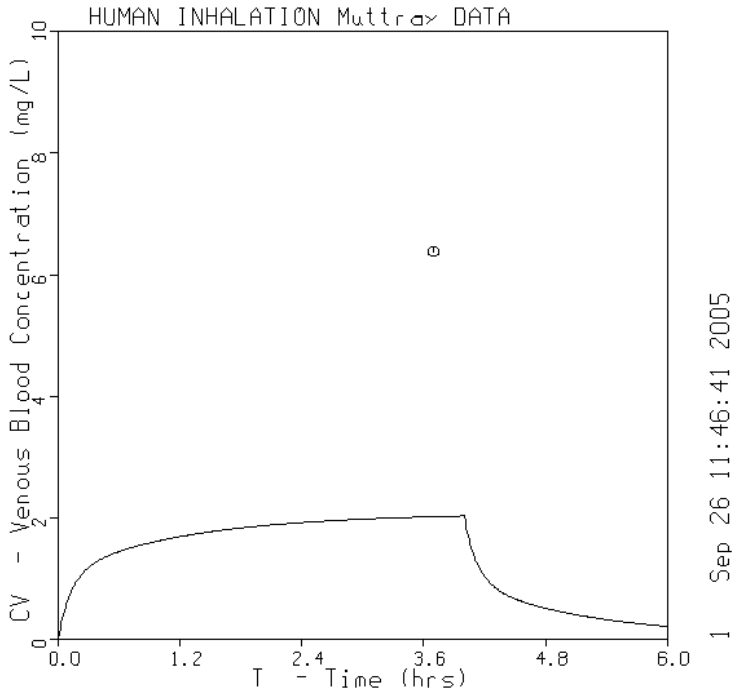


Figure 75. Simulation of the venous blood concentration of 1,1,1-trichloroethane in the Muttray *et al.* (2000) human study by the Reitz *et al.* (1988) model.

Gamberale and Hultengren (1973) study: Twelve healthy men, 20–30 years old, were exposed to 239, 338, 451, and 566 ppm (corresponding to the original target concentrations of 250, 350, 450, and 550 ppm) 1,1,1-trichloroethane sequentially in four 30-minute periods. The increase in concentrations from 239 to 338 ppm and from 451 to 566 ppm was performed without interruption in exposure. There was a 5-minute break between the 338 and 451 ppm exposures. Alveolar air concentrations of 1,1,1-trichloroethane were measured; it was reported that alveolar air concentration correlated well with arterial blood concentration. Psychophysiological functions including reaction time, perceptual speed, and manual dexterity were studied. The published study does not provide a statement describing the protocol for ethical conduct followed by the study investigators; however, the study was conducted by the Swedish National Board of Occupational Safety and Health at exposure concentrations below, or only briefly (30 minutes) above the occupational limit for repeated exposure (threshold limit value, TLV, of 350 ppm), and appears to have been conducted consistent with the ethical standards prevailing at the time of the study. These psychophysiological functions were all impaired during exposure to 338 ppm 1,1,1-trichloroethane or higher. As shown in Figure 76, our PBPK model prediction was much higher than the experimental data. Proper modifications in the blood:air partition coefficient, cardiac output rate constant, and alveolar ventilation rate constant improved the simulation; however, to simulate the data well required such a large change in each of those parameters that it became biologically implausible.

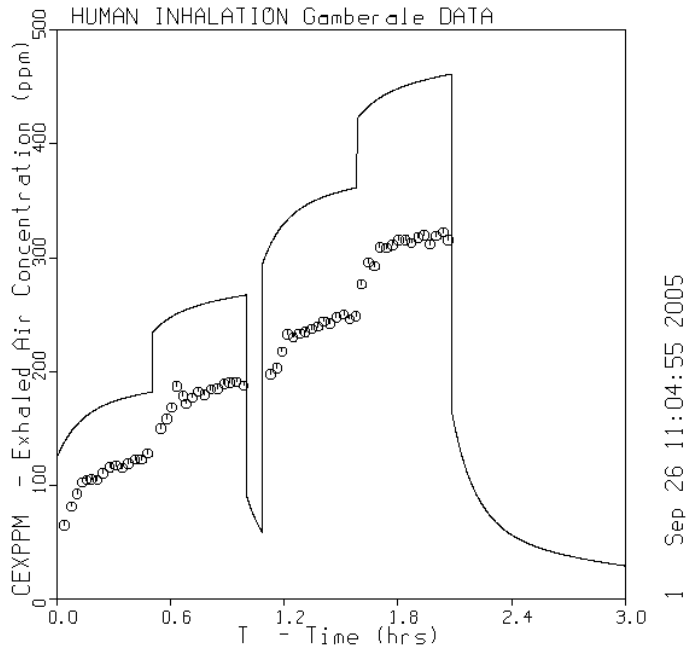


Figure 76. Simulation of the concentration of 1,1,1-trichloroethane in the expired air in the Gamberale and Hultengren (1973) human study by the Reitz *et al.* (1988) model.

Salvini *et al.* (1971) study: In one additional human study by Salvini *et al.* (1971), six male students (20–23 years old) were exposed to a control atmosphere and 450 ppm 1,1,1-trichloroethane (average value with a range of 400–500 ppm) in a 48 m^3 chamber on different days. The exposure pattern was 4 hours in the morning (8:30 a.m. – 12:30 p.m.) and 4 hours in the afternoon (2–6 p.m.) with 1.5 hours in between. Salvini et al. did not provide a statement describing their protocol for ethical conduct; however, the study was conducted by the Institute of Preventive Medicine for Workers and Applied Psychology at the University of Pavia, Italy, using a single exposure at or just above the TLV, and appears to have been conducted consistent with the ethical standards prevailing at the time of the study. Psychophysiological functions were measured; however, no pharmacokinetic data except a figure containing published data from other investigators was provided in the paper. We were unable to do any PBPK modeling with this study.

Conclusions Regarding Simulations of Acute Human Pharmacokinetic Data: The Reitz *et al.* (1988) PBPK model simulated well some, but not all, data sets from human intentional dosing studies. Because internal doses of 1,1,1-trichloroethane could not be reliably modeled in all instances, this PBPK analysis does not appear to support a comparison of human intentional dosing studies on an internal dose basis.

V.2.2. Calculating Internal Dose Using PBPK Modeling and Mackay *et al*. (1987) Data

The Mackay *et al*. (1987) study was selected by EPA as the principal study for derivation of acute RfC values. The study provides evidence of neurobehavioral effects in humans at a relatively low exposure concentration. Further, changes in neurobehavioral test scores were related both to exposure concentration and duration. In addition, the study provides pharmacokinetic data collected at time

points concurrent with tests of neurobehavioral performance. Finally, our human PBPK model simulations were consistent with the Mackay *et al.* experimental data.

Consideration was given to whether the area under the concentration vs. time curve (AUC) or the peak blood concentration (Cmax) constitutes the better internal dose metric in the case of the Mackay *et al.* (1987) study. Four blood samplings at 20, 60, 120, and 180 minutes were carried out and neurobehavioral tests were conducted on the human subjects immediately after each blood sampling (Mackay *et al.,* 1987). Strictly speaking, there is only one Cmax in any given concentration vs. time pharmacokinetic curve unless for some reason there are multiple, but equal, peaks. As shown in Figure 1 of the Mackay *et al.* (1987) study, the Cmax is at or near the end of the exposure period around 180 minutes. Since changes in psychomotor performance scores were observed as early as 20 minutes following exposure, it is more appropriate to use the concentration in the blood at time t (Ct), instead of Cmax, as a possible internal dose metric.

Additional support for the use of Ct as the appropriate dose metric is as follows:

1. Several laboratory animals studies of 1,1,1-trichloroethane have shown a correlation between blood and brain 1,1,1-trichloroethane concentrations and certain neurological deficits. Warren *et al.* (1998, 2000) found that blood and brain concentrations (expressed either as Cmax or AUC) were strongly correlated with operant performance in the rat receiving acute inhalation exposures to 1,1,1-trichloroethane for up to 100 minutes and with locomotor activity in the mouse at acute inhalation exposures up to 30 minutes in duration. In both studies, the investigators noted that Cmax and AUC were both equally suitable for predicting 1,1,1-trichloroethane-induced response rate changes.

2. Studies of trichloroethylene (TCE) have shown that acute neurological deficits in rats (as measured by changes in performance of a behavioral signal detection task or changes in visual evoked potentials) are related to the momentary concentrations of TCE in blood or brain at the time of the neurobehavioral assessment and not to the total amount of TCE exposure expressed as AUC. Preliminary evidence suggests a similar relationship exists for toluene (Boyes *et al.*, 2003, 2005, Bushnell *et al.,* 2005).

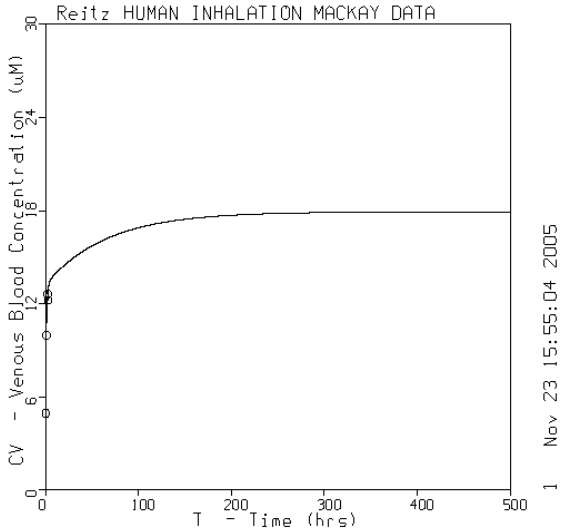
3. There is strong correlation between blood and brain concentrations, and, therefore, blood concentrations are an appropriate measure for CNS effects and a brain compartment is not needed for the PBPK model (see Section V.1).

4. Since Mackay *et al.* (1987) had precise measurements of blood concentrations at the time of neurobehavioral testing, Ct, as a form of internal dose metric, was already available (see Mackay.cmd file in Appendix III for values of blood concentrations at various time points derived from digiMatic). Thus, there was no need to perform PBPK model simulation to derive those values.

Mackay *et al.* (1987) discussed in their paper certain discrepancies between absence and presence of neurobehavioral effects in some of the earlier studies; they suggested that neurobehavioral effects from 1,1,1-trichloroethane may not necessarily correlate with the blood levels at the time of neurobehavioral testing. Accordingly, we believed that calculation of AUCs or time-weighted averages of 1,1,1-trichloroethane concentrations in the blood at different time periods, in addition to Ct, would prove informative.

Mackay *et al.* (1987) identified the lower (950 mg/m^3 or 175 ppm) of two exposure concentrations as the lowest-observed-adverse-effect level (LOAEL). There was no no-observed-adverse-effect level (NOAEL) in this study. A test battery was used to assess neurobehavioral performance before subjects entered the test chamber and at four time periods during the exposure. Changes in test performance were observed at an exposure concentration of 950 mg/m^3 as early as 20 minutes. Based on evidence from human intentional dose studies as a whole, however, EPA concluded that biologically significant changes could more reasonably be associated with an exposure to 950 mg/m^3 for 60 minutes. As shown in Appendix II, simple and choice reaction times were assessed by Mackay *et al.* (1987), Savolainen *et al.* (1981, 1982a,b), and Gamberale and Hultengren (1973). After 4 hours of continuous exposure to a concentration of 400 ppm, Savolainen *et al.* (1981, 1982a,b) found no significant changes in simple reaction time in exposed volunteers. Gamberale and Hultengren (1973) reported no significant changes in tests of simple and choice reaction time following 30 minutes of exposure to 250 ppm 1,1,1-trichloroethane but did see changes after 1 hour to a time-weighted average concentration of 300 ppm (250 ppm for 30 minutes followed by 350 ppm for 30 minutes). The Salvolainen *et al.* (1981, 1982a,b) and Gamberale and Hultengren (1973) studies do not confirm a finding of neurobehavioral effects following 20 minutes of exposure; however, the Gamberale and Hultengren (1973) findings are generally supportive of changes in neurobehavioral performance after one hour of exposure.

Using the extrapolated human PBPK model based on the Reitz *et al.* (1988) model, we first simulated the venous blood concentration under the exposure condition of 950 mg/m^3 (175 ppm) for up to 500 hours to illustrate the approximate time when steady state is reached (Figure 77). As shown in the two plots (the first in linear timescale and the next in log timescale) in Figure 77 and Table 6, the steady state venous blood concentration appears to be reached at around 168 hours or soon thereafter.



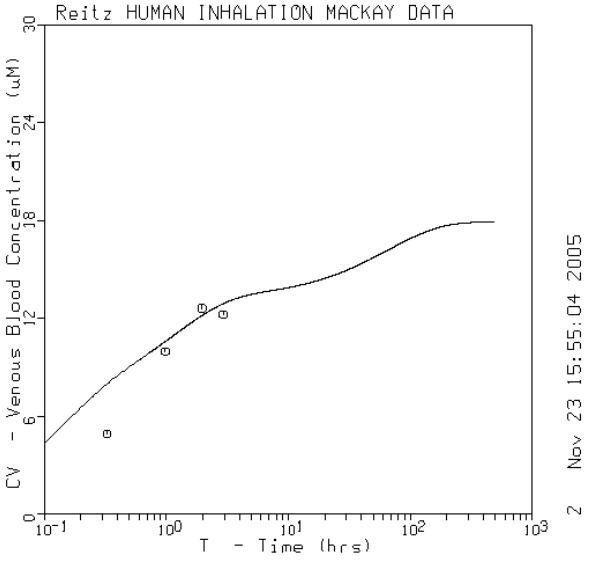


Figure 77. Simulations of the venous blood concentration of 1,1,1-trichloroethane in the Mackay *et al.* (1987) human study by the Reitz *et al.* (1988) model up to 1000 hrs. The first plot is in a linear scale; the x-axis (time) in the second plot is in a log scale.

Table 6. 1,1,1-Trichloroethane Concentration in Venous Blood at Various Time Points

Time (hr)	CV (µM)	CV/CV* (%) (CV*=17.92)
1	10.63	59
4	13.30	74
8	13.76	77
24	14.67	82
48	15.66	87
96	16.83	94
168	17.56	98
336	17.90	99.9
500	17.92	100

We then used this human PBPK model to calculate the Internal Doses (CV and AUC) at 1 hour. In line with EPA's conclusion above that biologically significant changes occur when humans are exposed to 1,1,1-trichloroethane at 950 mg/m^3 for 1 hour, we therefore used the internal dose of CV or AUC at 1 hour as a basis for further calculating the exposure concentrations for 4, 8, and 24 hours to reach such target internal doses as shown in Table 7.

Table 7. Predicted Exposure Concentration at Different Exposure Durations for Target Internal Doses

Exposure duration (hr)	1,1,1-Trichloroethane exposure concentration (mg/m^3 or ppm) based on	
	CV[a]	AUC[b]
1	**950 mg/m^3 (or 175 ppm)**	**950 mg/m^3 (or 175 ppm)**
4	**715.28 mg/m^3 (or 131 ppm)**	**174.7 mg/m^3 (or 32 ppm)**
8	**693.4 mg/m^3 (or 127 ppm)**	**76.4 mg/m^3 (or 14 ppm)**
24	**649.75 mg/m^3 (or 119 ppm)**	**24 mg/m^3 (or 4.4 ppm)**

[a]Target internal dose CV = 1.33 mg/L (or 9.97 μM).
[b]Target internal dose AUCCV = 1.09 mg/L × hr.

V.2.3. Comparison of Internal Doses and Exposure Concentrations

The human model was run at different internal doses in order to describe the relationship between the human internal dose-metric and human exposure concentration. If the relationship is linear, it was expected that log spacing of modeled exposures would be adequate because they would yield a straight line; otherwise, closer spacing would be needed. Because 1,1,1-trichloroethane metabolism is minimal, it was expected that this relationship would be linear. The results of this analysis are presented below.

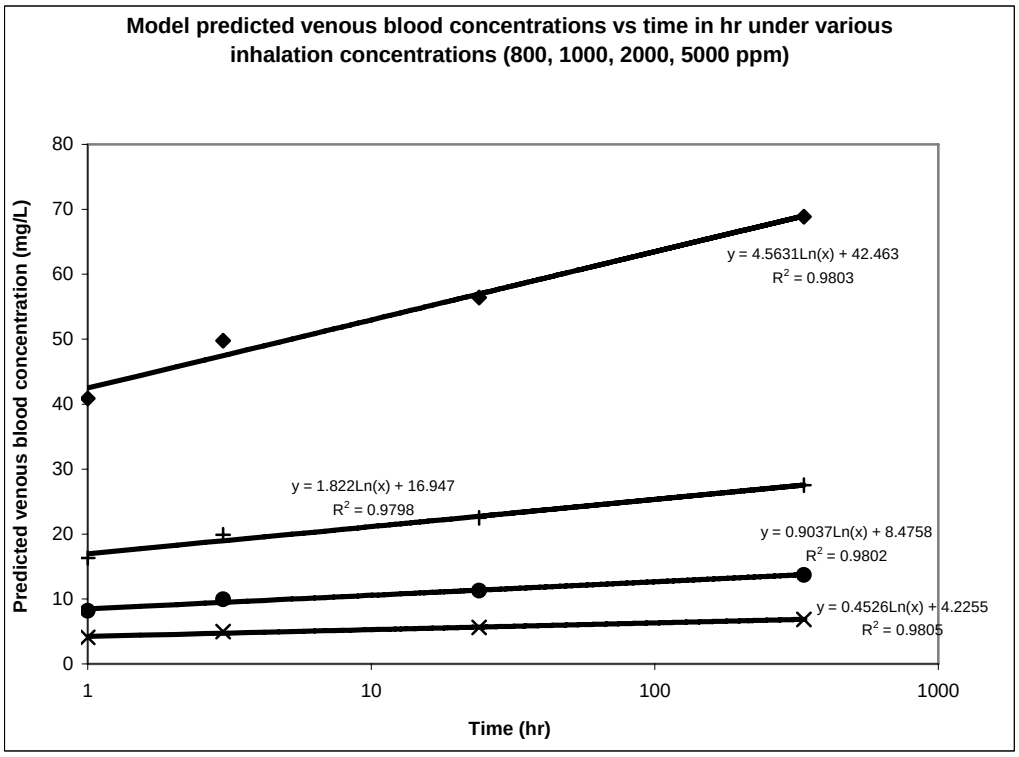


Figure 78. Relationship between the venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the time (hr) in a log scale. The predictions were obtained at exposure levels of 800-5,000 ppm.

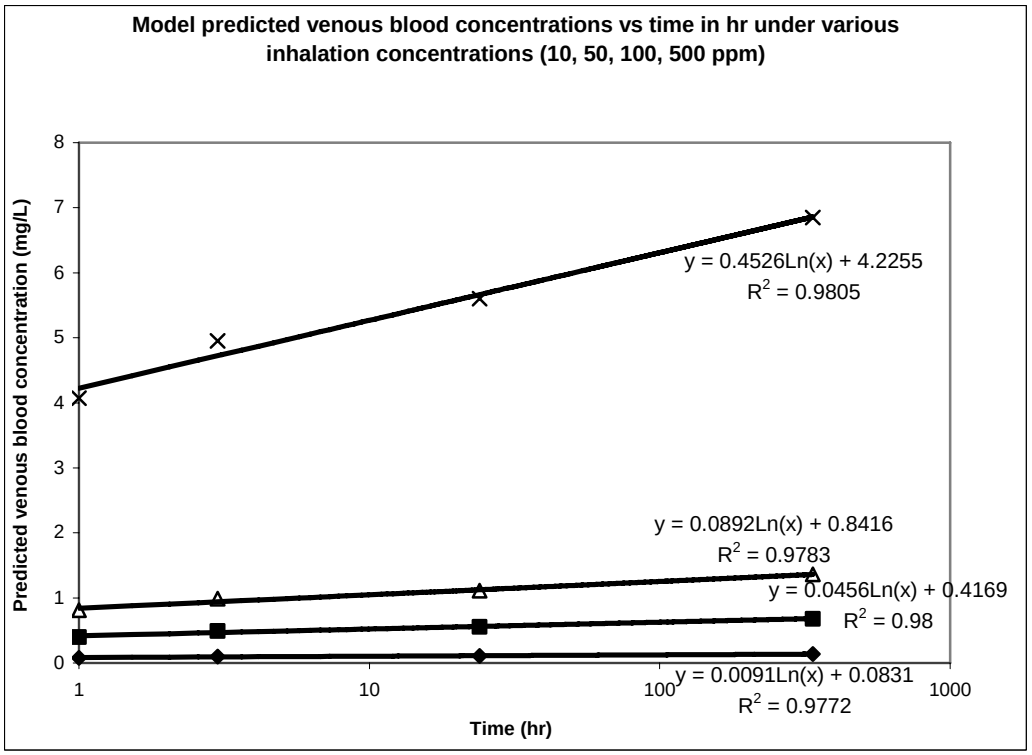


Figure 79. Relationship between the venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the time (hr) in a log scale. The predictions were obtained at exposure levels of 10-500 ppm.

Figures 78 and 79 provide PBPK model predicted venous blood concentrations under continuous inhalation with respect to time (*i.e.*, Ct) for a wide range of inhalation exposure concentrations. In each graph the lines represent, from top to bottom, the highest concentration to the lowest concentration. The four symbols associated with the lines are PBPK model predicted Ct at four time points under a given inhalation concentration. The four time points are 1, 3, 24, and 336 hours, which cover the time frame of rapid rising phase to steady state in Ct. As shown above, the predicted Ct is linear with time on a log scale within the range of time points (*i.e.*, 1 to 336 hours) studied. In the above plots, the log scale for time may have obscured the tendency for showing steady state plateau, particularly at the highest concentration level. It is anticipated that, if the simulation had gone on for longer time at the highest concentration, the steady state plateau would have been apparent.

Ct (*i.e.*, internal dose metrics) against exposure concentrations were then plotted to illustrate the relationship between the internal and external doses. As shown in Figures 80 through 83, a linear relationship between "internal dose" and inhalation "exposure concentration" exists for all four time points.

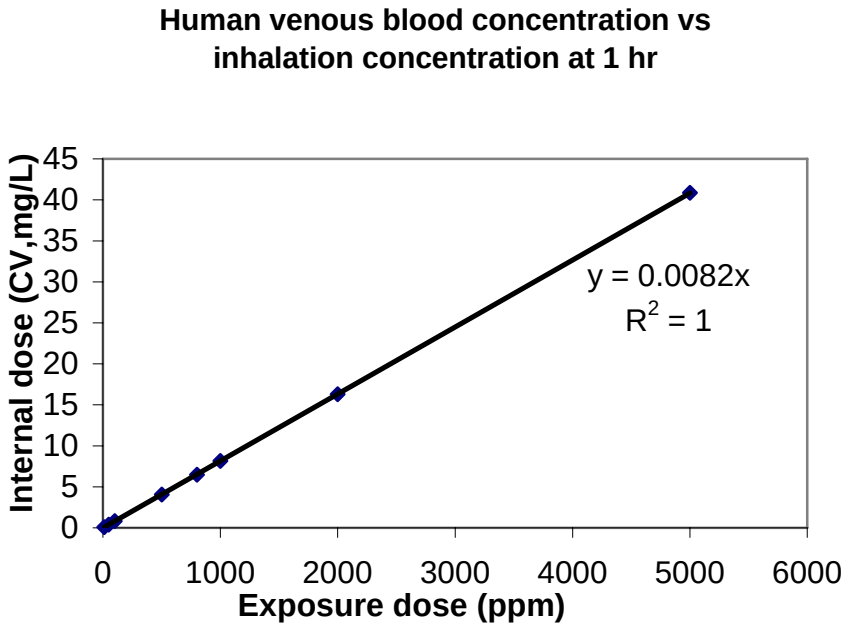


Figure 80. Relationship between the 1-hr venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the hypothetical exposure levels of 0-5,000 ppm.

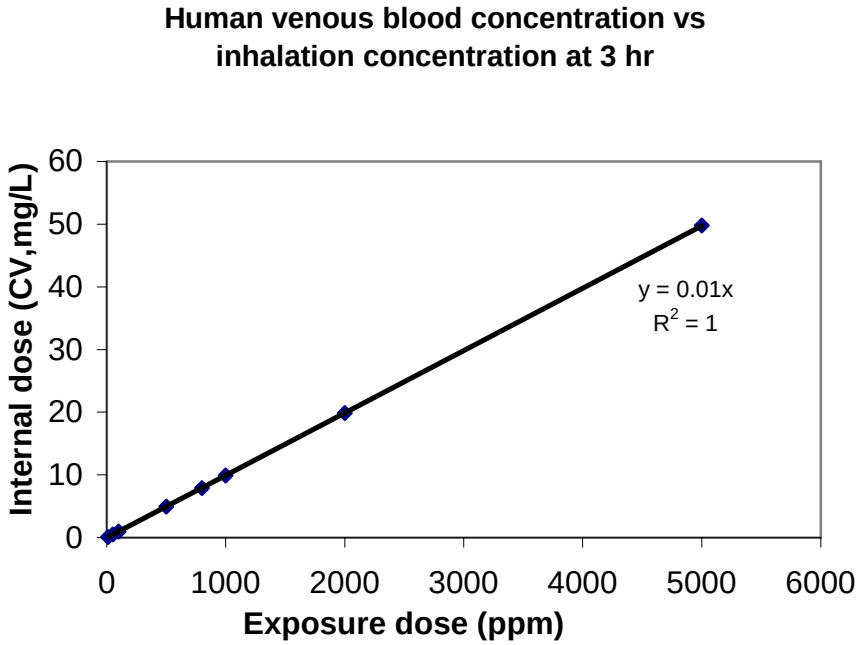


Figure 81. Relationship between the 3-hr venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the hypothetical exposure levels of 0-5,000 ppm.

