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**Expanded Development and Application of an
Array-Based Mathematical Model for
Fuels Exposure and Dosimetry**

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PREFACE

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The principal investigator for the project was Elaine A. Merrill, PhD (711HPW/RHBAF). Dr. Merrill left RHBAF in March 2022 and is currently with the Navy and Marine Corp Public Health Center (NMCPHC). The cross-service partner for this project was Gunda Reddy, PhD (Army Public Health Center (APHC)); Dr. Reddy retired in January 2020. Team member Peter J. Robinson, PhD, retired from HJF in November 2020.

Data utilized in this report were gathered from published literature. No novel animal or human data were collected.

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1.0 SUMMARY

The overall objective of this project is the development and validation of a quantitative model to predict internal dosimetry of volatile jet fuel components in target tissues, based upon the fuel's composition and exposure levels. An array physiologically-based pharmacokinetic (PBPK) model represents an unconventional way to quantify dosimetry of multiple compounds from exposure to a mixture. In a previous project (Sternner *et al.*, 2017), an array PBPK model was coded to simulate rat inhalation exposures in order to simultaneously predict internal dosimetry of multiple volatile components of jet fuel. The array model described target tissue dosimetry for five volatile JP-8 fuel hydrocarbon components: toluene, ethyl benzene, xylenes, nonane, and decane. The model structure included the brain (temporal lobe, brain stem and remaining areas), cochlea, fat, liver, rapidly perfused, and slowly perfused tissues; diffusion or flow limitation could be utilized for each tissue. The model was parameterized with partition coefficient (PC) values for these five JP-8 jet fuel hydrocarbon components in various tissues. Blood flows and tissue volumes were taken from the literature. The model was validated with available pharmacokinetic data, also from the literature. The model successfully described absorption, distribution, metabolism, and elimination of each compound in tissues associated with auditory signaling: cochlea, brain stem, and temporal lobe.

In the current effort, naphthalene was added to the array, based upon a previous rat and human naphthalene model (Merrill *et al.*, 2019) that had been validated against available literature data. The model structure required updating to account for metabolism in the lung as well as the liver. The resulting model satisfactorily simulated naphthalene circulating blood levels and tissue dosimetry resulting from inhalation exposures. Additionally, the alteration to the original array model did not adversely impact simulations of the other five JP-8 components when compared to available kinetic data.

The model was then utilized to predict tissue levels of all six compounds in the venous blood, lung, liver, and auditory signaling tissues (cochlea, brain stem, and temporal lobe) for rats exposed to 1000 milligrams/meter (mg/m)³ JP-8 for six hours, to mirror a published study (Guthrie *et al.*, 2014). The model was also utilized to predict potential tissue levels of the six components in rats if exposed at the established occupational exposure limit (OEL, 200 mg/m³) for JP-8 and a 50:50 blend of JP-8 with Virent Synthesized Aromatic Kerosene (SAK), to demonstrate the array model's usefulness to compare the potential tissue burdens resulting from the use of greener alternative fuels.

2.0 INTRODUCTION

Exposure to multiple chemical or nonchemical stressors is part of everyday life. Recently, more attention has been paid to the risk assessment of such exposures. Specifically, given the frequency of exposure to jet fuels among flight line workers, mechanics, pilots, etc., inhalation exposure to the volatile components of fuels remains a concern to the Air Force. Petroleum hydrocarbon mixtures like jet fuels typically contain hundreds of compounds. These include aliphatic and aromatic hydrocarbons plus military required additives. Multiple laboratory studies using rodents have studied JP-8 and other aviation fuels but effects, when seen, were at concentrations that are only possible in an inhalation chamber (*i.e.*, 2000 mg/m³) (Mattie and Sterner, 2011; Mattie *et al.*, 2018; Sterner *et al.*, 2020; Mattie *et al.*, 2020). The ACGIH® (formerly the American Conference of Governmental Industrial Hygienists) proposed an 8-hour threshold limit value (TLV) time-weighted average (TWA) of 200 mg/m³ for kerosene and jet fuel vapors in 2003 (ACGIH, 2021); this value is still current. A TLV of 5 mg/m³ for kerosene and middle distillate fuel aerosols was concurrently recommended by the National Research Council (NRC) Committee on Toxicology, based on the value set by ExxonMobil Biosciences (NRC, 2003). The U.S. Air Force's OEL and the ACGIH TLV for JP-8 is currently at 200 mg/m³. Tools for assessing body burden of fuels and hydrocarbon mixtures are needed to ensure that exposure limits remain protective for military personnel.

With the development of PBPK modeling, determining internal dosimetry of one or a few compounds representing a mixture became possible. Traditional mixtures models are coded as parallel models with lines of code for each individual chemical in the mixture, multiplied by every tissue in the model (*e.g.*, Martin *et al.*, 2012). Increasing the number of chemicals rapidly increases the model complexity and the lines of code required (Figure 1). Parallel modeling is a tedious practice and results in many opportunities to incorporate errors. Furthermore, individual models often incorporate different aspects of the underlying physiology, leading to potential inconsistencies when the physiological conditions are changed. Despite this complexity, when appropriate data are available, PBPK modeling is a far better tool than other methods to simulate different exposure scenarios, study chemical interactions, and extrapolate from animals (rats) to humans. These models can address episodic and chronic exposures, and provide individual component dosimetry for target tissues. With adequate data regarding chemical mechanisms of action, these models can account for component interactions, such as inhibition of a detoxifying enzyme or competition for a neuronal receptor (Sweeney and Gearhart, 2020).

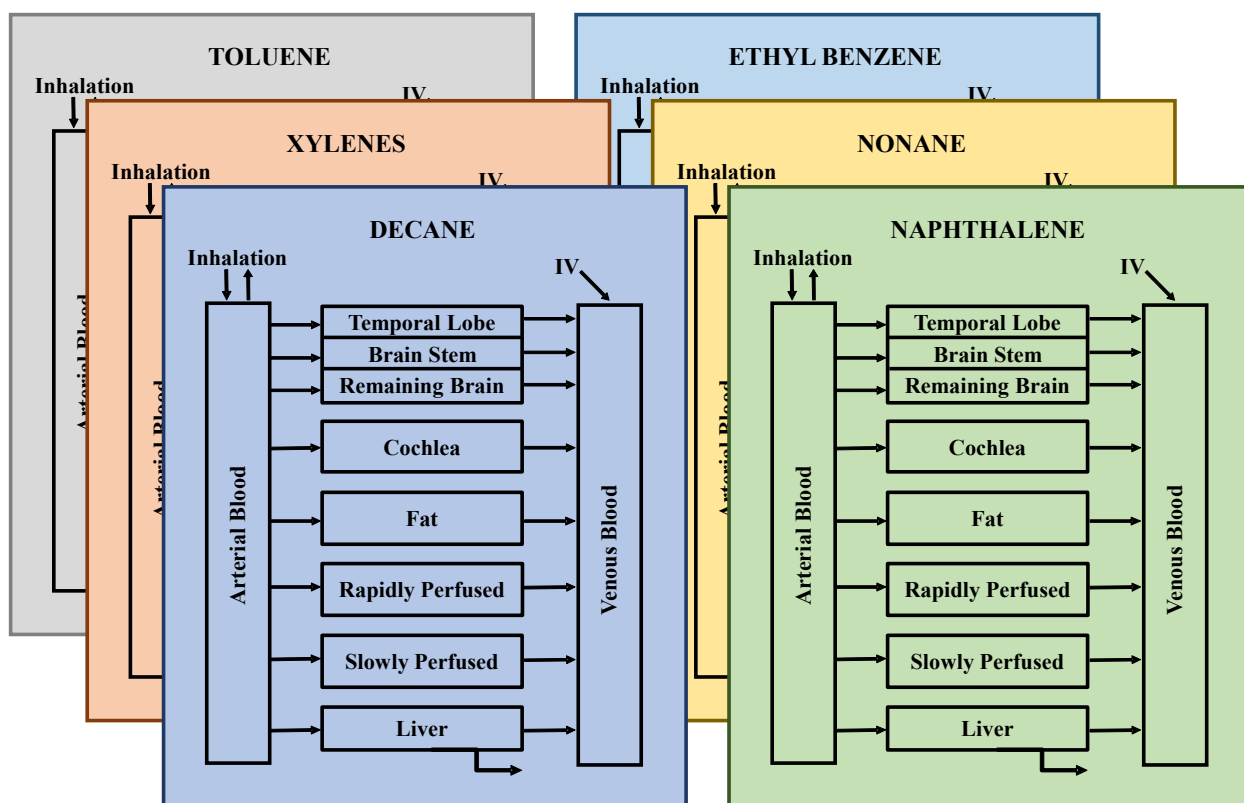


Figure 1. Traditional Modeling Approach Illustration. Note the number of compartments, parameters and distinct parameter names that would be involved in modeling a dose metric from a mixture of six chemicals using a traditional PBPK modeling approach.

The array PBPK model developed by Sterner *et al.* (2017) allows simulation of kinetic information for multiple components simultaneously using an identical model structure. The model uses species-specific physiological parameters and chemical-specific characteristics to simultaneously solve for concentrations of each modeled compound in the featured tissues. Changes to the model structure require just one set of equations, as opposed to a special set of equations and parameter names for each chemical modeled, decreasing the time required writing equations and the likelihood of introduced error. Further, increasing the number of compounds can be as simple as changing the array size and adding chemical-specific parameters, provided that the current model structure meets the kinetic needs of the newly added compound.

Naphthalene is a common exposure in the DoD as it is a component (up to 1 percent) of the single battle fuel, JP-8 (Egeghy *et al.*, 2003). JP-8 is the largest chemical exposure experienced by warfighters (NRC, 2003). Naphthalene is an occupational exposure concern as it is currently listed by the U.S. Environmental Protection Agency as a possible human carcinogen (U.S. EPA, 1998) due to its metabolism to reactive intermediates which can form deoxyribonucleic acid (DNA) adducts shown to injure nasal olfactory epithelium in mice (Van Winkle *et al.*, 1995). The integration of naphthalene into the array model published by Sterner *et al.* (2017) is critical for the overall assessment of fuel toxicity.

Naphthalene, however, requires a different model structure. Although rats and primates do not metabolize this compound to the same extent as mice in the nasal tissues (Van Winkle *et al.*, 1995), significant amounts of naphthalene are metabolized in the lung of these target species (Campbell *et al.*, 2014). The addition of naphthalene to the array model required adding a lung compartment and metabolic capacity in the lung.

The objectives of this effort were to:

- 1) expand the original array model (Sterner *et al.*, 2017) structure to include lung tissue and metabolism;
- 2) use the model to simulate naphthalene kinetics using parameters previously validated (Merrill *et al.*, 2019) and calculated parameters; and
- 3) utilize the array model to compare JP-8 to another fuel to predict organ and tissue dosimetry for all six key volatile components.

3.0 APPROACH

3.1 PBPK Model Structure

A PBPK model is a mix of algebraic and ordinary differential equations. The latter are mass balance equations, which describe the rate of change of a chemical within a model compartment. Taken together, the mass balance equations for all compartments describe how the chemical distributes within the body. The amount of a chemical within a single tissue compartment at any time should equal the amount of that chemical entering the compartment in the arterial blood stream, plus the amount taken up within the tissue, and minus the amount leaving the compartment in the venous blood stream and any amount excreted (or metabolized) (Fisher *et al.*, 2020). Figure 2 diagrams the transfer of the chemicals. The equations were coded in acslX (AEgis Technologies, Huntsville AL). By design requirement, the array model has the same structure (equations) for all six chemicals in the mixture. Physiological parameters that would not change based on the chemical are defined as scalar values, but chemical-specific parameters and physico-chemical properties, which cause each chemical in the model to behave differently, are defined as vectors. Examples of these properties include molecular weights, tissue:blood PC values, and metabolic constants (Sterner *et al.*, 2017).

The array model was coded to simulate the kinetics of six chemicals simultaneously in multiple tissues and blood dynamic tissue types including: fat, liver, lung, rapidly perfused tissues, slowly perfused tissues, cochlea, and brain, which was further split into three parallel tissues (brainstem, temporal lobe, and remaining brain tissue, Figure 2). The inclusion of the cochlea and distinct brain regions was maintained from the original array model (Sterner *et al.*, 2017) due to the implication of volatile jet fuel components combined with noise in exacerbating peripheral and central auditory hearing loss (Fechter *et al.*, 2010, 2012; Guthrie, 2022; Guthrie *et al.*, 2014, 2015, 2022).

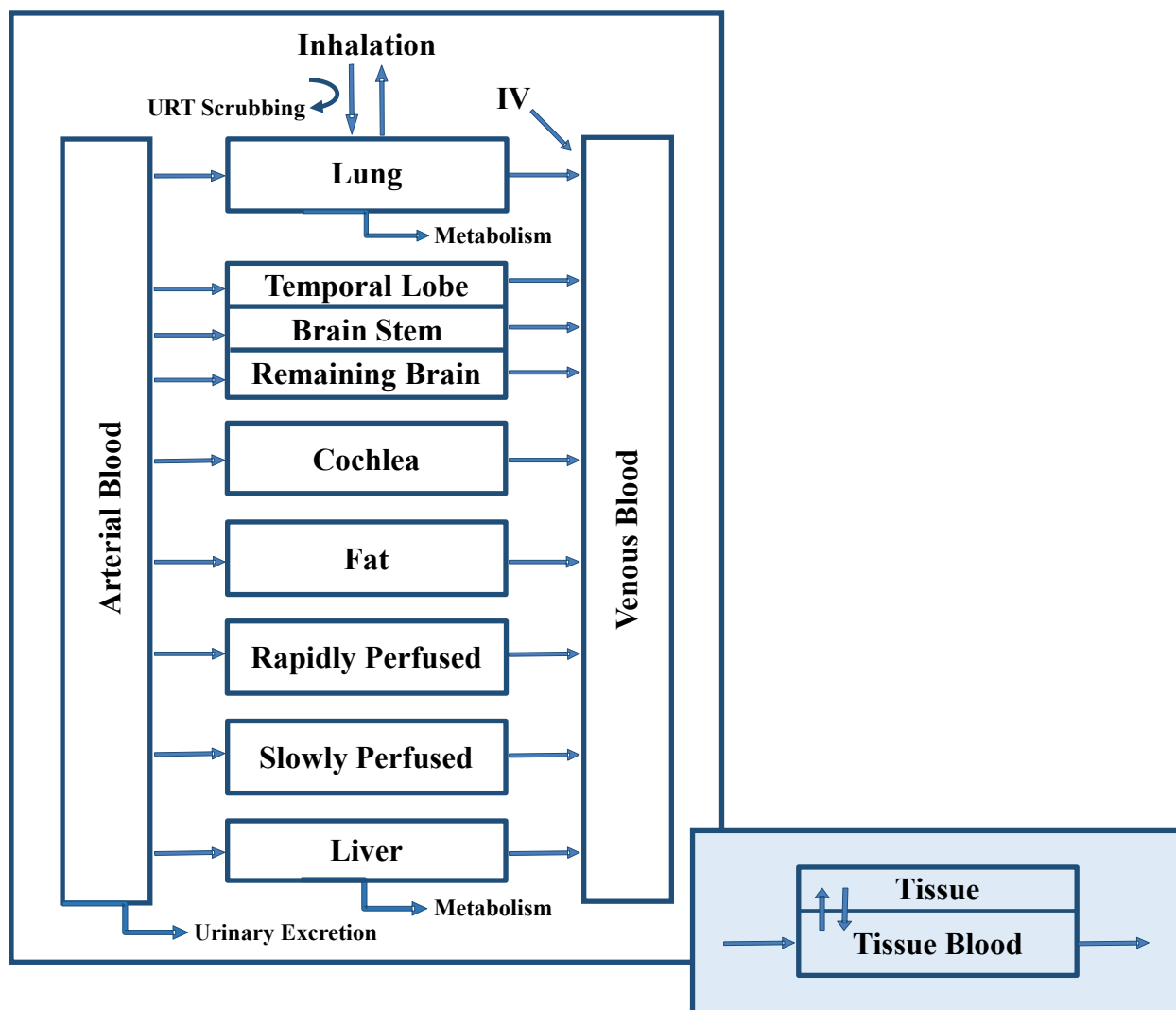


Figure 2. Physiologically-Based Pharmacokinetic Model Schematic. The general model schematic (white box) indicates the tissues in the model structure. Each tissue in the general schematic is divided into the tissue itself and the tissue blood (blue box). This convention allows the model to simulate diffusion limited chemicals as needed. URT = upper respiratory tract

Diffusion limited distribution was included in each tissue compartment. For compartments without metabolism or excretion, the rate of change in the amount of chemical in diffusion-limited compartments with respect to time was described as being proportional to the cell membrane permeability coefficient (permeability:area affinity constant PAT_{tiss}), as shown in Equations 1 and 2, and illustrated in Figure 2 (blue box). Diffusion limitation in each tissue compartment can be negated by setting the PAT_{tiss} to a very high number (e.g., 10000) to closely approximate flow limitation.

$$VT_{tissB} \frac{dCVT_{tiss}}{dt} = QT_{tiss}(C_{Art} - CVT_{tiss}) + PAT_{tiss}(C_{Tiss}^{CT} / PT_{tiss} - CVT_{tiss})$$

Equation 1

$VTiss$ represented the tissue volume and $QTiss$ was tissue blood flow, with the subscript denoting which tissue. C_{Art} was arterial concentration and $CVTiss$ was the tissue's venous (capillary bed) blood concentration, equivalent to the concentration in the tissue ($CTiss$) divided by the tissue:blood PC ($PTiss$).

$VTissB$ was the volume of blood in the tissue. The $CTiss$ was then derived from the $CVTiss$ using Equation 2.

$$VTiss \frac{dCTiss}{dt} = PATiss(CVTiss - \frac{CTiss}{PTiss}) \quad \text{Equation 2}$$

To model the formation and elimination of metabolites in the liver and lung compartments, the equation for the rate of change in the compound's concentration within these compartments included a term for saturable metabolism (Equation 3). For example, the liver was described below using flow limitation and saturable metabolism of the parent compound to a metabolite(s).

$$VLiv \frac{dCLiv}{dt} = QLiv \left(C_{Art} - \frac{CLiv}{PLiv} \right) - \frac{Vmax \times CVLiv}{Km + CVLiv} \quad \text{Equation 3}$$

$CLiv$ was the concentration of the parent compound in the liver tissue and $CVLiv$ was the concentration of the parent chemical in the liver capillary bed ($CVLiv = CLiv/PLiv$), where $PLiv$ was the liver:blood PC. $Vmax$ and Km were the liver tissue Michaelis Menten maximum velocity and affinity constants, respectively, for the conversion of the parent compound to metabolite. Note that the $Vmax$ was the result of converting the respective $VmaxC$ value, which was scaled by body weight (BW) ($Vmax = VmaxC \times BW^{0.75}$). Metabolism may be turned off in either tissue by assigning a value of zero to the respective $VmaxC$ parameter.

Naphthalene was the only compound of the six modeled for which significant metabolism was expected in the lung compartment. The model described the loss of naphthalene due to saturable metabolism as the conversion to naphthalene oxide, an intermediate product. Because metabolism within the lung of the other five compounds is of minor significance, their $VmaxLuC$ parameters were assigned a value of zero (Table 3).

The model included the inhalation and intravenous (IV) routes of exposure (Figure 2). IV injection was modeled as a zero-order rate into venous blood, based upon the length of the injection time. Inhalation was modeled using the species-specific ventilation rate multiplied by the air concentration, based upon blood:air PC values. Oral (gavage) and drinking water dosing equations were retained in the code from prior projects but were not parameterized for this model.

3.2 PBPK Model Parameters

The physiological and chemical specific parameters used in the model are listed in Tables 1 through 3. The parameterization of the original array model (Stern *et al.*, 2017) and that of naphthalene (Merrill *et al.*, 2019) are discussed in those reports.

Table 1. Physiological Constants

Constant	Constant Name	Rat	Human
<i>BW</i>	Body weight (kg) ^a	0.3	70.0
<i>QCC</i>	Cardiac output (L/(hour*kg ^{0.75}))	14.6	12.89
Tissue Blood Flows [fraction of cardiac output]			
<i>QPC</i>	Alveolar (pulmonary)	24.75	27.75
<i>QFatC</i>	Fat	0.07	0.052
<i>QLivC</i>	Liver	0.183	0.227
<i>QLuC</i>	Lung	0.021 ^b	0.025 ^b
<i>QRapC</i>	Rapidly perfused	0.536	0.394
<i>QSlwC</i>	Slowly perfused	0.16996	0.188
<i>QBrC</i>	Remainder of brain tissues	0.013	0.07182 ^b
<i>QStmC</i>	Brainstem	0.004	0.0228 ^{b,h}
<i>QTLC</i>	Temporal lobe	0.003	0.01938 ^{b,i}
<i>QCocC</i>	Cochlea	0.00004 ^c	rat value
Tissue Volumes [fraction of BW]			
<i>VAlvC</i>	Alveolar blood	0.007	0.0079
<i>VFatC</i>	Fat	0.10	0.214
<i>VLivC</i>	Liver	0.034	0.026
<i>VLuC</i>	Lung	0.005 ^b	0.0076 ^b
<i>VRapC</i>	Rapidly perfused	0.039	0.0284
<i>VSlwC</i>	Slowly perfused	0.65	0.536
<i>VBrnC</i>	Remainder of brain tissue	0.004 ^d	0.0162
<i>VStmC</i>	Brainstem	0.001 ^d	0.0004 ⁱ
<i>VTLC</i>	Temporal lobe	0.001 ^e	0.0034 ⁱ
<i>VCocM</i>	Cochlea, based on mass	0.00007*BW ^{0.2348} ^e	← rat equation ^e
Tissue Blood Volumes [fraction of tissue volume]			
<i>VFatBldC</i>	Fat	0.0154 ^b	0.02 ^b
<i>VLivBldC</i>	Liver	0.21 ^{b,f}	0.11 ^c
<i>VLuBldC</i>	Lung	0.36 ^b	rat value
<i>VRapBC</i>	Rapidly perfused	0.2075	0.17 ^b
<i>VSlwBldC</i>	Slowly perfused	0.0333 ^b	0.04 ^b
<i>VBrnBldC</i>	Remainder of brain tissue	0.03 ^{b,f}	0.04 ^b
<i>VStmBldC</i>	Brain stem	0.03 ^{b,f}	0.04 ^b
<i>VTLBldC</i>	Temporal lobe	0.03 ^{b,f}	0.04 ^b
<i>VCocBldC</i>	Cochlea	0.0183 ^g	0.0183 ^g

Notes: All tissue volumes and blood flows taken from Clewell *et al.* (2001), unless noted otherwise. ^aModel used study specific BW whenever provided. Source: ^bBrown *et al.* (1997). ^cRobinson *et al.* (2013), rat value. ^dDelp *et al.* (1991). ^eStern *et al.* (2017). ^fStern *et al.* (2013). ^gMorizono *et al.* (1968), guinea pig value. ^hVanderah and Gould (2016). ⁱLukies *et al.* (2017).

Table 2. Array PBPK Partition Coefficients and Permeability:Area Affinity Constants for Key Hydrocarbons

Constant	Constant Name	Toluene	Ethyl benzene	Xylenes	Nonane	Decane	Naphthalene (rat & human)
<i>PB</i>	Blood: Air PC	18.0 ^a	42.7 ^a	46.0 ^a	5.2 ^d	5.0 ^d	571.0 ^g
Tissue:Blood Partition Coefficients (unitless)							
<i>PBrn</i>	Brain	2.0 ^d	1.22 ^d	1.38 ^d	5.0 ^d	10.0 ^d	3.5 ⁱ
<i>PStm</i>	Brain stem	2.87 ^d	1.93 ^d	2.29 ^d	8.5 ^d	8.9 ^d	3.5 ⁱ
<i>PTL</i>	Temporal lobe	2.13 ^d	1.44 ^d	1.61 ^d	7.6 ^d	6.6 ^d	3.5 ⁱ
<i>PCoc</i>	Cochlea	0.54 ^d	0.44 ^d	0.47 ^d	1.45 ^d	2.15 ^d	0.47 ⁱ
<i>PFat</i>	Fat	56.7 ^a	36.4 ^a	40.4 ^a	282.0 ^d	328.0 ^d	49.0 ^g
<i>PLiv</i>	Liver	4.64 ^a	1.96 ^a	1.98 ^a	8.0 ^d	3.0 ^d	1.6 ^g
<i>PLu</i>	Lung	4.64 ^c	1.41 ^c	1.98 ^c	2.0 ^e	3.0 ^e	3.5 ^g
<i>PRap</i>	Rapidly perfused	4.64 ^d	1.41 ^d	1.98 ^a	2.0 ^d	3.0 ^d	3.5 ^g
<i>PShw</i>	Slowly perfused	1.54 ^a	0.61 ^a	0.91 ^a	4.0 ^d	0.85 ^d	3.5 ^g
Permeability:Area Affinity Constants (L/hour/kg^{0.75})							
<i>PABrn</i>	Brain	10000 ^f	10000 ^f	10000 ^f	0.5 ^d	0.005 ^d	10000 ^f
<i>PAStm</i>	Brain stem	10000 ^f	10000 ^f	10000 ^f	0.5 ^d	0.005 ^d	10000 ^f
<i>PATL</i>	Temporal lobe	10000 ^f	10000 ^f	10000 ^f	0.5 ^d	0.005 ^d	10000 ^f
<i>PACoc</i>	Cochlea	10000 ^f	10000 ^f	10000 ^f	1.0 ^d	1.0 ^d	10000 ^f
<i>PAFat</i>	Fat	10000 ^f	10000 ^f	10000 ^f	0.5 ^d	0.07 ^d	0.2*BW ^{0.75j}
<i>PALiv</i>	Liver	10000 ^f	10000 ^f	10000 ^f	0.07 ^d	0.15 ^d	10000 ^f
<i>PALu</i>	Lung	10000 ^f	10000 ^f	10000 ^f	1.0 ^d	0.005 ^d	10000 ^f
<i>PARap</i>	Rapidly perfused	10000 ^f	10000 ^f	10000 ^f	1.0 ^d	0.005 ^d	10000 ^f
<i>PAShw</i>	Slowly perfused	10000 ^f	10000 ^f	10000 ^f	0.5 ^d	0.14 ^d	2.0*BW ^{0.75j}

Notes: ^aHaddad *et al.* (1999); ^bSterner *et al.* (2004); ^cSchlosser *et al.* (2010); ^dSterner *et al.* (2017); ^eLung parameters = rapidly perfused tissues, in the absence of data; ^fNo diffusion limitation; ^gCampbell *et al.* (2014); ^hSchwarz and Wasik (1977); ⁱCalculated using Ruark *et al.* (2014) with tissue data from Sterner *et al.* (2017); ^jMerrill *et al.* (2019), values were not pre-scaled to BW

Table 3. Array PBPK Inhalation, Metabolic, and Clearance Parameters for Key Hydrocarbons

Constant	Constant Name	Toluene	Ethyl benzene	Xylenes	Nonane	Decane	Naphthalene	
							Rat	Human
V_{maxC}	Maximal Rate of Reaction – Liver (mg/hour/kg ^{0.75})	3.44 ^a	6.39 ^a	6.49 ^a	0.1 ^c	0.005 ^c	(8.28/(BW ^{0.75})) x BW ^{*d}	(0.775/(BW ^{0.75})) x BW ^{*d}
K_m	Affinity Constant – Liver (mg/L)	0.13 ^a	1.04 ^c	0.45 ^a	0.1 ^c	0.1 ^c	2.18 ^d	2.94 ^d
V_{maxLuC}	Maximal Rate of Reaction – Lung (mg/hour/kg ^{0.75})	0 ^b	0 ^b	0 ^b	0 ^b	0 ^b	(0.45/(BW ^{0.75})) *BW ^d	(0.0035/(BW ^{0.75})) *BW ^d
K_{mLu}	Affinity Constant – Lung (mg/L)	0.13 ^b	1.04 ^b	0.45 ^b	0.1 ^b	0.1 ^b	2.18 ^d	8.7 ^d
Cl_{UrC}	Urinary Clearance (L/hour/kg ^{0.75})	0.004 ^c	0.04 ^c	0.004 ^c	0.04 ^c	0.004 ^c	0 ^d	0 ^d
$Scrub$	Upper Respiratory Tract Scrubbing (fraction)	0 ^c	0 ^c	0 ^c	0.4 ^c	0.7 ^c	0 ^d	0 ^d

Notes: ^aHaddad *et al.* (1999); ^bAssumption of no significant metabolism in lung ($V_{MaxLuC} = 0$ & $K_{mLu} = K_m$); ^cSterner *et al.* (2017); ^dMerrill *et al.* (2019); *Merrill *et al.* (2019) reported the maximum rate of reaction values in mg/hour/kg; this equation allows use of these units in the updated array model, which scales to BW^{0.75}.

Although the naphthalene model (Merrill *et al.*, 2019) provided most human and rat parameters, it did not include the cochlea or brain compartments. PCs for these tissues were calculated using Ruark *et al.* (2014) with tissue data from Sterner *et al.* (2017) and were assumed to be the same for rats and humans. Due to the lack of data on human cochlea volume, this parameter was calculated using the same quantitative algorithm based on body weight as measured for rats in Sterner *et al.* (2017). The Merrill *et al.* (2019) model was not parameterized based on allometric scaling but the Sterner *et al.* (2017) required allometry. Therefore, permeability:area affinity constant (PA), V_{maxC} , and V_{maxLuC} values were scaled in the model for naphthalene prior to using them in equations.

3.3 PBPK Model Validation

Altering the model structure to include a lung compartment required re-validation of the new model for all compounds. Animal studies described and simulated in Sterner *et al.* (2017) were compared against new simulations with the updated model structure. Likewise, published animal and human studies simulated for naphthalene, described in Merrill *et al.* (2019), were compared to the new model simulations.

3.4 PBPK Model Predictions

Following validation of documented simulations for each compound, the model was utilized to predict target tissue concentrations following JP-8 exposure. Guthrie *et al.* (2014) exposed male Long-Evans rats to 1000 mg/m³ JP-8 for 6 hours per day, 5 days a week, for 4 weeks, with and without noise. The Guthrie study used a JP-8 fuel blend referred to as POSF 4658, which is maintained at the Air Force Research Laboratory Fuels and Energy Branch (AFRL/RQTF) located at Wright-Patterson Air Force Base, OH. RQTF was formerly known as the Air Force Wright Aeronautical Laboratories fuel lab (AFWAL/POSF); fuels are still identified using POSF log book numbers. Predictions of the key components in this exposure scenario were based upon their percent by volume in POSF 4658 fuel, assuming standard temperature and pressure (STP). The percent weight values were measured using tandem gas chromatography (GC x GC) analysis (Shafer *et al.*, 2006) and are shown in Table 4.

Table 4. Percent Weight Values of Key Components in JP-9 and Virent SAK

Compound	Compound Percent by Weight: JP-8	Compound Percent by Weight: Virent SAK	Compound Percent by Weight: 50-50 Blend
Toluene	0.16	0.30	0.23
Ethyl benzene	0.11	0.17*	0.14
Xylene	0.67	0.50*	0.59
Nonane	1.14	0.09	0.62
Decane	2.55	0.13	1.34
Naphthalene	0.12	0.02	0.07

Note: *The total C2-benzene content in Virent SAK is 0.67 percent (%) by weight. This category includes ethyl benzene and xylenes. To derive a representative number, the total C2-benzene content was divided by four, the number of compounds possible in the category. One portion of the content was assigned to ethyl benzene and the remaining three portions were assigned to o-, m-, and p- xylene, combined.

The model was then utilized to predict rat tissue concentrations at the JP-8 OEL (200 mg/m³) for both JP-8 and a 50:50 mixture of Virent SAK. Percent weight values of the six key components in Virent SAK are also shown in Table 4, as well as the values for the 50:50 blend of the two fuels.

4.0 RESULTS

4.1 Model Validation

Due to the large number of simulations required to validate the new model structure against published data and previously recorded simulation graphs (Sternner *et al.*, 2017; Merrill *et al.*, 2019), these results are recorded in Appendix A. In general, good fidelity was found between the simulations generated with the updated model structure and those from prior iterations. Model simulations for ethyl benzene and xylenes appeared to be identical; no statistical method was applied to determine model agreement. Simulated toluene, nonane, and decane maximal concentrations were found to be slightly higher for the updated model as compared to the Sternner *et al.* (2017) version. The newer predictions were still visually close to their predecessors. Naphthalene predictions varied the most between the prior model (Merrill *et al.*, 2019) and the updated version for some validation data sets. This variation was likely due to differences in the model code; parameters were not altered to achieve better results, and the fits, while different, were considered to be sufficient for use in the array model.

Appendix B contains the acslX model code (.csl) file and Appendix C contains the script (.m) files needed to run the model and specify parameters. Appendix D contains the script files for the validation simulations. Inclusion of these lengthy files ensures the ability to reconstruct the model.

4.2 Guthrie *et al.* (2014) Tissue Predictions

Figure 3 contains predictions of the six volatile hydrocarbons following exposure to 1000 mg/m³ JP-8 (POSF 4658) used in the Guthrie *et al.* (2014) rat study. The Y-axis on each graph is plotted on the same scale to facilitate tissue comparisons. Appendix E contains the script file for running the Guthrie study predictions.

4.3 Comparison of Tissue Concentrations at OEL

To demonstrate the adaptability of the array model in predicting tissue concentrations for different fuels and the potential health effects of integrating alternative (non-petroleum) fuels into the supply chain, the updated model code was used to predict key component rat tissue concentrations for JP-8 and a 50:50 blend of Virent SAK:JP-8. This comparison is shown in Figures 4 and 5. The Y-axes in Figure 4 match, as do those in Figure 5, in order facilitate comparisons; however, each figure set has a different Y-axis scale to better highlight the chemical curve changes. The script files for these predictions are also located in Appendix E.

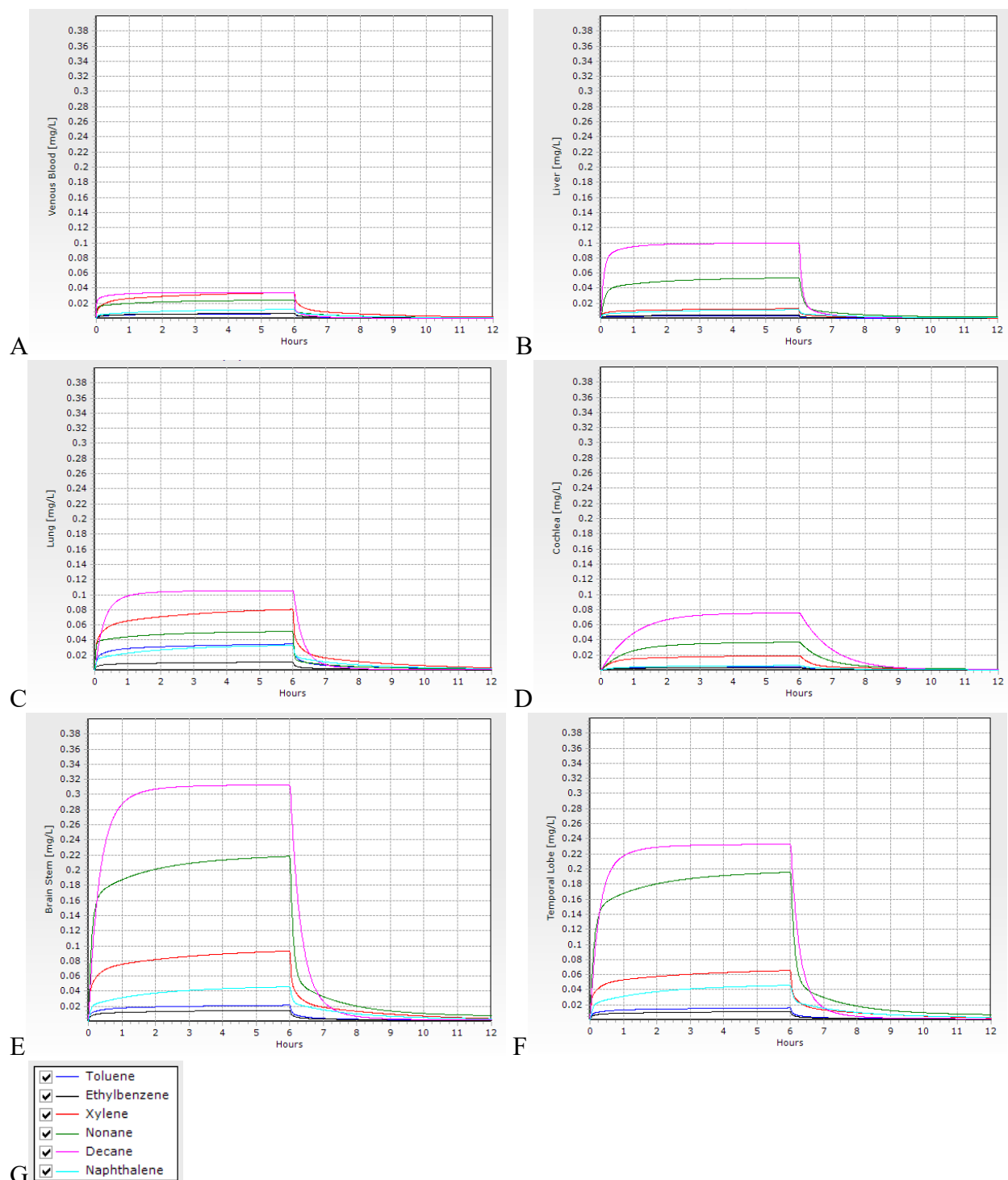


Figure 3. Predictions of Toluene, Ethyl Benzene, Xylene, Nonane, Decane, and Naphthalene Tissue Concentrations. The graphs show updated model predicted concentrations in A) venous blood, B) liver, C) lung, D) cochlea, E) brain stem, and F) temporal lobe following inhalation of 1000 mg/m³ of jet fuel (POSF 4658) by rats for 6 hours (Guthrie *et al.*, 2014). G) Compound identification is differentiated by line color.