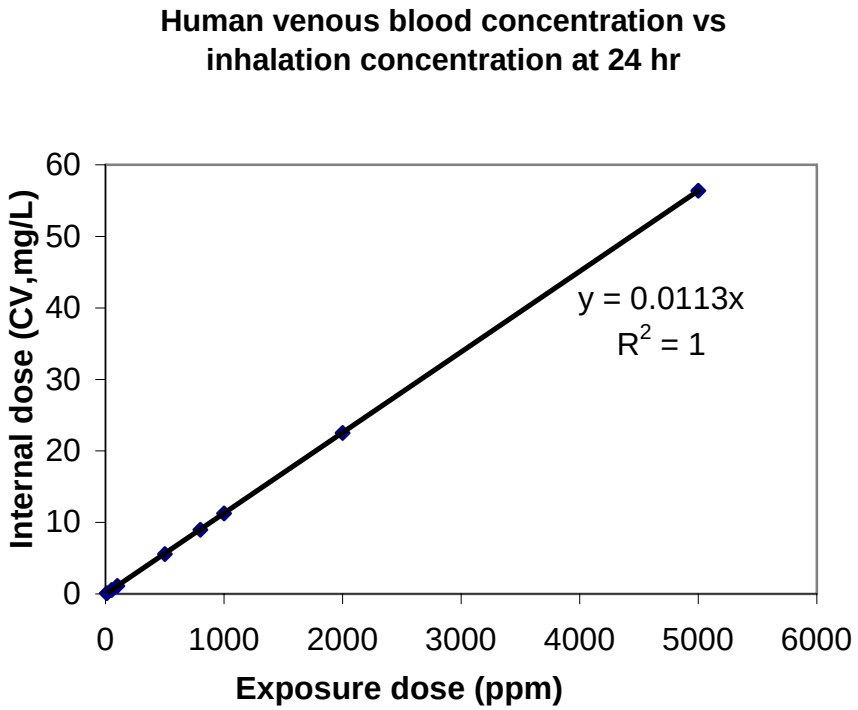


Figure 82. Relationship between the 24-hr venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the hypothetical exposure levels of 0-5,000 ppm.

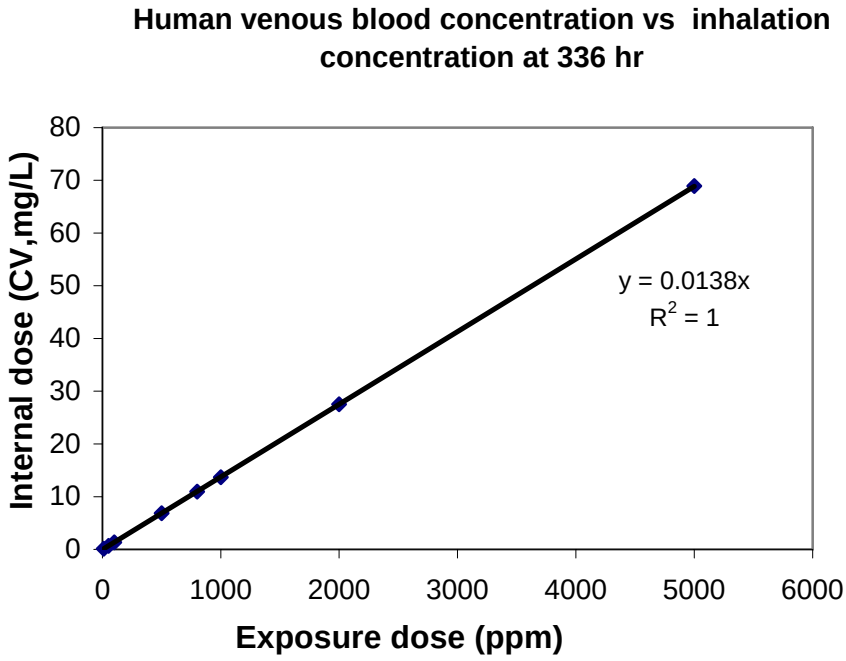


Figure 83. Relationship between the 336-hr venous blood concentrations of 1,1,1-trichloroethane predicted by the Reitz *et al.* (1988) human model and the hypothetical exposure levels of 0-5,000 ppm.

V.3. Application of PBPK Modeling to Explore Route-to-Route Extrapolation for Acute Exposure

Consideration was given to whether or not extrapolation of findings from human intentional dosing studies involving acute inhalation exposures could be extrapolated to the oral exposure route. As noted previously (Sections III.3 and IV.2.7), the Reitz *et al.* (1988) PBPK model did not simulate very well oral gavage results generated by their own laboratory nor the oral gavage data of Bruckner (personal communication). Further, a human value for the GI absorption rate constant (Ka) is not available. Therefore, it would appear that use of a PBPK model to extrapolate from the acute inhalation route to the acute oral route is not supported.

V.4. Application of PBPK Modeling to Support Derivation of Chronic Reference Values

V.4.1. Internal Dose Calculation of Quast *et al.* (1988) Study Using PBPK Modeling

The Quast *et al.* (1988) study was selected by EPA as a candidate principal study for derivation of a chronic inhalation RfC. Quast *et al.* exposed male and female Fischer 344 rats to 0, 150, 500 or 1500 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week, for 2 years. Additional animals were designated for interim sacrifice at 6, 12, and 18 months of exposure. Slight histopathological changes of the liver were observed in male and female high-dose (1500 ppm or 8190 mg/m^3) rats at 6, 12, and 18 months of exposure; no differences from the controls were observed at 2 years because of confounding geriatric changes. There was no increase in incidence or severity of the hepatic changes after 6 months.

The Reitz *et al.* (1988) PBPK model was used to estimate the internal dose at the exposure concentration equivalent to the mid-dose group (*i.e.,* 2730 mg/m^3, 6 hours/day, 5 days/week); this is the level in the Quast *et al.* (1988) study, where no hepatic changes were seen in any of the time periods. Since histopathologic changes were seen as early as 6 months, we provide calculations for 6 months of exposure (365 days/2 = 182.5 days; or 4380 hours). Because chronic exposure to 1,1,1-trichloroethane may result in neurotoxicity and/or hepatic lesions, we provide calculations based on both blood concentration and liver concentration as internal doses.

Given below are several plots (Figures 84-88) from our simulations under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year.

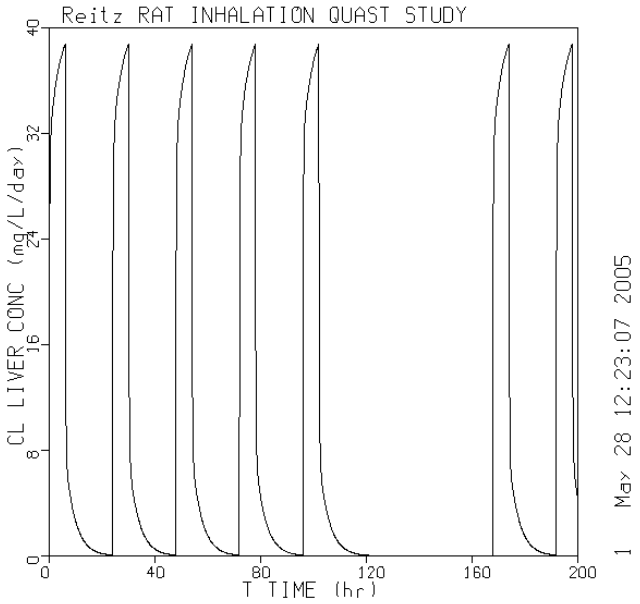


Figure 84. Simulation of the liver 1,1,1-trichloroethane concentration by the Reitz *et al.* (1988) model under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year. Note that only the first 200 hrs is shown for a satisfactory resolution.

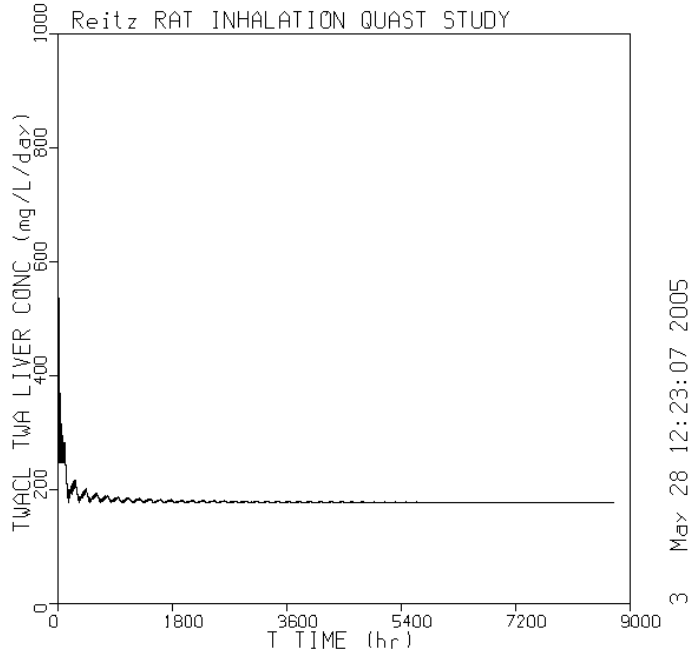


Figure 85. Simulation of the time-weighted average liver 1,1,1-trichloroethane concentration by the Reitz *et al.* (1988) model under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year.

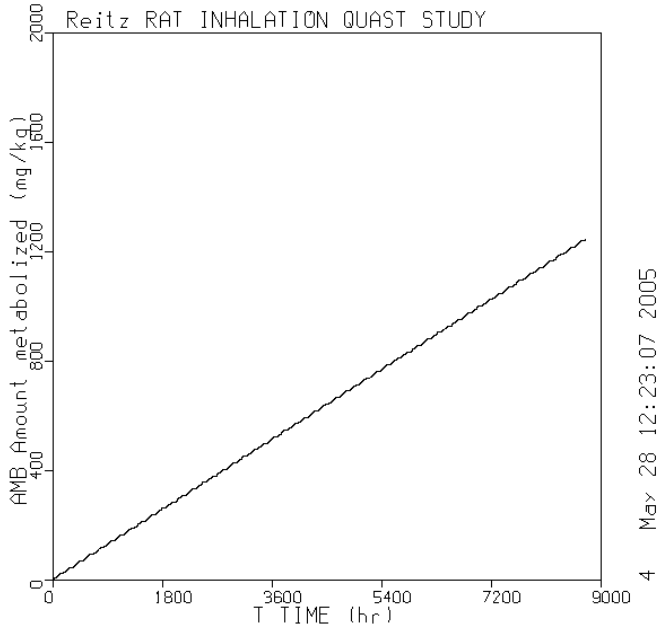


Figure 86. Simulation of the body weight-standardized amount of 1,1,1-trichloroethane metabolized by the Reitz *et al.* (1988) model under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year.

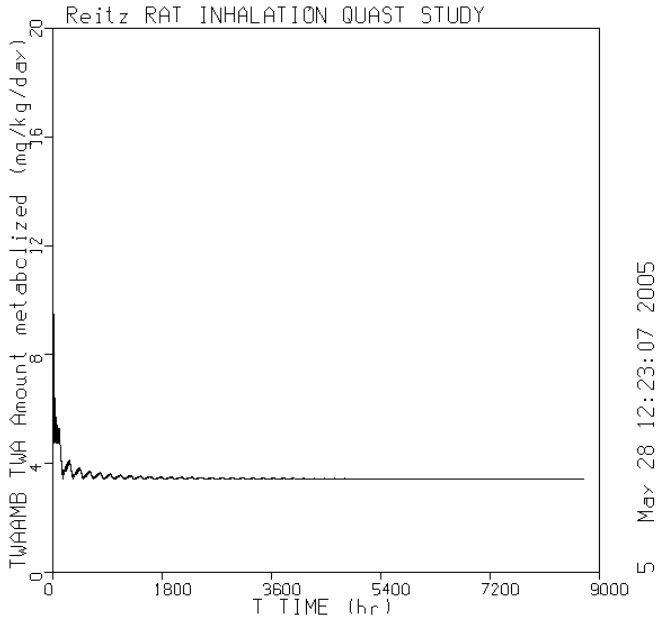


Figure 87. Simulation of the time-weighted average body weight-standardized amount of 1,1,1-trichloroethane metabolized by the Reitz *et al.* (1988) model under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year.

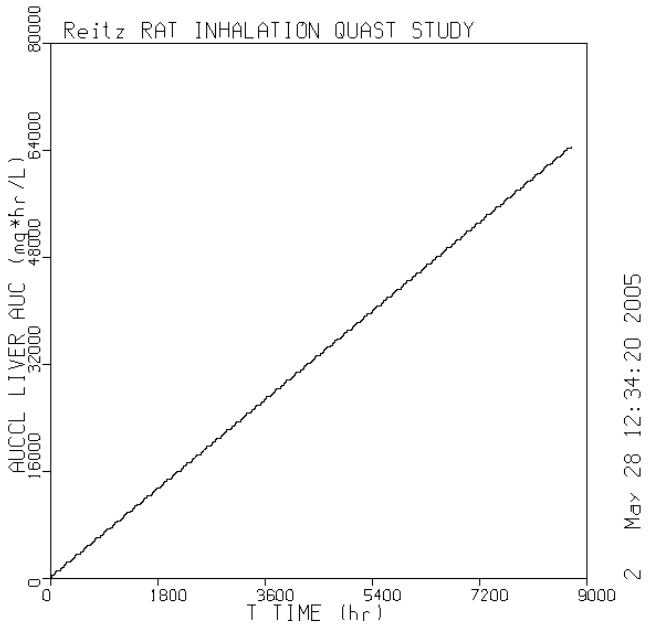


Figure 88. Simulation of the area-under-the-liver-concentration-curve (AUCCV) by the Reitz *et al.* (1988) model under the condition of inhalation exposure at 875 ppm, 6 hours/day, 5 days/week for up to 1 year.

Using Blood Concentrations as Internal Doses

The CSL and CMD files (ReitzRatIDs.CSL, ReitzRatIDs.CMD, ReitzHumanRfC.CSL, ReitzHumanRfC.CMD) for the following simulation/calculation are in Appendix III. Blood internal doses correspond to the exposure level of 2730 mg/m^3 (500 ppm) for 6 hours/day, 5 days/week.

Male Fischer 344 rats:

At t = 4380 hours (6 months), AUC-Venous blood = 12,800.2 mg × hr/L
TWA AUC-Venous blood = 70.14 mg/L-day

Female Fischer 344 rats (calculated separately because of differences in body weights):
At t = 4380 hours (6 months), AUC-Venous blood = 12,757.3 mg × hr/L
TWA AUC-Venous blood = 69.9 mg/L-day

Implications: Sex does not affect the TWA AUC-venous blood concentration, and hence the internal dose for male rat is used in subsequent calculations; the TWA AUC is stabilized at 6 months, and further exposure does not change its value.

Using Liver Concentrations as Internal Doses

Liver internal doses correspond to the exposure level of 2730 mg/m^3 (500 ppm) for 6 hours/day, 5 days/week.

Male Fischer 344 rats:
At t = 4380 hours (6 months), AUC-Liver = 19,002.5 mg × hr/L
TWA AUC-Liver = 104.12 mg/L-day

Female Fischer 344 rats (calculate separately because of differences in body weights):
At t = 4380 hours (6 months), AUC- Liver = 18,938.5 mg × hr/L
TWA AUC-Liver = 103.77 mg/L-day

Implications: Sex does not affect the TWA AUC-liver concentration, and hence the internal dose for male rat is used in subsequent calculations; the TWA is stabilized at 6 month, and further exposure does not change its value.

V.4.2. Interspecies Extrapolation for Derivation of Human Equivalent Concentrations for Chronic Inhalation Exposures

The Reitz *et al.* (1988) model was used to calculate human inhalation exposure concentrations (as a continuous exposure) corresponding to an exposure concentration in the rat of 2730 mg/m^3, 6 hours/day, 5 days/week, as well as a range of concentrations above and below 2730 mg/m^3. Tables 8 and 9 provide the human equivalent concentrations for chronic inhalation exposures.

Table 8. Relationship Between Exposure Concentration and Internal Dose in Rat Blood

Exposure concentration (mg/m^3)	Predicted AUC – venous blood in the rat[a] (mg × hr/L)	Predicted TWA AUC – venous blood in the rat[a] (mg/L-day)	UF	Calculated human exposure concentration (ppm)[c]	Calculated human exposure concentration (mg/m^3)[c]
27.3	121.6	0.7	--	2.15	11.74
273	1,264.4	6.9	--	21.2	115.75
2730	12,799.9	70.1	--	214	1,174
2730	12,799.9	70.1	30[b]	7.18	39.2
27,300	129,333	708.7	--	2,152	11,744.7
273,000	1,300,900	7128.4	--	21,600	117,939

[a]At t = 4380 hours (6 months); parameters for male Fischer 344 rat used (volume fraction of fat remaining constant during the calculation). We found that incorporation of the body weight-dependent fat volume fraction (VFC) change does not significantly affect the results and thus are not reported here. This comment also applies to Tables 9-11.
[b]AUC divided by 30 before calculating corresponding human exposure concentration.
[c]Calculated based on TWA AUCs-venous blood in humans equivalent to the respective rat internal doses (TWA AUCs in third column) under inhalation exposure conditions up to 4380 hours.

Table 9. Relationship Between Exposure Concentration and Internal Dose in Rat Liver

Exposure concentration (mg/m^3)	Predicted AUC – liver in the rat[a] (mg × hr/L)	Predicted TWA AUC – liver in the rat[a] (mg/L-day)	UF	Calculated human exposure concentration (ppm)[c]	Calculated human exposure concentration (mg/m^3)[c]
27.3	187.3	1.03	--	0.94	5.1
273	1862.9	10.2	--	9.3	50.8
2730	19,002	104.1	--	95	518.7
2730	19,002	104.1	30[b]	3.17	17.3
27,300	192,874	1,056.8	--	948	5,176
273,000	1,942,100	10,641.7	--	9,480	51,762

[a]At t = 4380 hours (6 months); parameters for male Fischer 344 rat used (volume fraction of fat remaining constant during the calculation).
[b]AUC divided by 30 before calculating corresponding human exposure concentration.
[c]Calculated based on TWA AUCs-liver in humans equivalent to the respective rat internal doses (TWA AUCs in third column) under inhalation exposure conditions up to 4380 hours.

V.4.3. Route-to-Route Extrapolation for Derivation of Human Equivalent Doses for Chronic Oral Exposures

V.4.3.1. PBPK Model Simulation of Human Internal Dose Under Different Exposure Scenarios

Consideration was given to whether or not chronic inhalation rat data could be extrapolated to the oral route. A GI absorption rate constant (Ka) is available for the rat but not the human. The following analyses were performed to help evaluate whether route-to-route extrapolation is appropriate: (1) run the human model as a continuous GI tract infusion and (2) run the human model as six equally divided bolus doses within a 24-hour period. In the case of constant infusion, continuous oral infusion was modeled under two different scenarios for comparison: (1) 24 hours/day, 7 days/week and (2) 8 hours/day, 7 days/week. An assumption of 100% absorption was made in all these simulations.

The rationale behind the above suggested PBPK modeling warrants some discussion. Since intake of environmental pollutants via the oral route is likely to be associated with food, water, or soil (*e.g.,* children playing on the ground and ingesting soil unintentionally), the uptake of the chemical of interest is generally episodic and at irregular intervals. It is difficult to do PBPK modeling with such irregularity. Thus, one commonly accepted way is to consider constant infusion directly into the liver from the GI tract as a result of such oral intake; the assumption here is that the absorption is rapid for the constantly available small amount of chemicals in the GI tract. The other commonly accepted way is to divide the total estimated intake by a chosen number (*e.g.,* 4, 6, 12, 24) and consider that number of episodic but equal oral bolus doses happened during the day or whatever set period of time. Discussions on this subject in relation to PBPK modeling can be found in the literature (see for instance Reitz *et al.*, 1987, 1988; NRC, 1989).

Modeling of constant infusion and six bolus doses under the scenarios described above should lead to steady state or pseudo-steady state under repeated exposure conditions. If the two approaches (*i.e.,* constant infusion vs. six bolus doses) produced different outcomes, the conclusion could reasonably be reached that the chronic oral PBPK model is too uncertain to perform route-to-route extrapolation. Another important consideration is related to the relatively poor simulation results of acute oral dosing using both the Reitz *et al.* (1988) data (Figure 4) and Bruckner (personal communication) data (Section

IV.2.7). Given the relatively poor model simulation results for acute oral dosing, there was some concern that the estimation of the absorption rate constant, Ka, would not be accurate. If, however, it could be demonstrated that steady state is achieved rapidly with both simulation approaches proposed above, the precise value of the Ka does not matter.

The simulations of venous blood 1,1,1-trichloroethane in humans following continuous oral/liver infusion at the rate of 0.01, 0.1, 1, 5, 25, and 100 mg/kg/hour, 24 hours/day, 7 days/week, by the Reitz *et al.* (1988) human model are shown in Figure 89 in a semi-log scale and in Figure 90 in a log-log scale.

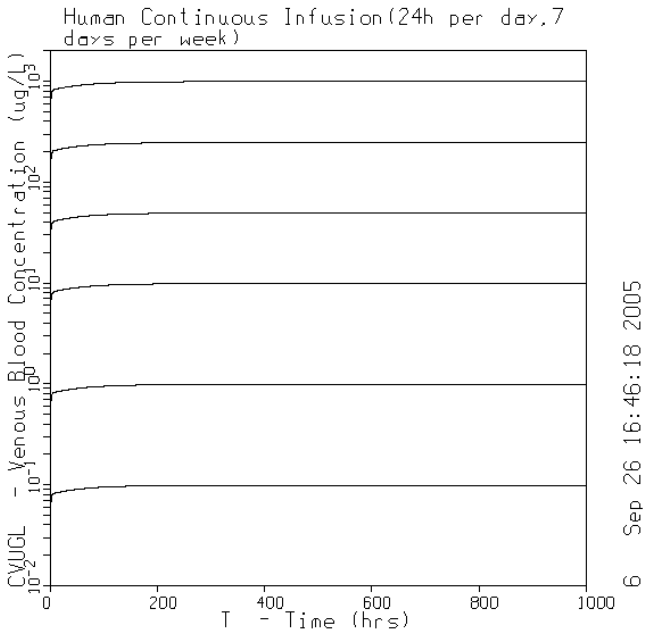


Figure 89. Simulations of the venous blood 1,1,1-trichloroethane following continuous oral/liver infusion at the rate of 0.01, 0.1, 1, 5, 25, and 100 mg/kg/hour (from the bottom to the top), 24 hours/day, 7 days/week by the Reitz *et al.* (1988) human model.

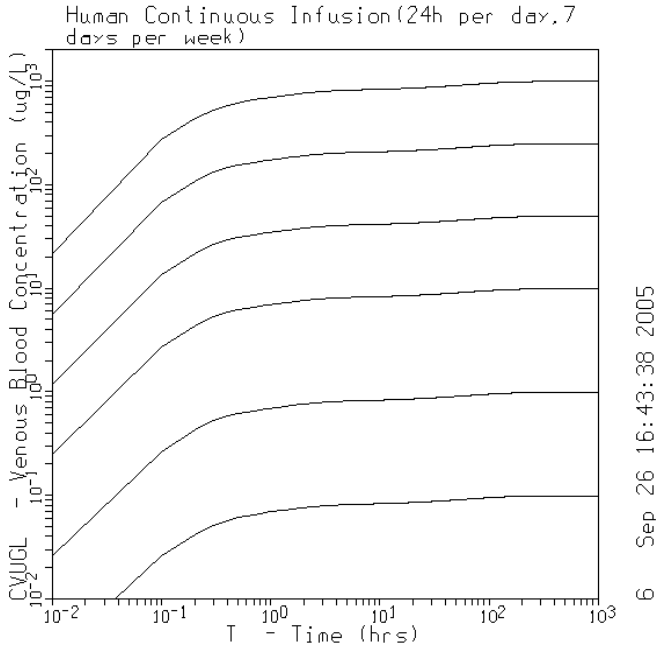


Figure 90. Simulations of the venous blood 1,1,1-trichloroethane following continuous oral/liver infusion at the rate of 0.01, 0.1, 1, 5, 25, and 100 mg/kg/hour (from the bottom to the top), 24 hours/day, 7 days/week by the Reitz *et al.* (1988) human model. Please note that both axes are in log scales.

Figures 91 and 92 show human intermittent oral/liver infusion at the rate of 0.01, 0.1, 1, 5, 25, 100 mg/kg/hour, 8 hours/day, 7 days/week.

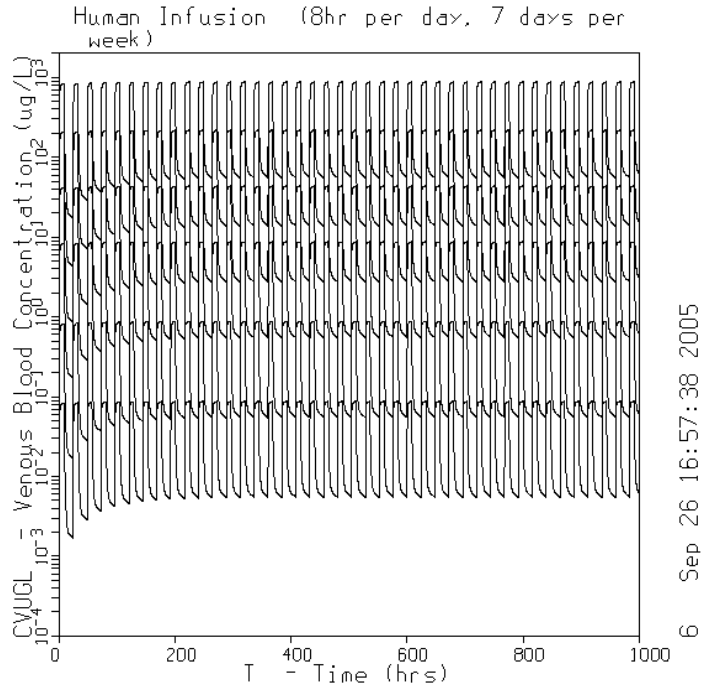


Figure 91. Simulations of the venous blood 1,1,1-trichloroethane following intermittent oral/liver infusion at the rate of 0.01, 0.1, 1, 5, 25, and 100 mg/kg/hour (from the bottom to the top), 8 hours/day, 7 days/week, by the Reitz *et al.* (1988) human model.