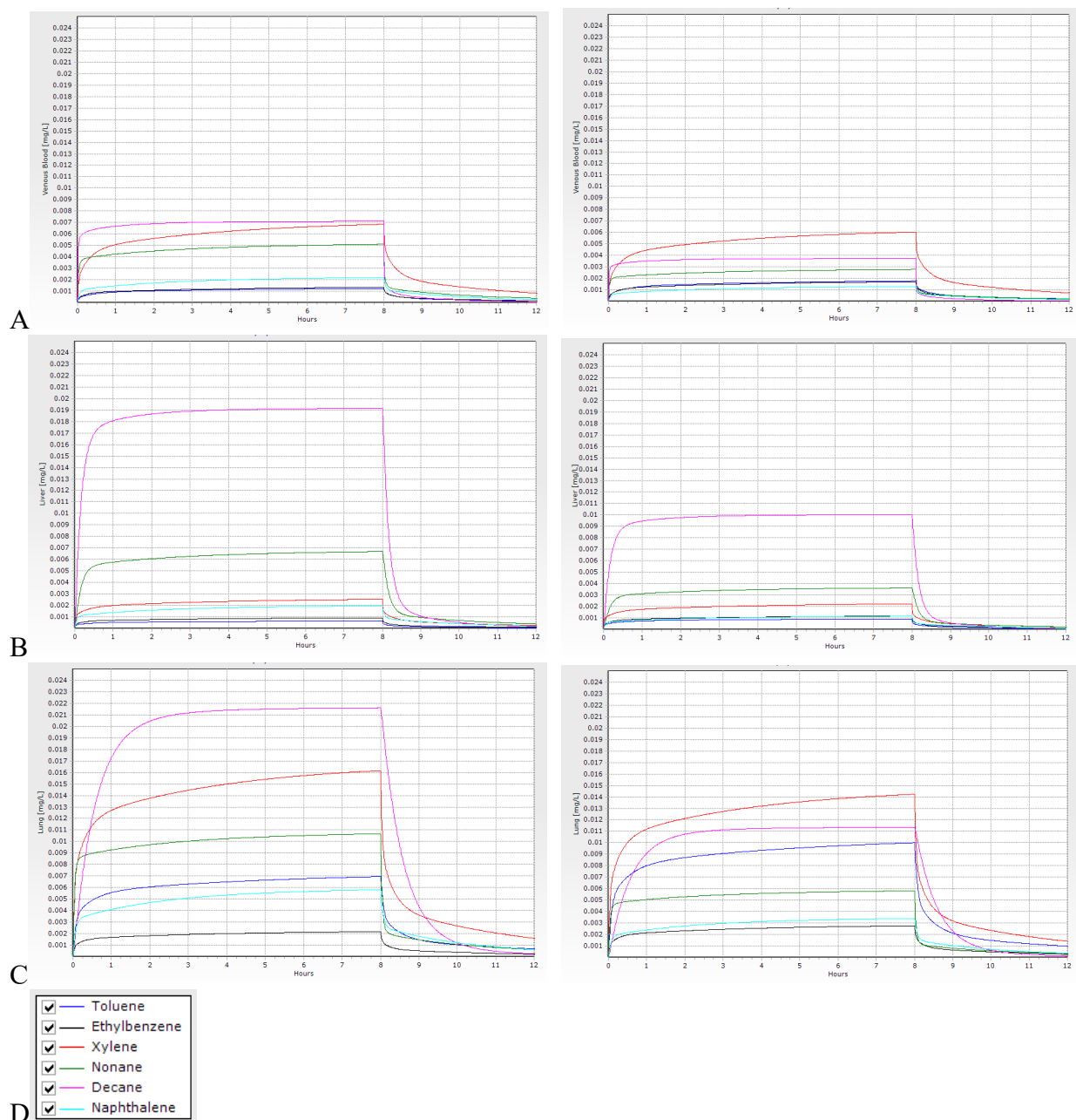


Figure 4. Comparison of General Tissue Concentration Predictions in Rats for JP-8 and 50:50 Virent:JP-8 Mixture at the OEL. The graphs show predictions for A) venous blood, B) liver, and C) lung concentrations for exposure to 200 mg/m³ JP-8 (left) or a Virent:JP-8 mixture (right). D) Compound identification is differentiated by line color.

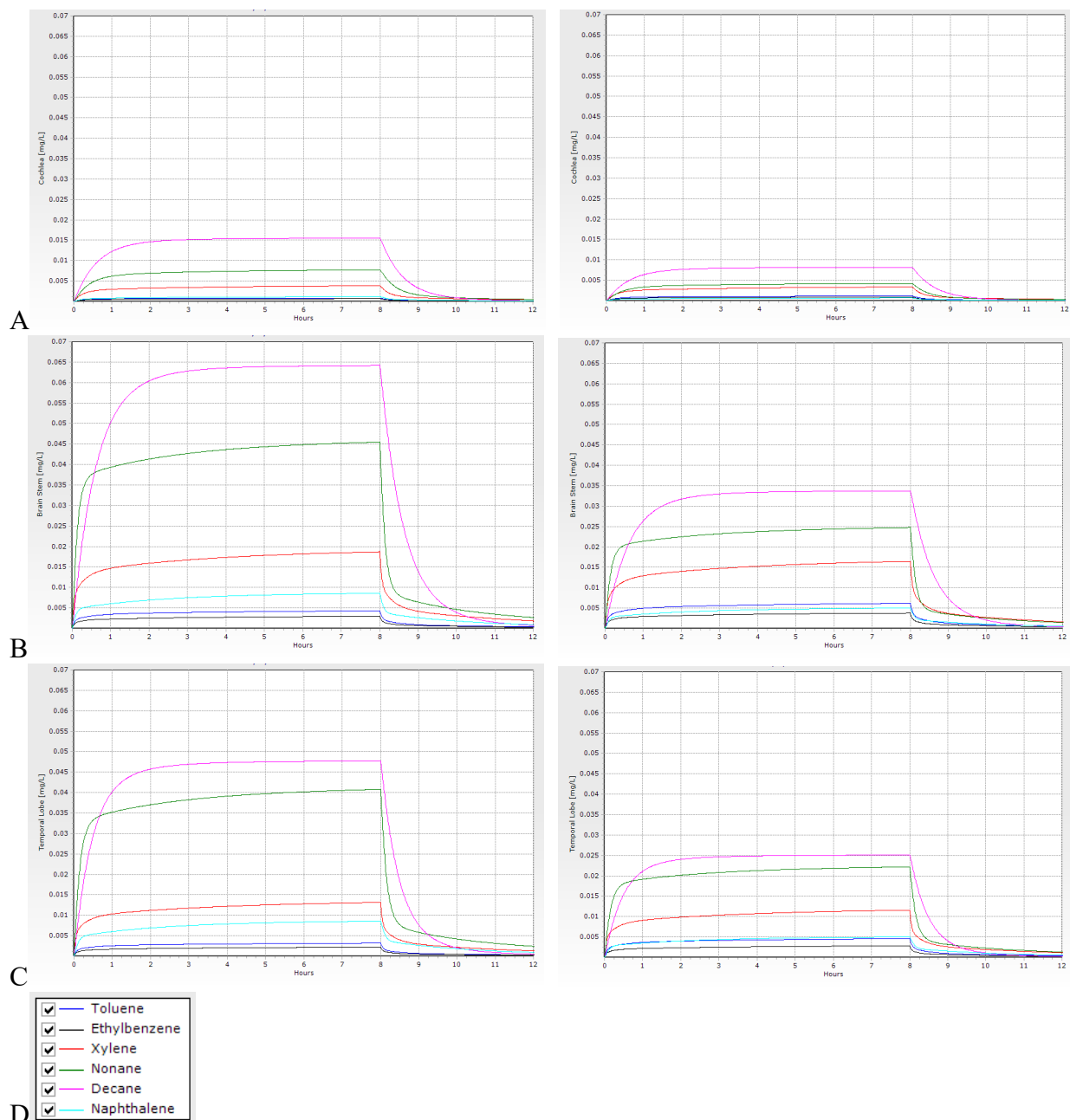


Figure 5. Comparison of Auditory Tissue Concentration Predictions in Rats for JP-8 and 50:50 Virent:JP-8 Mixture at the OEL. The graphs show predictions for A) cochlea, B) brain stem, and C) temporal lobe concentrations for exposure to 200 mg/m³ JP-8 (left) or a Virent:JP-8 mixture (right), with each exposure set at 200 mg/m³. D) Compound identification is differentiated by line color.

5.0 DISCUSSION

In the current effort, naphthalene was added to the array model originally developed by Sterner *et al.* (2017). The naphthalene model was based upon a previous rat and human naphthalene model by Merrill *et al.* (2019). The Sterner *et al.* (2017) model structure required updating to account for metabolism in the lung as well as the liver. The updated model successfully simulated available literature data for six key components in rats and naphthalene in humans. These model results can be found in Appendix A.

The model was then utilized to predict tissue levels of all six compounds in the venous blood, lung, liver, and auditory signaling tissues (cochlea, brain stem, and temporal lobe) for rats exposed to 1000 mg/m³ JP-8 for six hours, to mirror a published study (Guthrie *et al.*, 2014). In this study, the jet fuel plus noise exposure resulted in central auditory system (CAS) deficits but not peripheral hearing changes (cochlea hair cell damage); CAS effects occurred in the brainstem and temporal lobe along the auditory neural pathway. The predictions in Figure 3 indicate the increased potential for high concentrations of the modeled JP-8 components in the brain regions that house the nuclei of the auditory neural pathway. The CAS damage identified in subsequent publications (Guthrie, 2022; Guthrie *et al.*, 2015, 2022) was located in the nuclei of the brainstem, where the concentrations of decane and nonane are predicted to be the highest. Nonane and decane are major components of white spirits, a solvent known to affect the CAS pathway (Lund *et al.*, 1996; SCOEL, 2007).

Virent SAK (POSF 10326) is an alternative fuel derived from bio-based feed stocks using their BioForming® process. This fuel is in the ASTM International (formerly known as American Society for Testing and Materials) process for approval. A jet engine test flight was successfully completed using Virent SAK in 2016 (Virent, 2022).

An in-house tool was developed to compare jet fuels, both visually and numerically. Users select GC x GC data profiles from a list of different POSF fuels; the tool then compares the similarity in terms of the GC x GC carbon number groupings delineated by the Shafer *et al.* (2006) method (Figure 6). The tool can also generate a graphic using principal component analysis (PCA) techniques. This graphic shows the distance between two fuels (red dots) and their relationship to other jet fuels (blue dots) in the database (Figure 7). The tool can help prioritize the inclusion of additional compounds or compound groups in the array model, based on abundance, potential toxicity or other properties, as new fuels are developed. Figure 6 indicates that Virent SAK and JP-8 POSF 4658 are very different fuels (173/200 or 87 percent difference and 13% similar); Virent SAK contains relatively few aliphatics (paraffins) and only a subset of the aromatics found in JP-8.

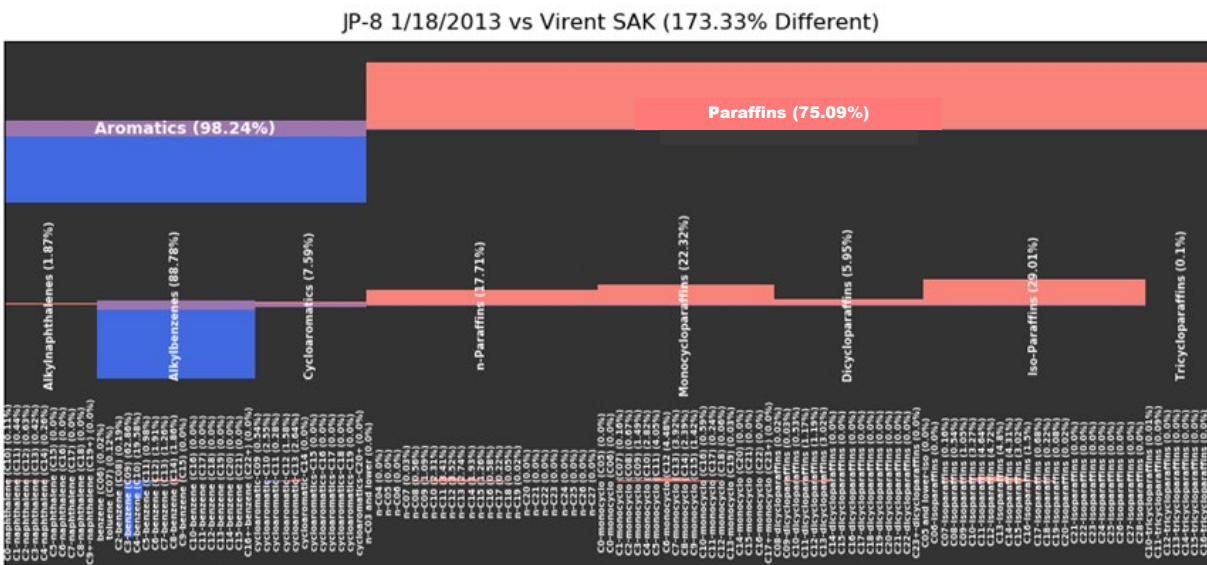


Figure 6. Comparison of JP-8 and Virent SAK using Jet Fuel Comparer Tool. The top bar is a simple representation of the aromatic and paraffinic overlap between JP-8 (1-18-2013 = POSF 4658) and Virent SAK, where the purple area indicates common compounds, the blue indicates compounds present in Virent SAK (mostly aromatic) and red indicates JP-8 components (highly paraffinic/aliphatic). The middle bar graph indicates the chemical classes present in each fuel. Virent SAK contains very few paraffins, which are not visible on the graph. The bottom graph lists the 38 aromatic and 108 paraffinic GC x GC carbon number groupings. The blue area behind the grouping names indicates that Virent SAK mainly falls into just two groups.

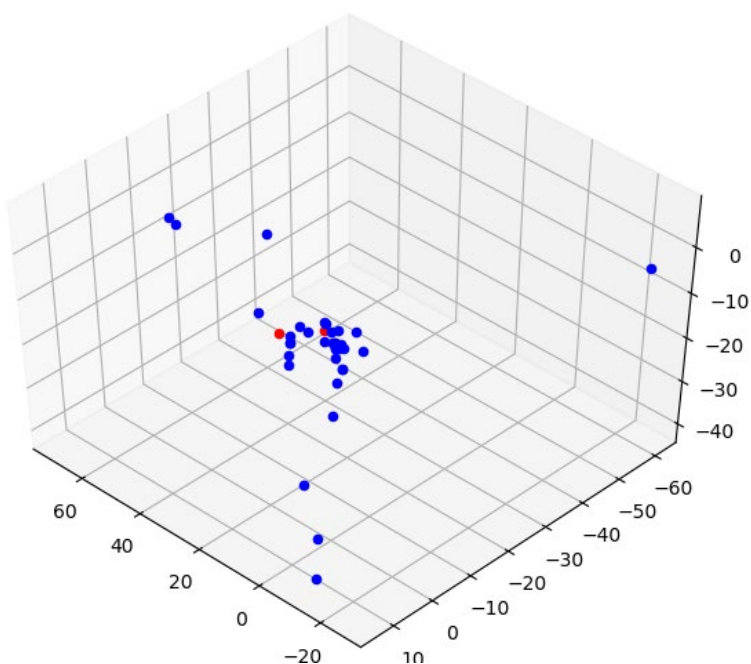


Figure 7. Comparison of JP-8 and Virent SAK using PCA. Graphic representation of PCA distance between the two fuels (red dots, with JP-8 on the right and Virent SAK on the left) and other fuels in the database (blue dots). Virent SAK is relatively closer to JP-8 POSF 4658 than many alternative fuels.

Virent SAK has been evaluated for dermal irritation potential and bacterial mutagenicity. Virent SAK with a standard additive package (when combined is identified as POSF 10330) has a similar to slightly stronger potential to be a dermal irritant, compared to JP-8 (POSF 4658+, where + indicates the presence of the same additives). Both fuels were graded as “slightly irritating”, whether occluded or non-occluded following exposure (Sterner *et al.*, 2014). In the *Salmonella/Escherichia coli* bacterial reverse mutation assay (Ames test), both Virent SAK with additives (POSF 10330) and JP-8 (POSF 4658+) were found to be non-mutagenic (Mumy *et al.*, 2016).

The array model was used to predict tissue levels of the six components for rats exposed at the established occupational exposure level (200 mg/m³) for JP-8 and a 50:50 blend of JP-8 with Virent SAK to demonstrate the array model’s usefulness to explore the potential tissue burdens resulting from the use of greener alternative fuels. In general, Figures 4 and 5 indicate that the 50:50 blend results in lower tissue concentrations of nonane and decane, the compounds more likely to result in central auditory processing deficits. These decreases are most clearly seen in the brain stem and temporal lobe (Figure 5B and C). Switching to this 50:50 blend could improve protection against hearing effects in exposed Airmen.

5.1 Future Modeling Opportunities

Naphthalene was the only compound modeled herein with pre-validated human parameters in an in-house model, allowing rapid simulation of published data and prediction of potential human tissue levels following real-life exposure scenarios. Human literature kinetic data exist for the remaining five components featured in the array model. Validating the model using human parameters for these chemicals is the next step for developing the array approach and applying it to Air Force exposure scenarios. Future expansion of the model may target trimethylbenzenes, major components of Virent SAK.

Many jet fuel components exhibit qualitatively similar pharmacokinetic properties in living organisms, which makes them suitable to lump with similar components for modeling. This concept has been explored using traditional PBPK modeling techniques (Dennison *et al.*, 2003; Martin *et al.*, 2012). The array model concept could be utilized to track specific components of interest, such as naphthalene for regulatory purposes or nonane and decane for hearing loss potential, along with lumped fractions to model the whole fuel. The lump designations could be tied to the equivalent carbon fractions set up by the Total Petroleum Hydrocarbon Working Group (TPHCWG) (Gustafson *et al.*, 1997). Although the TPHCWG chemical groupings were established for soil cleanup purposes, the fractions were outlined based on general chemical properties, which not only influence the migration of the compounds in soil and groundwater, but also affect their partitioning in tissues.

Jet fuel components are metabolized by relatively few pathways. Aromatic class compound metabolism is primarily mediated by cytochrome P450 mixed function oxidase system, subfamily CYP2E1. Lighter weight aliphatics such as n- and iso-alkanes are metabolized through CYP1A2 and CYP2B6 pathways (Martin *et al.*, 2012). Competition for these enzymes and the resulting decrease in metabolism once the enzymes are saturated can be accounted for in PBPK models. Competitive metabolic inhibition has not yet been added to the array model. Sufficient binary mixture data exist for two-component mixtures of toluene, ethyl benzene, and xylenes in rats (Haddad *et al.*, 1999). The predicted maximal venous blood concentrations (Figures 4 and 5) are below the K_m values (Table 3); calculated competitive metabolic inhibition would essentially be zero. Similarly, metabolic interaction was not seen in humans exposed to pairs of these compounds (toluene, ethyl benzene, and xylenes), with respect to expected metabolism data from single compound exposures (Marchand *et al.*, 2015, 2016). Competitive metabolic inhibition could be added in future iterations of the model. This would become important if the whole fuel is accounted for through lumping, thereby increasing the additive metabolic load on each cytochrome subfamily.