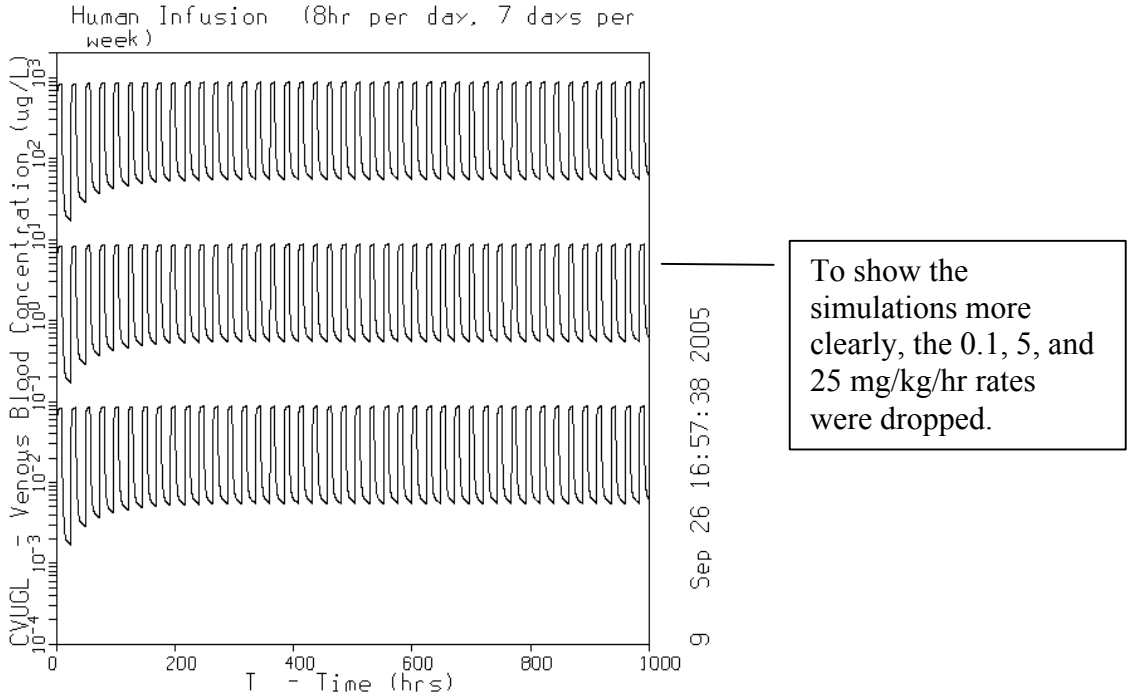


Figure 92. Simulations of the venous blood 1,1,1-trichloroethane following intermittent oral/liver infusion at the rate of 0.1, 5, 25 mg/kg/hour (from the bottom to the top), 8 hours/day, 7 days/week, by the Reitz *et al.* (1988) human model. Please note that both axes are in log scales.

Figures 93 and 94 show human intermittent oral bolus at the rate of 0.04, 4, and 400 mg/kg/hour every 4 hours.

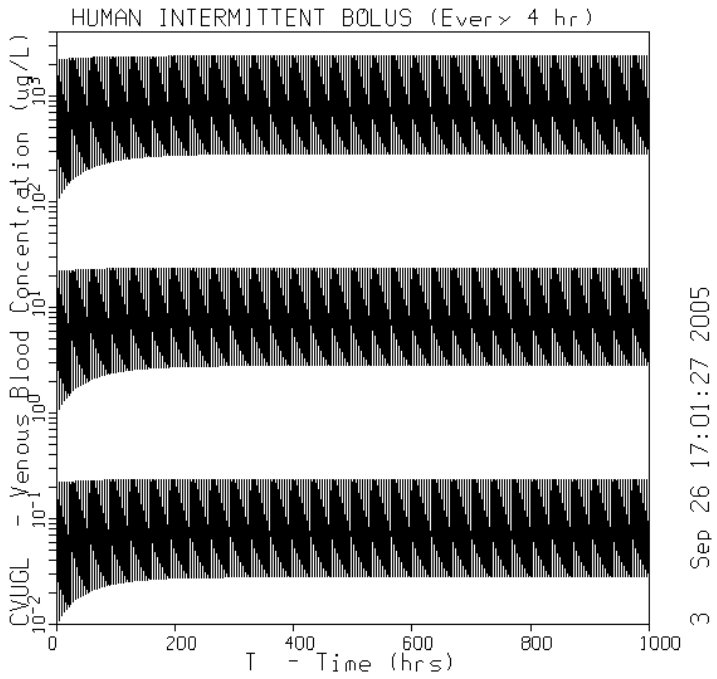


Figure 93. Simulations of the venous blood 1,1,1-trichloroethane following human intermittent oral bolus at the rate of 0.04, 4, and 400 mg/kg/hour (from the bottom to the top) every 4 hours by the Reitz *et al.* (1988) human model.

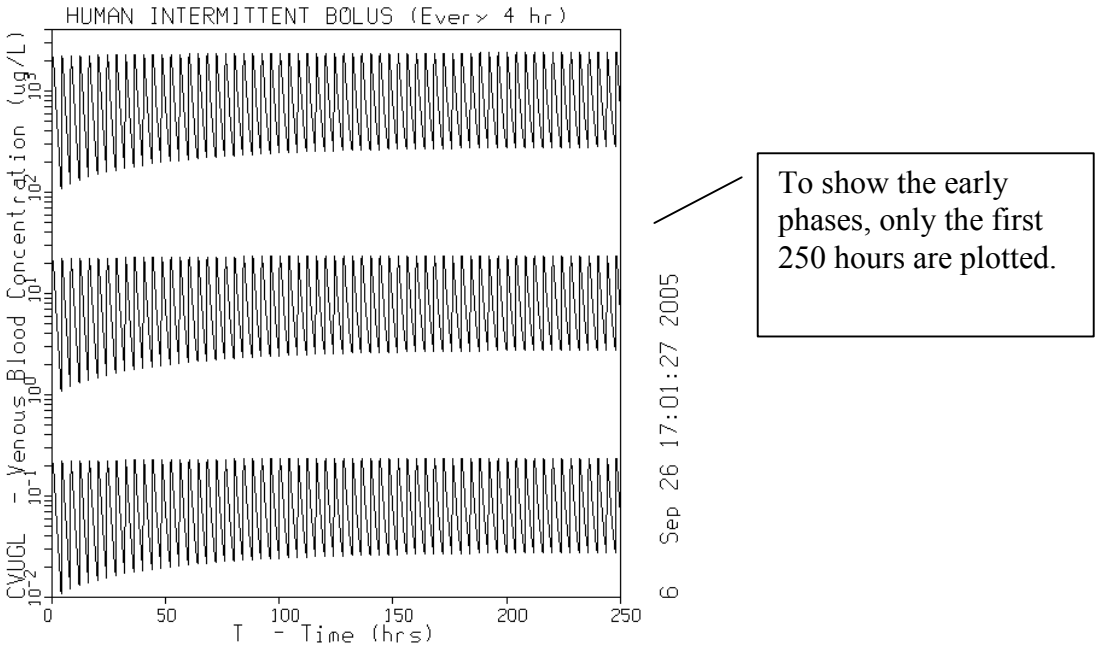


Figure 94. Simulations of the venous blood 1,1,1-trichloroethane following human intermittent oral bolus at the rate of 0.04, 4, and 400 mg/kg/hour (from the bottom to the top) every 4 hours by the Reitz *et al.* (1988) human model. Only the first 250 hours are plotted for a satisfactory resolution.

The above exercise demonstrates that steady state is reached under all exposure scenarios in a relatively short period of time. Thus, in a repeated oral dosing situation, particularly for a relatively long exposure time, it is reasonable to consider dose to be independent of the precise value of the absorption rate constant, Ka.

V.4.3.2. Model Prediction of Human Equivalent Doses

The Reitz *et al.* (1988) model was used to calculate human chronic oral doses corresponding to the internal doses under an exposure concentration in the rat of 2730 mg/m^3, 6 hours/day, 5 days/week, as well as a range of concentrations above and below 2730 mg/m^3. Tables 10 and 11 provide the human equivalent doses for chronic oral dose administration (The codes HumanOral.CSL and HumanOral.CMD are attached in Appendix III).

Table 10. Relationship Between External Exposure and Internal Dose in Blood

Rat exposure concentration (mg/m^3)	Predicted AUC – venous blood in the rat[a] (mg × hr/L)	Predicted TWA AUC – venous blood in the rat[a] (mg/L-day)	UF	Calculated human oral dose (mg/kg-day)[c]
27.3	121.6	0.7	--	72
273	1,264.4	6.9	--	698.4
2730	12,799.9	70.1	--	7,025.5
2730	12,799.9	70.1	30[b]	237.1
27,300	129,333	708.7	--	70,224
273,000	1,300,900	7128.4	--	704,400

[a]At t = 4380 hours (6 months); parameters for male Fischer 344 rat used (volume fraction of fat remaining constant during the calculation).
[b]AUC of rats divided by 30 before calculating corresponding human oral dose.
[c]Calculated based on TWA AUCs-venous blood in humans equivalent to the rat internal doses (TWA AUCs in third column) under continuous infusion conditions up to 4380 hours.

Table 11. Relationship Between External Exposure and Internal Dose in Liver

Rat exposure concentration (mg/m^3)	Predicted AUC – liver in the rat[a] (mg × hr/L)	Predicted TWA AUC – liver in the rat[a] (mg/L-day)	UF	Calculated human oral dose (mg/kg-day)[c]
27.3	187.3	1.03	--	16.2
273	1862.9	10.2	--	160.8
2730	19,002	104.1	--	1,627.2
2730	19,002	104.1	30[b]	54.48
27,300	192,874	1,056.8	--	16,296
273,000	1,942,100	10,641.7	--	163,008

[a]At t = 4380 hours (6 months); parameters for male Fischer 344 rat used (volume fraction of fat remaining constant during the calculation).
[b]AUC divided by 30 before calculating corresponding human oral dose.
[c]Calculated based on TWA AUCs-liver in humans equivalent to the respective rat internal doses (TWA AUCs in third column) under continuous infusion conditions up to 4380 hours.

VI. OVERALL CONCLUSIONS

In support of the health assessment of 1,1,1-trichloroethane by the EPA IRIS Program we carried out a project aimed at incorporating PBPK modeling into the health assessment process. Fourteen published PBPK models were considered for reconstruction and nine were reconstructed based on published information in the literature. In one case, the model code was provided in SimuSolv by Dr. Richard Reitz and in another case the original code of Gargas *et al.* model was provided by Dr. Lisa Sweeney. All PBPK models were written in ACSL code, and simulations were carried out using this software. The digiMatic software was used to capture experimental data from graphic representations in published papers. Of the nine reconstructed models, two were selected for further evaluation based on a number of criteria (*e.g.*, quality of the study, the number of routes of exposure in the model, extent and quality of experimental data, similarity with other available models). This final evaluation was performed by comparing simulation results against the same eleven data sets (seven from laboratory animals and four from human studies). Based on the versatility of inter-route and interspecies extrapolations and the consistency of model simulation as compared to the eleven data sets, the Reitz *et al.* (1988) model was selected to be the final model for supporting the health assessment of 1,1,1-trichloroethane. Although this reestablished PBPK model is not able to simulate all the data sets in the literature, it is versatile and useful in that it can be used for interspecies-, route-to-route, and inter-dose extrapolations for most exposure scenarios. The two general limitations of this model are its limitation in simulating tri-exponential decay kinetics of 1,1,1-trichloroethane and its limitation in simulating acute oral dosing data for 1,1,1-trichloroethane. It was outside the scope of this project, however, to address these limitations through model refinement. Using this PBPK model, simulations were carried out based on the experimental conditions of a large number of human studies and a chronic toxicity study in rats. Internal dose metrics for both humans and rats were derived from PBPK model simulation based on the exposure scenarios associated with the specific studies selected. The use of PBPK modeling permits the movement away from default extrapolation (uncertainty) factors in the health assessment for 1,1,1-trichloroethane.

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Appendix I

Model code (CSL files) and data (CMD files) for Reconstructed or Original PBPK Models

Note: For further evaluation of the Gargas et al. (1986a) and the Reitz et al. (1988) models, the CSL files (model code) for these two respective models given here in Appendix I were used to do the simulations in Section V of this Report with appropriate input functions. These CSL files are not separately listed in the Appendices.

Model codes

1.Gargas et al. 1986
PROGRAM: Gargas.CSL

```
!Initially created by Lohitnavy M and Lu Y, 12/2004,for EPA contract. First editting by Lu Y
!12/23/2004. Reviewed by Lu Y 5/22/2005

!Gargas M,Andersen ME,Clewell HJ,3rd,1986. A physiologically based simulation approach for
!determining metabolic constants from gas uptake data. Toxicol Appl Pharmacol,86,341-352.

!Details of the simulated exposure conditions: Male F344 rats,200-250g;closed chamber.
!Four compartments:liver,fat,richly and slowly perfused;Flow-limited;
!First order metabolism in the liver.

!Original code provided by Dr. Lisa Sweeney on April 27th, 2006, and was modified into this format by
!Yasong LU. 5/4/06

INITIAL

!Physiological Parameters **********************************
CONSTANT BW = 0.22     !Mean body weight (kg)/rat; Gargas 1986.
CONSTANT Nrat=3.       !Number of rats in the chamber; Gargas 1986.
CONSTANT QPC = 14      !Alveolar ventilation rate constant (L/hr/kg^0.74); Gargas 1986.
       QCC = QPC      !Cardiac output rate constant (L/hr/kg^0.74); Gargas 1986.
  !Blood flow fractions
CONSTANT QLC = 0.25     !Fractional blood flow to liver; Gargas 1986.
CONSTANT QFC = 0.09     !Fractional blood flow to fat; Gargas 1986.
CONSTANT QRC = 0.51     !Fractional blood flow to richly perfused; Gargas 1986.
CONSTANT QSC = 0.15     !Fractional blood flow to slowly perfused; Gargas 1986.
  !Volume fractions
CONSTANT VLC = 0.04     !Fraction liver tissue; Gargas 1986.
CONSTANT VFC = 0.07     !Fraction fat tissue; Gargas 1986.
CONSTANT VRC = 0.05     !Fraction richly perfused tissues; Gargas 1986.
CONSTANT VSC = 0.75     !Fraction slowly perfused; Gargas 1986.

!Chemical specific parameters ******************************
  !Partition coefficients;experimentally determined
CONSTANT PB = 5.76      !Blood/air; Gargas 1986.
CONSTANT PL = 1.49      !Liver/blood; Gargas 1986.
CONSTANT PF = 45.66     !Fat/blood; Gargas 1986.
       PR = PL        !Richly perfused/blood;assumption, not clarified in Gargas 1986.
CONSTANT PS = 0.55      !Slowly perfused/blood; Gargas 1986.
  !Metabolism;visual optimization
CONSTANT VMAX = 0.      !Capacity of saturable metabolism (mg/hr);ignored in Gargas 1986.
CONSTANT KM = 0.5       !Affinity of saturable metabolism (mg/L);ignored in Gargas 1986.
CONSTANT KFC=5.0        !First order metabolism rate constant (/hr/BW^-0.3); Gargas 1986.

!Scaled parameters
   QC = QCC*BW**0.74    !Cardiac output per rat (L/hr)
```

```
  QP = QPC*BW**0.74    !Ventilation rate per rat (L/hr)
  BWtotal = BW * Nrat        !total body weight of 3 rats in chamber (kg)
  VF = VFC * BWtotal   !Fat volume of 3 rats(L)
  VL = VLC * BWtotal   !Liver volume of 3 rats(L)
  VR = VRC * BWtotal         !Richly perfused volume of 3 rats(L)
  VS = 0.91*BWtotal-VL-VF-VR  !Slowly perfused volume of 3 rats(L)
  QPtotal = QP * Nrat  !Alveolar ventilation of 3 rats(L/hr)
  QCtotal = QC * Nrat  !Cardiac output of 3 rats(L/hr)
  QL = QLC * QCtotal   !Liver blood flow (L/hr)
  QF = QFC * QCtotal   !Fat blood flow (L/hr)
  QR = QRC * QCtotal         !Richly Perfused blood flow (L/hr)
  QS = QCtotal-QF-QL-QR!Slowly Perfused  blood flow (L/hr)
  KF = KFC*BW**(-0.3)     !First order metabolism rate constant (/hr); Gargas 1986.

!Parameters for simulation of experiment**********************
CONSTANT MW = 133.5   !Molecular weight (g/mol)
CONSTANT VCHAMBER0=9.1 !Total chamber volume (L).
         VCHAMBER= VCHAMBER0 - BWtotal !Net volume of the gas.
CONSTANT KL = 0.001   !Non-specific loss from the chamber (/hr)
CONSTANT CONC0 = 0.2  !Initial concentration in chamber (ppm)
       CIN0 = CONC0*MW/24450.  !Initial concentration in chamber (mg/L)
       ACHM0 = CIN0*VCHAMBER   !Initial amount in chamber(mg)

!Timing commands
CONSTANT TSTOP = 6.   !Length of experiment (hrs)
CINTERVAL CINT = 0.1  !Communication interval (hrs)

!Method of integration
ALGORITHM IALG = 2    !Gear method for stiff systems

END              !End of INITIAL

DYNAMIC
DERIVATIVE

    !Mass balance in the chamber (mg)
    RACHM = QPtotal * (CEX-CIN) - KL*ACHM
     ACHM = INTEG(RACHM,ACHM0)
     CIN = ACHM/VCHAMBER
     CINPPM = CIN*24450./MW

    !Mass balance OF non-specific loss from the chamber (mg)
    RALOSS= KL*ACHM
     ALOSS= INTEG(RALOSS,0.)

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS
```

```
      !AR = Amount in Richly Perfused Tissues (mg)
      RAR = QR*(CA-CR/PR)
       AR = INTEG(RAR,0.)
       CR = AR/VR

      !AF = Amount in fat tissue (mg)
      RAF = QF*(CA-CF/PF)
       AF = INTEG(RAF,0.)
       CF = AF/VF

      !AL = Amount in liver tissue (mg)
      RAL = QL*(CA-CL/PL)-RAM
       AL = INTEG(RAL,0.)
       CL = AL/VL

      !AM = Amount metabolized (mg)
      RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
       AM = INTEG(RAM,0.)

      !Blood concentrations (mg/L)
       CV = (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QCtotal
       CA = (QCtotal*CV+QPtotal*CIN)/(QCtotal+QPtotal/PB)
       CEX = CA/PB
       CEXPPM = (0.7*CEX+0.3*CIN)*24450./MW

      !TMASS = mass balance (mg)
       TMASS = AF+AL+AS+AR+AM+ALOSS+ACHM
       ERROR=(TMASS-ACHM0)/ACHM0*100

TERMT(T.GE.TSTOP)
END      !End of derivative
END      !End of dynamic
END      !End of program
```

```
!Gargas.CMD for Gargas 1986 TCA model reproduction
!Initially created by Lohitnavy M and Lu Y, 12/2004.First editting by Lu Y 12/23/2004
!Reviewed by Lu Y 5/22/2005
!Information in the original code incorporated here. Yasong LU, 5/4/06

PREPAR /ALL

SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.
SET HVDPRN=.T.

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED LOWEST
SET CONC0 = 0.19
START
SET TITLE ='TCA INHALATION IN RATS - 0.2 PPM'
PLOT /DATA=LOWEST CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=1
END

!Digitized by Lohitnavy from Fig.4a,Gargas et al. 1986.
DATA LOWEST (t,CINPPM)
0.167       0.17
 0.333       0.14
 0.500       0.12
 0.667       0.10
 0.833       0.09
 1.000       0.09
 1.167       0.08
 1.333       0.11
 1.500       0.08
 1.667       0.08
 1.833       0.07
 2.000       0.07
 2.167       0.07
 2.333       0.06
 2.500       0.06
 2.667       0.06
 2.833       0.05
 3.000       0.05
 3.167       0.05
 3.333       0.05
 3.500       0.05
 3.667       0.05
```

```
 3.833       0.06
 4.000       0.05
 4.167       0.05
 4.333       0.05
END

PROCED SECONDLOW
SET CONC0=1.1
START
SET TITLE ='TCA INHALATION IN RATS - 1.0 PPM'
PLOT /DATA=SECONDLOW CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=2
END

!Digitized by Lohitnavy from Fig.4a,Gargas et al. 1986.
DATA SECONDLOW (t,CINPPM)
0.083       1.04
 0.167       0.85
 0.333       0.79
 0.500       0.66
 0.667       0.63
 0.833       0.58
 1.000       0.54
 1.167       0.51
 1.333       0.47
 1.500       0.46
 1.667       0.42
 1.833       0.42
 2.000       0.39
 2.167       0.39
 2.333       0.37
 2.500       0.36
 2.667       0.35
 2.833       0.34
 3.000       0.32
 3.250       0.31
 3.333       0.30
 3.500       0.29
 3.667       0.29
 3.833       0.28
 4.000       0.26
 4.167       0.33
 4.333       0.27
 4.500       0.26
 4.667       0.25
 4.833       0.24
 5.000       0.24
 5.167       0.23
```

```
 5.333      0.24
 5.500      0.25
 5.667      0.24
 5.833      0.22
 6.000      0.21
END

PROCED SECONDHIGH
SET CONC0=9.5
START
SET TITLE ='TCA INHALATION IN RATS - 10.0 PPM'
PLOT /DATA=SECONDHIGH CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=3
END

!Digitized by Lohitnavy from Fig.4a,Gargas et al. 1986.
DATA SECONDHIGH (T,CINPPM)
0.083      8.70
 0.167      7.77
 0.333      6.65
 0.500      5.82
 0.667      5.34
 0.833      4.95
 1.000      4.66
 1.167      4.40
 1.333      4.24
 1.500      4.07
 1.667      3.91
 1.833      3.74
 2.000      3.66
 2.167      3.60
 2.333      3.51
 2.500      3.48
 2.667      3.39
 2.833      3.35
 3.000      3.30
 3.167      3.25
 3.333      3.20
 3.500      3.15
 3.667      3.12
 3.833      3.07
 4.000      3.03
 4.167      3.00
 4.333      2.91
 4.500      2.89
 4.667      2.88
 4.833      2.75
 5.000      2.84
```

```
 5.167       2.76
END

PROCED HIGHEST
SET CONC0=210.
START
SET TITLE ='TCA INHALATION IN RATS - 210.0 PPM'
PLOT /DATA=HIGHEST CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=5
END

PROCED ALL !Plot all plots together
SET CONC0=210.
START
s defplt=.t.
SET TITLE ='TCA Inhalation;Reproduction of Gargas'
PLOT /DATA=HIGHEST CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=5
SET CONC0=10.
START
s defplt=.t.
PLOT /DATA=secondhigh CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=3
SET CONC0=1.
START
s defplt=.t.
PLOT /DATA=secondlow CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=2
SET CONC0=0.2
START
s defplt=.f.
PLOT /DATA=lowest CINPPM /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=1
END

!Digitized by Lohitnavy from Fig.4a,Gargas et al. 1986.
DATA HIGHEST (T,CINPPM)
.083      199.
.167    182.
.333    154.
.5      138.
.667    125.
.83     117.
1.0     110.
```

1.167 106
1.333 100.
1.5 95.6
1.667 93.4
1.83 89.6
2.0 88.0
2.167 86.7
2.333 82.7
2.5 83.0
2.667 80.9
2.83 79.2
3.0 78.6
3.167 76.7
3.333 76.1
3.5 74.5
3.667 72.4
3.83 72.8
4.0 71.3
4.167 71.3
4.333 71.5
4.5 69.9
4.667 67.8
4.83 68.5
5.0 67.6
5.167 66.0
5.333 66.4
5.5 65.5
5.667 65.2
5.83 65.1
6.0 63.7
END