Additional activities would improve the model's validity and versatility. A sensitivity analysis would help determine which parameters would need further research to improve the predictability of circulating levels of specific fuel components. Monte Carlo analysis could be utilized to predict a range of individual kinetics of the six volatiles using population variability. In addition, the array model could be integrated with the Jet Fuel Comparison Tool, to automatically upload parameters for each new fuel based on the GC x GC data within the application.

6.0 CONCLUSIONS

The addition of naphthalene to the PBPK array model expanded the capability of the model to predict kinetics of compounds with notable metabolism in the lung. Additionally, successful simulation of the naphthalene human data, demonstrated the interspecies extrapolation capability of the model. The majority of parameters utilized within the model are based on literature studies, allowing for minimal need to fit values. The ability of the model to extrapolate across species and routes (intravenous and inhalation) with so few fitted parameters, gives greater confidence in the model predictions.

PBPK model predictions are useful for visualizing and comparing concentrations in tissues of concern. For example, model predictions indicate the potential for significantly higher concentrations of nonane and decane in the brainstem (Figure 3E) than could be predicted using blood levels. The array model can be quickly adapted to model exposures to alternative fuels (Figures 4 and 5) as the various formulations are tested and qualified for use by ASTM.

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APPENDIX A: VALIDATION SIMULATIONS FOR KEY COMPONENTS

Validation simulations are simple visual comparisons between a prior published graph and the output from the updated model. No statistical method was applied to determine differences. References are listed in the main report.

For all figures in this appendix, the simulations on the left are from the Sterner *et al.* (2017) or the Merrill *et al.* (2019) models. The simulations on the right are from the updated array model. Descriptions of all studies are found in either Sterner *et al.* (2017) or Merrill *et al.* (2019).

Toluene Rat Validation Simulations

As is shown in Figures A-1 through A-4, the peak height is slightly different, indicating that the maximum concentration of toluene in the tissue is slightly higher in the updated model. However, the model's overall fit to the data is not impacted and the model fit is judged to be adequate.

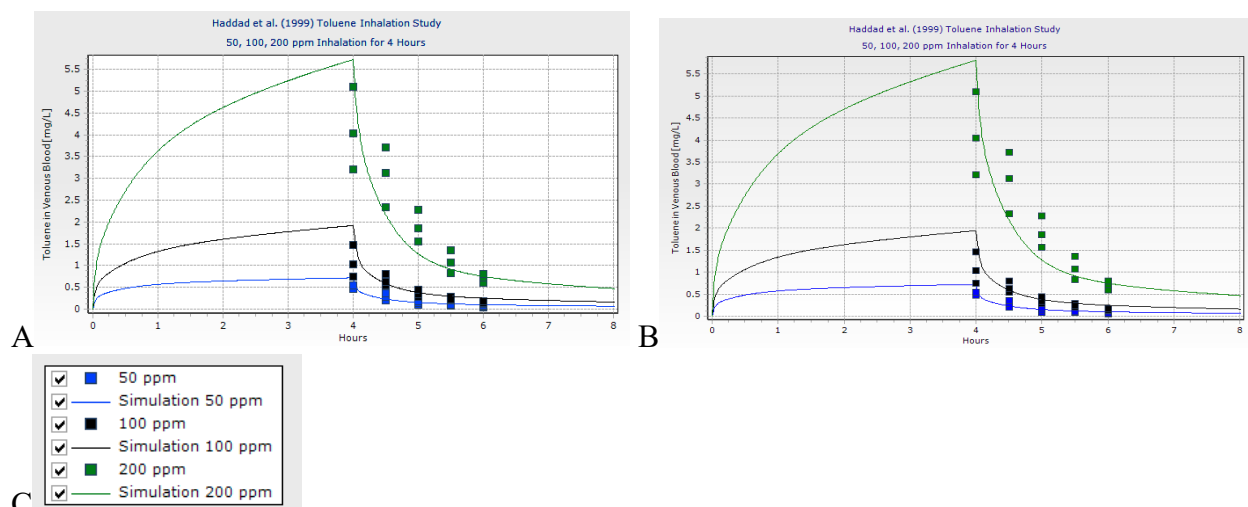


Figure A-1. Comparison Simulations of the Haddad *et al.* (1999) Toluene Whole Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

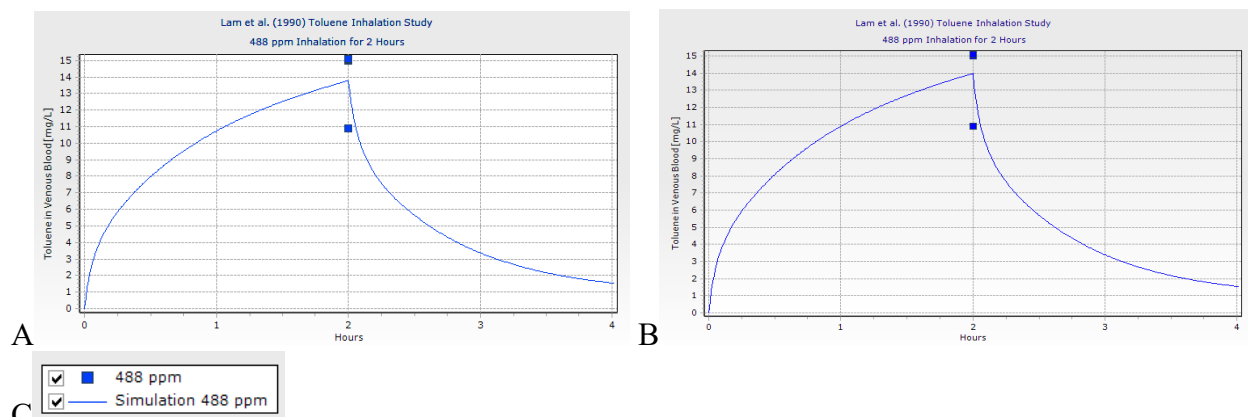


Figure A-2. Comparison Simulations of the Lam *et al.* (1990) Toluene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

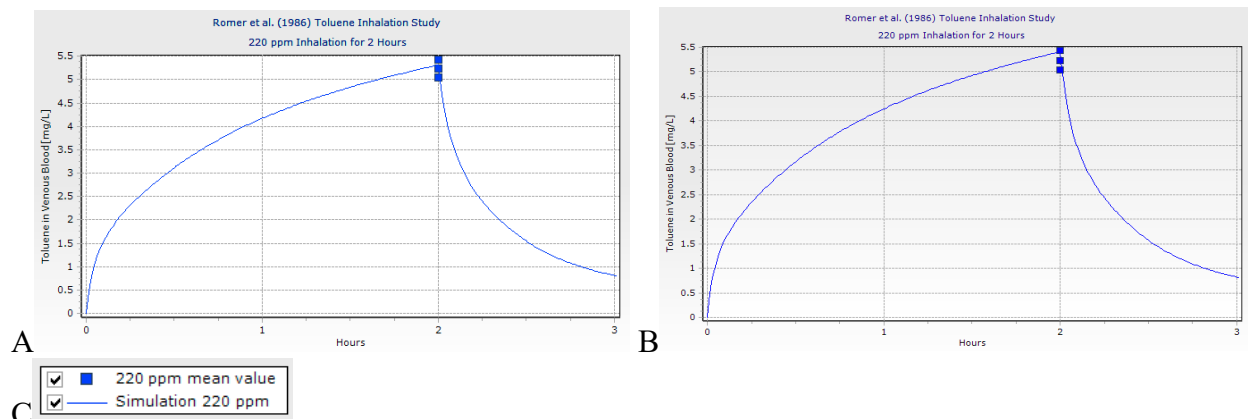


Figure A-3. Comparison Simulations of the Romer *et al.* (1986) Toluene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

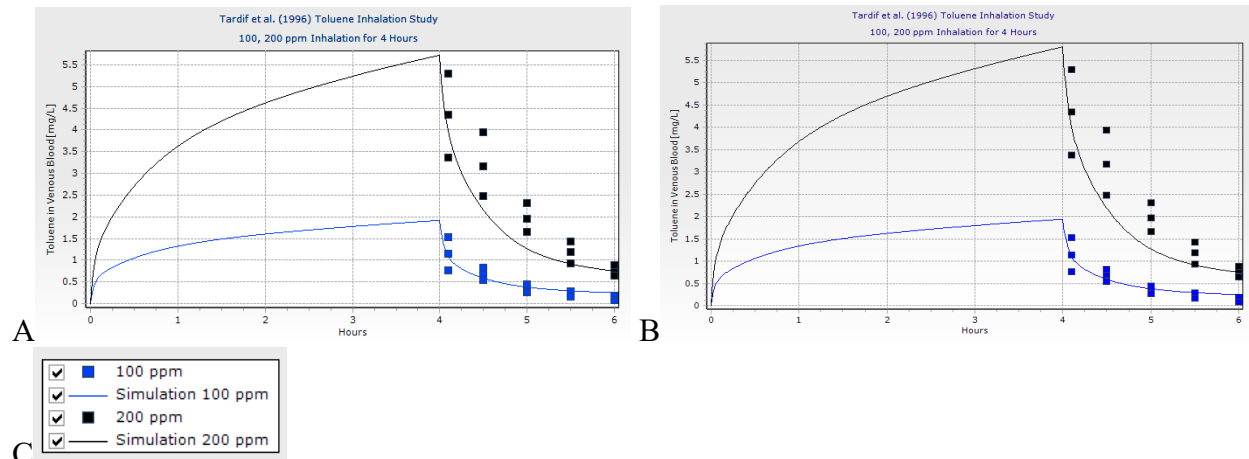


Figure A-4. Comparison Simulations of the Tardif *et al.* (1996) Toluene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

Ethyl Benzene Rat Validation Simulations

The simulations in Figures A-5 through A-6 are essentially the same using both models.

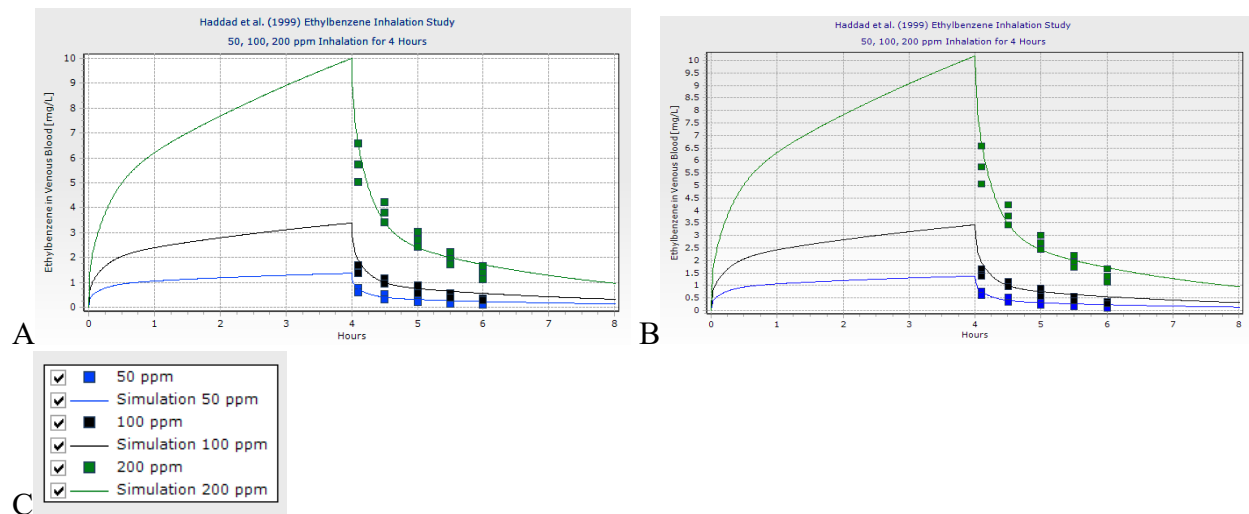


Figure A-5. Comparison Simulations of the Haddad *et al.* (1999) Ethyl Benzene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

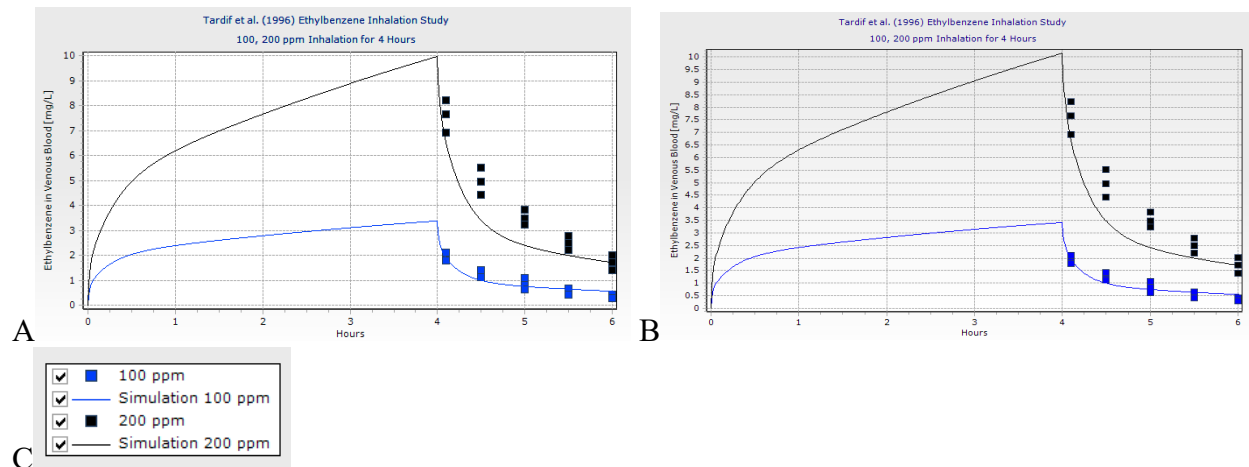


Figure A-6. Comparison Simulations of the Tardif *et al.* (1996) Ethyl Benzene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

Xylenes Rat Validation Simulations

As is shown in Figures A-7 through A-8, the simulations are essentially the same using both models.

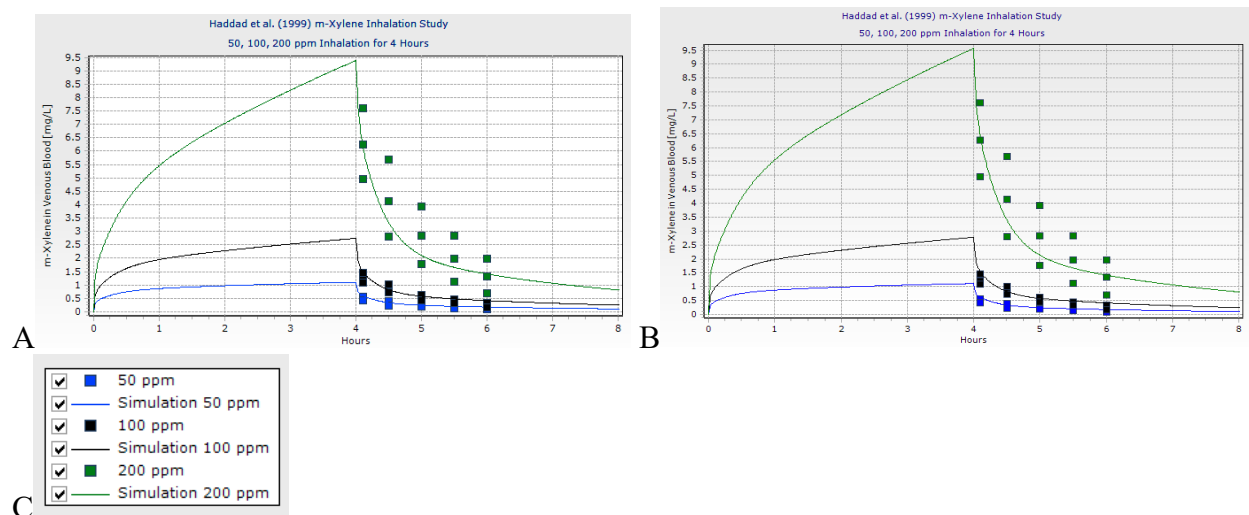


Figure A-7. Comparison Simulations of the Haddad *et al.* (1999) m-Xylene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

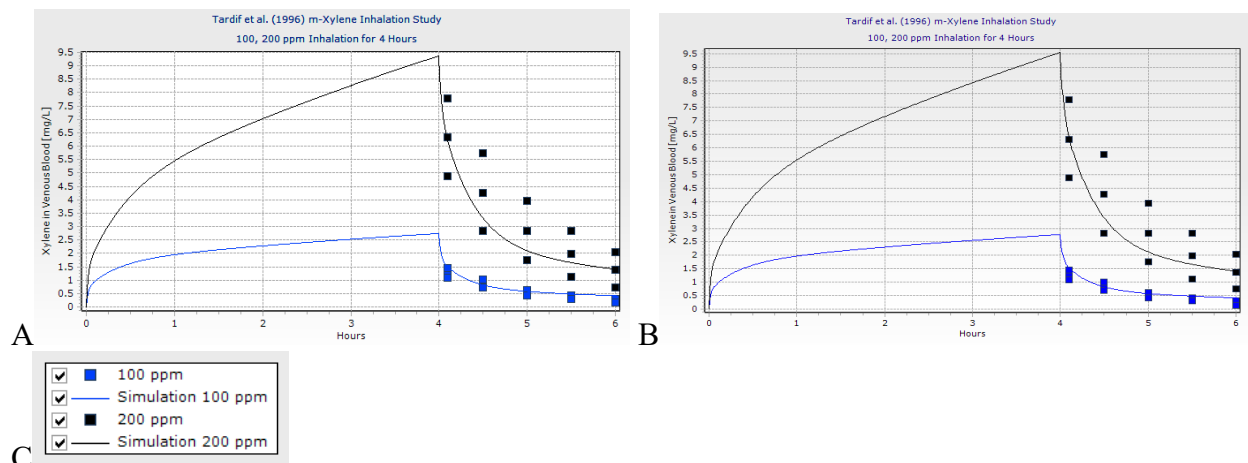


Figure A-8. Comparison Simulations of the Tardif *et al.* (1996) m-Xylene Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

Nonane Rat Validation Simulations

As is shown in Figures A-9 through A-15, the peak height is slightly different, indicating that the simulated maximum concentration of nonane in the tissue is slightly higher for the updated model. However, the model's overall fit to the data is not impacted and the model fit is judged to be adequate.

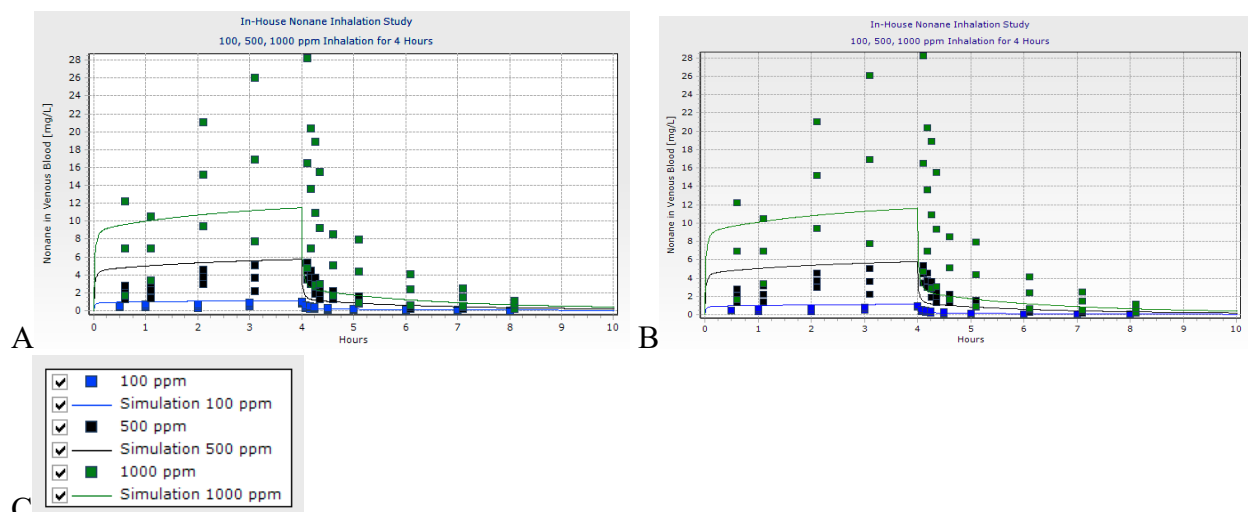


Figure A-9. Comparison Simulations of the Robinson and Merrill (2008) Nonane Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

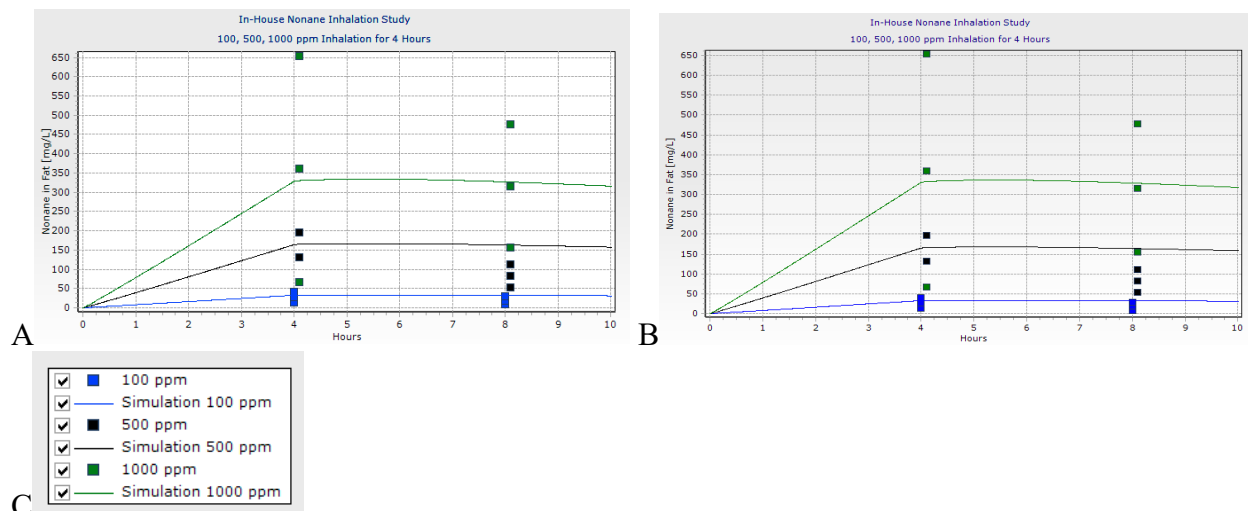


Figure A-10. Comparison Simulations of the Robinson and Merrill (2008) Nonane Fat Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

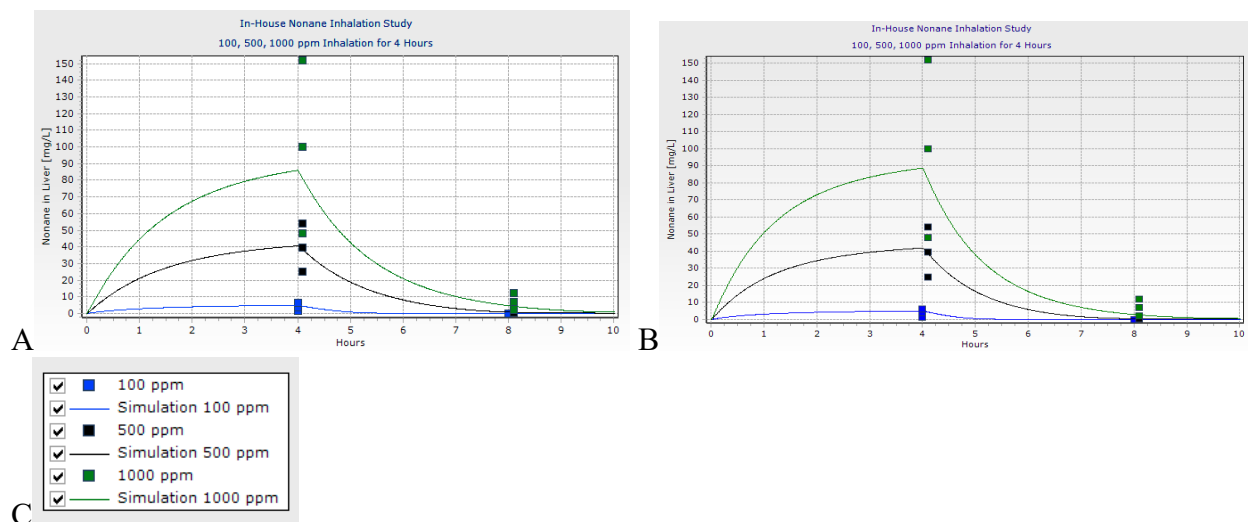


Figure A-11. Comparison Simulations of the Robinson and Merrill (2008) Nonane Liver Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

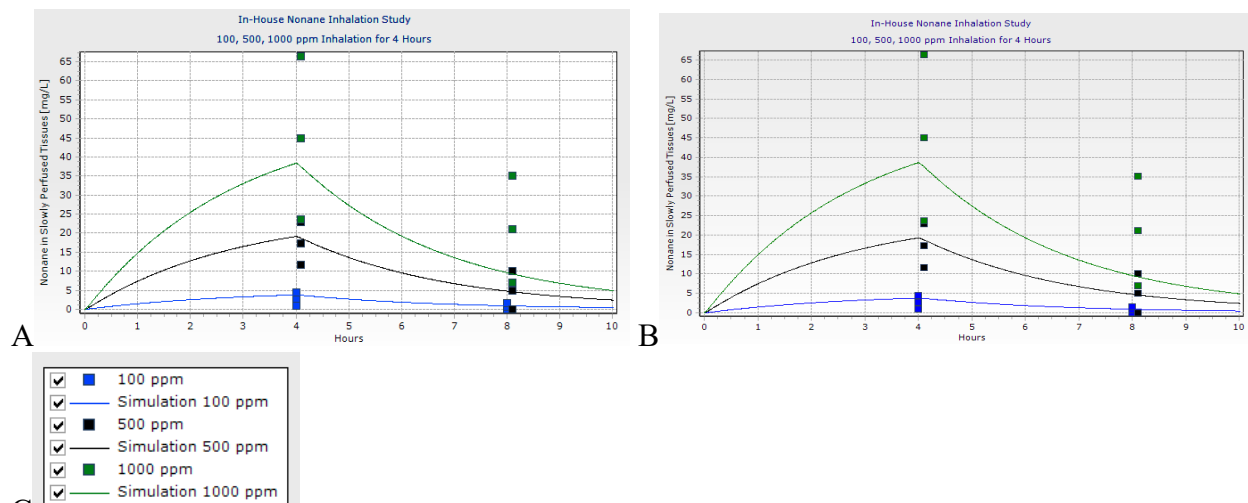


Figure A-12. Comparison Simulations of the Robinson and Merrill (2008) Nonane Slowly Perfused Tissue Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

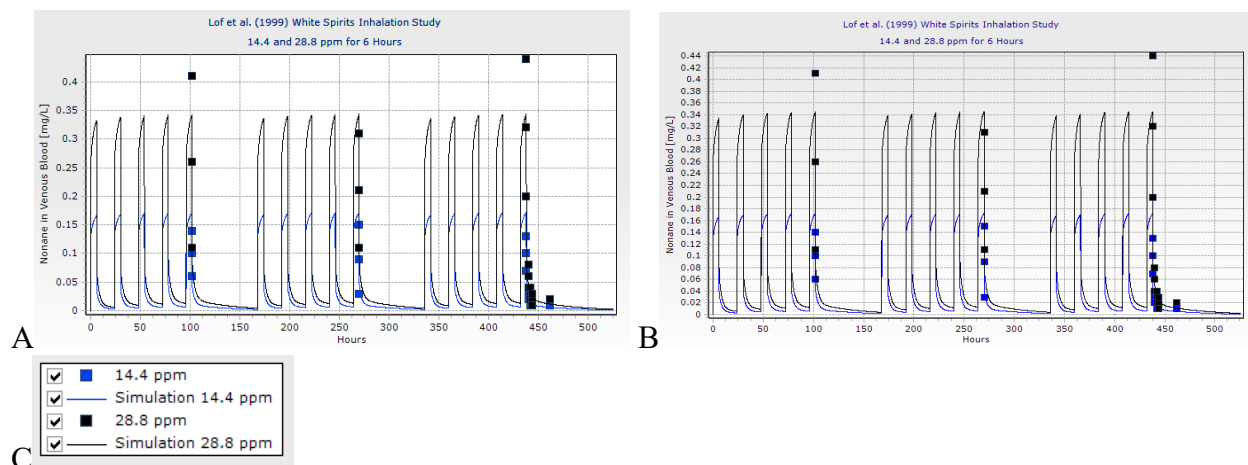


Figure A-13. Comparison Simulations of the Lof *et al.* (1999) Nonane in White Spirits Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

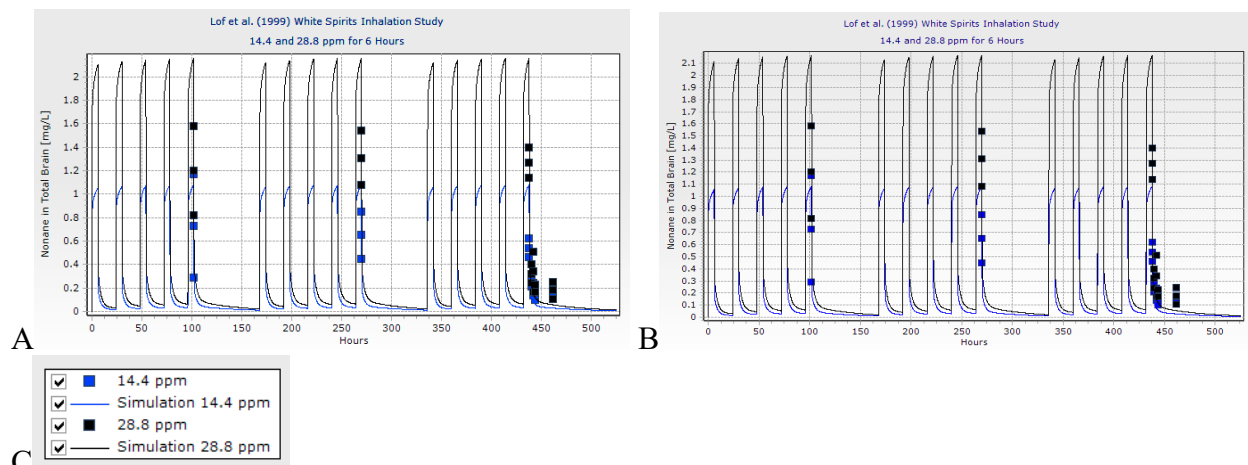


Figure A-14. Comparison Simulations of the Lof *et al.* (1999) Nonane in White Spirits Total Brain Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

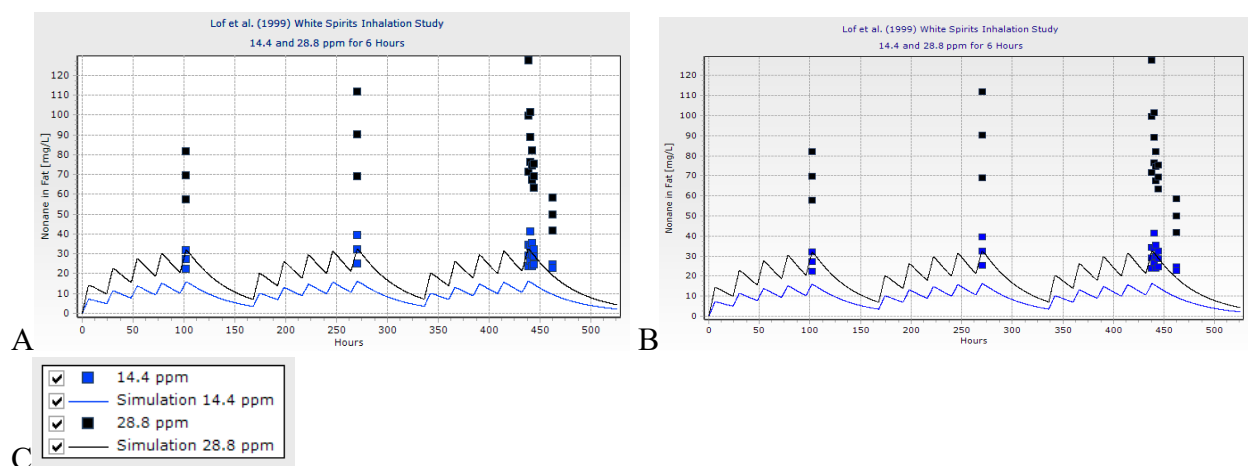


Figure A-15. Comparison Simulations of the Lof *et al.* (1999) Nonane in White Spirits Fat Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

Decane Rat Validation Simulations

As is shown in Figures A-16 through A-27, the peak height is slightly different, indicating that the simulated maximum concentration of decane in the tissue is slightly higher for the updated model. The overall fit of the model to the data, however, is not impacted and the model fit is judged to be adequate.

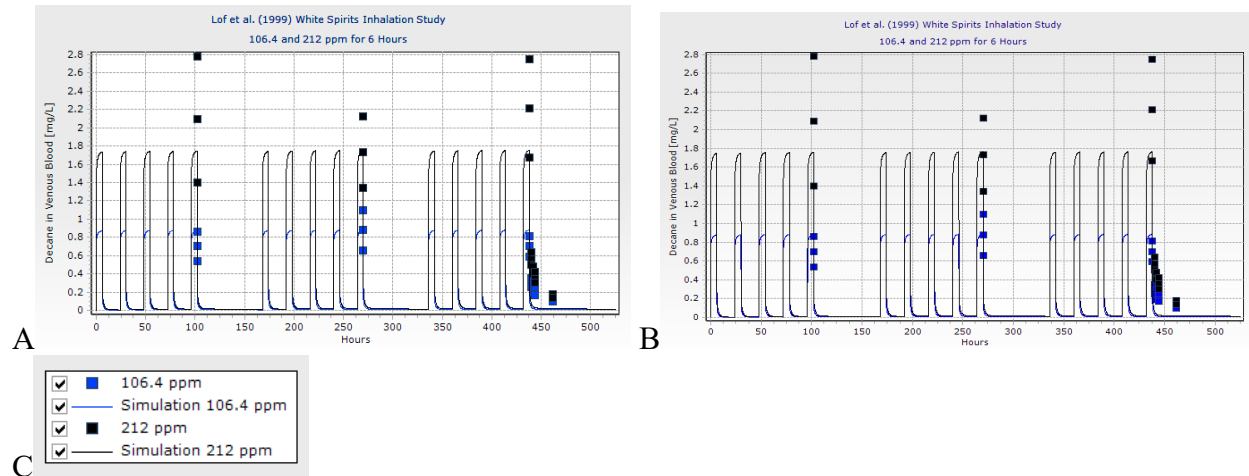


Figure A-16. Comparison Simulations of the Lof *et al.* (1999) Decane in White Spirits Venous Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

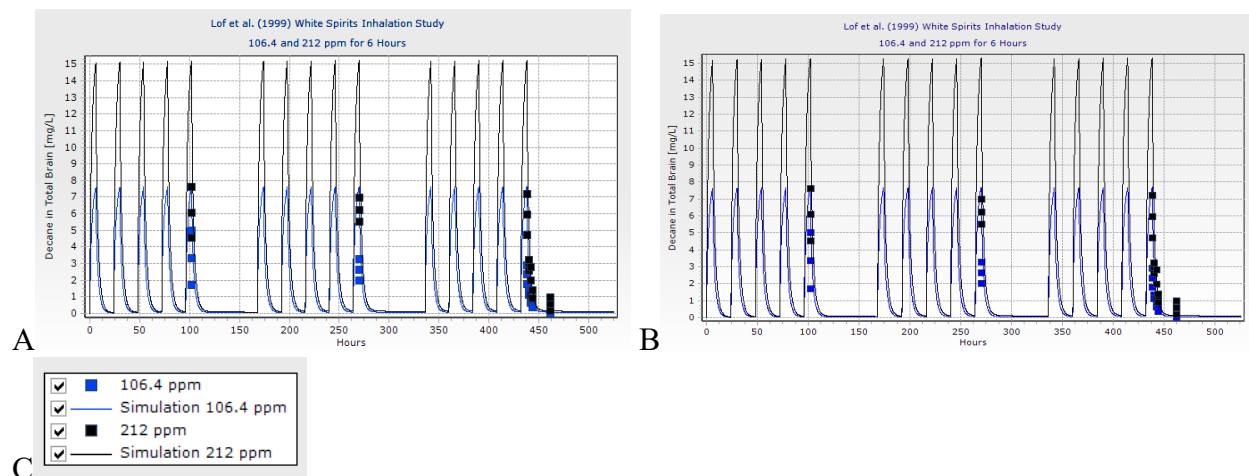


Figure A-17. Comparison Simulations of the Lof *et al.* (1999) Decane in White Spirits Total Brain Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

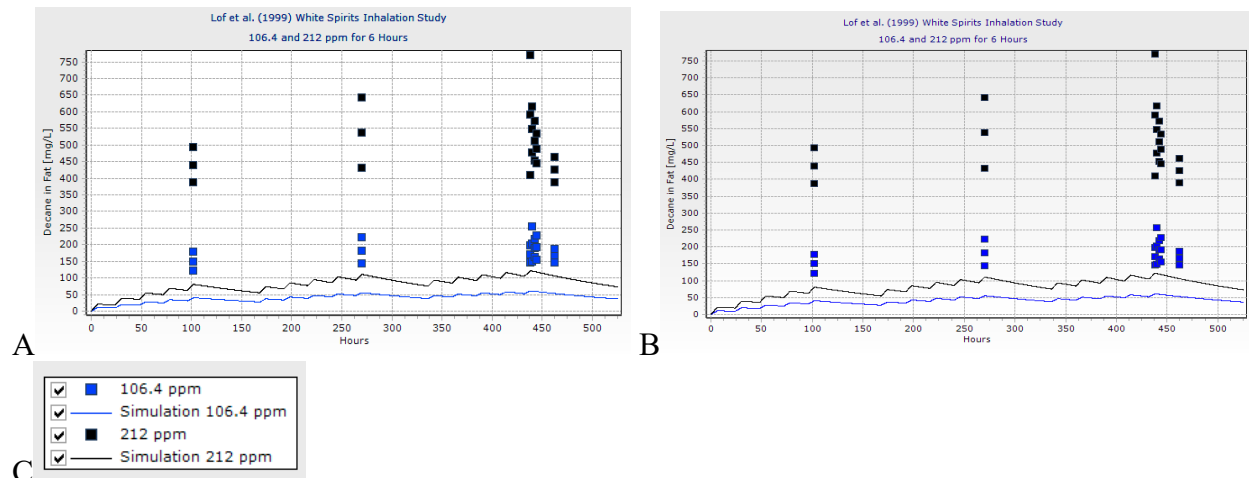


Figure A-18. Comparison Simulations of the Lof *et al.* (1999) Decane in White Spirits Fat Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