2. Reitz et al. 1988
PROGRAM: Reitz.CSL

```
!Original code supplied by Reitz. Modified the SimuSolv format into ACSL Tox format by Lu Y.
!12/2004.
!Reitz RH,McDougal JN,Himmelstein MW,Nolan RJ,Schumann AM. 1988 Physiologically based
!pharmacokinetic modelling with methylchloroform: Implications for interspecies,high dose/low
!dose, and dose route extrapolations. Toxicol.Appl. Pharmacol.1988,95:185-199
!Edited by Lu Y 12/23/2004; Dennison 04/06/05

!Reviewd by Lu Y 5/23/2005
!Runs only under the condition of "single precision".

INITIAL

!Physiological Parameters **********************************
!Constants set for the rat
CONSTANT BW = 0.233       !Mean body weight (kg);Reitz code.
                !Although in Reitz 1988 BW=0.215,it seems 0.233 is the correct value
                !according to the calculation of QC and QP.
CONSTANT QCC= 15.         !Cardiac output constant (L/hr/kg^0.74);Reitz 1988.
CONSTANT QPC= 15.         !Alveolar ventilation constant (L/hr/kg^0.74);Reitz 1988.
  !Blood flow fractions
CONSTANT QLC = 0.24       !Fractional blood flow to liver;Reitz 1988.
CONSTANT QFC = 0.05       !Fractional blood flow to fat;Reitz 1988.
CONSTANT QSC = 0.18       !Fractional blood flow to slowly perfused;Reitz 1988.
 QRC=1.0-(QFC+QSC+QLC)    !Fractional blood flow to rapidly perfused;Reitz 1988.
  !Volume fractions
CONSTANT VLC = 0.04       !Fraction liver tissue;Reitz 1988.
CONSTANT VFC = 0.07       !Fraction fat tissue;Reitz 1988.
CONSTANT VRC = 0.05       !Fraction richly perfused tissues;Reitz 1988.
 VSC = 0.91-VLC-VFC-VRC   !Fraction slowly perfused;Reitz 1988.

!Chemical specific parameters ******************************
  !Partition coefficients
CONSTANT PB = 5.76        !Blood/air;Reitz 1988.
CONSTANT PLA = 8.6        !Liver/air;Reitz 1988.
CONSTANT PFA = 263.       !Fat/air;Reitz 1988.
CONSTANT PRA = 8.6        !Richly perfused/air;Reitz 1988.
CONSTANT PSA = 3.15       !Slowly perfused/air;Reitz 1988.
  PL=PLA/PB
  PF=PFA/PB
  PR=PRA/PB
  PS=PSA/PB

  !Metabolism;saturable;estimated from Schumann data and Reitz drinking water study
CONSTANT VMAXC = 0.419 !Capacity of saturable metabolism (mg/hr/kg^0.7);Reitz 1988.
CONSTANT KM = 5.75     !Affinity of saturable metabolism (mg/L);Reitz 1988.
CONSTANT KF=0.         !First order metabolism (/hr);ignored in Reitz 1988.
```

```
!Oral IA and IV parameters
CONSTANT BDOSE = 0.     !Oral bolus dose (mg/kg)
  KA = 1.25          !Rat oral uptake rate (/hr);Reitz 1988.
CONSTANT DRINK = 0.     !Rat uptake rate from drinking (mg/kg/hr)
CONSTANT DTIME = 8.     !time in which animal has access to water (hr);Reitz 1988.
CONSTANT IVDOSE = 0.    !iv dose (mg/kg)
CONSTANT TINF = 0.01    !length of iv infusion (hr)
CONSTANT RATS = 1.0     !Number of rats in metabolic chamber
CONSTANT FCH = 30.0     !Flow thru metabolic chamber (L/hr)
CONSTANT VCHC = 6.1     !Total volume of metabolic chamber (L)
CONSTANT IADOSE = 0.0  !IA bolus dose at Bruckner lab (mg/kg)
CONSTANT TINFIA = 0.01 !length of IA infusion (hr)
CONSTANT TCHNG = 6.     !Length of inhalation exposure (hrs)both rat and human

!Scaled parameters
  QC = QCC*BW**0.74      !Cardiac output (L/hr);Reitz 1988.
  QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);Reitz 1988.
  VF = VFC*BW           !Fat volume (L)
  VL = VLC*BW           !Liver volume (L)
  VR = VRC*BW                !Richly Perfused volume (L)
  VS = VSC*BW               !Slowly Perfused volume (L)
  QL = QLC*QC           !Liver blood flow (L/hr)
  QF = QFC*QC           !Fat blood flow (L/hr)
  QR = QRC*QC                !Richly Perfused blood flow (L/hr)
  QS = QSC*QC               !Slowly Perfused blood flow (L/hr)
  VMAX=VMAXC*BW**0.7     !Capacity of saturable metabolism (mg/hr);Reitz 1988.
  ODOSE = BDOSE*BW        !Oral bolus dose (mg)
  DDOSE = DRINK*BW        !Dose rate from drinking water (mg/hr)
  IVR = IVDOSE*BW/TINF   !IV rate (mg/hr)
  VCH = VCHC - RATS*BW   !Net chamber volume (L)
  IAR = IADOSE*BW/TINFIA !IA rate (mg/hr)

    IF (BDOSE.EQ.0.) KA = 0.  !'Parenteral dosing'
    ODOSE = BDOSE*BW          !Oral dose, mg
    IF(VCH .LE. 0.0) VCH=1.0

'Other Compound Specific Parameters'
 CONSTANT   MW = 133.5   !'Molecular weight (g/mol)'
 CONSTANT   CONC=150.0   !'Inhaled concentration (ppm)'
   CIN = CONC*MW/24450.   !mg/L

'Timing commands'
CONSTANT   TSTOP = 72.  !'Length of experiment (hrs)'
CINTERVAL  CINT  = 0.01 !Communication interval

!Method of integration
ALGORITHM IALG = 2  !Gear method for stiff systems
END                 !End of initial
```

```
DYNAMIC

 !Rat and human inhalation exposure in dynamic chamber
  IF (T.LT.TCHNG) THEN
    CIN = CONC*MW/24450.
   ELSE
    CIN = 0
  ENDIF

 !IV = Intravenous infusion rate (mg/hr)
  IF (T.LT.TINF) THEN
    IV = IVR
   ELSE
    IV = 0
  ENDIF

 !IA = Intra-arterial infusion rate (mg/hr)
  IF (T.LT.TINFIA) THEN
    IA = IAR
   ELSE
    IA = 0
  ENDIF

 !Drinking water exposure (mg/hr)
  IF (T.LT.DTIME) THEN
    RDRINK = DDOSE
   ELSE
    RDRINK = 0
  ENDIF

DERIVATIVE

    !RACH = rate of amount in metabolism chamber (postexposure)
    !used for exhalation Fig. 4 Reitz 1988
    !Note CCH is different from CIN
     RACH = QP*RATS*(CEX-CCH) - FCH*CCH
      ACH = INTEG(RACH, 0.0)
      CCH = ACH / VCH
    RLOSS = FCH*CCH
    ALOST = INTEG(RLOSS,0.0)

    !Amount inhaled
      RAIN = QP*CIN
       AIN = INTEG(RAIN,0.)
    !Amount exhaled
      RAEX = QP*CEX
       AEX = INTEG(RAEX,0.)

     !MR = Amount remaining in stomach (mg)
```

```
    T2 = AMIN1(T,50.0)
    MR = ODOSE*EXP(-KA*T2)
  !exponential decrease in the amount in stomach

   !RAO = Rate of input to liver from stomach
    RAO = KA*MR

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR
     CRmol=CR/MW*1000.

    !AF = Amount in fat (mg)
    RAF = QF*(CA-CF/PF)
     AF = INTEG(RAF,0.)
     CF = AF/VF
     CFmol=CF/MW*1000.

    !AL = Amount in liver (mg)
    RAL = QL*(CA-CL/PL)-RAM + RAO + RDRINK
     AL = INTEG(RAL,0.)
     CL = AL/VL
     CLmol=CL/MW*1000.
     DRINKDOSE = RDRINK*DTIME   !Uptake from drinking water

    !AM = Amount metabolized (mg)
    RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
     AM = INTEG(RAM,0.)

    !Blood concentrations (mg/L)
    CV= (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR+IV+IA)/QC
    CVUGL=CV*1000     !mg/L converted to ug/L
    CA=(QC*CV+QP*CIN)/(QC+QP/PB)
    CEX = CA/PB
    CEXPPM = (0.667*CEX+0.333*CIN)*24450./MW !ppm
    CEXMGL=0.667*CEX+0.333*CIN         !mg/L

    !TMASS = mass balance (mg)
    !Amount in the body
    AINTOBODY=AIN-AEX+IVDOSE*BW+IADOSE*BW+ODOSE+DRINKDOSE
    !Amount in the body,summation of all compartments
    AINCAL=AF+AL+AS+AR+AM
    ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100
```

```
TERMT(T.GE.TSTOP)       !'Sets Termination Condition'
END     !'End of derivative'
END     !'End of dynamic'
END     !'End of program'
```

```
!This Reitz.cmd file is originally from Reitz,and is modified into the form
!that ACSL TOX 11.8 requires by Yasong LU on April 7,2005.
!Reviewd by Lu Y 5/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

!Set rat's parameters
PROCED RAT
  SET BW=0.233,QPC=15.0,QCC=15.0,QLC=0.24,QFC=0.05,QSC=0.18, ...
     VLC=0.04,VFC=0.07,VRC=0.05, ...
     PLA=8.6,PFA=263.0,PSA=3.15,PRA=8.6,PB=5.76, ...
     VMAXC=0.419,KM=5.75
END  !'of proced rat'

PROCED RATinh
!Simulate Schumann 1982 rat inhalation data
 !Rat Inhalation 150ppm
  S CONC=150.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
  START
  SET TITLE='Rat inhalation Schumann 1982'
  SET DEFPLT=.T.      !Defer Plot
  PLOT /DATA=RATinh150ppm CV /XLO=0 /XHI=12 /CHAR=1...
    /LOG /LO=0.1 /HI=100 /TAG='Venous Conc (mg/L)' /xtag='Time (hr)'
 !Rat Inhalation 1500ppm
  S CONC=1500.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
  START
  SET DEFPLT=.F.
  PLOT /DATA=RATinh1500ppm CV /XLO=0 /XHI=12 /CHAR=2...
    /LOG /LO=0.1 /HI=100 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
END  ! 'of proced RATinh'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 1, 150ppm
DATA RATinh150ppm (T,CV)
4       2.133
5       2.983
6       2.64
6.09    1.93
6.17    1.823
6.25    1.333
6.34    1.353
```

```
6.42    1.273
6.5     1.207
6.75    0.94
7       0.983
7.3     0.81
7.6     0.757
7.76    0.763
8       0.643
8.51    0.563
9.03    0.463
END

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 1, 1500ppm
DATA RATinh1500ppm (T,CV)
4       18.5
5       24.3
6       23.1
6.09    15.9
6.17    19.2
6.25    17.2
6.34    18.3
6.42    15.2
6.51    14.3
6.75    13
7.02    9.67
7.28    8.27
7.51    8.43
7.77    6.83
8.03    6.5
8.57    5.87
9.03    5.57
END

PROCED RATIV
!Simulate Reitz 1988 rat IV data
 !Rat IV1:8.84 mg/kg
   S CONC=0.0,DRINK=0.0,BDOSE=0.0,IVDOSE=8.84,CINT=0.001
   S BW=0.256,TSTOP=4
   START
   SET TITLE='  Rat Intravenous Reitz 1988'
   SET DEFPLT=.T.  !Defer Plot
   PLOT /DATA=RATIV8.84mgperkg CV /XLO=0 /XHI=4 ...
    /LOG /LO=0.01 /HI=100 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)' /CHAR=2
 !Rat IV2:25.3 mg/kg
   S CONC=0.0,DRINK=0.0,BDOSE=0.0,IVDOSE=25.6
   S BW=0.233,TSTOP=4
   START
   SET DEFPLT=.T.  !Defer Plot
```

```
  PLOT /DATA=RATIV25.3mgperkg CV /XLO=0 /XHI=4 ...
   /LOG /LO=0.01 /HI=100 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)' /CHAR=1
!Rat IV3: 47 mg/kg
  S CONC=0.0,DRINK=0.0,BDOSE=0.0,IVDOSE=47.0
  S BW=0.268,TSTOP=4
  START
  SET DEFPLT=.F.
  PLOT /DATA=RATIV47mgperkg CV /XLO=0 /XHI=4 ...
    /LOG /LO=0.01 /HI=100 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)' /CHAR=3
END !'of proced RATIV'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 2, 8.8mg/kg
DATA RATIV8.84mgperkg (T,CV)
0.033   5.27
0.1     3
0.1667  1.8
0.333   0.83
0.5     0.62
1       0.35
1.5     0.22
2       0.15
4       0.1
END

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 2, 26mg/kg
DATA RATIV25.3mgperkg (T,CV)
0.033   13.56
0.1     7.07
0.1667  4.7
0.333   2.29
0.5     1.56
1       0.66
1.5     0.57
2       0.47
4       0.2
END

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 2, 47mg/kg
DATA RATIV47mgperkg (T,CV)
0.033   29.8
0.1     15.7
0.1667  9.1
0.333   4.2
0.5     2.3
1       1.1
1.5     0.9
```

```
2       0.6
4       0.39
END

PROCED RATgavage  !Oral gavage
  SET BDOSE=14.2,IVDOSE=0.0,CONC=0.0,DRINK=0.0
  SET BW=0.268, TSTOP=4.0, KA=1.25
  SET CINT=0.001
  SET TITLE='   Rat Oral Gavage Reitz 1988'
  START
  PLOT /DATA=RATgavage CV /XLO=0 /XHI=4 /LOG /LO=0.1 /HI=10 ...
       /CHAR=1 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
END !'OF PROCED'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 3 gavage
DATA RATgavage (T,CV)
0.033   0.93
0.1     2.75
0.167   2.35
0.333   1.6
0.5     1.05
1       0.78
1.5     0.52
2       0.33
4       0.18
END

PROCED RATdrink  !rat drinking water exposure
   S BDOSE=0.0,IVDOSE=0.0,CONC=0.0,DRINK=14.4  !'mg/kg/hr'
   S BW=0.25,DTIME=8.0,TSTOP=30.0,CINT=0.01
   SET TITLE='Rat Drinking Water Reitz 1988'
   START
   PLOT /DATA=RATDRINKING RLOSS /XLO=0 /XHI=30 /CHAR=1...
    /LOG /LO=0.001 /HI=10 /TAG='Elimination Rate (mg/hr)' /xtag='Time (hr)'
END !'of proced drink'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 4 Drinking water
DATA RATDRINKING (T,RLOSS)
2       1.81
6       5.75
9       0.36
11      0.144
14      0.108
18      0.0417
22      0.0284
28      0.0138
38      0.00207
```

```
50      0.00237
END

PROCED MICEINH
  SET BW=0.029,QPC=15.0,QCC=15.0,QLC=0.24,QFC=0.02,QSC=0.18, ...
     VLC=0.04,VFC=0.04,VRC=0.05, ...
     PLA=8.6,PFA=263.0,PSA=3.15,PRA=8.6,PB=10.8, ...
     VMAXC=0.419,KM=5.75
 !Mice inhalation 150ppm
  S CONC=150.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
   START
   SET TITLE='Mice Inhalation Schumann 1982'
   SET DEFPLT=.T. !Defer Plot
   PLOT /DATA=MICEINH150PPM CV /XLO=6 /XHI=10 /CHAR=1...
        /LOG /LO=0.1 /HI=1000 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
 !Mice inhalation 1500ppm
  S CONC=1500.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
  START
   SET DEFPLT=.F.
   PLOT /DATA=MICEINH1500PPM CV /XLO=6 /XHI=10 /CHAR=2...
        /LOG /LO=0.1 /HI=1000 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
END ! 'OF PROCED MICEINH'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 5 150PPM
DATA MICEINH150PPM (T,CV)
6.04    9.27
6.09    4.58
6.19    3.59
6.36    2.12
6.78    1.2
7.52    0.872
END

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 5 1500PPM
DATA MICEINH1500PPM (T,CV)
6.03    111.6
6.1     28.1
6.18    24.7
6.27    23.7
6.36    14.4
6.49    13.6
6.53    19.8
6.77    8.78
7.01    7
7.29    5.93
7.52    4.43
7.76    4.23
```

```
8.04    5.73
8.53    4.18
9.02    3.85
END

PROCED HUMAN  !Inhalatin, Nolan study 1984;setting parameters
  SET BW=83.0,QPC=15.0,QCC=15.0,QLC=0.24,QFC=0.09,QSC=0.18, ...
     VLC=0.031,VFC=0.231,VRC=0.037, ...
     PLA=8.6,PFA=263.0,PSA=3.15,PRA=8.6,PB=2.53, ...
     VMAXC=0.419,KM=5.75
END  !'of proced HUMANinh'

PROCED HUMANCV  !Simulate human experiment data
 !Human 35ppm inhalation,CV
  SET CONC = 35.0,IVDOSE=0.0,BDOSE=0.0,DRINK=0.0
  SET TSTOP=120.0
  START
  SET TITLE='  Human inhalation Nolan 1984'
  SET DEFPLT=.T.  !Defer Plot
  PLOT /DATA=HUMANINH35PPM CV /XLO=0 /XHI=240 /CHAR=1...
     /LOG /LO=0.001 /HI=10 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
 !Human 350ppm inhalation,CV
  SET CONC = 350.0,IVDOSE=0.0,BDOSE=0.0,DRINK=0.0
  SET TSTOP=240.0
  START
  SET DEFPLT=.F.
  PLOT /DATA=HUMANINH350PPM CV /XLO=0 /XHI=240 /CHAR=2...
    /LOG /LO=0.001 /HI=10 /TAG='Venous Conc(mg/L)' /xtag='Time (hr)'
END ! 'of proced HUMANcv'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 6B 35PPM
DATA HUMANINH35PPM (T,CV)
0.08    0.0265
0.29    0.0584
0.53    0.0863
0.97    0.134
1.5     0.139
3       0.114
4.02    0.13
5.8     0.151
6.1     0.116
6.3     0.101
6.5     0.0868
6.8     0.0814
7.5     0.0614
9       0.041
10      0.0316
11      0.0278
```

```
22.8    0.0115
31.1    0.00602
46.5    0.0047
118.4   0.00168
END

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 6B 350PPM
DATA HUMANINH350PPM (T,CV)
0.1     0.304
0.3     0.741
0.52    1.11
0.94    1.41
1.5     1.62
3       1.79
4       1.65
5.85    1.75
6.09    1.48
6.29    1.1
6.51    0.906
6.89    0.854
7.5     0.679
9       0.46
10      0.4
11      0.32
22.4    0.114
31.4    0.0692
46.4    0.0414
118.6   0.0134
166.3   0.0073
214.3   0.00498
END

PROCED HUMANCEX  !Simulate human experiment data
 !Human 35ppm inhalation,cex
  SET CINT=0.1
  SET CONC = 35.0,IVDOSE=0.0,BDOSE=0.0,DRINK=0.0
  SET TSTOP=240.0
  SET TITLE='  Human inhalation Nolan 1984'
  START
  SET DEFPLT=.T.
  PLOT /DATA=HUMANINH35PPMCEX CEXMGL /XLO=0 /XHI=240 /CHAR=1...
     /LOG /LO=0.0001 /HI=10 /TAG='Exh Conc(mg/L)' /xtag='Time (hr)'
 !Human 350ppm inhalation,cex
  SET CONC = 350.0,IVDOSE=0.0,BDOSE=0.0,DRINK=0.0
  SET TSTOP=240.0
  START
  SET DEFPLT=.F.
  PLOT /DATA=HUMANINH350PPMCEX CEXMGL /XLO=0 /XHI=240 /CHAR=2...
```

```
    /LOG /LO=0.0001 /HI=10 /TAG='Exh Conc(mg/L)' /xtag='Time (hr)'
END   !'End of proced HUMANCEX'

PROCED HUMANCEXINSET  !Simulate human experiment data
 !Human 35ppm inhalation,cex
  SET CINT=0.1
  SET CONC = 35.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
  SET TSTOP=240.0
  SET TITLE='Human inhalation inset Schumann 1982'
  START
  SET DEFPLT=.T.
  PLOT /DATA=HUMANINH35PPMCEX CEXMGL /XLO=0 /XHI=8 /CHAR=1...
    /LOG /LO=0.01 /HI=10 /TAG='Exh Conc' /xtag='Time (hr)'
 !Human 350ppm inhalation,cex
  SET CONC = 350.0, IVDOSE=0.0, BDOSE=0.0, DRINK=0.0
  SET TSTOP=240.0
  START
  SET DEFPLT=.F.
  PLOT /DATA=HUMANINH350PPMCEX CEXMGL /XLO=0 /XHI=8 /CHAR=2...
    /LOG /LO=0.01 /HI=10 /TAG='Exh Conc' /xtag='Time (hr)'
END   !'End of proced HUMANCEX'

!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 6A 35PPM
DATA HUMANINH35PPMCEX (T,CEXMGL)
0.08    0.1054
0.29    0.1186
0.53    0.1266
0.97    0.1342
1.5     0.1428
3       0.1475
4.02    0.1493
5.8     0.1501
6.1     0.0474
6.3     0.03866
6.5     0.03067
6.8     0.02689
7.5     0.02123
9       0.01371
10      0.01091
11      0.00941
22.8    0.00307
31.1    0.00188
46.5    0.00127
118.4   0.00354
166.6   0.000187
214.9   0.000128
END
```

```
!Obtained as original data from Reitz cmd file
!Reitz (1988) Fig 6A 350PPM
DATA HUMANINH350PPMCEX (T,CEXMGL)
0.1     0.9903
0.3     1.096
0.52    1.215
0.94    1.205
1.5     1.279
3       1.375
4       1.407
5.85    1.483
6.09    0.4365
6.29    0.3194
6.51    0.2681
6.89    0.2312
7.5     0.1876
9       0.1243
10      0.1038
11      0.08767
22.4    0.03297
31.4    0.02
46.4    0.01202
118.6   0.00345
166.3   0.00172
214.3   0.00164
END
```

```
3. Dallas et al. (1989)
PROGRAM: Dallas.CSL
!Reproduce Dallas et al. model. 11/22/05 by Lu Y.
!Dallas, C. E., Ramanathan, R., Muralidhara, S., Gallo, J. M., and
!Bruckner, J. V. (1989). The uptake and elimination of 1,1,1-trichloroethane
!during and following inhalation exposures in rats. Toxicol Appl Pharmacol
!98, 385-97.

INITIAL

!Physiological Parameters **********************************
CONSTANT BW = 0.34    !Mean body weight (kg);Dallas 1989;
  QC = 106.4*60/1000  !Cardiac output (L/hr);Dallas 1989;
CONSTANT QP= 7.56     !Rat alveolar ventilation (L/hr);Dallas 1989;
  !Blood flows
  QL = 39.8*60/1000   !Blood flow to liver(L/hr);Dallas 1989;
  QF = 9.4*60/1000    !Blood flow to fat(L/hr);Dallas 1989;
  QS = 12.8*60/1000   !Blood flow to slowly perfused(L/hr);Dallas 1989;
  QR = 44.4*60/1000   !Blood flow to rapidly perfused(L/hr);Dallas 1989;
  !Volumes
CONSTANT VL = 0.0136  !liver(L);Dallas 1989;
CONSTANT VF = 0.0305  !fat (L);Dallas 1989;
CONSTANT VR = 0.017   !richly perfused tissues(L);Dallas 1989;
CONSTANT VS = 0.248   !poorly perfused tissues(L);Dallas 1989;
CONSTANT VB = 0.0254  !blood (L);Dallas 1989;
CONSTANT VLG= 0.00397 !lung (L);Dallas 1989;
CONSTANT VALV=0.002   !alveolar (L);Dallas 1989;

!Chemical specific parameters ********************************
  !Partition coefficients
CONSTANT PLGA = 8.6   !Lung/air; Dallas 1989;
CONSTANT PLG= 1.49    !Lung/blood; Dallas 1989;
CONSTANT PL = 1.49    !Liver/blood; Dallas 1989;
CONSTANT PF = 47.7    !Fat/blood; Dallas 1989;
CONSTANT PR = 1.49    !Richly perfused/blood; Dallas 1989;
CONSTANT PS = 0.55    !Slowly perfused/blood; Dallas 1989;
  !Metabolism constants
KF=0.115*60  !1st-order metabolism rate constant(/hr);Dallas 1989;
  !Mass transfer in alveolar area
 K = 500*60/1000      !L/hr, Dallas 1989;

!Exposure conditions
CONSTANT TCHNG = 2.     !Length of inhalation exposure (hrs);
CONSTANT MW = 133.5     !TCA molecular weight (g/mol);
CONSTANT CONC= 50.0     !Inhaled concentration (ppm);
  CIN = CONC*MW/24450.  !Convert ppm to mg/L;

!Timing commands
CONSTANT  TSTOP = 6.    !Length of experiment (hrs);
```

```
CINTERVAL CINT  = 0.01  !Communication interval;

!Method of integration
ALGORITHM IALG = 2 !Gear method for stiff systems,default of PBPK modeling;
END             !End of initial;

DYNAMIC
!Rat and human inhalation exposure in dynamic chamber
  IF (T.LT.TCHNG) THEN
    CIN = CONC*MW/24450.
   ELSE
    CIN = 0
  ENDIF

DERIVATIVE
!Subblock for differential calculations
!Amount inhaled
   RAIN = QP*CIN
    AIN = INTEG(RAIN,0.)
 !Amount exhaled
   RAEX = QP*CALV  !Dr. Lisa Sweeney suggested this correction; she was right.
    AEX = INTEG(RAEX,0.)
 !Amount in alveolar space (mg)
   RALV = QP*(CIN-CALV)+K*(CLG/PLGA-CALV)
    ALV = INTEG(RALV,0.)
    CALV= ALV/VALV
 !Amount in lung (mg)
   RALG = QC*(CVB-CLG/PLG)+K*(CALV-CLG/PLGA)
    ALG = INTEG(RALG,0.)
    CLG = ALG/VLG
 !Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CVS)
     AS = INTEG(RAS,0.)
     CS = AS/VS
    CVS = CS/PS
 !Amount in Rapidly Perfused Tissues (mg)
    RAR = QR*(CA-CVR)
     AR = INTEG(RAR,0.)
     CR = AR/VR
    CVR = CR/PR
 !Amount in fat (mg)
    RAF = QF*(CA-CVF)
     AF = INTEG(RAF,0.)
     CF = AF/VF
    CVF = CF/PF
 !Amount in liver (mg)
    RAL = QL*(CA-CVL)-RAM
     AL = INTEG(RAL,0.)
     CL = AL/VL
```

```
    CVL = CL/PL
 !Amount metabolized in liver (mg)
    RAM = KF*CVL*VL
     AM = INTEG(RAM,0.)
 !Venous Blood concentrations (mg/L)
     RAVB = QL*CVL+QS*CVS+QF*CVF+QR*CVR-QC*CVB
      AVB = INTEG(RAVB,0.)
      CVB = AVB/VB
 !Arterial blood
     RAAB = QC*(CLG/PLG-CA)
      AAB = INTEG(RAAB,0.)
       CA = AAB/VB
  CEX = 0.5*CALV+0.5*CIN !Concentration in expired air,mg/L

 !Check mass balance (mg)
 !Amount in the body
   AINTOBODY = AIN-AEX
 !Amount in the body calculated,summation of all compartments
   AINCAL = ALV+ALG+AF+AL+AS+AR+AM+AAB+AVB
    ERROR = (AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100
  TERMT(T.GE.TSTOP)          !Termination Condition
END      !of derivative
END      !of dynamic
END      !of program
```

```
!Dallas.CMD
!Reproduce Dallas et al. data sets. 11/22/05 by Lu Y.

SET GRDCPL=.F.
START
PREPAR /ALL

!PROCEDURE to run a group of commands
PROCED CHECK
START
PLOT ERROR
END

!Simulate Dallas 1989 rat inhalation data
PROCED DallasCA
 !Rat Inhalation 50ppm
   S CONC=50.0,QP=7.56
   START
   SET TITLE='Rat inhalation Dallas 1989'
   SET DEFPLT=.T.      !Defer Plot
   PLOT /DATA=Dallas50ppmCA CA /XLO=0 /XHI=6 /CHAR=1...
     /LOG /LO=0.01 /HI=100 /TAG='Arterial Conc (mg/L)' /xtag='Time (hr)'
 !Rat Inhalation 500ppm
   S CONC=500.0,QP=7.08
   START
   SET DEFPLT=.F.
   PLOT /DATA=Dallas500ppmCA CA /XLO=0 /XHI=6 /CHAR=2...
      /LOG /LO=0.01 /HI=100 /TAG='Arterial Conc(mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCA'
DATA Dallas50ppmCA (T,CA)
0.063333333   0.32
0.096666667   0.34
0.168333333   0.43
0.245   0.42
0.33     0.47
0.485   0.57
0.731666667   0.64
0.985   0.64
1.23     0.66
1.483333333   0.71
1.736666667   0.7
1.983333333   0.78
2.021666667   0.58
2.046666667   0.45
2.086666667   0.45
2.158333333   0.39
2.241666667   0.33
2.326666667   0.23
2.481666667   0.27
```

```
2.741666667   0.24
2.986666667   0.19
3.246666667   0.15
3.5       0.13
3.751666667   0.11
4.005   0.09
4.496666667   0.07
4.996666667   0.06
5.515   0.07
END

DATA Dallas500ppmCA (T,CA)
0.061666667   2.8
0.098333333   3.6
0.13      4.3
0.173333333   4.8
0.255   5.1
0.335   6.4
0.423333333   5.9
0.503333333   6.4
0.758333333   7
1.008333333   7
1.25      7.9
1.505   8.3
1.761666667   8.8
2.01      8.3
2.046666667   5.6
2.078333333   4.8
2.11      3.9
2.185   2.9
2.265   3.2
2.346666667   3.1
2.433333333   2.5
2.508333333   2.4
2.77      2
3.018333333   1.8
3.273333333   1.3
3.535   1.2
3.771666667   1.1
4.021666667   0.9
4.525   0.7
5.016666667   0.7
5.508333333   0.4
END

PROCED DallasCEX
 !Rat Inhalation 50ppm
   S CONC=50.0,QP=7.56
   START
```

```
  SET TITLE='Rat inhalation Dallas 1989'
  SET DEFPLT=.T.      !Defer Plot
  PLOT /DATA=Dallas50ppmCEX CEX /XLO=0 /XHI=6 /CHAR=1...
    /LOG /LO=0.001 /HI=10 /TAG='Exhaled Conc (mg/L)' /xtag='Time (hr)'
!Rat Inhalation 500ppm
  S CONC=500.0,QP=7.08
  START
  SET DEFPLT=.F.
  PLOT /DATA=Dallas500ppmCEX CEX /XLO=0 /XHI=6 /CHAR=2...
    /LOG /LO=0.001 /HI=10 /TAG='Exhaled Conc(mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCEX'

DATA Dallas50ppmCEX (T,CEX)
0         0.131
0.026   0.168
0.065166667   0.178
0.15     0.183
0.234833333   0.189
0.313166667   0.196
0.469666667   0.194
0.645833333   0.207
0.809   0.205
0.972166667   0.217
1.141833333   0.208
1.3115 0.221
1.4745 0.208
1.637666667   0.212
1.813833333   0.21
1.977   0.213
2.009666667   0.081
2.029166667   0.056
2.074833333   0.05
2.1075 0.055
2.153166667   0.036
2.486   0.024
2.740333333   0.022
2.988333333   0.017
3.242833333   0.015
3.503833333   0.011
3.751833333   0.01
3.999666667   0.007
4.495666667   0.007
END


DATA Dallas500ppmCEX (T,CEX)
0.006183333   1.318
0.037183333   1.5
0.074383333   1.657
```

```
0.161166667   1.802
0.24795       1.814
0.32855       1.814
0.502116667   1.85
0.6695 1.802
0.843066667   2.008
1.016633333   2.153
1.177816667   2.141
1.3452 2.153
1.512566667   2.141
1.692333333   2.298
1.847316667   2.25
2.0085 2.262
2.033283333   0.725
2.064283333   0.435
2.095283333   0.375
2.138666667   0.35
2.182066667   0.278
2.26885       0.254
2.516816667   0.157
2.764783333   0.145
3.01895       0.108
3.2731 0.12
3.521066667   0.084
4.0232 0.06
4.519116667   0.024
5.00885       0.036
END

PROCED DallasCAlow
 !Rat Inhalation 50ppm
   S CONC=50.0,QP=7.56
   START
   SET TITLE='Rat inhalation Dallas 1989'
   PLOT /DATA=Dallas50ppmCA CA /XLO=0 /XHI=6 /CHAR=1...
     /LO=0 /HI=1 /TAG='Arterial Conc (mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCA'

PROCED DallasCAhi
 !Rat Inhalation 500ppm
   S CONC=500.0,QP=7.08
   START
   SET TITLE='Rat inhalation Dallas 1989'
   PLOT /DATA=Dallas500ppmCA CA /XLO=0 /XHI=6 /CHAR=1...
     /LO=0 /HI=9 /TAG='Arterial Conc (mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCA'

PROCED DallasCEXlow
 !Rat Inhalation 50ppm
```

```
  S CONC=50.0,QP=7.56
  START
  SET TITLE='Rat inhalation Dallas 1989'
  PLOT /DATA=Dallas50ppmCEX CEX /XLO=0 /XHI=6 /CHAR=1...
    /LO=0 /HI=0.3 /TAG='Exhaled Conc (mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCEX'

PROCED DallasCEXhi
 !Rat Inhalation 500ppm
  S CONC=500.0,QP=7.08
  START
  SET TITLE='Rat inhalation Dallas 1989'
  PLOT /DATA=Dallas500ppmCEX CEX /XLO=0 /XHI=6 /CHAR=1...
    /LO=0 /HI=3 /TAG='Exhaled Conc (mg/L)' /xtag='Time (hr)'
END  ! 'of proced DallasCEX'
```