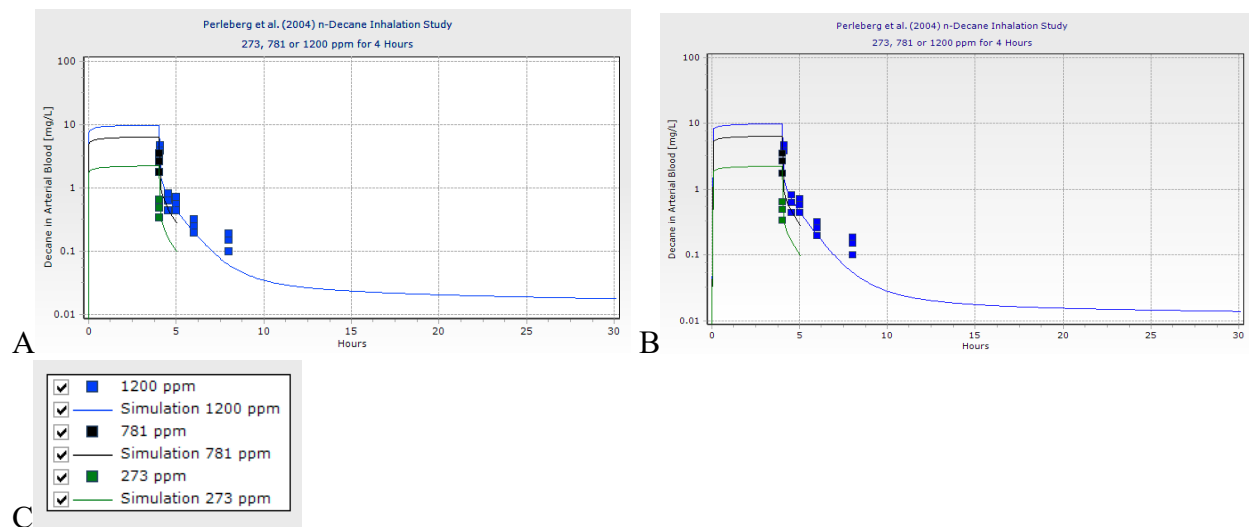


Figure A-19. Comparison Simulations of the Perleberg *et al.* (2004) Decane Arterial Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

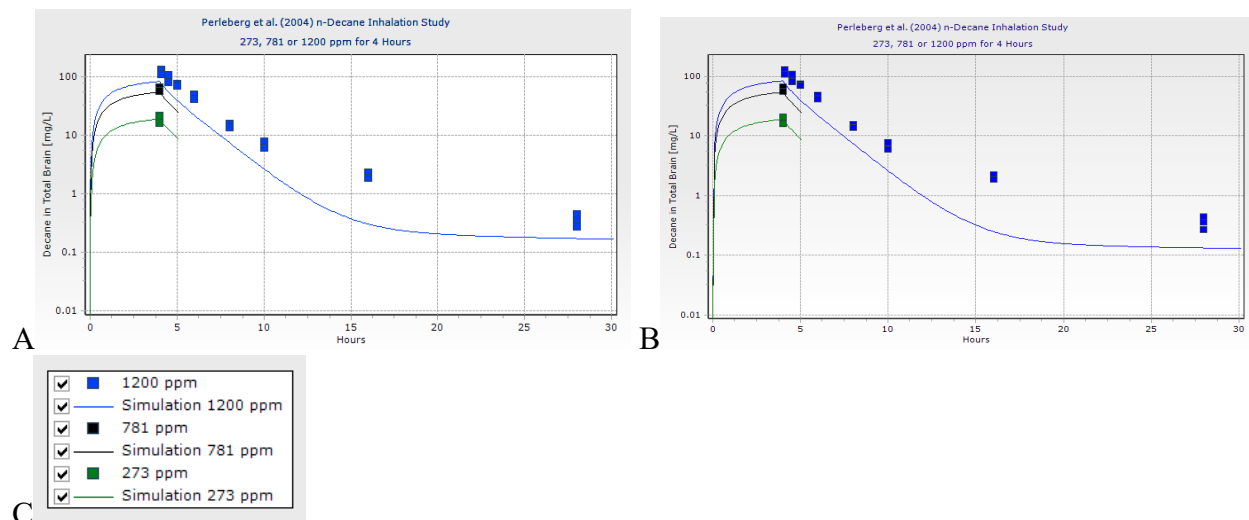


Figure A-20. Comparison Simulations of the Perleberg *et al.* (2004) Decane Total Brain Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

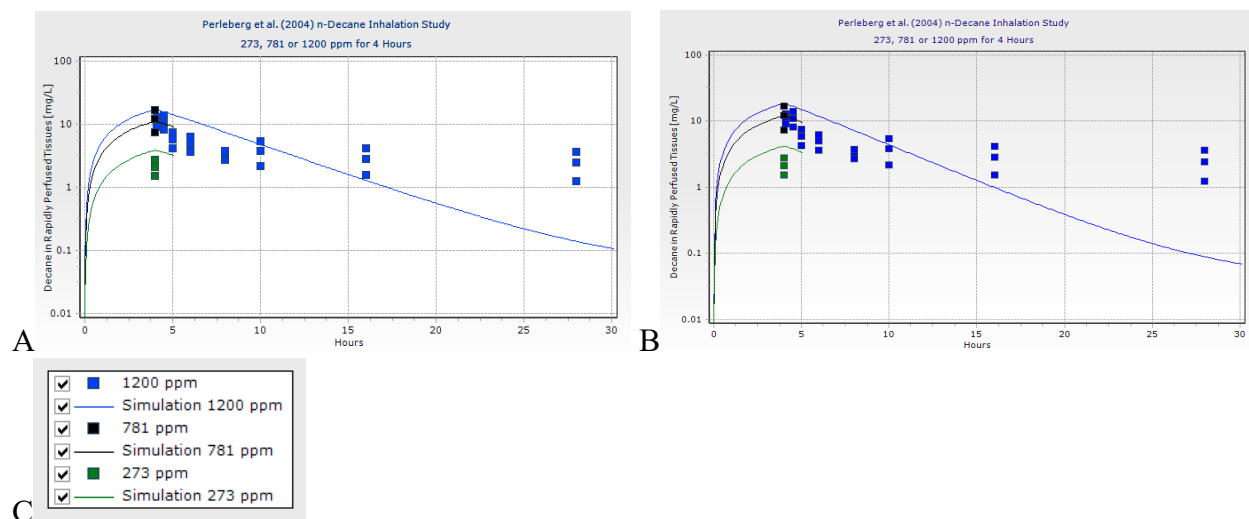


Figure A-21. Comparison Simulations of the Perleberg *et al.* (2004) Decane Kidney (Rapidly Perfused Tissue) Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

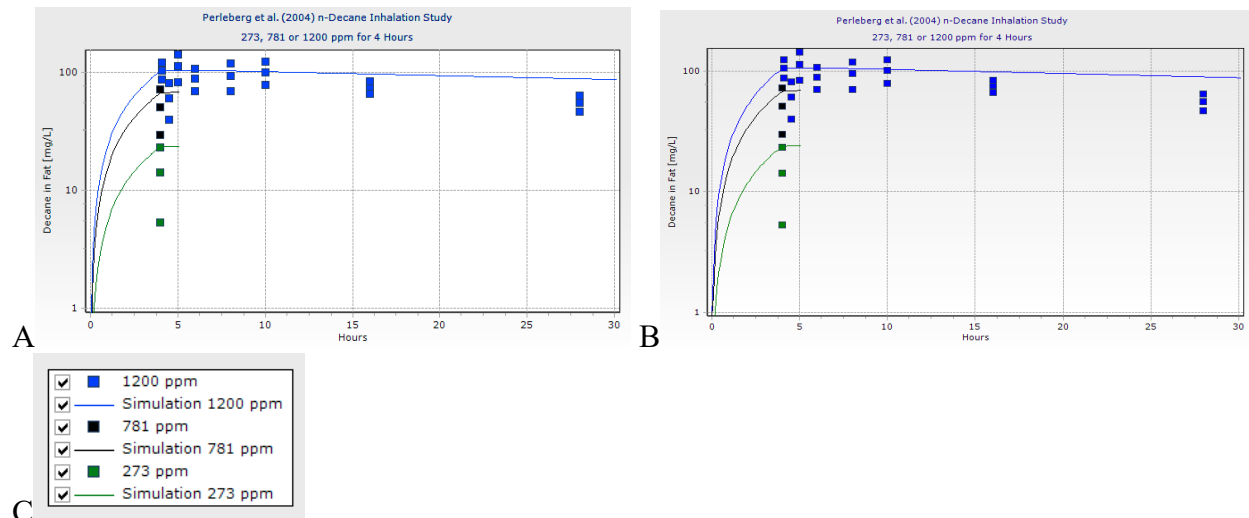


Figure A-22. Comparison Simulations of the Perleberg *et al.* (2004) Decane Fat Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

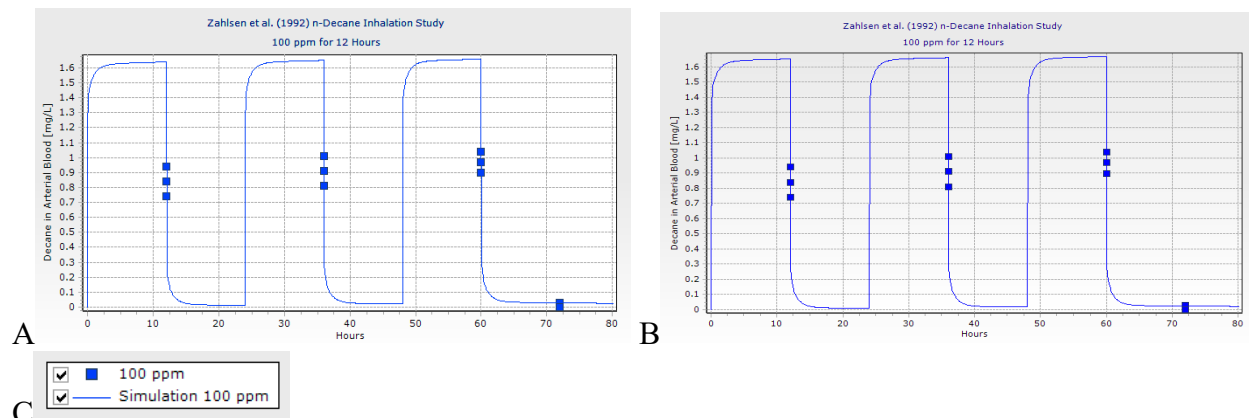


Figure A-23. Comparison Simulations of the Zahlsen *et al.* (1992) Decane Arterial Blood Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

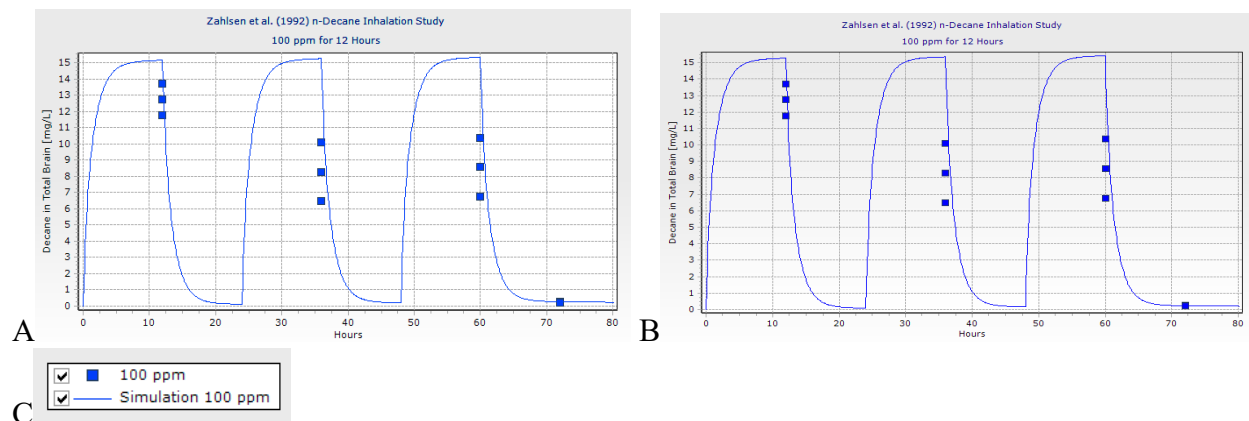


Figure A-24. Comparison Simulations of the Zahlsen *et al.* (1992) Decane Total Brain Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

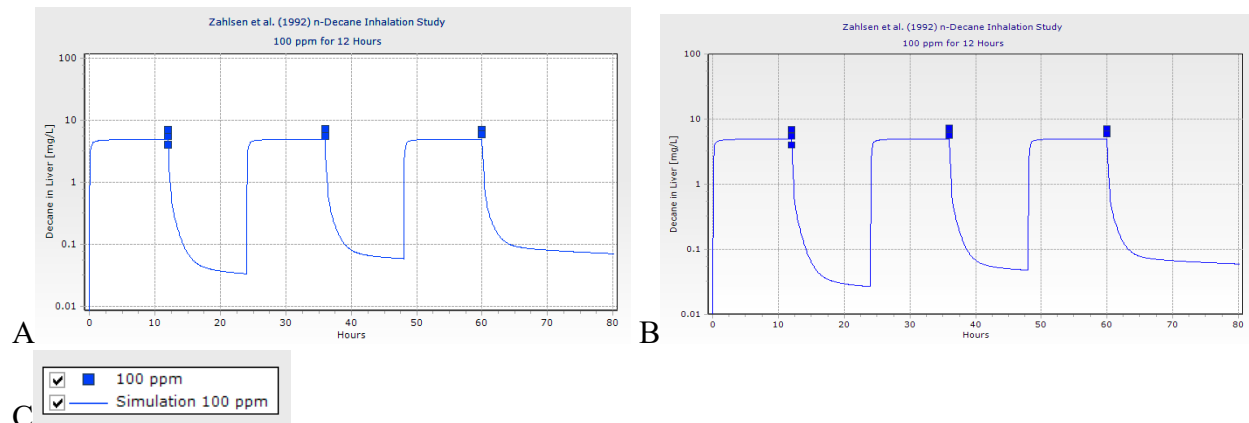


Figure A-25. Comparison Simulations of the Zahlsen *et al.* (1992) Decane Liver Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

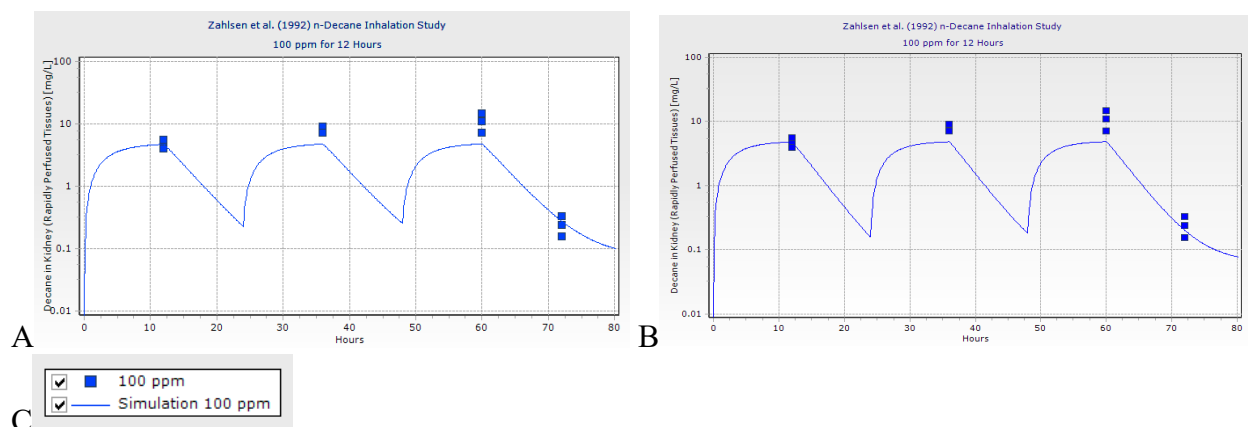


Figure A-26. Comparison Simulations of the Zahlsen *et al.* (1992) Decane Kidney (Rapidly Perfused Tissue) Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

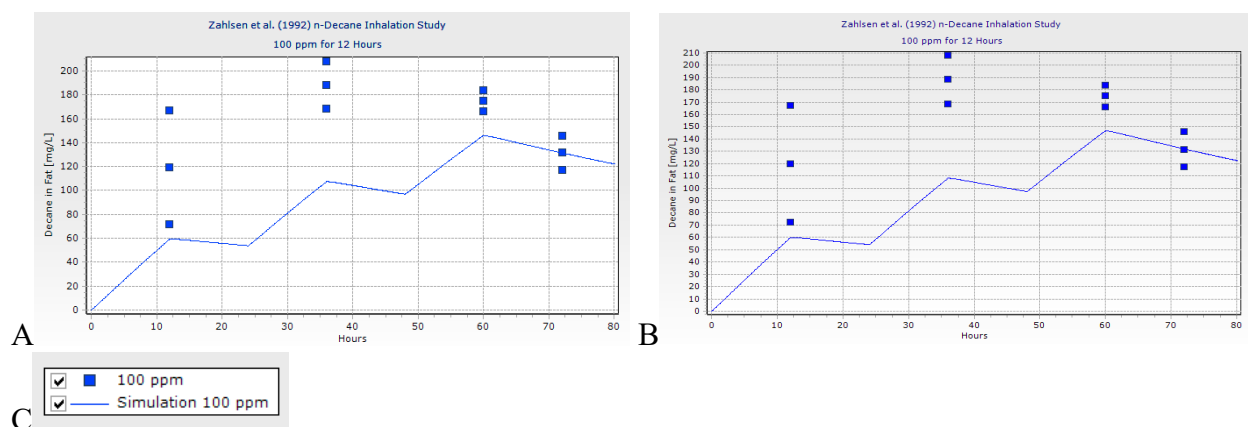


Figure A-27. Comparison Simulations of the Zahlsen *et al.* (1992) Decane Fat Data. Simulations are from A) Sterner *et al.* (2017) and B) the updated array model. C) The legend applies to both graphs.

Naphthalene Human Validation Simulation

Only one naphthalene exposure human data set with measured exhaled air concentrations was found in the literature (Egeghy *et al.*, 2003). All other human data used in Merrill *et al.* (2019) measured excreted naphthols. Excretion of specific metabolites is not a current function of the updated array model. Figure A-28 indicates a good fit to data with the updated model, although the curve is slightly different from the Merrill *et al.* (2019) simulation. Note that the lag time in the older simulation (flat leading portion of the curve) cannot be replicated by the array model at this time; exposure is assumed to begin instantly.