4. Leung 1992

```
PROGRAM: Leung.CSL
!Created by M.Lohitnavy and Y.Lu 12/24/04.
!Leung H. 1992. Use of physiologically based pharmacokinetic models to establish biological
!exposure indexes. Am Ind Hyg Assoc J 53:369-374.
!Human inhalation exposure resembling industrial scenario, 350ppm 8hr/day,5days/week.
!50W exercise during working and rest between shifts.
!Metabolites are not traced.

!Reviewed by Lu Y 5/23/2005

INITIAL

!Physiological Parameters **********************************
CONSTANT BW = 70.        !Body weight (kg);Leung 1992
 QP=1320.     !Alveolar ventilation at work (L/hr);Leung 1992
 QC=603.      !Cardiac output at work (L/hr);Leung 1992
   !Blood flow to tissues at work
 QL=96.5      !Blood flow to liver (L/hr);Leung 1992
 QF=36.2      !Blood flow to fat (L/hr);Leung 1992
 QR=162.8     !Blood flow to richly perfused (L/hr);Leung 1992
 QS=307.5     !Blood flow to slowly perfused (L/hr);Leung 1992
  !Volume Of tissues
CONSTANT VL=2.2       !Volume of liver (L);Leung 1992
CONSTANT VF=16.2      !Volume of fat (L);Leung 1992
CONSTANT VR=4.1       !Volume of rapidly perfused tissue (L);Leung 1992
CONSTANT VS=41.2      !Volume of slowly perfused tissue (L);Leung 1992

!Chemical specific parameters ******************************
  !Partition coefficients
CONSTANT PB = 2.53   !Blood/air;Leung 1992
CONSTANT PL = 3.4    !Liver/blood;Leung 1992
CONSTANT PF = 104.   !Fat/blood;Leung 1992
CONSTANT PR = 3.4    !Richly perfused tissue/blood;Leung 1992
CONSTANT PS = 1.25   !Slowly perfused tissue/blood;Leung 1992
  !Metabolism
CONSTANT VMAX = 8.22  !Capacity of saturable metabolism (mg/hr);Leung 1992
CONSTANT KM = 5.75    !Affinity of saturable metabolism (mg/L);Leung 1992

!Parameters for simulation of experiment**********************
CONSTANT MW = 133.5    !Molecular weight of 1,1,1,-trichloroethane (g/mol)
  OEL=350             !Occupational exposure limit (ppm);Leung 1992
    CIN=OEL*MW/24450   !Conc in atmosphere (mg/L)

!Timing commands
CONSTANT   TSTOP = 125. !5 workdays (hr)
CINTERVAL  CINT  = 0.01 !Communication interval

!Method of integration
```

```
ALGORITHM IALG = 2        !Gear method for stiff systems

END                       !End of INITIAL

DYNAMIC

!Exposure scenario
IF (T.LT.8.) THEN
  QP=1320.     !Alveolar ventilation at work (L/hr);Leung 1992
  QC=603.      !Cardiac output at work (L/hr);Leung 1992
  QL=96.5      !Blood flow to liver (L/hr);Leung 1992
  QF=36.2      !Blood flow to fat (L/hr);Leung 1992
  QR=162.8     !Blood flow to richly perfused (L/hr);Leung 1992
  QS=307.5     !Blood flow to slowly perfused (L/hr);Leung 1992
  OEL=350      !Exposure
  CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
 ELSE IF (T.GE.8.AND.T.LE.24) THEN
  QP = 348     !Alveolar ventilation at rest (L/hr);Leung 1992
  QC = 347.9   !Cardiac output at rest (L/hr);Leung 1992
  QL = 87.     !Blood flow to liver (L/hr);Leung 1992
  QF = 17.4    !Blood flow to fat (L/hr);Leung 1992
  QR = 177.4   !Blood flow to richly perfused (L/hr);Leung 1992
  QS = 66.1    !Blood flow to slowly perfused (L/hr);Leung 1992
  OEL= 0       !No exposure
  CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
 ELSE IF (T.GT.24.AND.T.LE.33) THEN
  QP=1320.     !Alveolar ventilation at work (L/hr)
  QC=603.      !Cardiac output at work (L/hr)
  QL=96.5      !Blood flow to liver (L/hr)
  QF=36.2      !Blood flow to fat (L/hr)
  QR=162.8     !Blood flow to richly perfused (L/hr)
  QS=307.5     !Blood flow to slowly perfused (L/hr)
  OEL=350
  CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
 ELSE IF (T.GT.33.AND.T.LE.48) THEN
  QP = 348     !Alveolar ventilation at rest (L/hr);Leung 1992
  QC = 347.9   !Cardiac output at rest (L/hr);Leung 1992
  QL = 87.     !Blood flow to liver (L/hr);Leung 1992
  QF = 17.4    !Blood flow to fat (L/hr);Leung 1992
  QR = 177.4   !Blood flow to richly perfused (L/hr);Leung 1992
  QS = 66.1    !Blood flow to slowly perfused (L/hr);Leung 1992
  OEL= 0       !No exposure
  CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
 ELSE IF (T.GT.48.AND.T.LE.56) THEN
  QP=1320.     !Alveolar ventilation at work (L/hr)
  QC=603.      !Cardiac output at work (L/hr)
  QL=96.5      !Blood flow to liver (L/hr)
  QF=36.2      !Blood flow to fat (L/hr)
  QR=162.8     !Blood flow to richly perfused (L/hr)
```

```
 QS=307.5     !Blood flow to slowly perfused (L/hr)
 OEL=350
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ELSE IF (T.GT.56.AND.T.LE.72) THEN
 QP = 348     !Alveolar ventilation at rest (L/hr);Leung 1992
 QC = 347.9   !Cardiac output at rest (L/hr);Leung 1992
 QL = 87.     !Blood flow to liver (L/hr);Leung 1992
 QF = 17.4    !Blood flow to fat (L/hr);Leung 1992
 QR = 177.4   !Blood flow to richly perfused (L/hr);Leung 1992
 QS = 66.1    !Blood flow to slowly perfused (L/hr);Leung 1992
 OEL= 0       !No exposure
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ELSE IF (T.GT.72.AND.T.LE.80) THEN
 QP=1320.     !Alveolar ventilation at work (L/hr)
 QC=603.      !Cardiac output at work (L/hr)
 QL=96.5      !Blood flow to liver (L/hr)
 QF=36.2      !Blood flow to fat (L/hr)
 QR=162.8     !Blood flow to richly perfused (L/hr)
 QS=307.5     !Blood flow to slowly perfused (L/hr)
 OEL=350
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ELSE IF (T.GT.80.AND.T.LE.96) THEN
 QP = 348     !Alveolar ventilation at rest (L/hr);Leung 1992
 QC = 347.9   !Cardiac output at rest (L/hr);Leung 1992
 QL = 87.     !Blood flow to liver (L/hr);Leung 1992
 QF = 17.4    !Blood flow to fat (L/hr);Leung 1992
 QR = 177.4   !Blood flow to richly perfused (L/hr);Leung 1992
 QS = 66.1    !Blood flow to slowly perfused (L/hr);Leung 1992
 OEL= 0       !No exposure
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ELSE IF (T.GT.96.AND.T.LE.104) THEN
 QP=1320.     !Alveolar ventilation at work (L/hr)
 QC=603.      !Cardiac output at work (L/hr)
 QL=96.5      !Blood flow to liver (L/hr)
 QF=36.2      !Blood flow to fat (L/hr)
 QR=162.8     !Blood flow to richly perfused (L/hr)
 QS=307.5     !Blood flow to slowly perfused (L/hr)
 OEL=350
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ELSE IF (T.GT.104) THEN
 QP = 348     !Alveolar ventilation at rest (L/hr);Leung 1992
 QC = 347.9   !Cardiac output at rest (L/hr);Leung 1992
 QL = 87.     !Blood flow to liver (L/hr);Leung 1992
 QF = 17.4    !Blood flow to fat (L/hr);Leung 1992
 QR = 177.4   !Blood flow to richly perfused (L/hr);Leung 1992
 QS = 66.1    !Blood flow to slowly perfused (L/hr);Leung 1992
 OEL= 0       !No exposure
 CIN=OEL*MW/24450 !Conc in atmosphere (mg/L)
ENDIF
```

```
DERIVATIVE

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR

    !AF = Amount in fat tissue (mg)
    RAF = QF*(CA-CF/PF)
     AF = INTEG(RAF,0.)
     CF = AF/VF

    !AL = Amount in liver tissue (mg)
    RAL = QL*(CA-CL/PL)-RAM
     AL = INTEG(RAL,0.)
     CL = AL/VL
     CVL= CL/PL

    !AM = Amount of 1,1,1-trichloroethane metabolized (ug)
    RAM = VMAX*CL/PL/(KM+CL/PL)
     AM = INTEG(RAM,0.)

        !Amount inhaled (ug)
        RAIN = QP*CIN
        AIN = INTEG(RAIN,0.)

        !Amount exhaled (ug)
        RAEX=QP*CEX
        AEX=INTEG(RAEX,0.)
        CEX=CA/PB
        CEXPPM = (2*CEX/3+CIN/3)*24450./MW

      !Blood concentrations (mg/L)
    CV=(QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC !mg/L
    CVM=CV/MW    !mmol/L
    CA=(QC*CV+QP*CIN)/(QC+QP/PB) !mg/L

  !TMASS = mass balance (mg)
  !Amount in the body,difference b/t inhalation and exhalation
   AINTOBODY=AIN-AEX
  !Amount in the body,summation of all compartments
   AINCAL=AF+AL+AS+AR+AM
  ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100
```

```
TERMT(T.GE.TSTOP)
END     !End of derivative
END     !End of dynamic
END     !End of program
```

```
!FILE Leung.CMD FOR TCA MODEL REPRODUCTION PREPARED BY Y.LU AND
!M.LOHITNAVY DEC. 24rd, 2004. Reviewed by Lu Y 5/23/2005

PREPAR /ALL

SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.
START

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED Leung
START
SET TITLE ='TCA EXPOSURE IN HUMANS'
!s defplt=.t.
PLOT /DATA=Leung CV /LO=0.0 /HI=10. ...
    /TAG=' - Venous Concentrations (mg/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=120 /CHAR=1
PLOT /DATA=Leung CEXppm /LOG /LO=0.1 /HI=1000.  ...
    /TAG=' - Exhaled Concentrations (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=120 /CHAR=1
END

!Leung's calculation, not real human data.
DATA Leung (t,CV,CEXppm)
8       4.56    337.8
24      ?       3.4
96      ?       9.09
END
```

5. Yoshida 1993

```
PROGRAM: Yoshida.CSL PHYSIOLOGICAL MODEL
!By M.Lohitnavy and Y.Lu 12/24/04.
!Yoshida K. 1993. Preliminary exposure assessment of volatile chlorinated
!hydrocarbons in Japan. Chemosphere 27(4):621-630.

!Reviewed by Lu Y 5/23/2005

INITIAL

!Physiological Parameters **********************************
CONSTANT BW = 70.       !Body weight (kg);Yoshida 1993
         QC=6.2*60      !L/hr-convert from L/min to L/hr;Yoshida 1993
         QP=7.5*60      !L/hr-convert from L/min to L/hr;Yoshida 1993
  !Blood flow to tissues
 QL = 1.55*60   !Blood flow to liver (L/hr)-convert from L/min to L/hr;Yoshida 1993
 QF = 0.31*60   !Blood flow to fat (L/hr)-convert from L/min to L/hr;Yoshida 1993
 QR = 2.77*60   !Blood flow to richly perfused (L/hr)-convert from L/min to L/hr
 QS = 1.57*60 !Blood flow to slowly perfused (L/hr)-convert from L/min to L/hr
  !Volume Of tissues
CONSTANT VL=1.7             !Volume of liver (L);Yoshida 1993
CONSTANT VF=14.0            !Volume of fat (L);Yoshida 1993
CONSTANT VR=3.5             !Volume of rapidly perfused tissue (L);Yoshida 1993
CONSTANT VS=43.4            !Volume of slowly perfused tissue (L);Yoshida 1993

!Chemical specific parameters ********************************
  !Partition coefficients
CONSTANT PB = 2.53   !Blood/air;Yoshida 1993
CONSTANT PL = 3.4    !Liver/blood;Yoshida 1993
CONSTANT PF = 104.   !Fat/blood;Yoshida 1993
CONSTANT PR = 3.4    !Richly perfused tissue/blood;Yoshida 1993
CONSTANT PS = 1.25   !Slowly perfused tissue/blood;Yoshida 1993
  !Metabolism;Yoshida 1993
VMAX = 0.1*60  !Capacity of saturable metabolism (mg/hr)-convert from mg/min to mg/hr
CONSTANT KM = 6.43   !Affinity of saturable metabolism (mg/L)

!Parameters for simulation of experiment**********************
CONSTANT MW = 133.4    !Molecular weight of 1,1,1,-trichloroethane (g/mol)
CONSTANT CATM=1.5e-3   !Conc in atmospheric air (ug/L);Yoshida 1993
         CIN=CATM
CONSTANT WATER=7.5e-3  !Ingestion rate from water (ug/hr);Yoshida 1993
CONSTANT FISH=2.e-3    !Ingestion rate from fish (ug/hr);Yoshida 1993
CONSTANT VEGGIE=5.e-3  !Ingestion rate from vegetables (ug/hr);Yoshida 1993
        DIN=WATER+FISH+VEGGIE !Cumulative ingestion (ug/hr)

!Timing commands
CONSTANT   TSTOP = 200.   !Yoshida assumed steady state (hr)
CINTERVAL  CINT  = 0.01   !Communication interval
```

```
!Method of integration
ALGORITHM IALG = 2       !Gear method for stiff systems

END                      !End of INITIAL

DYNAMIC

DERIVATIVE

    !AS = Amount in Slowly Perfused Tissues (ug)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (ug)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR

    !AF = Amount in fat tissue (ug)
    RAF = QF*(CA-CF/PF)
     AF = INTEG(RAF,0.)
     CF = AF/VF

    !AL = Amount in liver tissue (ug)
    RAL = QL*(CA-CL/PL)-RAM+DIN
     AL = INTEG(RAL,0.)
     CL = AL/VL
     CVL= CL/PL

    !AM = Amount of 1,1,1-trichloroethane metabolized (ug)
    RAM = VMAX*1000*CL/PL/(KM*1000+CL/PL)
     AM = INTEG(RAM,0.)

        !Total amount from ingestion (ug)
        ADIN=integ(DIN,0.)

        !Amount inhaled (ug)
        RAIN = QP*CIN
        AIN = INTEG(RAIN,0.)

        !Amount exhaled (ug)
        RAEX=QP*CEX
        AEX=INTEG(RAEX,0.)
        CEX=CA/PB
        CEXPPM = (0.7*CEX+0.3*CIN)*24450./MW

      !Blood concentrations (mg/L)
    CV=(QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
```

```
    CVM=CV/MW    !mmol/L
    CA=(QC*CV+QP*CIN)/(QC+QP/PB)

  !TMASS = mass balance (mg)
  !Amount in the body,difference b/t inhalation and exhalation
   AINTOBODY=AIN-AEX+ADIN
  !Amount in the body,summation of all compartments
   AINCAL=AF+AL+AS+AR+AM
  ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)
END      !End of derivative
END      !End of dynamic
END      !End of program
```

```
!FILE Yoshida.CMD FOR TCA MODEL REPRODUCTION PREPARED BY Y.LU
!AND M.LOHITNAVY DEC. 23rd, 2004.Reviewed by Lu Y 5/24/2005.

PREPAR /ALL
SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.
SET HVDPRN=.T.

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED Yoshida
START
SET TITLE ='TCA EXPOSURE IN HUMANS'
s defplt=.t.
PLOT /DATA=Yoshida CV /LOG /LO=0.0001 /HI=1 ...
    /TAG=' - Venous Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.t.
PLOT /DATA=Yoshida CEX /LOG /LO=0.0001 /HI=1  ...
    /TAG=' - Exhaled Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.t.
PLOT /DATA=Yoshida CA /LOG /LO=0.0001 /HI=1 ...
    /TAG=' - Arterial Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.t.
PLOT /DATA=Yoshida CL /LOG /LO=0.0001 /HI=1  ...
    /TAG=' - Liver Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.t.
PLOT /DATA=Yoshida CF /LOG /LO=0.0001 /HI=1. ...
    /TAG=' - Fat Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.t.
PLOT /DATA=Yoshida CR /LOG /LO=0.0001 /HI=1  ...
    /TAG=' - Rapidly Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
s defplt=.f.
PLOT /DATA=Yoshida CS /LOG /LO=0.0001 /HI=1 ...
    /TAG='Tissue Concentrations (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=200 /CHAR=1
END
!Yoshida's calculation, not real human data
DATA Yoshida (t,CV,CEX,CA,CL,CF,CR,CS)
198. 3.81E-3 1.49E-3 3.78E-3 13.3E-3 393.E-3 12.9E-3 4.72E-3
END
```