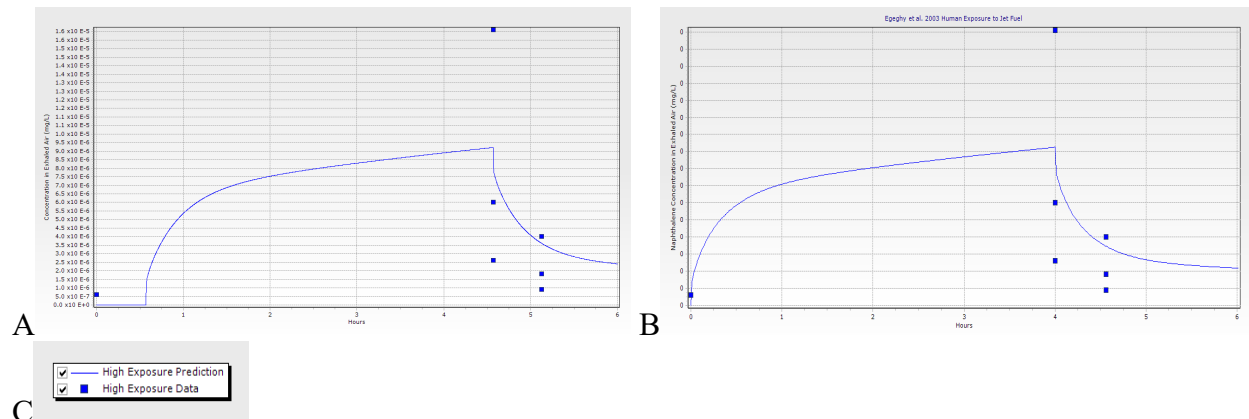


Figure A-28. Comparison Simulations of the Egeghy *et al.* (2003) Human Naphthalene Exhaled Air Data. Simulations are from A) Merrill *et al.* (2019) and B) the updated array model. C) The legend applies to both graphs.

Naphthalene Rat Validation Simulations

As is shown in the rat simulations in Figures A-29 through A-31, the simulation peak heights are somewhat different and the curves are slightly altered. The overall fit of the model to the data, however, is not affected and the model fit is judged to be adequate.

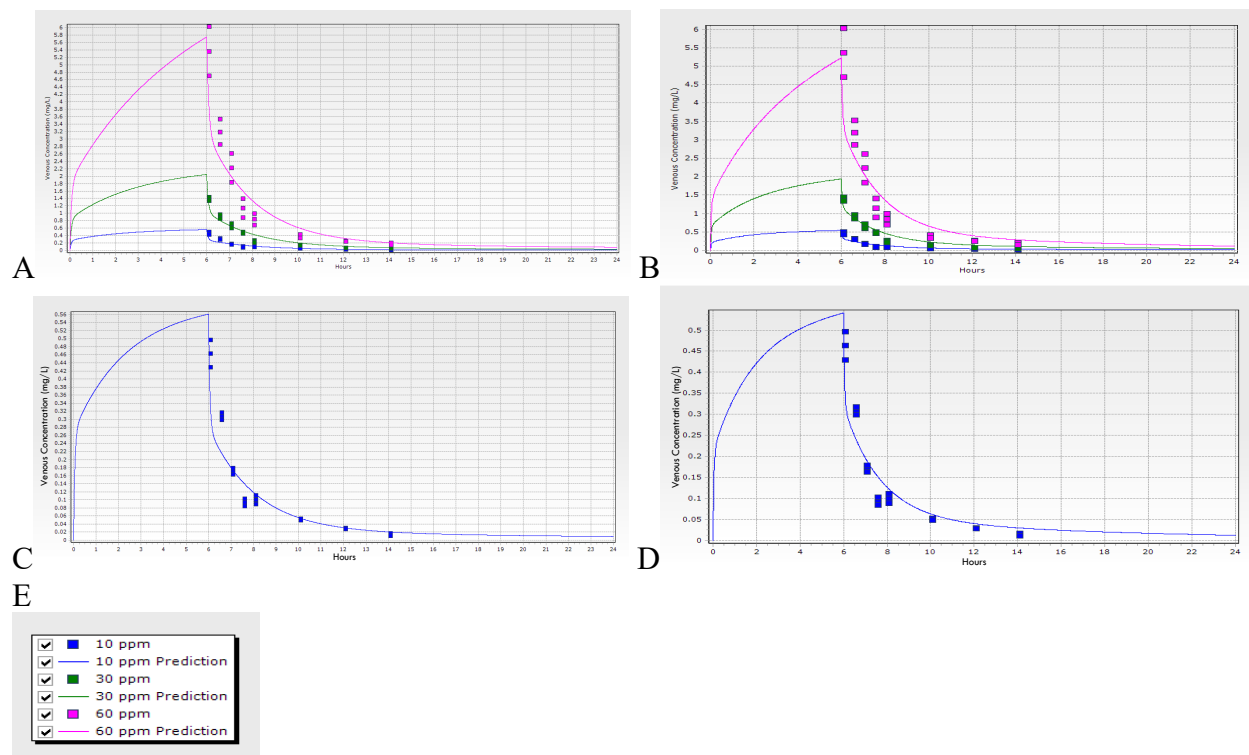


Figure A-29. Comparison Simulations of the NTP (2000) Rat Single-dose Naphthalene Venous Blood Data. Simulations are from A) Merrill *et al.* (2019) and B) the updated array model. Comparison simulations of the lowest exposure concentration (10 ppm) data alone are shown in C) and D), from Merrill *et al.* (2019) and the updated array model, respectively. E) The legend applies to both graphs.

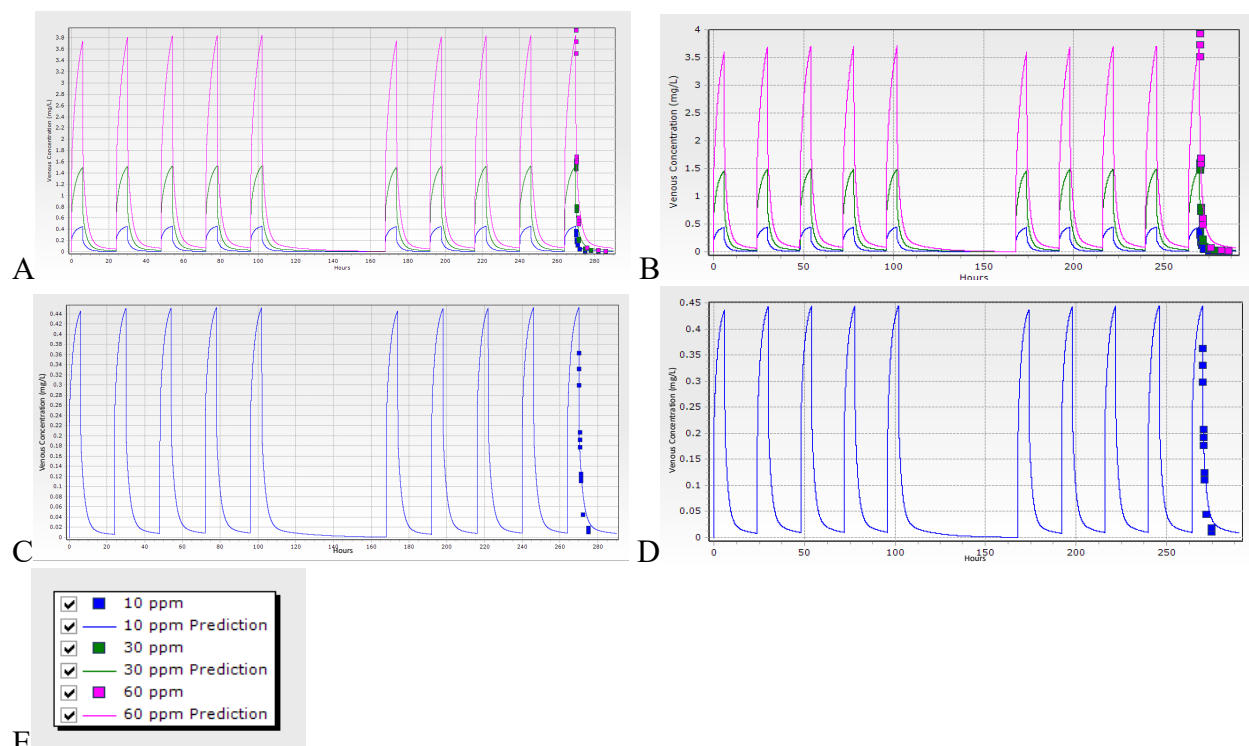
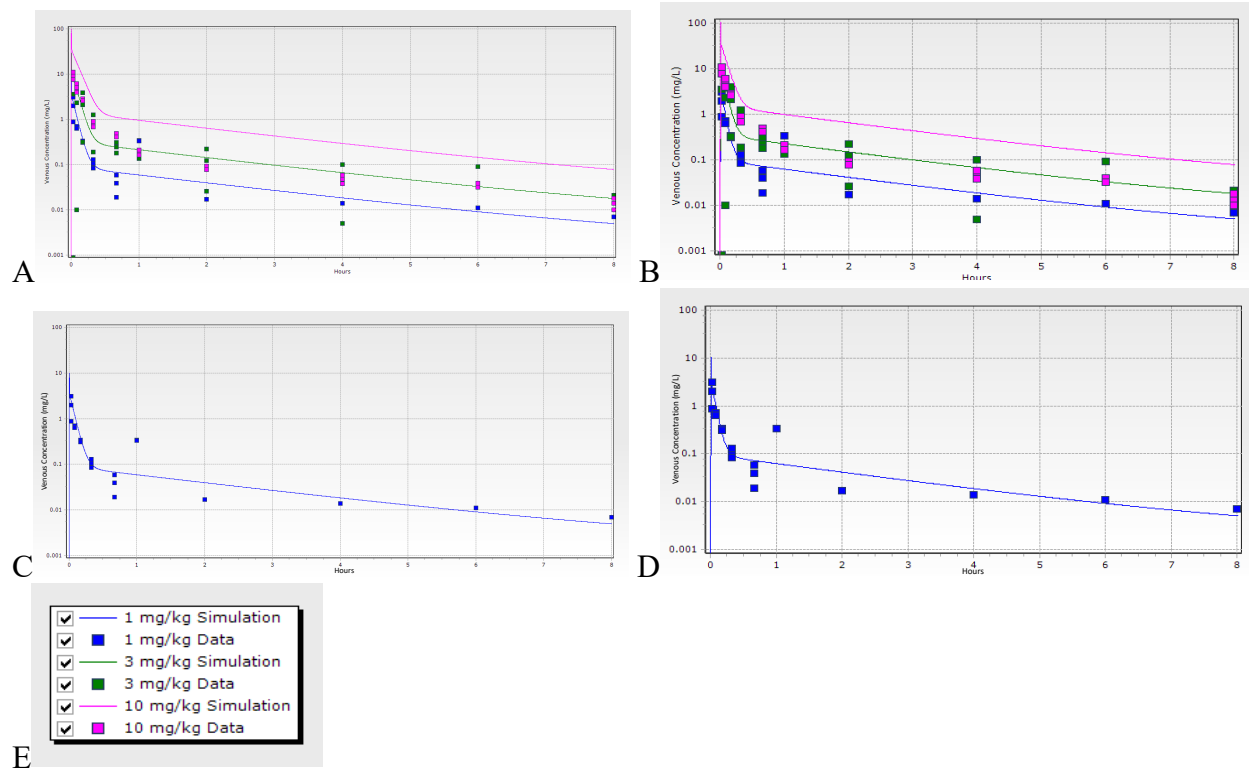


Figure A-30. Comparison Simulations of the NTP (2000) Rat Repeated-dose Naphthalene Venous Blood Data. Simulations are from A) Merrill *et al.* (2019) and B) the updated array model. Comparison simulations of the lowest exposure concentration (10 ppm) data alone are shown in C) and D), from Merrill *et al.* (2019) and the updated array model, respectively. E) The legend applies to both graphs.



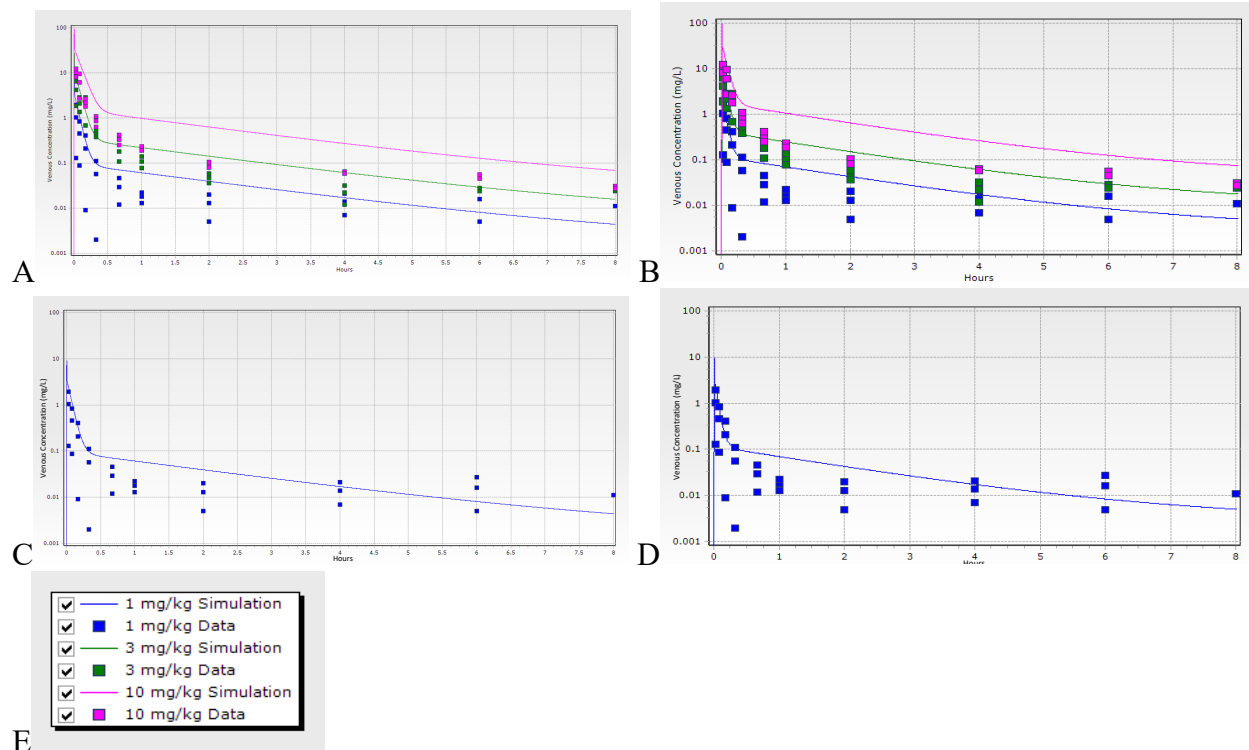


Figure A-31. Comparison Simulations of the RTI (1996) Female Rat Intravenous Naphthalene Venous Blood Data. Simulations are from A) Merrill *et al.* (2019) and B) the updated array model. Comparison simulations of the lowest exposure concentration (1 mg/kg) data alone are shown in C) and D), from Merrill *et al.* (2019) and the updated array model, respectively. E) The legend applies to both graphs.