6. Lapare et al. 1995
PROGRAM: Lapare.CSL PHYSIOLOGICAL MODEL

```
!Prepared by Lohitnavy M and Lu Y 12/18/04.Reviewed by LU Y 5/22/2005.
!Lapare et al. 1995. Effect of various exposure scenarios on the biological monitoring
!of organic solvents in alveolar air. II. 1,1,1-trichloroethane and trichloroethylene.
!Int Arch Occup Environ Health 67:375-394.
!Metabolites are not tracked here.

INITIAL

!Physiological Parameters **********************************
CONSTANT  BW = 60.5      !Body weight (kg);Lapare 1995
  QPC = 15.5      !Alveolar ventilation at rest (L/hr/kg^0.7);Lapare 1995
  QCC = 19.0      !Cardiac output at rest (L/hr/kg^0.7);Lapare 1995
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.069    !Fractional arterial blood flow to liver
   QFC = 0.053    !Fractional blood flow to fat
   QRC = 0.379    !Fractional blood flow to richly perfused tissues
   QSC = 0.063    !Fractional blood flow to slowly perfused tissues
   QSHUNTC= 0.151 !Fractional blood flow to shunt
   QMC = 0.114    !Fractional blood flow to muscle and skin
   QGIC= 0.171    !Fractional blood flow to GI
  !Volume fractions;Lapare 1995
CONSTANT  VFC = 0.211    !Fat
CONSTANT  VLC = 0.023    !Liver
CONSTANT  VRC = 0.030    !Richly perfused
CONSTANT  VSC = 0.085    !Poorly perfused
CONSTANT  VLUNGC=0.029   !Lung
CONSTANT  VGIC=0.019     !GI tract
CONSTANT  VMC = 0.415    !Muscle

!Chemical specific parameters ******************************
  !Partition coefficients;Lapare 1995
CONSTANT  PB = 4.35      !Blood/air partition coefficient
CONSTANT  PLA=16.        !Liver/air partition coefficient
CONSTANT  PFA=251.       !Fat/air partition coefficient
CONSTANT  PRA=8.3        !Richly/air partition coefficient
CONSTANT  PSA=6.7        !Poorly/air partition coefficient
CONSTANT  PMA=6.7        !Muscle/air partition coefficient
CONSTANT  PGIA=16.       !GI/air partition coefficient
CONSTANT  PLUNGA=4.7     !Lung/air partition coefficient
    PL = PLA/PB          !Liver/blood partition coefficient
    PF = PFA/PB          !Fat/blood partition coefficient
    PR = PRA/PB          !Richly perfused tissue/blood partition coefficient
    PS = PSA/PB          !Poorly perfused tissue/blood partition coefficient
    PM = PMA/PB          !Muscle and Skin/blood partition coefficient
    PGI = PGIA/PB        !GI/blood Partition coefficient
    PLUNG = PLUNGA/PB    !Lung partition coefficient
  !Metabolism;saturable
```

```
CONSTANT  MW = 133.5     !Molecular weight of 1,1,1,-trichloroethane (g/mol)
CONSTANT  VMAXC = 0.42   !Capacity of saturable metabolism (mg/hr/kg^0.74)
CONSTANT  KM = 5.75      !Affinity of saturable metabolism (mg/L)

!Scaled parameters
   QC = QCC*BW**0.7     !Cardiac output (L/hr)
   QP = QPC*BW**0.7     !Alveolar ventilation (L/hr)
   QL = QLC*QC          !Liver arterial blood flow - L/hr
   QF = QFC*QC          !Fat blood flow - L/hr
   QR = QRC*QC                  !Richly Perfused Tissue blood flow - L/hr
   QS = QSC*QC          !Slowly Perfused Tissue blood flow - L/hr
   QSHUNT =QSHUNTC*QC           !Shunt blood flow - L/hr
   QM = QMC*QC                  !Muscle and Sking blood flow - L/hr
   QGI= QGIC*QC      !GI blood flow - L/hr
   QLUNG=QC             !Lung - L/hr
   VF = VFC*BW          !Volume of fat - L
   VL = VLC*BW          !Liver volume - L
   VR = VRC*BW                  !Richly Perfused Tissue volume - L
   VS = VSC*BW               !Slowly Perfused Tissue volume - L
   VLUNG= VLUNGC*BW   !Lung volume- L
   VGI= VGIC*BW     !GI Volume- L
   VM = VMC*BW                  !Muscle and Skin volume- L
   VMAX=VMAXC*BW**0.74  !Metabolism- mg/hr

!Parameters for simulation of experiment**********************
CONSTANT  exposure=87.5       !ppm
 conc0ppm=exposure
 CIN =CONC0ppm*MW/24450.  !Initial conc in chamber (mg/l)
logical EXERCISE
CONSTANT EXERCISE = .FALSE.  !Not exercise, at rest;define exposure scenarios

!Timing commands
CONSTANT   TSTOP = 300. !Length of experiment (hrs)
CINTERVAL  CINT  = 0.1  !Communication interval

!Method of integration
ALGORITHM IALG = 2         !Gear method for stiff systems

END     !End of initial

DYNAMIC
!Exposure scenario:intermitten, at rest
IF (EXERCISE) GOTO 35
If (t.le.7) then
   conc0ppm=exposure
 else if (t.ge.24.and.t.le.31) then
   conc0ppm=exposure
 else if (t.ge.48.and.t.le.55) then
   conc0ppm=exposure
```

```
 else
   conc0ppm=0.
ENDIF
CIN =CONC0ppm*MW/24450.  !Initial conc in chamber (mg/l)

35:CONTINUE
!Intermitten exercise and rest
IF (EXERCISE) THEN
If (t.ge.1.8333.and.t.le.2) then
   QCC=31.89
   QPC=65.31
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.038    !Fractional arterial blood flow to liver
   QFC = 0.077    !Fractional blood flow to fat
   QRC = 0.272    !Fractional blood flow to richly perfused tissues
   QSC = 0.036    !Fractional blood flow to slowly perfused tissues
   QSHUNTC= 0.164 !Fractional blood flow to shunt
   QMC = 0.318    !Fractional blood flow to muscle and skin
   QGIC= 0.095    !Fractional blood flow to GI
 else if (t.ge.2.8333.and.t.le.3) then
   QCC=31.89
   QPC=65.31
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.038    !Fractional arterial blood flow to liver
   QFC = 0.077    !Fractional blood flow to fat
   QRC = 0.272    !Fractional blood flow to richly perfused tissues
   QSC = 0.036    !Fractional blood flow to slowly perfused tissues
   QSHUNTC= 0.164 !Fractional blood flow to shunt
   QMC = 0.318    !Fractional blood flow to muscle and skin
   QGIC= 0.095    !Fractional blood flow to GI
 else if (t.ge.4.8333.and.t.le.5) then
   QCC=31.89
   QPC=65.31
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.038    !Fractional arterial blood flow to liver
   QFC = 0.077    !Fractional blood flow to fat
   QRC = 0.272    !Fractional blood flow to richly perfused tissues
   QSC = 0.036    !Fractional blood flow to slowly perfused tissues
   QSHUNTC= 0.164 !Fractional blood flow to shunt
   QMC = 0.318    !Fractional blood flow to muscle and skin
   QGIC= 0.095    !Fractional blood flow to GI
 else if (t.ge.6.3333.and.t.le.6.5) then
   QCC=31.89
   QPC=65.31
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.038    !Fractional arterial blood flow to liver
   QFC = 0.077    !Fractional blood flow to fat
   QRC = 0.272    !Fractional blood flow to richly perfused tissues
   QSC = 0.036    !Fractional blood flow to slowly perfused tissues
```

```
   QSHUNTC= 0.164 !Fractional blood flow to shunt
   QMC = 0.318    !Fractional blood flow to muscle and skin
   QGIC= 0.095    !Fractional blood flow to GI
 else
   QCC=19.
   QPC=15.5
  !Blood flow to tissues;add to 1.0;Lapare 1995
   QLC = 0.069    !Fractional arterial blood flow to liver
   QFC = 0.053    !Fractional blood flow to fat
   QRC = 0.379    !Fractional blood flow to richly perfused tissues
   QSC = 0.063    !Fractional blood flow to slowly perfused tissues
   QSHUNTC= 0.151 !Fractional blood flow to shunt
   QMC = 0.114    !Fractional blood flow to muscle and skin
   QGIC= 0.171    !Fractional blood flow to GI
ENDIF
!Recalculate scaled parameters
    QC = QCC*BW**0.7     !Cardiac output (L/hr)
    QP = QPC*BW**0.7     !Alveolar ventilation (L/hr)
    QL = QLC*QC          !Liver arterial blood flow - L/hr
    QF = QFC*QC          !Fat blood flow - L/hr
    QR = QRC*QC                  !Richly Perfused Tissue blood flow - L/hr
    QS = QSC*QC          !Slowly Perfused Tissue blood flow - L/hr
    QSHUNT =QSHUNTC*QC           !Shunt blood flow - L/hr
    QM = QMC*QC                  !Muscle and Sking blood flow - L/hr
    QGI= QGIC*QC      !GI blood flow - L/hr
    QLUNG=QC             !Lung
IF (T.GT.7) THEN
conc0ppm=0
CIN =CONC0ppm*MW/24450.  !Initial conc in chamber (mg/l)
ENDIF
ENDIF

DERIVATIVE

      !AS = Amount in Slowly Perfused Tissues (mg)
      RAS = QS*(CA-CS/PS)
       AS = INTEG(RAS,0.)
       CS = AS/VS

      !AR = Amount in Richly Perfused Tissues (mg)
      RAR = QR*(CA-CR/PR)
       AR = INTEG(RAR,0.)
       CR = AR/VR

      !AF = Amount in fat tissue (mg)
      RAF = QF*(CA-CF/PF)
       AF = INTEG(RAF,0.)
       CF = AF/VF
```

```
      !AL = Amount in liver tissue (mg)
      RAL = QL*CA+QGI*CGI/PGI-(QL+QGI)*CVL-RAM
       AL = INTEG(RAL,0.)
       CL = AL/VL
       CVL=CL/PL

      !AM = Amount of 1,1,1-trichloroethane metabolized (mg)
      RAM = VMAX*CL/PL/(KM+CL/PL)
       AM = INTEG(RAM,0.)

      !AMUS = Amount in muscle and skin tissue (mg)
           RAMUS = QM*(CA-CM/PM)
           AMUS = INTEG(RAMUS,0.)
           CM   = AMUS/VM

      !AGI = Amount in GI tissue (mg)
           RAGI= QGI*(CA-CGI/PGI)
         AGI=INTEG(RAGI,0.)
            CGI=AGI/VGI

           !Amount inhaled (mg)
           RAIN = QP*CIN
           AIN = INTEG(RAIN,0.)

           !Amount exhaled (mg)
           RAEX=QP*CEX
           AEX=INTEG(RAEX,0.)
           CEX=CA/PB
           CEXPPM = (0.7*CEX+0.3*CIN)*24450./MW

           !ALUNG = Amount in lung tissue (mg)
           RLUNG= QLUNG*(CV-CLUNG/PLUNG)+(RAIN-RAEX)
           ALUNG= INTEG(RLUNG,0.)
           CLUNG= ALUNG/VLUNG
           CA=CLUNG/PLUNG

      !CA = Blood concentration (mg/L)
      CV = ((QL+QGI)*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR+QM*CM/PM+QSHUNT*CA)/QC

    !TMASS = mass balance (mg)
     AINTOBODY=AIN-AEX
     AINCAL=AF+AL+AS+AR+AM+AMUS+AGI+ALUNG
     ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)
END       !End of derivative
END       !End of dynamic
END       !End of program
```

```
!FILE Lapare.CMD FOR TCA MODEL REPRODUCTION BY Y.LU AND M.LOHITNAVY
!DEC. 17TH, 2004. Reviewed by LU Y 5/22/2005

SET TITLE ='TCA TIME-COURSE'
PREPAR /ALL

SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.

PROCED CHECK
START
PLOT ERROR
END

!At rest
PROCED TCALOW
S EXPOSURE=87.5
S EXERCISE=.F.
START
SET TITLE ='TCA INHALATION IN HUMANS - 87.5 PPM'
PLOT /DATA=LOWESTCV CV /LOG /LO=.001 /HI=10 ...
    /TAG=' - Venous Blood Concentration (mg/l)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
PLOT /DATA=LOWESTAIR CEXppm /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Alveolar Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
END
!Data digitized from Lapare 1995 using digiMatic by Lohitnavy M
DATA LOWESTCV (t,CV)
6.5     1.53
7.5     0.79
30.5    1.67
31.5    0.82
54.5    1.65
55.5    0.87
END

!Data digitized from Lapare 1995 using digiMatic by Lohitnavy M
DATA LOWESTAIR (t,CEXppm)
6.5     58.4
7.5     20.2
8.      13.4
30.5    61.4
31.5    20.7
32.     17.6
54.5    63.7
55.5    21.7
56.     16.6
79.     3.4
END
```

```
PROCED TCAHIGH
S EXPOSURE=175.
START
SET TITLE ='TCA INHALATION IN HUMANS - 175 PPM'
PLOT /DATA=HIGHCV CV /LOG /LO=.001 /HI=10 ...
    /TAG=' - Venous Blood Concentration (mg/l)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
PLOT /DATA=HIGHAIR CEXppm /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Alveolar Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
END

!Data digitized from Lapare 1995 using digiMatic by Lohitnavy M
DATA HIGHCV (t,CV)
6.5     3.
7.5     1.56
30.5    2.66
31.5    1.2
54.5    2.68
55.5    1.4
END

!Data digitized from Lapare 1995 using digiMatic by Lohitnavy M
DATA HIGHAIR (t,CEXppm)
6.5     124.8
7.5     40.6
8.      28.3
30.5    125.5
31.5    45.2
32.     31.4
54.5    125.9
55.5    45.3
56.     33.9
79.     5.7
END

PROCED TCACV
S EXPOSURE=87.5
START
SET TITLE ='TCA INHALATION IN HUMANS'
SET DEFPLT=.T.
PLOT /DATA=LOWESTCV CV /LOG /LO=.001 /HI=10 ...
    /TAG=' - Venous Blood Concentration (mg/l)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
S EXPOSURE=175.
START
SET DEFPLT=.F.
PLOT /DATA=HIGHCV CV /LOG /LO=.001 /HI=10 ...
```

```
    /TAG=' - Venous Blood Concentration (mg/l)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
END

PROCED TCAAIR
S EXPOSURE=87.5
START
SET DEFPLT=.T.
SET TITLE ='TCA INHALATION IN HUMANS'
PLOT /DATA=LOWESTAIR CEXppm /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Alveolar Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
S EXPOSURE=175.
START
SET DEFPLT=.F.
PLOT /DATA=HIGHAIR CEXppm /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Alveolar Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=420 /CHAR=1
END


!Lapare exercise and rest
PROCED TCAEXER
SET exposure=83.1
S EXERCISE=.T.
START
SET TITLE ='TCA INHALATION IN HUMANS - 83.1 PPM'
PLOT /DATA=exerCV CV /LOG /LO=.001 /HI=10 ...
    /TAG=' - Venous Blood Concentration (mg/l)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
PLOT /DATA=exerAIR CEXppm /LOG /LO=.01 /HI=1000 ...
    /TAG=' - Alveolar Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END

!Data from bottom line of table 4 in Lapare 1995
DATA exerCV (t,CV)
6.5     1.95
7.5     0.92
END

!Data from table 10 in Lapare 1995
DATA exerAIR (t,CEXppm)
1.8     52.21
2       61.75
2.8     58.67
3       66.79
4.8     59.3
5       65.28
```

6.3 62.36
6.5 66.5
7.5 23.7
8. 16.7
END

7. Loizou et al. 1996

```
PROGRAM: Loizou.CSL PHYSIOLOGICAL MODEL
!PREPARED BY Y.LU AND M.LOHITNAVY FOR EPA CONTRACT 01/05/2005.
!Reviewed by LU Y 5/22/2005.
!Loizou GD,Eldirdiri NI,King LJ.(1996)Physiologically based pharmacokinetics of
!uptake by inhalation of a series of 1,1,1-trihaloethanes:correlation with various
!physiochemical parameters. Inhalation Toxicology, 8,1-19.

INITIAL

!Physiological Parameters **********************************
CONSTANT   BW1rat = 0.215    !Body weight (kg);Range = 0.165-0.265 (Table 1)
CONSTANT   NRAT=1.       !number of rat housed in the chamber.
CONSTANT   QCC = 15.    !Cardiac output (L/hr/kg^0.74)
CONSTANT   QPC = 15.    !Alveolar ventilation (L/hr/kg^0.74)
CONSTANT   QLC = 0.24   !Fractional blood flow to liver
CONSTANT   QFC = 0.06   !Fractional blood flow to fat
CONSTANT   QRC = 0.51   !Fractional blood flow to richly perfused tissues
CONSTANT   QSC = 0.19   !Fractional blood flow to slowly perfused tissues
CONSTANT   VLC = 0.04   !Fraction liver tissue
CONSTANT   VFC = 0.07   !Fraction fat tissue
CONSTANT   VRC = 0.07   !Fraction richly perfused tissues
CONSTANT   VSC = 0.73   !Fraction slowly perfused tissues

!Chemical specific parameters ******************************
!Partition coefficients
CONSTANT   PB = 5.55    !Blood/air partition coefficient
CONSTANT   PL = 1.42    !Liver/blood partition coefficient
CONSTANT   PF = 40.5    !Fat/blood partition coefficient
CONSTANT   PR = 1.42    !Richly perfused tissue/blood partition.
CONSTANT   PS = 0.50    !Slowly perfused tissue/blood partition
CONSTANT   MW = 133.5   !Molecular weight (g/mol)
!Metabolism
CONSTANT   KFC=6.         !first order metabolism rate constant (/hr/kg**(-0.3))
                !Erroneously marked in Loizou 1996
!Calculated parameters
    BW=BW1rat*NRAT       !total body weight of the 1 rat in the chamber (kg)
    VF = VFC*BW              !Volume of fat - L
    VL = VLC*BW              !Liver volume - L
    VR = VRC*BW              !Richly Perfused Tissue volume - L
    VS = 0.91*BW-VL-VF-VR        !Slowly Perfused Tissue volume - L
    QC1rat = QCC*BW1rat **0.74    !Cardiac output - L/hr
    QP1rat = QPC*BW1rat **0.74    !Alveolar ventilation - L/hr
    QP = QP1rat*NRAT
    QC = QC1rat*NRAT
    QL = QLC*QC           !Liver blood flow - L/hr
    QF = QFC*QC           !Fat blood flow - L/hr
    QR = QRC*QC          !Richly Perfused Tissue blood flow - L/hr
    QS = QSC*QC           !Slowly Perfused Tissue blood flow - L/hr
```

```
    KF = KFC*BW1rat **(-0.3)    !First-order metabolism rate constant

!Parameters for simulation of experiment**********************
CONSTANT VCHAMBER0=1.16    !volume of the chamber used (L).
  VCHAMBER= VCHAMBER0-BW  !Net chamber volume after housing 1 rats
CONSTANT KL=0.001          !non-specific loss from the chamber (/hr)
CONSTANT CONC = 2000.      !Initial concentration in chamber (ppm)
 CIN0 = CONC*MW/24450.    !Concentration in mg/l
 ACHM0 = CIN0*VCHAMBER         !initial amount of tca in the chamber (mg)

!Timing commands

CONSTANT   TSTOP = 4.   !Length of experiment (hrs)

!Exposure Definitions
cinterval   CINT  = 0.01  !Communication interval

!Method of integration
ALGORITHM IALG = 2         !Gear method for stiff systems

END     !End of initial

DYNAMIC

DERIVATIVE

!Mass balance in the chamber
RACHM = QP*(CEX-CIN)-KL*ACHM  !AMOUNT OF TCA IN THE CHAMBER (mg).
ACHM = INTEG(RACHM,ACHM0)     !CALCULATION OF TCA AMOUNT IN THE CHAMBER
CIN = ACHM/VCHAMBER
CINPPM = CIN*24450./MW

!MASS BALANCE OF NON-SPECIFIC LOSS TO THE CHAMBER.
RALOSS= KL*ACHM                  !RATE OF TCA LOSS FROM NON-SPECIFIC LOSS (mg/hr)
ALOSS= INTEG(RALOSS,0.) !AMOUNT OF TCA LOSS FROM NON-SPECIFIC LOSS (mg)

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR

    !AF = Amount in fat tissue (mg)
    RAF = QF*(CA-CF/PF)
     AF = INTEG(RAF,0.)
```

```
      CF = AF/VF

      !AL = Amount in liver tissue (mg)
      RAL = QL*(CA-CL/PL)-RAM
       AL = INTEG(RAL,0.)
       CL = AL/VL

      !AM = Amount metabolized (mg)
      RAM = KF*CL/PL*VL
       AM = INTEG(RAM,0.)

      !CA = Blood concentration (mg/L)
       CV = (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
       CA = (QC*CV+QP*CIN)/(QC+QP/PB)
       CEX = CA/PB
     CEXPPM = (0.7*CEX+0.3*CIN)*24450./MW

    !TMASS = mass balance (mg)
     TMASS = AF+AL+AS+AR+AM+ALOSS+ACHM
    ERROR=(TMASS-ACHM0)/ACHM0*100

   TERMT(T.GE.TSTOP)

END      !End of derivative
END      !End of dynamic
END      !End of program
```

```
!FILE Loizou.CMD FOR TCA MODEL REPRODUCTION PREPARED BY Y.LU AND
M.LOHITNAVY
!Jan. 5th, 2005
!Reviewed by LU Y 5/22/2005.

SET TITLE ='TCA TIME-COURSE'
PREPAR /ALL
START
SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.
SET HVDPRN=.T.

PROCED CHECK
START
PLOT ERROR
END

PROCED ALL
SET CONC=25000.
START
s defplt=.t.
SET TITLE ='TCA INHALATION IN RATS'
PLOT /DATA=C5ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=5
SET CONC=15000.
START
s defplt=.t.
SET TITLE ='TCA INHALATION IN RATS'
PLOT /DATA=C4ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=3
SET CONC=8000.
START
s defplt=.t.
SET TITLE ='TCA INHALATION IN RATS'
PLOT /DATA=C3ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=2
SET CONC=4000.
START
s defplt=.t.
SET TITLE ='TCA INHALATION IN RATS'
PLOT /DATA=C2ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=4
SET CONC=2000.
START
s defplt=.f.
SET TITLE ='TCA INHALATION IN RATS'
```

```
PLOT /DATA=C1ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
END

PROCED lowest
START
SET TITLE ='TCA INHALATION IN RATS'
PLOT /DATA=C1ppm CINPPM /LOG /LO=100. /HI=100000 ...
    /TAG=' - Chamber Concentration (PPM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
END

!Digitized by Lohitnavy from Fig4a in Loizou 1996
DATA C5ppm (T,CINPPM)
0.1402 18020.5993
0.2917 14000.8320
0.4319 10877.7346
0.5778 9152.4731
0.7237 7498.9420
0.8751 6566.1030
1.0154 5749.3054
1.1669 5238.7873
1.3183 4902.1276
1.4642 4648.4449
1.6100 4407.8902
1.7671 4292.3221
1.9130 4235.6793
2.0589 4016.4850
2.2103 3963.4823
2.3618 3911.1789
2.5525 3859.5659
2.6591 3758.3740
2.8050 3708.7774
2.9509 3611.5389
3.1079 3516.8500
3.2594 3516.8500
3.3997 3424.6436
3.5511 3379.4510
3.6970 3247.4200
END

DATA C4ppm (T,CINPPM)
0.1402 11023.2001
0.2861 7599.2237
0.4319 5749.3054
0.5834 4902.1276
0.7293 4466.8359
0.8751 4016.4850
```

1.0210 3659.8352
1.1612 3563.8800
1.3127 3424.6436
1.4642 3204.5660
1.6157 3120.5472
1.7559 2959.0605
1.9130 2959.0605
2.0589 2920.0118
2.2159 2768.9026
2.3562 2843.4536
2.5582 2732.3634
2.6647 2696.3063
2.8050 2732.3634
2.9565 2696.3063
3.1079 2625.6133
3.2594 2625.6133
3.3941 2590.9649
3.5511 2523.0338
3.6914 2456.8837
END

DATA C3ppm (T,CINPPM)
0.1402 4124.6263
0.2861 2881.4785
0.4375 2298.9973
0.5834 1986.4467
0.7349 1786.1711
0.8751 1649.3305
1.0210 1543.3397
1.1612 1483.0433
1.3183 1425.1026
1.4698 1369.4256
1.6100 1315.9238
1.7727 1264.5123
1.9242 1247.8254
2.0645 1199.0744
2.2159 1167.6365
2.3674 1152.2280
2.5133 1107.2119
2.6704 1092.6008
2.8162 1049.9142
2.9621 1049.9142
3.1079 982.4437
3.2538 982.4437
3.3997 969.4791
3.5511 931.6027
3.6970 895.2061
END

```
DATA C2ppm (T,CINPPM)
0.1402 3247.4200
0.2917 1883.6490
0.4375 1406.2965
0.5890 1152.2280
0.7293 1036.0593
0.8751 956.6855
1.0210 907.1775
1.1612 871.7352
1.3183 837.6776
1.4698 815.7150
1.6213 773.5021
1.7784 753.2221
1.9242 743.2823
2.0701 714.2432
2.2272 695.5169
2.3730 677.2815
2.5133 668.3439
2.6647 668.3439
2.8162 659.5242
2.9677 633.7574
3.1136 617.1413
3.2706 600.9608
3.4053 585.2045
3.5511 577.4820
3.7026 562.3413
END

DATA C1ppm (t,CINPPM)
0.1402 907.1775
0.2973 677.2815
0.4431 526.2036
0.5890 442.7451
0.7349 398.1071
0.8863 367.6077
1.0266 326.1831
1.1669 297.2192
1.3183 289.4266
1.4810 281.8382
1.6213 270.8272
1.7727 260.2463
1.9242 250.0788
2.0757 237.1373
2.2272 234.0080
2.3730 227.8727
2.5189 218.9699
2.6704 216.0804
2.8162 213.2289
2.9677 210.4151
```

3.1136 204.8983
3.2594 202.1944
3.4053 196.8932
3.5568 194.2949
3.7026 186.7040
END

```
8. DeJongh et al. 1998
PROGRAM: DeJongh.CSL PHYSIOLOGICAL MODEL
!By M.Lohitnavy and Y.Lu 12/23/04.
!DeJongh J,Verhaar H,Hermens J.1998.Role of kinetics inf acute lethality of
!nonreactive volatile organic compounds (VOCs). Toxicol.Sci.45:26-32.
!Reviewed by Lu Yasong 5/22/2005.

INITIAL

!Physiological Parameters **********************************
CONSTANT BW = 0.35       !Body weight (kg);DeJongh 1998
CONSTANT QCC=14          !L/hr/kg^0.7;DeJongh 1998
CONSTANT QPC=14          !L/hr/kg^0.7;DeJongh 1998
  !Blood flow fractions
CONSTANT QLC = 0.25      !Fractional blood flow to liver;DeJongh 1998
CONSTANT QFC = 0.09      !Fractional blood flow to fat;DeJongh 1998
CONSTANT QRC = 0.52      !Fractional blood flow to richly perfused;DeJongh 1998
CONSTANT QSC = 0.11      !Fractional blood flow to slowly perfused;DeJongh 1998
CONSTANT QBRC= 0.03      !Fractional blood flow to brain;DeJongh 1998
  !Volume fractions
CONSTANT VLC=0.04        !Fractional volume of liver;DeJongh 1998
CONSTANT VFC=0.07        !Fractional volume of fat;DeJongh 1998
CONSTANT VBRC=0.006      !Fractional volume of brain;DeJongh 1998
CONSTANT VBRwaterC=0.85          !Fractional volume of brain water;DeJongh 1998
CONSTANT VBRlipidC=0.15          !Fractional volume of brain lipid;DeJongh 1998
    VRC=0.09-VLC-VBRC    !Fractional volume of richly perfused;DeJongh 1998
    VSC=0.82-VFC       !Fractional volume of slowly perfused;DeJongh 1998

!Chemical specific parameters ********************************
  !Partition coefficients
CONSTANT KOW= 302    !Octanol/water,10**2.48;DeJongh 1998
CONSTANT PB = 5.76   !Blood/air;DeJongh 1998
CONSTANT PL = 1.49   !Liver/blood;DeJongh 1998
CONSTANT PF = 45.66  !Fat/blood;DeJongh 1998
   PR = PL          !Richly perfused tissue/blood;NOT clarified by DeJongh 1998
CONSTANT PS = 0.55   !Poorly perfused tissue/blood;DeJongh 1998
CONSTANT PBR =2.39   !Brain/blood;DeJongh 1998
CONSTANT PBRL=15.64  !Brain/brain lipid;DeJongh 1998
  !Metabolism
CONSTANT VMAXC = 0.  !Capacity of saturable metabolism (mg/kg/hr^0.7);
CONSTANT KM = 0.001  !Affinity of saturable metabolism (mg/L);
CONSTANT KFC= 5.0    !First order metabolism (/h/kg^(-0.3));DeJongh 1998

!Scaled parameters
   VF = VFC*BW          !Fat volume (L)
   VL = VLC*BW          !Liver volume (L)
   VR = VRC*BW          !Richly Perfused volume (L)
   VS = VSC*BW              !Slowly Perfused volume (L)
   VBR= VBRC*BW         !Brain volume (L)
```

```
  VBRwater=VBR*VBRwaterC !Brain water volume (L)
  VBRlipid=VBR*VBRlipidC !Brain lipid volume (L)

  QC = QCC*BW**0.7      !Cardiac output (L/hr);DeJongh 1998
  QP = QPC*BW**0.7      !Alveolar ventilation (L/hr);DeJongh 1998
  QL = QLC*QC           !Blood flow to liver (L)
  QF = QFC*QC           !Blood flow to fat (L)
  QR = QRC*QC           !Blood flow to richly perfused tissues (L)
  QS = QSC*QC           !Blood flow to slowly perfused tissues (L)
  QBR= QBRC*QC          !Blood flow to brain (L)

  KF=KFC*BW**(-0.3)     !First order metabolism (mg/hr);DeJongh 1998
  VMAX=VMAXC*BW**0.7    !Saturable metabolism (mg/hr);DeJongh 1998

!Parameters for simulation of experiment**********************
CONSTANT MW = 133.5      !Molecular weight of 1,1,1,-trichloroethane (g/mol)
CONSTANT conc0ppm=38000  !Exposure concentration (ppm)
  CIN=conc0ppm*MW/24450  !mg/L

!Timing commands
CONSTANT   TSTOP = 10.   !Length of experiment (hrs)
CINTERVAL  CINT  = 0.01  !Communication interval

!Method of integration
ALGORITHM IALG = 2       !Gear method for stiff systems

END                  !End of INITIAL

DYNAMIC

DERIVATIVE

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR

    !AF = Amount in fat tissue (mg)
    RAF = QF*(CA-CF/PF)
     AF = INTEG(RAF,0.)
     CF = AF/VF

    !AL = Amount in liver tissue (mg)
    RAL = QL*(CA-CL/PL)-RAM
```

```
      AL = INTEG(RAL,0.)
      CL = AL/VL
      CVL= CL/PL

     !AM = Amount of 1,1,1-trichloroethane metabolized (mg)
     RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
      AM = INTEG(RAM,0.)


     !Amount in whole brain (mg)
      RABR=QBR*(CA-CVBR)
       ABR=INTEG(RABR,0.)
       CBR=ABR/VBR
       CBRM=CBR/MW  !mmol/L
       CVBR=CBR/PBR
       CBRlipid=CBR/(VBRwaterC/KOW + VBRlipidC)
       CBRlipidM=CBRlipid/MW  !mmol/L

          !Amount inhaled (mg)
          RAIN = QP*CIN
          AIN = INTEG(RAIN,0.)

          !Amount exhaled (mg)
          RAEX=QP*CEX
          AEX=INTEG(RAEX,0.)
          CEX=CA/PB
          CEXPPM = (0.7*CEX+0.3*CIN)*24450./MW

        !Blood concentrations (mg/L)
      CV=(QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR+QBR*CVBR)/QC
      CVM=CV/MW    !mmol/L
      CA=(QC*CV+QP*CIN)/(QC+QP/PB)

    !TMASS = mass balance (mg)
    !Amount in the body,difference b/t inhalation and exhalation
     AINTOBODY=AIN-AEX
    !Amount in the body,summation of all compartments
     AINCAL=AF+AL+AS+AR+AM+ABR
    ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)
END      !End of derivative
END      !End of dynamic
END      !End of program
```

```
!FILE DeJongh.CMD FOR TCA MODEL REPRODUCTION BY.LU AND M.LOHITNAVY
!DEC. 23rd, 2004. Reviewed by LU Yasong 5/22/2005

PREPAR /ALL

SET FTSPLT=.T.,XINCPL=5.,SYMCPL=.F.,GRDCPL=.F.,WESITG=.F.
SET HVDPRN=.T.

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED CONC18000
SET conc0ppm = 18000
START
SET TITLE ='TCA INHALATION IN RATS - 18000 PPM'
s defplt=.t.
PLOT /DATA=CONC18000 CVM /LOG /LO=1 /HI=100 ...
    /TAG=' - Venous Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.t.
PLOT /DATA=CONC18000 CBRM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.f.
PLOT /DATA=CONC18000 CBRlipidM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Lipid Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END

PROCED CONC14250
SET conc0ppm = 14250
START
SET TITLE ='TCA INHALATION IN RATS - 14250 PPM'
s defplt=.t.
PLOT /DATA=CONC14250 CVM /LOG /LO=1 /HI=100 ...
    /TAG=' - Venous Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.t.
PLOT /DATA=CONC14250 CBRM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.f.
PLOT /DATA=CONC14250 CBRlipidM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Lipid Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END
```

```
PROCED CONC18400
SET conc0ppm = 18400
START
SET TITLE ='TCA INHALATION IN RATS - 18400 PPM'
s defplt=.t.
PLOT /DATA=CONC18400 CVM /LOG /LO=1 /HI=100 ...
    /TAG=' - Venous Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.t.
PLOT /DATA=CONC18400 CBRM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.f.
PLOT /DATA=CONC18400 CBRlipidM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Lipid Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END

PROCED CONC10300
SET conc0ppm = 10300
START
SET TITLE ='TCA INHALATION IN RATS - 10300 PPM'
s defplt=.t.
PLOT /DATA=CONC10300 CVM /LOG /LO=1 /HI=100 ...
    /TAG=' - Venous Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.t.
PLOT /DATA=CONC10300 CBRM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.f.
PLOT /DATA=CONC10300 CBRlipidM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Lipid Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END

PROCED CONC38000
SET conc0ppm = 38000
START
SET TITLE ='TCA INHALATION IN RATS - 38000 PPM'
s defplt=.t.
PLOT /DATA=CONC38000 CVM /LOG /LO=1 /HI=100 ...
    /TAG=' - Venous Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
s defplt=.t.
PLOT /DATA=CONC38000 CBRM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
```

```
s defplt=.f.
PLOT /DATA=CONC38000 CBRlipidM /LOG /LO=1 /HI=100 ...
    /TAG=' - Brain Lipid Concentrations (mmol/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=10 /CHAR=1
END

!Calculated values of DeJongh,not real experimental data.
DATA CONC18000 (T,CVM,CBRM,CBRlipidM)
3       3.2     8.      52.1
END

DATA CONC14250 (T,CVM,CBRM,CBRlipidM)
7       2.9     7.1     46.2
END

DATA CONC18400 (T,CVM,CBRM,CBRlipidM)
4       3.4     8.5     55.6
END

DATA CONC10300 (T,CVM,CBRM,CBRlipidM)
6       2.      5.      32.8
END

DATA CONC38000 (T,CVM,CBRM,CBRlipidM)
0.25    4.2     11.4    74.9
END
```

```
PROGRAM: Tardif.CSL
!Tardif, R., Charest-Tardif, G. (1999) The importance of measured end-points in
!demonstrating the occurrence of interactions: a case study with methylchloroform and
!m-xylene. Toxicol Sci 49, 312-7.
!Edited by Lu Y 5/4/2006

INITIAL

!Physiological Parameters **********************************
!Constants set for the rat
CONSTANT BW = 0.225       !Mean body weight (kg); Tardif 1999
CONSTANT QCC= 15.         !Cardiac output constant (L/hr/kg^0.74); Tardif 1999
CONSTANT QPC= 15.         !Alveolar ventilation constant (L/hr/kg^0.74); Tardif 1999
  !Blood flow fractions
CONSTANT QLC = 0.25       !Fractional blood flow to liver;Tardif 1999.
CONSTANT QFC = 0.09       !Fractional blood flow to fat;Tardif 1999.
CONSTANT QSC = 0.15       !Fractional blood flow to slowly perfused;Tardif 1999.
 QRC=1.0-(QFC+QSC+QLC)    !Fractional blood flow to rapidly perfused;Tardif 1999.
  !Volume fractions
CONSTANT VLC = 0.049      !Fraction liver tissue;Tardif 1999.
CONSTANT VFC = 0.09       !Fraction fat tissue;Tardif 1999.
CONSTANT VRC = 0.05       !Fraction richly perfused tissues;Tardif 1999.
CONSTANT VSC = 0.72       !Fraction poorly perfused tissues;Tardif 1999.

!Chemical specific parameters ********************************
  !Partition coefficients
CONSTANT PB = 5.76        !Blood/air;Tardif 1999.
CONSTANT PLA = 8.6        !Liver/air;Tardif 1999.
CONSTANT PFA = 263.       !Fat/air;Tardif 1999.
CONSTANT PRA = 8.6        !Richly perfused/air;Tardif 1999.
CONSTANT PSA = 3.15       !Slowly perfused/air;Tardif 1999.
  PL=PLA/PB
  PF=PFA/PB
  PR=PRA/PB
  PS=PSA/PB

  !Metabolism;saturable;estimated from Schumann data and Reitz drinking water study
CONSTANT VMAXC = 0.42 !Capacity of saturable metabolism (mg/hr/kg^0.7);Tardif 1999.
CONSTANT KM = 5.75     !Affinity of saturable metabolism (mg/L);Tardif 1999.
CONSTANT KF=0.          !First order metabolism (/hr);ignored in Tardif 1999.

!Scaled parameters
   QC = QCC*BW**0.74      !Cardiac output (L/hr);not clarified, assumption
   QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);not clarified, assumption
   VF = VFC*BW           !Fat volume (L)
   VL = VLC*BW           !Liver volume (L)
   VR = VRC*BW                 !Richly Perfused volume (L)
   VS = VSC*BW               !Slowly Perfused volume (L)
   QL = QLC*QC           !Liver blood flow (L/hr)
```

```
  QF = QFC*QC          !Fat blood flow (L/hr)
  QR = QRC*QC              !Richly Perfused blood flow (L/hr)
  QS = QSC*QC            !Slowly Perfused blood flow (L/hr)
  VMAX=VMAXC*BW**0.7    !Capacity of saturable metabolism (mg/hr);
                !not clarified, assumption

!Exposure Parameters
 CONSTANT   MW = 133.5   !Molecular weight (g/mol)
 CONSTANT   CONC=400     !Inhaled concentration (ppm)
   CIN = CONC*MW/24450.
 CONSTANT   TCHNG=4      !Inhalation time (hr)


!Timing commands
CONSTANT   TSTOP = 6.  !'Length of experiment (hrs)'
CINTERVAL  CINT  = 0.01 !Communication interval

!Method of integration
ALGORITHM IALG = 2  !Gear method for stiff systems
END                 !End of initial

DYNAMIC

 !Rat and human inhalation exposure in dynamic chamber
  IF (T.LT.TCHNG) THEN
   CIN = CONC*MW/24450.
  ELSE
   CIN = 0
  ENDIF

DERIVATIVE

   !Amount inhaled
    RAIN = QP*CIN
     AIN = INTEG(RAIN,0.)
   !Amount exhaled
    RAEX = QP*CEX
     AEX = INTEG(RAEX,0.)

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR
```

```
      !AF = Amount in fat (mg)
      RAF = QF*(CA-CF/PF)
       AF = INTEG(RAF,0.)
       CF = AF/VF

      !AL = Amount in liver (mg)
      RAL = QL*(CA-CL/PL)-RAM
       AL = INTEG(RAL,0.)
       CL = AL/VL

      !AM = Amount metabolized (mg)
      RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
       AM = INTEG(RAM,0.)

      !Blood concentrations (mg/L)
      CV= (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
      CA=(QC*CV+QP*CIN)/(QC+QP/PB)
      CEX = CA/PB
      CEXPPM = (0.667*CEX+0.333*CIN)*24450./MW !ppm
      CEXMGL=0.667*CEX+0.333*CIN        !mg/L

      !TMASS = mass balance (mg)
      !Amount in the body
      AINTOBODY=AIN-AEX
      !Amount in the body,summation of all compartments
      AINCAL=AF+AL+AS+AR+AM
      ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)       !'Sets Termination Condition'
END     !'End of derivative'
END     !'End of dynamic'
END     !'End of program'
```

```
!Tardif.cmd, editted by Lu Yasong 5/4/2006

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED RAT
!Simulate rat inhalation 400 ppm; not data reported.
  START
  SET TITLE='Rat inhalation Tardif 1999'
  PLOT CV /XLO=0 /XHI=6 /LOG /LO=1 /HI=50 ...
    /TAG='Venous Conc (mg/L)' /xtag='Time (hr)'
END

PROCED Human
!Simulate human inhalation 400 ppm
set BW=70  !not clarified; assumption
set QCC=18,QPC=18
set VLC=0.026,VFC=0.19,VRC=0.05,VSC=0.62
set QLC=0.26,QFC=0.05,QSC=0.25
set PB=2.53
  START
  SET TITLE='Human inhalation Tardif 1999'
  PLOT /DATA=HUMAN CV /XLO=0 /XHI=6 /LOG /LO=0.1 /HI=50 /char=1...
    /TAG='Venous Conc (mg/L)' /xtag='Time (hr)'
END

!Digitized from Tardif and Charest-Tardif 1999 Fig.1.left panel.
DATA human (T,CV)
1.1     3.05
2.4     3.05
3.75    4
END
```

Appendix II

Summary Table for Human Studies

Summary of Human Controlled-Exposure Studies and Findings for 1,1,1-Trichloroethane

Reference Exposure Duration / # of Subjects	Experimental Design	Measurements for 1,1,1-TCA?	Neurobehavioral Test Findings																		
			Simple reaction time	Choice reaction time	Stroop test	Digital step-input tracking	Stress arousal check list	EEG	Tiredness score	Visual evoked potential (VEP)	Body sway	Perception test (tachistoscopic task)	Wechsler memory scale	Complex reaction times	Manual dexterity	Perceptual speed (ident #)	Perceptual speed (spokes)	Hand tapping speed	Critical flicker fusion threshold	Gaze deviation nystagmus
Mackay *et al.* (1987) 3.5 hr / 12 males	0, 175, 350 ppm, 3.5 hours, continuous exposure NB testing: @ 0, 20, 60, 120 & 180 minutes	Blood: 20, 60, 120 & 180 minutes	X	X	X	X	neg														
Muttray *et al.* (2000) 4 hr / 12 males	20, 200 ppm, 4 hours, continuous exposure NB testing: @ 0 & 3.7 hours	Venous blood: 0 & 3.7 hours						X	X												
Laine *et al.* (1996) 5 hr / 9 males	Exposure day 1: 200 ppm, 3 hours exposure → 40-minute break → 40 min exposure. 10 minutes of exercise (bicycle ergometer) at beginning of morning and afternoon sessions. Exposure day 2: 135 ppm (baseline exposure) combined with transient peak concentration (400 ppm) Exposure day 3: control NB testing: EEG during 1st 20-min period (peak), body sway & reaction times during 2nd 20-min period (2nd peak). Repeated after 120 min in chamber and in afternoon session.	Venous blood: @ (morning session) 7, 9, 11, 13, 15, 20, 40, 60, 120, 180, (afternoon session) 220, 227, 229, 231, 233, 235, 240, 260 & 290 minutes						neg		neg	neg										
Savolainen *et al.* (1981, 1982a,b) 4 hr / 9 males	200, 400 ppm, 4 hours, continuous. NB testing: prior to exposure, between 20 min & 1 1/2 hour, and between 3 hours & 3 3/4 hours.	Venous blood: pre-exposure, 1 hour, 2 hours, 3.5 hours	neg								neg							neg	neg	neg
Salvini *et al.* (1971) 8 hr / 6 males	350, 450 ppm, 4 hours exposure → 1 ½ hour break → 4 hours exposure (8 hours total exposure time). Alternated activities as follows: 1 hr at rest, then 20 minutes physical exercise. NB testing: 0 & 8 hours (immediately after entering exposure room and before leaving exposure room).	–										neg	neg	neg	neg[1]					
Gamberale & Hultengren (1973) 0.5 hr / 12 males	250 ppm (30 min) → 350 ppm (30 min) → 450 ppm (30 min) → 550 ppm (30 min). NB testing: final 20 minutes of each exposure period.	Alveolar air: every other minute. Arterial blood (2 subjects): 37 measurements parallel to alveolar air samples.	X	X											X[2]	X	X			

X = positive finding.
[1]Threading needles in hole.
[2]Wire spiral.

Appendix III

Model code (CSL files) and Command files (CMD files) for the Calculation of Internal Doses

```
PROGRAM: ReitzRatIDs.CSL
!Original code supplied by Reitz. Modified the SimuSolv format into ACSL Tox format by Lu Y.
!12/2004.
!Reitz RH,McDougal JN,Himmelstein MW,Nolan RJ,Schumann AM. 1988 Physiologically based
!pharmacokinetic modelling with methylchloroform: Implications for interspecies,high dose/low
!dose, and dose route extrapolations. Toxicol.Appl. Pharmacol.1988,95:185-199
!Edited by Lu Y 12/23/2004; Dennison 04/06/05

!Reviewd by Lu Y 5/23/2005

!Trim this code to simulate only dynamic chamber inhalation exposures.
!Quast JF,Calhoun LL,Frauson LE. Fundam Appl Toxicol,1988,11:611-625. No PK data.
!Fischer 344 rats;150,500,1500 ppm,6 hr/day,5 days/week,24 month (516 exposure days).
!For RfC calculation.

INITIAL

!Physiological Parameters **********************************
!Constants set for the rat
!Male rat body weight (Digitized from Fig.2 in Quast 1988 by Lu Yasong)
TABLE BWMALET,1,25/0,720,1440,2160,2880,3600,4320,5040,5760,6480,7200,7920,&
        8640,9360,10080,10800,11520,12240,12960,13680,14400,15120,15840,&
        16560,17280,&
        0.229,0.282,0.32,0.346,0.364,0.382,0.394,0.413,0.427,0.435,0.44,&
        0.443,0.445,0.459,0.459,0.464,0.466,0.459,0.449,0.446,0.448,&
        0.442,0.441,0.428,0.425/
!Male rat body weight(Digitized from Fig.2 in Quast 1988 by Lu Yasong)
TABLE BWFEMALET,1,25/0,720,1440,2160,2880,3600,4320,5040,5760,6480,7200,7920,&
        8640,9360,10080,10800,11520,12240,12960,13680,14400,15120,15840,&
        16560,17280,&
        0.141,0.162,0.18,0.194,0.199,0.204,0.206,0.215,0.222,0.219,0.231,&
        0.234,0.24,0.251,0.256,0.26,0.265,0.272,0.257,0.264,0.266,&
        0.27,0.275,0.266,0.271/
 BWMALE = BWMALET(T)
 BWFEMALE = BWFEMALET(T)
LOGICAL SEX
CONSTANT SEX=.TRUE.  !male
IF (SEX) THEN
  BW = BWMALE
 ELSE             !female
  BW = BWFEMALE
ENDIF

CONSTANT QCC= 15.        !Cardiac output constant (L/hr/kg^0.74);Reitz 1988.
CONSTANT QPC= 15.        !Alveolar ventilation constant (L/hr/kg^0.74);Reitz 1988.
  !Blood flow fractions
CONSTANT QLC = 0.24      !Fractional blood flow to liver;Reitz 1988.
CONSTANT QFC = 0.05      !Fractional blood flow to fat;Reitz 1988.
CONSTANT QSC = 0.18      !Fractional blood flow to slowly perfused;Reitz 1988.
```

```
 QRC=1.0-(QFC+QSC+QLC)    !Fractional blood flow to rapidly perfused;Reitz 1988.
  !Volume fractions
CONSTANT VLC = 0.04       !Fraction liver tissue;Reitz 1988.
CONSTANT VFC = 0.07       !Fraction fat tissue;Reitz 1988.
CONSTANT VRC = 0.05       !Fraction richly perfused tissues;Reitz 1988.
 VSC = 0.91-VLC-VFC-VRC   !Fraction slowly perfused;Reitz 1988.

!Chemical specific parameters ******************************
  !Partition coefficients
CONSTANT PB = 5.76        !Blood/air;Reitz 1988.
CONSTANT PLA = 8.6        !Liver/air;Reitz 1988.
CONSTANT PFA = 263.       !Fat/air;Reitz 1988.
CONSTANT PRA = 8.6        !Richly perfused/air;Reitz 1988.
CONSTANT PSA = 3.15       !Slowly perfused/air;Reitz 1988.
  PL=PLA/PB
  PF=PFA/PB
  PR=PRA/PB
  PS=PSA/PB

  !Metabolism;saturable;estimated from Schumann data and Reitz drinking water study
CONSTANT VMAXC = 0.419 !Capacity of saturable metabolism (mg/hr/kg^0.7);Reitz 1988.
CONSTANT KM = 5.75     !Affinity of saturable metabolism (mg/L);Reitz 1988.
CONSTANT KF=0.         !First order metabolism (/hr);ignored in Reitz 1988.

!Inhalation duration
CONSTANT TCHNG = 6.     !Length of inhalation exposure (hrs)/day

!Scaled parameters
   QC = QCC*BW**0.74      !Cardiac output (L/hr);Reitz 1988.
   QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);Reitz 1988.
   VF = VFC*BW           !Fat volume (L)
   VL = VLC*BW           !Liver volume (L)
   VR = VRC*BW                 !Richly Perfused volume (L)
   VS = VSC*BW               !Slowly Perfused volume (L)
   QL = QLC*QC           !Liver blood flow (L/hr)
   QF = QFC*QC           !Fat blood flow (L/hr)
   QR = QRC*QC                 !Richly Perfused blood flow (L/hr)
   QS = QSC*QC               !Slowly Perfused blood flow (L/hr)
   VMAX=VMAXC*BW**0.7     !Capacity of saturable metabolism (mg/hr);Reitz 1988.

!Other Compound Specific Parameters
  CONSTANT   MW = 133.5   !'Molecular weight (g/mol)'
  CONSTANT  EXPOSURE=500.0   !'Inhaled concentration (ppm)',NOAEL,Quast 1988
  DAILYINDICATOR = 1  !either 1 or 0
  WEEKLYINDICATOR = 1 !either 1 or 0
    CONC = EXPOSURE * DAILYINDICATOR * WEEKLYINDICATOR
    CIN = CONC*MW/24450.  !mg/L
  I = 0  !counter for exposure setting
  K = 0  !another counter
```

```
!Timing commands
CONSTANT   TSTOP = 12500.  !'Length of experiment (hrs)'
CINTERVAL  CINT  = 0.1 !Communication interval

!Method of integration
ALGORITHM IALG = 2  !Gear method for stiff systems
END                 !End of initial

DYNAMIC
    !Setting exposure
    procedural
    IF(T.GE.168*K.AND.T.LT.(120+168*K)) THEN
      WEEKLYINDICATOR = 1
    ENDIF
     IF (T.GE.(24*I).and.t.le.(24*I+TCHNG)) THEN
       DAILYINDICATOR = 1
     ENDIF
      CONC = EXPOSURE*DAILYINDICATOR*WEEKLYINDICATOR
      CIN = CONC*MW/24450.  !mg/L
    end

DERIVATIVE

BWMALE = BWMALET(T)
 BWFEMALE = BWFEMALET(T)
IF (SEX) THEN
  BW = BWMALE
 ELSE             !female
  BW = BWFEMALE
ENDIF

!Scaled parameters
  QC = QCC*BW**0.74      !Cardiac output (L/hr);Reitz 1988.
  QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);Reitz 1988.
  VF = VFC*BW           !Fat volume (L)
  VL = VLC*BW           !Liver volume (L)
  VR = VRC*BW                 !Richly Perfused volume (L)
  VS = VSC*BW               !Slowly Perfused volume (L)
  QL = QLC*QC           !Liver blood flow (L/hr)
  QF = QFC*QC           !Fat blood flow (L/hr)
  QR = QRC*QC                 !Richly Perfused blood flow (L/hr)
  QS = QSC*QC               !Slowly Perfused blood flow (L/hr)
  VMAX=VMAXC*BW**0.7     !Capacity of saturable metabolism (mg/hr);Reitz 1988.

   !Amount inhaled
    RAIN = QP*CIN
     AIN = INTEG(RAIN,0.)
   !Amount exhaled
```

```
RAEX = QP*CEX
 AEX = INTEG(RAEX,0.)

!AS = Amount in Slowly Perfused Tissues (mg)
RAS = QS*(CA-CS/PS)
 AS = INTEG(RAS,0.)
 CS = AS/VS

!AR = Amount in Richly Perfused Tissues (mg)
RAR = QR*(CA-CR/PR)
 AR = INTEG(RAR,0.)
 CR = AR/VR

!AF = Amount in fat (mg)
RAF = QF*(CA-CF/PF)
 AF = INTEG(RAF,0.)
 CF = AF/VF

!AL = Amount in liver (mg)
RAL = QL*(CA-CL/PL)-RAM
 AL = INTEG(RAL,0.)
 CL = AL/VL
AUCCL=INTEG(CL,0.)
TWACL=AUCCL/(T/24+1E-30) !time-weighted avarage CL,mg/L/day

!AM = Amount metabolized (mg)
RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
 AM = INTEG(RAM,0.)
 AMB=AM/BW     !Standardized by BW
 TWAAMB=AMB/(T/24+1E-30) !time-weighted average AMB,mg/L/day

!Blood concentrations (mg/L)
CV= (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
CA=(QC*CV+QP*CIN)/(QC+QP/PB)
CEX = CA/PB
CEXPPM = (0.667*CEX+0.333*CIN)*24450./MW !ppm
CEXMGL=0.667*CEX+0.333*CIN        !mg/L
AUCCV=INTEG(CV,0.)
TWACV=AUCCV/(T/24+1E-30) !time-weighted avarage CV,mg*day/L

!TMASS = mass balance (mg)
!Amount in the body
AINTOBODY=AIN-AEX
!Amount in the body,summation of all compartments
AINCAL=AF+AL+AS+AR+AM
ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

!Setting exposure
procedural
```

```
      IF (T.GT.(24*I+TCHNG)) THEN
        DAILYINDICATOR = 0
        I = I+1
       ENDIF
      IF(T.GE.(120+168*K).AND.T.LT.(168+168*K)) THEN
        WEEKLYINDICATOR = 0
        K = K+1
      ENDIF
        CONC = EXPOSURE*DAILYINDICATOR*WEEKLYINDICATOR
        CIN = CONC*MW/24450.  !mg/L
      end

TERMT(T.GE.TSTOP)        !'Sets Termination Condition'
END      !'End of derivative'
END      !'End of dynamic'
END      !'End of program'
```

```
!This ReitzRatIDs.cmd file is originally from Reitz,and is modified into the form
!that ACSL TOX 11.8 requires by Yasong LU on April 7,2005.
!Reviewd by Lu Y 5/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

!Simulate Quast et al. 1988 exposure conditions
!Male rat
PROCED MALE
set cint=1
SET SEX=.T. !male
set exposure=500
START
SET TITLE='Reitz RAT INHALATION QUAST STUDY'
PLOT AUCCV /TAG='AUC OF VENOUS BLOOD CONC (mg*hr/L)' /XTAG='TIME (hr)'
END

PROCED FEMALE
set cint=1
SET SEX=.FALSE. !female
set exposure=500
START
SET TITLE='Reitz RAT INHALATION QUAST STUDY'
PLOT AUCCV /TAG='AUC OF VENOUS BLOOD CONC (mg*hr/L)' /XTAG='TIME (hr)'
END

PROCED COMPARE !with the results in the earlier PPRTV report
S EXPOSURE=875
S TSTOP=8760
SET SEX=.T. !male
START
SET TITLE='Reitz RAT INHALATION QUAST STUDY'
PLOT CL /TAG='LIVER CONC (mg/L/day)' /XTAG='TIME (hr)' /XHI=200
PLOT AUCCL /TAG='LIVER AUC (mg*hr/L)' /XTAG='TIME (hr)' /XHI=9000 /hi=80000
PLOT TWACL /TAG='TWA LIVER CONC (mg/L/day)' /XTAG='TIME (hr)' /XHI=9000
PLOT AMB /TAG='Amount metabolized (mg/kg)' /XTAG='TIME (hr)' /XHI=9000
PLOT TWAAMB /TAG='TWA Amount metabolized (mg/kg/day)' /XTAG='TIME (hr)' /XHI=9000
print t,twacv
END
```

```
PROGRAM: ReitzHumanInternalDose.CSL
!Original code supplied by Reitz. Modified the SimuSolv format into ACSL Tox format by Lu Y.
!12/2004.
!Reitz RH,McDougal JN,Himmelstein MW,Nolan RJ,Schumann AM. 1988 Physiologically based
!pharmacokinetic modelling with methylchloroform: Implications for interspecies,high dose/low
!dose, and dose route extrapolations. Toxicol.Appl. Pharmacol.1988,95:185-199
!Edited by Lu Y 12/23/2004; Dennison 04/06/05

!Reviewd by Lu Y 5/23/2005

!Trim this code to simulate only dynamic chamber inhalation exposures.
!Quast JF,Calhoun LL,Frauson LE. Fundam Appl Toxicol,1988,11:611-625. No PK data.
!Fischer 344 rats;150,500,1500 ppm,6 hr/day,5 days/week,24 month (516 exposure days).

!Simulate HUMAN life time continuous exposure; for RfC calculation.

INITIAL

!Physiological Parameters, redefined in CMD **********************************
CONSTANT BW = 70          !Assume
CONSTANT QCC= 15.         !Cardiac output constant (L/hr/kg^0.74);Reitz 1988.
CONSTANT QPC= 15.         !Alveolar ventilation constant (L/hr/kg^0.74);Reitz 1988.
  !Blood flow fractions
CONSTANT QLC = 0.24       !Fractional blood flow to liver;Reitz 1988.
CONSTANT QFC = 0.05       !Fractional blood flow to fat;Reitz 1988.
CONSTANT QSC = 0.18       !Fractional blood flow to slowly perfused;Reitz 1988.
 QRC=1.0-(QFC+QSC+QLC)    !Fractional blood flow to rapidly perfused;Reitz 1988.
  !Volume fractions
CONSTANT VLC = 0.04       !Fraction liver tissue;Reitz 1988.
CONSTANT VFC = 0.07       !Fraction fat tissue;Reitz 1988.
CONSTANT VRC = 0.05       !Fraction richly perfused tissues;Reitz 1988.
 VSC = 0.91-VLC-VFC-VRC   !Fraction slowly perfused;Reitz 1988.

!Chemical specific parameters ********************************
  !Partition coefficients, redefined in CMD
CONSTANT PB = 5.76        !Blood/air;Reitz 1988.
CONSTANT PLA = 8.6        !Liver/air;Reitz 1988.
CONSTANT PFA = 263.       !Fat/air;Reitz 1988.
CONSTANT PRA = 8.6        !Richly perfused/air;Reitz 1988.
CONSTANT PSA = 3.15       !Slowly perfused/air;Reitz 1988.
  PL=PLA/PB
  PF=PFA/PB
  PR=PRA/PB
  PS=PSA/PB

  !Metabolism;saturable;estimated from Schumann data and Reitz drinking water study
CONSTANT VMAXC = 0.419 !Capacity of saturable metabolism (mg/hr/kg^0.7);Reitz 1988.
CONSTANT KM = 5.75     !Affinity of saturable metabolism (mg/L);Reitz 1988.
CONSTANT KF=0.         !First order metabolism (/hr);ignored in Reitz 1988.
```

```
!Oral IA and IV parameters

!Scaled parameters
  QC = QCC*BW**0.74      !Cardiac output (L/hr);Reitz 1988.
  QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);Reitz 1988.
  VF = VFC*BW            !Fat volume (L)
  VL = VLC*BW            !Liver volume (L)
  VR = VRC*BW                  !Richly Perfused volume (L)
  VS = VSC*BW                  !Slowly Perfused volume (L)
  QL = QLC*QC            !Liver blood flow (L/hr)
  QF = QFC*QC            !Fat blood flow (L/hr)
  QR = QRC*QC                  !Richly Perfused blood flow (L/hr)
  QS = QSC*QC                  !Slowly Perfused blood flow (L/hr)
  VMAX=VMAXC*BW**0.7     !Capacity of saturable metabolism (mg/hr);Reitz 1988.

!Other Compound Specific Parameters
 CONSTANT   MW = 133.5   !'Molecular weight (g/mol)'
 CONSTANT  EXPOSURE=1500.0   !'Inhaled concentration (ppm)',changed in CMD
  CIN = EXPOSURE*MW/24450
!Timing commands
CONSTANT   TSTOP = 120.  !'Length of experiment (hrs)',changed in CMD
CINTERVAL  CINT  = 0.1 !Communication interval,changed in CMD

!Method of integration
ALGORITHM IALG = 2  !Gear method for stiff systems
END                 !End of initial

DYNAMIC
DERIVATIVE

   !Amount inhaled
    RAIN = QP*CIN
     AIN = INTEG(RAIN,0.)
   !Amount exhaled
    RAEX = QP*CEX
     AEX = INTEG(RAEX,0.)

    !AS = Amount in Slowly Perfused Tissues (mg)
    RAS = QS*(CA-CS/PS)
     AS = INTEG(RAS,0.)
     CS = AS/VS

    !AR = Amount in Richly Perfused Tissues (mg)
    RAR = QR*(CA-CR/PR)
     AR = INTEG(RAR,0.)
     CR = AR/VR

    !AF = Amount in fat (mg)
```

```
      RAF = QF*(CA-CF/PF)
       AF = INTEG(RAF,0.)
       CF = AF/VF

      !AL = Amount in liver (mg)
      RAL = QL*(CA-CL/PL)-RAM
       AL = INTEG(RAL,0.)
       CL = AL/VL
      AUCCL=INTEG(CL,0.)
      TWACL=AUCCL/(T/24+1E-30) !time-weighted avarage CL,mg*day/L

      !AM = Amount metabolized (mg)
      RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
       AM = INTEG(RAM,0.)
       AMB=AM/BW

      !Blood concentrations (mg/L)
      CV= (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
      CA=(QC*CV+QP*CIN)/(QC+QP/PB)
      CEX = CA/PB
      CEXPPM = (0.667*CEX+0.333*CIN)*24450./MW !ppm
      CEXMGL=0.667*CEX+0.333*CIN        !mg/L
      AUCCV=INTEG(CV,0.)
      TWACV=AUCCV/(T/24+1E-30) !time-weighted avarage CV,mg/L/day

      !TMASS = mass balance (mg)
      !Amount in the body
      AINTOBODY=AIN-AEX
      !Amount in the body,summation of all compartments
      AINCAL=AF+AL+AS+AR+AM
      ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)       !'Sets Termination Condition'
END     !'End of derivative'
END     !'End of dynamic'
END     !'End of program'
```

```
!This ReitzHumanInternalDose.cmd file is originally from Reitz,and is modified into
!the form that ACSL TOX 11.8 requires by Yasong LU on April 7,2005.
!Reviewd by Lu Y 5/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED HUMAN !Reitz parameters
  SET BW=70.0,QPC=15.0,QCC=15.0,QLC=0.24,QFC=0.09,QSC=0.18, ...
     VLC=0.031,VFC=0.231,VRC=0.037, ...
     PLA=8.6,PFA=263.0,PSA=3.15,PRA=8.6,PB=2.53, ...
     VMAXC=0.419,KM=5.75
S EXPOSURE = 0.59  !ppm;hypothetical value to get desired human TWA-CV.
S CINT=1
S TSTOP=613200     !human lifetime,70 years
START
SET TITLE='Reitz HUMAN LIFETIME INHALATION'
!PLOT AUCCV /TAG='AUC OF VENOUS BLOOD CONC (mg*hr/L)' /XTAG='TIME (hr)'
!PLOT TWACV /TAG='TWA VENOUS BLOOD CONC (mg/L/day)' /XTAG='TIME (hr)'
PRINT T,TWACL
END
```

```
PROGRAM: HumanOral.CSL
!Original code supplied by Reitz. Modified the SimuSolv format into ACSL Tox format by Lu Y.
!12/2004.
!Reitz RH,McDougal JN,Himmelstein MW,Nolan RJ,Schumann AM. 1988 Physiologically based
!pharmacokinetic modelling with methylchloroform: Implications for interspecies,high dose/low
!dose, and dose route extrapolations. Toxicol.Appl. Pharmacol.1988,95:185-199
!Edited by Lu Y 12/23/2004; Dennison 04/06/05

!Reviewd by Lu Y 5/23/2005
!8/18/05. Modified to simulate continuous human infusion scenario.

INITIAL

!Physiological Parameters **********************************
!Constants set for the rat
CONSTANT BW = 70  !Assumption of a reference human,kg
CONSTANT QCC= 15.        !Cardiac output constant (L/hr/kg^0.74);Reitz 1988.
CONSTANT QPC= 15.        !Alveolar ventilation constant (L/hr^0.74);Reitz 1988.
  !Blood flow fractions
CONSTANT QLC = 0.24       !Fractional blood flow to liver;Reitz 1988.
CONSTANT QFC = 0.09       !Fractional blood flow to fat;Reitz 1988.
CONSTANT QSC = 0.18       !Fractional blood flow to slowly perfused;Reitz 1988.
 QRC=1.0-(QFC+QSC+QLC)    !Fractional blood flow to rapidly perfused;Reitz 1988.
  !Volume fractions
CONSTANT VLC = 0.031       !Fraction liver tissue;Reitz 1988.
CONSTANT VFC = 0.231       !Fraction fat tissue;Reitz 1988.
CONSTANT VRC = 0.037       !Fraction richly perfused tissues;Reitz 1988.
 VSC = 0.91-VLC-VFC-VRC   !Fraction slowly perfused;Reitz 1988.

!Chemical specific parameters ********************************
  !Partition coefficients
CONSTANT PB = 2.53        !Blood/air;Reitz 1988.
CONSTANT PLA = 8.6        !Liver/air;Reitz 1988.
CONSTANT PFA = 263.       !Fat/air;Reitz 1988.
CONSTANT PRA = 8.6        !Richly perfused/air;Reitz 1988.
CONSTANT PSA = 3.15       !Slowly perfused/air;Reitz 1988.
  PL=PLA/PB
  PF=PFA/PB
  PR=PRA/PB
  PS=PSA/PB

  !Metabolism;saturable;estimated from Schumann data and Reitz drinking water study
CONSTANT VMAXC = 0.419 !Capacity of saturable metabolism (mg/hr^0.7);Reitz 1988.
CONSTANT KM = 5.75     !Affinity of saturable metabolism (mg/L);Reitz 1988.
CONSTANT KF=0.          !First order metabolism (/hr);ignored in Reitz 1988.

!Scaled parameters
   QC = QCC*BW**0.74      !Cardiac output (L/hr);Reitz 1988.
   QP = QPC*BW**0.74      !Alveolar ventilation (L/hr);Reitz 1988.
```

```
   VF = VFC*BW          !Fat volume (L)
   VL = VLC*BW          !Liver volume (L)
   VR = VRC*BW              !Richly Perfused volume (L)
   VS = VSC*BW             !Slowly Perfused volume (L)
   QL = QLC*QC          !Liver blood flow (L/hr)
   QF = QFC*QC          !Fat blood flow (L/hr)
   QR = QRC*QC              !Richly Perfused blood flow (L/hr)
   QS = QSC*QC             !Slowly Perfused blood flow (L/hr)
   VMAX=VMAXC*BW**0.7     !Capacity of saturable metabolism (mg/hr);Reitz 1988.

!Continous human oral infusion
CONSTANT INFUSION0 = 14.4 !Oral infusion,mg/kg/day,rate in Reitz rat study 1988.
 INFUSION = INFUSION0/24  !mg/kg/hr

!'Timing commands'
CONSTANT   TSTOP = 4381.  !'Length of experiment (hrs)'
CINTERVAL  CINT  = 1. !Communication interval

!Method of integration
ALGORITHM IALG = 2  !Gear method for stiff systems
END                 !End of initial

DYNAMIC

DERIVATIVE
   !Amount inhaled
     RAIN = QP*CIN
      AIN = INTEG(RAIN,0.)
   !Amount exhaled
     RAEX = QP*CEX
      AEX = INTEG(RAEX,0.)

     !AS = Amount in Slowly Perfused Tissues (mg)
     RAS = QS*(CA-CS/PS)
      AS = INTEG(RAS,0.)
      CS = AS/VS

     !AR = Amount in Richly Perfused Tissues (mg)
     RAR = QR*(CA-CR/PR)
      AR = INTEG(RAR,0.)
      CR = AR/VR

     !AF = Amount in fat (mg)
     RAF = QF*(CA-CF/PF)
      AF = INTEG(RAF,0.)
      CF = AF/VF

     !AL = Amount in liver (mg)
     RAL = QL*(CA-CL/PL)-RAM + INFUSION
```

```
      AL = INTEG(RAL,0.)
      CL = AL/VL
     AUCCL=INTEG(CL,0.)
     TWACL=AUCCL/(T/24+1E-30)

     !AM = Amount metabolized (mg)
     RAM = VMAX*CL/PL/(KM+CL/PL)+KF*CL/PL*VL
      AM = INTEG(RAM,0.)

     !Blood concentrations (mg/L)
     CV= (QL*CL/PL+QS*CS/PS+QF*CF/PF+QR*CR/PR)/QC
     CVUM=CV/MW*1000
     CVUGL=CV*1000     !mg/L converted to ug/L
     CA=(QC*CV+QP*CIN)/(QC+QP/PB)
     CEX = CA/PB
     CEXPPM = (0.667*CEX+0.333*CIN)*24450./MW !ppm
     CEXMGL=0.667*CEX+0.333*CIN         !mg/L

     AUCCV=INTEG(CV,0.) !mg/L
     TWACV=AUCCV/(T/24+1E-30)

     !TMASS = mass balance (mg)
     !Infusion amount
     InfuAmount = INTEG(INFUSION,0.)
     !Amount in the body
     AINTOBODY=AIN-AEX+InfuAmount
     !Amount in the body,summation of all compartments
     AINCAL=AF+AL+AS+AR+AM
     ERROR=(AINTOBODY-AINCAL)/(AINTOBODY+1E-30)*100

TERMT(T.GE.TSTOP)        !'Sets Termination Condition'
END       !'End of derivative'
END       !'End of dynamic'
END       !'End of program'
```

```
!This cmd file is originally from Reitz,and is modified into the form
!that ACSL TOX 11.8 requires by Yasong LU on April 7,2005.
!Reviewd by Lu Y 5/23/2005
!Simulate continous human infusion

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END
```

The following CMD files were written for reconstruction of some human models. They are not essential for this report. We present these files for EPA's convenience in case these data are needed in the future.

```
!Mackay.cmd file
!Reviewd by Lu Y 5/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

!Test Mackay et al. data
PROCED MACKAY !set parameters
S BW=70  !No clarified in in the paper; hypothetical value
S Nrat=1.!Track TCA in 1 human.
!S QC = 274.5       !Cardiac output (L/hr); Scalde from Reitz 1988,QC=QCC*BW**0.75
!S QP = 274.5       !Alveolar ventilation (L/hr); Reitz 1988,QP=QPC*BW**0.75
SET QLC=0.24,QFC=0.09,QSC=0.18
SET VLC=0.031,VFC=0.231,VRC=0.037
SET PB=2.53
S TCHNG=3.5 !hr
!SET KF=1.4  !Scaled accoring to the function in Table 2,Gargas 1986
SET TSTOP=4. !hr
START
END

PROCED MACKAYCVlog
S CONC=175 !ppm
START
SET DEFPLT=.T.
SET TITLE ='Reitz HUMAN INHALATION MACKAY DATA'
PLOT /DATA=LOWESTCV CVUM /LOG /LO=.1 /HI=50 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
S CONC=350 !ppm
START
SET DEFPLT=.F.
PLOT /DATA=HIGHCV CVUM /LOG /LO=.1 /HI=50 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
END

PROCED MACKAYCV
S CONC=175 !ppm
START
```

```
SET DEFPLT=.T.
SET TITLE ='Reitz HUMAN INHALATION MACKAY DATA'
PLOT /DATA=LOWESTCV CVUM /LO=0 /HI=40 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
S CONC=350 !ppm
START
SET DEFPLT=.F.
PLOT /DATA=HIGHCV CVUM /LO=0 /HI=40 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=4 /CHAR=1
END

!Data digitized from Mackay 1987 using digiMatic by Lohitnavy M
DATA LOWESTCV (t,CVUM)
0.328325        4.9342
0.97854         9.9671
1.963518333     12.6315
2.948496667     12.2368
END

DATA HIGHCV(T,CVUM)
0.341201667     12.5328
1.004291667     20.0328
1.976393333     23.7828
3.019311667     24.5723
END
```

```
!Gamberale.cmd file
!Reviewd by Lu Y 9/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED GamberaleCEXPPM
START
SET TITLE ='HUMAN INHALATION Gamberale DATA'
PLOT /DATA=GCEXPPM CEXPPM /HI=500...
    /TAG=' - Exhaled Air Concentration (ppm)'...
  /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=3 /CHAR=1
END

!Data digitized from Fig2 in Stewart 1969
DATA GCEXPPM (t,CEXPPM)
0.037198333   64.611
0.074396667   81.2144
0.105031667   92.5047
0.133478333   102.4667
0.15536       104.4592
0.181618333   105.1233
0.212253333   104.4592
0.2407        110.4364
0.277898333   115.7495
0.310721667   117.0777
0.343543333   115.0853
0.376366667   119.0702
0.411378333   122.3908
0.4442        122.3908
0.479211667   127.7039
0.549233333   149.6204
0.579868333   158.2542
0.603938333   168.2163
0.632385      186.8121
0.665206667   178.1783
0.682713333   171.537
0.713346667   176.85
0.74617       182.1631
0.778993333   179.5066
0.811815      184.1555
0.849015      184.8197
```

0.881836667	188.8045
0.912471667	190.1328
0.947483333	190.7969
0.984681667	187.4762
1.126913333	197.4383
1.161925	202.7514
1.188183333	217.3624
1.21663	232.6375
1.247263333	229.981
1.280086667	233.3017
1.310721667	234.6299
1.345731667	237.2865
1.378555	239.2789
1.40919	243.9278
1.442011667	241.9354
1.474835	247.2485
1.514221667	249.9051
1.544856667	245.9203
1.57768	248.5768
1.608315	276.4705
1.643325	295.7305
1.676148333	292.4098
1.704595	309.0132
1.739605	308.3491
1.772428333	311.0056
1.80525	315.6546
1.840261667	315.6546
1.870896667	312.9981
1.908095	317.647
1.93873	319.6394
1.969365	311.6698
2.002186667	318.9753
2.039386667	322.296
2.065645	315.6546

END

```
!Laine.cmd file
!Reviewed by Lu Y 9/23/05; to simulate Laine 1996 data.

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED LaineCV
S NonCONSTANTCONC=.F. !constant concentration
START
SET DEFPLT=.T.
SET TITLE ='HUMAN INHALATION Laine DATA'
PLOT /DATA=constantCV CVUM /HI=60 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=1
S NonCONSTANTCONC=.T. !NOT constant concentration
START
SET DEFPLT=.F.
PLOT /DATA=NOTconstantCV CVUM /HI=60 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=2
END

PROCED constantconc
S NonCONSTANTCONC=.F. !constant concentration
START
SET TITLE ='HUMAN INHALATION Laine DATA'
PLOT /DATA=constantCV CVUM /HI=30 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=1
END

PROCED nonconstantconc
S NonCONSTANTCONC=.T. !NOT constant concentration
START
PLOT /DATA=NOTconstantCV CVUM /HI=60 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=2
END

!Data provided in Laine 1996
!Unit umol/L
DATA constantCV (t,CVUM)
```

```
0.116667    9.9
0.150000    6.4
0.183333    14.3
0.216667    17.9
0.250000    19.9
0.333333    16.5
0.666667    14.3
1.000000    15.5
2.000000    15.4
3.000000    18.2
3.666667    5.7
3.783333    14.3
3.816667    17.5
3.850000    20.4
3.883333    21.3
3.916667    21.5
4.000000    20.2
4.333333    18.5
4.833333    6
END

DATA NOTconstantCV(T,CVUM)
0.116667    15.1
0.150000    18.5
0.183333    26
0.216667    35.9
0.250000    34
0.333333    25.9
0.666667    17.7
1.000000    21.5
2.000000    15.2
3.000000    14.4
3.666667    9.2
3.783333    26.4
3.816667    38.2
3.850000    42.9
3.883333    46.7
3.916667    49.1
4.000000    34
4.333333    29.2
4.833333    11
END
```

```
!Savolainen.cmd file
!Reviewd by Lu Y 9/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED SavolainenCV
S CONC=200 !ppm
START
SET DEFPLT=.T.
SET TITLE ='  HUMAN INHALATION Savolainen DATA'
PLOT /DATA=LOWESTCV CVUM /HI=40 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=1
S CONC=400 !ppm
START
SET DEFPLT=.F.
PLOT /DATA=HIGHCV CVUM /HI=40 ...
    /TAG=' - Venous Blood Concentration (uM)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=6 /CHAR=2
END

!Data provided in Savolainen 1981
!The unit of the concentrations was not clarified in the paper;but
!the predictions agree with the unit of umol/L
!The unit, umol/L, mentioned in another paper(1982) by the same group.
DATA LOWESTCV (t,CVUM)
1.1     11.4
2.3     13.3
3.45    16.4
END

DATA HIGHCV(T,CVUM)
1.1     25.7
2.3     25.4
3.45    31.5
END
```

```
!Stewart.cmd file; Reviewd by Lu Y 9/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED StewartCEXPPM
START
SET TITLE ='  HUMAN INHALATION Stewart DATA'
PLOT /DATA=StCEXPPM CEXPPM /LOG /HI=600 /LO=0.3...
    /TAG=' - Exhaled Air Concentration (ppm)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=340 /CHAR=1
END

!Data digitized from Fig2 in Stewart 1969
DATA StCEXPPM (t,CEXPPM)
3       80
6.5     101
9       40.1
24      11
27      79.8
31      91
33      49
48      17
52      103
55      120
57      60
72      25
76      100
79      118
91      50
96      24
100     102
103     103
106     42
119     21
166     5.8
190     4.98
214     2.7
238     2.05
262     1.65
334     0.88
END
```

```
!Wallace.cmd
!Reviewd by Lu Y 9/23/2005

SET GRDCPL=.F.
START
PREPAR /ALL

PROCED CHECK
START
PLOT ERROR
print t,error
END

PROCED WallaceScenario1  !Conditions in CSL file
S VFC=0.26
S CONC=1100
S TCHNG=10
S TSTOP=35
START
SET TITLE =' HUMAN INHALATION Wallace DATA'
PLOT /DATA=WDATA1 CEXUGM /HI=1300 ...
    /TAG=' - Exhaled concentration (ug/m^3)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=35 /CHAR=1
END

PROCED WallaceScenario2
S VFC=0.26
S CONC=800
S TCHNG=2
S TSTOP=7
START
SET TITLE =' HUMAN INHALATION Wallace DATA'
PLOT /DATA=WDATA2 CEXUGM /HI=1000 ...
    /TAG=' - Exhaled concentration (ug/m^3)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=7 /CHAR=1
END

PROCED WallaceScenario3
S VFC=0.16
S CONC=800
S TCHNG=2
S TSTOP=7
START
SET TITLE =' HUMAN INHALATION Wallace DATA'
PLOT /DATA=WDATA3 CV /HI=10 ...
    /TAG=' - Venous Blood Concentration (ug/L)'...
    /XTAG = ' - Time (hrs)' /COLOR=0 /XHI=7 /CHAR=1
END
```

```
!Data provided in Wallace 1997
DATA WDATA1 (t,CEXUGM)
0.5695      390
1.5375      470
6.0612      630
9.5167      680
10.0375     670
10.0375     670
10.1805     420
10.2653     380
10.5138     300
11.0153     210
11.8458     180
14.0153     120
16.0192     110
18.0137     74
22.0138     64
26.0230     47
26.0230     45
34.0125     34
END

!Data provided in Wallace 1997
DATA WDATA2 (t,CEXUGM)
0.507       240
1.5345      370
2.0000      310
4.0412      320
4.0412      210
4.1272      190
4.2038      160
4.2828      140
4.5137      120
5.0112      100
5.5103      100
6.0095      100
6.0095      84
7.0138      60
END

!Data provided in Wallace 1997
DATA WDATA3 (t,CV)
2.0395      7.38
2.0395      7.28
2.1800      7.67
2.2678      7.54
2.2678      5.05
2.5133      3.37
2.5133      4.31
```

3.0105	3.1
3.8422	3.07
3.8422	2.51
6.0130	1.56

END