APPENDIX B: ACSLX ARRAY MODEL CODE

```
PROGRAM: JFHL_6HCB.CSL
! Dec 2019: (a)Removed SQ dosing; (b)Added lung and naphthalene, added lung parameters to other 5
HC
! June 2016: Adds cochlea to diffusion limited array model
! August 2016: Adds brain regions important to hearing to diffusion limited array model
! September 2016: Adds SQ dosing
! NOTE: CINT is only 2x TSQInf - may have to decrease CINT for SQ simulations
! October 2016: Changed cochlea volume to regression derived calculation from BW
! October 2016: Updated from JFHL_SQ to include scrubbing for decane

! Adapted from version of Isopropanol/Acetone model using arrays and from 4 Chem model
!   Removed skin dosing code and changed slow parameters to real values (not array)
!   Removed HalfLife discrete blocks
!   ASt changed to (INTVC(RASt, IASt)) and is replaced in other equations with (TotDose(i) -
ASt(i)) since ASt
!   could not be defined as (TotDose - INTVC(RASt, 0.0))

! Model currently set up to run for 6 chemicals
! Will run for fewer chemicals without modifications as long as parameters are set accordingly
! Can change the model to run for more or less by only changing the "6" in the line "PARAMETER
(NChem=6) "

! ***** SET INIT.M TO LOAD AT RUN TIME *****

INITIAL
  INTEGER NChem
  PARAMETER (NChem=6)

  DIMENSION MW(NChem), PB(NChem), PLq(NChem), PMuc(NChem), PBrn(NChem), PStm(NChem), PTL(NChem)
  DIMENSION PCoc(NChem), PFat(NChem), PLiv(NChem), PRap(NChem), PSlw(NChem), PLu(NChem),
PALu(NChem)
  DIMENSION PABrn(NChem), PASTm(NChem), PATL(NChem), PACoc(NChem), PAFat(NChem), PALiv(NChem),
PARap(NChem), PASlw(NChem)
  DIMENSION VMaxC(NChem), KM(NChem), KFC(NChem), VMaxLuC(NChem), KmLu(NChem), CLurC(NChem),
kUrtC(NChem), Scrub(NChem)
  DIMENSION kAD(NChem), kAS(NChem), kTD(NChem), kTSD(NChem)
  DIMENSION Conc(NChem), IVDose(NChem), PDose(NChem), PDrink(NChem)
  DIMENSION VMax(NChem), KF(NChem), VMaxLu(NChem), CLur(NChem), kUrt(NChem)
  DIMENSION IAArt(NChem), IABrn(NChem), IABrnBld(NChem), IASTm(NChem), IASTmBld(NChem),
IATL(NChem), IATLBld(NChem)
  DIMENSION IACoc(NChem), IACocBld(NChem), IAFat(NChem), IAFatBld(NChem), IALiv(NChem),
IALivBld(NChem)
  DIMENSION IARap(NChem), IARapBld(NChem), IASlw(NChem), IASlwBld(NChem), IALu(NChem),
IALuBld(NChem)
  DIMENSION AI0(NChem), Drink(NChem), IVR(NChem), TotDose(NChem)
  DIMENSION IAExh(NChem), IAMuc(NChem), IAO(NChem), IAExc(NChem), IADu(NChem), IASt(NChem),
IAMet1(NChem), IAMet2(NChem)
  DIMENSION IAURN(NChem), IAUCcArt(NChem), IAUCcBrn(NChem), IATotInh(NChem), IATotIV(NChem),
IATotDrink(NChem), IAMetLu(NChem)
  DIMENSION DAUCcArt(NChem), DAUCcBrn(NChem), PAUCcArt(NChem), PAUCcBrn(NChem)
  DIMENSION Calv(NChem), CalvPPM(NChem), CP(NChem), CEnd(NChem), CEndPPM(NChem), PerEnd(NChem),
CMix(NChem), CMixPPM(NChem), PerMix(NChem)
  DIMENSION RACH(NChem), RAMuc(NChem), RAArt(NChem), RAExh(NChem), RABrn(NChem), RABrnBld(NChem),
RAStm(NChem), RAStmBld(NChem)
  DIMENSION RATL(NChem), RATLBld(NChem), RACoc(NChem), RACocBld(NChem), RAFat(NChem),
RAFatBld(NChem)
  DIMENSION RAO(NChem), RAExc(NChem), RADu(NChem), RASl(NChem), RALu(NChem), RALuBld(NChem)
  DIMENSION RALiv(NChem), RALivBld(NChem), RAMet1(NChem), RAMet2(NChem), RAMetLu(NChem),
RARap(NChem), RARapBld(NChem)
  DIMENSION RASlw(NChem), RASlwBld(NChem), RAURN(NChem), RATotInh(NChem)
  DIMENSION Cinh(NChem), CMuc(NChem), CArt(NChem), CBrn(NChem), CBrnBld(NChem), CBrnDif(NChem)
  DIMENSION CStm(NChem), CStmBld(NChem), CStmDif(NChem), CTL(NChem), CTLBld(NChem), CTLDif(NChem)
  DIMENSION CCoc(NChem), CCocBld(NChem), CCocDif(NChem), CFat(NChem), CFatDif(NChem),
CFatBld(NChem)
  DIMENSION CLiv(NChem), CLivBld(NChem), CLivDif(NChem), CRap(NChem), CRapBld(NChem),
CRapDif(NChem)
```

```

    DIMENSION CSFC(NChem), CSlw(NChem), CSlwBld(NChem), CSlwDif(NChem), CLu(NChem), CLuBld(NChem),
    CLuDif(NChem)
    DIMENSION CVen(NChem)
    DIMENSION ACh(NChem), AMuc(NChem), AArt(NChem), AUCCArt(NChem), AExh(NChem), ABrn(NChem),
    ABrnBld(NChem), AUCCBrn(NChem)
    DIMENSION AStm(NChem), AStmBld(NChem), ATL(NChem), ATLBld(NChem), ACoc(NChem), ACocBld(NChem)
    DIMENSION AFat(NChem), AFatBld(NChem), AO(NChem), AExc(NChem), ADu(NChem), ASt(NChem),
    ALu(NChem), ALuBld(NChem)
    DIMENSION ALiv(NChem), ALivBld(NChem), AMet1(NChem), AMet2(NChem), AMetLu(NChem), ARap(NChem),
    ARapBld(NChem)
    DIMENSION ASlw(NChem), ASlwBld(NChem), AUrn(NChem)
    DIMENSION ATotInh(NChem), ATotIV(NChem), ATotDrink(NChem)
    DIMENSION CBrnTotBld(NChem), CBrnTot(NChem), TDose(NChem), AmtBody(NChem), MassBal(NChem)

    INTEGER i, j1, j2, j3, j4, j5, i1, i2, i3, i4, i5, i6, i7, i8, i9, i10, i11, i12, i13, i14,
    i15, i16, i17, i18
    LOGICAL CC                                ! To control whether closed or open chamber

! Total Pulmonary Ventilation Rate (L/hr for 1 kg animal)
CONSTANT    QPC = 24.75                      ! Total pulmonary ventilation (L/hr - 1 kg)

! Blood Flows (fraction of cardiac output)
CONSTANT    QCC = 14.6                      ! Cardiac output (L/hr - 1 kg animal)
CONSTANT    QBrnC = 0.013                  ! Brain Remainder (0.02 - QStmC - QTLC)
    CONSTANT    QStmC = 0.004              ! Brain Stem
    CONSTANT    QTLC = 0.003              ! Temporal Lobe
CONSTANT    QCocC = 0.00004              ! Cochlea pair
CONSTANT    QFatC = 0.07                  ! Fat
CONSTANT    QLivC = 0.183                ! Liver
CONSTANT    QLuC = 0.021                ! Lung (Brown et al 1997)
CONSTANT    QRapC = 0.536                ! Rapidly perfused (0.557 - Lung)
CONSTANT    QSlwC = 0.16996            ! Slowly perfused (includes skin compartment)

! Tissue Volumes (fraction of body weight)
CONSTANT    BW = 0.22                    ! Body weight (kg)
CONSTANT    VALvC = 0.007                ! Alveolar blood
CONSTANT    VBrnC = 0.004                ! Brain Remainder (0.006 - VStmC - VTLC)
    CONSTANT    VStmC = 0.001            ! Brain Stem
    CONSTANT    VTLC = 0.001            ! Brain Temporal Lobe
CONSTANT    VFatC = 0.10                 ! Fat
CONSTANT    VLivC = 0.034                ! Liver
CONSTANT    VLuC = 0.005                 ! Lung (Brown et al 1997)
CONSTANT    VMucC = 0.0001              ! Mucous
CONSTANT    VRapC = 0.039                ! Rapidly perfused (0.044 - Lung)
CONSTANT    VSlwC = 0.65                 ! Slowly perfused (includes skin, cochlea)
CONSTANT    DS = 0.15                   ! Dead space volume (fraction)

!Tissue Volumes (fraction of tissue volume)
CONSTANT    VBrnBldC = 0.03              ! Brain Remainder
    CONSTANT    VStmBldC = 0.03          ! Brain Stem
    CONSTANT    VTLBldC = 0.03          ! Brain Temporal Lobe
CONSTANT    VCocBldC = 0.0183           ! Cochlea
CONSTANT    VFatBldC = 0.0154           ! Fat
CONSTANT    VLivBldC = 0.21             ! Liver
CONSTANT    VLuBldC = 0.36              ! Lung (Brown et al., 1997)
CONSTANT    VRapBldC = 0.2075           ! Rapidly Perfused Tissues
CONSTANT    VSlwBldC = 0.0333          ! Slowly Perfused Tissues

! Molecular Weights (mg/mmmole)
CONSTANT    MW = NChem*1.0

! Tissue/Blood Partition Coefficients
CONSTANT    PB = NChem*1.0              ! Blood/air
CONSTANT    PLq = NChem*1.0            ! Saline/air
CONSTANT    PMuc = NChem*1.0           ! Mucous/air
CONSTANT    PBrn = NChem*1.0           ! Brain Remainder
    CONSTANT    PStm = NChem*1.0        ! Brain Stem
    CONSTANT    PTL = NChem*1.0        ! Brain Temporal Lobe
CONSTANT    PCoc = NChem*1.0           ! Cochlea
CONSTANT    PFat = NChem*1.0           ! Fat

```

```

CONSTANT    PLiv = NChem*1.0      ! Liver
CONSTANT    PLu  = NChem*1.0      ! Lung
CONSTANT    PRap = NChem*1.0      ! Rapidly perfused tissue
CONSTANT    PSlw = NChem*1.0      ! Slowly perfused tissue

! Tissue Permeability Coefficients
CONSTANT    PABrn = NChem*1000.0  ! Brain remainder diffusion limitation
  CONSTANT  PASTm = NChem*1000.0  ! Brain stem diffusion limitation
  CONSTANT  PATL  = NChem*1000.0  ! Brain temporal lobe diffusion limitation
CONSTANT    PACoc = NChem*1000.0  ! Cochlea diffusion limitation
CONSTANT    PAFat = NChem*1000.0  ! Fat diffusion limitation
CONSTANT    PALiv = NChem*1000.0  ! Liver diffusion limitation
CONSTANT    PALu  = NChem*1000.0  ! Lung diffusion limitation
CONSTANT    PARap = NChem*1000.0  ! Rapidly perfused tissues diffusion limitation
CONSTANT    PASlw = NChem*1000.0  ! Slowly perfused tissues diffusion limitation

! Metabolism Parameters
  CONSTANT  VMaxC = NChem*0.0      ! Michaelis-Menten maximum reaction rat for lung
metabolism
  CONSTANT  KM    = NChem*1.0      ! M-M Affinity coefficient (mg/L)
  CONSTANT  KFC   = NChem*0.0      ! First order rate constant (/hr)
  CONSTANT  VMaxLuC = NChem*0.0    ! Michaelis-Menten maximum reaction rat for lung
metabolism
  CONSTANT  KMLu  = NChem*1.0      ! M-M Affinity coefficient (mg/L)

! Uptake and Clearance Parameters
  CONSTANT  ClUrC = NChem*0.0      ! Urinary clearance (L/hr)
  CONSTANT  kUrtC = NChem*0.0      ! URT uptake into mucus (L/hr)
  CONSTANT  Scrub = NChem*0.0      ! Fraction of inhaled dose scrubbed (not absorbed into
blood or mucus)
  CONSTANT  kAD   = NChem*0.0      ! Absorption from duodenum (/hr)
  CONSTANT  kAS   = NChem*0.0      ! Absorption from stomach (/hr)
  CONSTANT  kTD   = NChem*0.0      ! Excretion (/hr)
  CONSTANT  kTSD  = NChem*0.0      ! Transfer - stomach to duodenum (/hr)

! Dosing Parameters
  CONSTANT  Conc  = NChem*0.0      ! Inhaled concentration (ppm)
  CONSTANT  IVDose = NChem*0.0      ! IV dose (mg/kg)
  CONSTANT  PDose  = NChem*0.0      ! Oral dose (mg/kg)
  CONSTANT  PDrink = NChem*0.0      ! Drinking water dose (mg/kg/day)
  CONSTANT  TChng  = 0.0           ! Length of inhalation exposure (hrs)
  CONSTANT  DaysWk = 1.0           ! Number of exposure days per week
  CONSTANT  TMax   = 24.0          ! Maximum time for exposures
  CONSTANT  TInf   = 0.20          ! Length of IV injection (hrs)
  CONSTANT  Rats   = 1.0           ! Number of animals in experiment

! Chamber Parameter
  CONSTANT  CC     = .FALSE.        ! Default to open chamber
  CONSTANT  VChC   = 9.1           ! Volume of closed chamber
  CONSTANT  kLCC   = 0.0           ! Chamber loss

! Simulation Control Parameters
  CONSTANT  TStop  = 24.0
  CINTERVAL  CINT  = 0.01

! Set Chamber Volume and Loss for Open and Closed Chamber Exposures
  IF (.NOT. CC) THEN
    VCh = 1.0e+20                ! Large chamber = open chamber
    kLC = 0.0
  ELSE
    VCh = VChC - (Rats * BW)      ! Calculate net chamber volume
    kLC = kLCC
  ENDIF

! Scaled Pulmonary Ventilation Rate (L/hr)
  QCN  = QCC * (BW**0.75)
  QP   = QPC * (BW**0.75)
  QAlv = 0.67 * QP

! Scaled Blood Flows (L/hr) and Tissue Volumes (L)

```

```

QBrn = QBrnC * QCN
QStm = QStmC * QCN
QTL = QTLc * QCN
QCoc = QCocC * QCN      ! cochlea pair
QFat = QFatC * QCN
QLiv = QLivC * QCN
QLu = QLuC * QCN
QRap = QRapC * QCN

VAlv = VAlvC * BW
VMuc = VMucC * BW
VBrn = (VBrnC * (1 - VBrnBldC)) * BW
VStm = (VStmC * (1 - VStmBldC)) * BW
VTL = (VTLC * (1 - VTLBldC)) * BW
VCocM = 0.00007 * (BW**0.2348)      ! Data based calculation of cochlea pair mass
(kg)
VCoc = VCocM * (1 - VCocBldC)
VFat = (VFatC * (1 - VFatBldC)) * BW
VLiv = (VLivC * (1 - VLivBldC)) * BW
VLu = (VLuC * (1 - VLuBldC)) * BW
VRap = (VRapC * (1 - VRapBldC)) * BW
VSlw = ((VSlwC * BW) - VCocM) * (1.0 - VSlwBldC)

VBrnBld = VBrnBldC * (VBrnC * BW)
VStmBld = VStmBldC * (VStmC * BW)
VTLBld = VTLBldC * (VTLC * BW)
VCocBld = VCocBldC * VCocM
VFatBld = VFatBldC * (VFatC * BW)
VLivBld = VLivBldC * (VLivC * BW)
VLuBld = VLuBldC * (VLuC * BW)
VRapBld = VRapBldC * (VRapC * BW)
VSlwBld = ((VSlwC * BW) - VCocM) * VSlwBldC

QSlw = (QSlwC * QCN)
QC = QBrn + QStm + QTL + QCoc + QFat + QLiv + QLu + QRap + QSlw
QTot = QCN - QC

VTotTis = VBrn + VStm + VTL + VCoc + VFat + VLiv + VLu + VRap + VSlw
VTotBld = VBrnBld + VStmBld + VTLBld + VCocBld + VFatBld + VLivBld + VLuBld + VRapBld +
VSlwBld
VTot = (VTotTis + VTotBld)/BW

DO 1030 i=1, NChem
! Scaled Metabolism Parameters
VMax(i) = VMaxC(i) * (BW**0.75)
KF(i) = KFC(i) / (BW**0.25)
VMaxLu(i) = VMaxLuC(i) * (BW**0.75)

! Scaled Clearance Rates
ClUr(i) = ClUrC(i) * (BW**0.75)
kUrt(i) = (min(kUrtC(i), QPC)) * (BW**0.75)

! Initial Amounts (mg)
IAArt(i) = 0.0
IABrn(i) = 0.0
IAStm(i) = 0.0
IATL(i) = 0.0
IABrnBld(i) = 0.0
IAStmBld(i) = 0.0
IATLBld(i) = 0.0
IACoc(i) = 0.0
IACocBld(i) = 0.0
IAFat(i) = 0.0
IAFatBld(i) = 0.0
IALiv(i) = 0.0
IALivBld(i) = 0.0
IALu(i) = 0.0
IALuBld(i) = 0.0
IARap(i) = 0.0
IARapBld(i) = 0.0

```

```

IASlw(i) = 0.0
IASlwBld(i) = 0.0

! Scaled and Initial Doses
  AI0(i) = (Conc(i) * VCh * MW(i)) / 24450.0      ! Initial amount in chamber
  Drink(i) = (PDrink(i) * BW) / 24.0             ! Drinking water dose
(mg/hr)
  IVR(i) = 0.0                                     ! IV dose
  TotDose(i) = 0.0                                 ! Facilitate mass balance
check

! Initialize Initial Values for Integrating State Variables
  IAEsh(i) = 0.0
  IAMuc(i) = 0.0
  IAO(i) = 0.0
  IAEsh(i) = 0.0
  IADu(i) = 0.0
  IAST(i) = 0.0
  IAMet1(i) = 0.0
  IAMet2(i) = 0.0
  IAMetLu(i) = 0.0
  IAUrn(i) = 0.0
  IAUCCart(i) = 0.0
  IAUCBrn(i) = 0.0
  IATotInh(i) = 0.0
  IATotIV(i) = 0.0
  IATotDrink(i) = 0.0

! Initialize Starting Values
  DAUCCart(i) = 0.0
  DAUCBrn(i) = 0.0
  PAUCCart(i) = 0.0
  PAUCBrn(i) = 0.0
  PerEnd(i) = 0.0
  PerMix(i) = 0.0
1030: CONTINUE

! Initialize Starting Values
  CIZone = 1.0
  CSFZone = 0.0
  DayExp = 1.0

END                                ! End of Initial

DYNAMIC
  ALGORITHM  IALG = 2              ! Gear stiff method

DISCRETE DoseOn    ! Start dosing
  INTERVAL DoseInt = 24.0          ! Interval to repeat dosing
  SCHEDULE DoseOffIV .AT. T + TInf
  SCHEDULE DoseOffIhl .AT. T + TChng

  IF ((T .LT. TMax) .AND. (DayExp .LE. DaysWk)) .OR. CC) THEN
    CIZone = 1.0
  ENDIF

  DayExp = DayExp + 1.0

  IF (DayExp .GT. 7.0) THEN
    DayExp = 0.5
  ENDIF

DO 1040 j1=1, NChem
  IF (T .LE. TInf) THEN
    IVR(j1) = (IVDose(j1) * BW) / TInf      ! Rate of intravenous dosing (mg/hr)
    TotDose(j1) = TotDose(j1) + (PDose(j1) * BW)
  ENDIF
1040: CONTINUE

```

END

```
DISCRETE DoseOffIV
DO 1050 j2=1, NChem
    IVR(j2) = 0.0
1050: CONTINUE
END
```

```
DISCRETE DoseOffIhl
    IF (.NOT. CC) THEN
        CIZone = 0.0
    ENDIF
END
```

```
DISCRETE Calc      ! Calculate daily average AUC (D) using previous value (P)
! Note that this is calculated for the Brain Remainder and not the whole brain
INTERVAL CalcInt = 24.0
```

```
DO 1060 j3=1, NChem
    DAUCCArt(j3) = (AUCCArt(j3) - PAUCCArt(j3)) / (CalcInt / 24.0)
    DAUCCBrn(j3) = (AUCCBrn(j3) - PAUCCBrn(j3)) / (CalcInt / 24.0)

    IF (T .GT. 0.0) THEN
        PAUCCArt(j3) = AUCCArt(j3)
        PAUCCBrn(j3) = AUCCBrn(j3)
    ENDIF
1060: CONTINUE
END      ! End of Calc
```

```
!----- Calculate Parameters Used for Plotting -----
-----
```

```
    Hours = T
    Minutes = T * 60.0
    Days = T / 24.0
```

```
DO 2010 i1=1, NChem
! Concentration in Alveolar Air (mg/L and ppm)
    CALv(i1) = CArt(i1) / PB(i1)
    CALvPPM(i1) = (CArt(i1) / PB(i1)) * (24450.0 / MW(i1))

! Concentration in Inhaled Air (ppm)
    CP(i1) = (CInh(i1) * 24450.0) / MW(i1)

! Concentration in End-Exhaled Air (mg/L, ppm and percent)
    CEnd(i1) = RAExh(i1) / QAlv
    CEndPPM(i1) = CEnd(i1) * (24450.0 / MW(i1))

    IF (Conc(i1) .GT. 0.0) THEN
        PerEnd(i1) = (CEnd(i1) / ((Conc(i1) * MW(i1)) / 24450.0)) * 100.0
    ENDIF
```

```
! Concentration in Mixed Exhaled Air (mg/L, ppm and percent)
    CMix(i1) = ((1.0 - DS) * CEnd(i1)) + (DS * CInh(i1))
    CMixPPM(i1) = CMix(i1) * (24450.0 / MW(i1))

    IF (Conc(i1) .GT. 0.0) THEN
        PerMix(i1) = (CMix(i1) / ((Conc(i1) * MW(i1)) / 24450.0)) * 100.0
    ENDIF
2010: CONTINUE

    CArtTot = 0.0
    AExhAll = 0.0
```

```
DO 2020 i2=1, NChem
! Total Concentration in Arterial Blood (mg/L)
    CArtTot = CArtTot + CArt(i2)
```

```

! Total Amount Exhaled (mg)
  AExhAll = AExhAll + AExh(i2)
2020: CONTINUE

DERIVATIVE
!-----
! Amount in Inhaled Air (mg)
  ACh = INTVC(RACh, AI0)

! Concentration in Inhaled Air (mg/L) and Rate of Change in Chamber Concentration (mg/hr)
  PROCEDURAL (CInh, RACh = QAlv, VCh, kLC, kUrt, CIZone, CMuc, CArt)
DO 3030 i3=1, NChem
  CInh(i3) = ( (ACh(i3) / VCh) * (1-Scrub(i3)) ) * CIZone
  RACh(i3) = (Rats * ((-QAlv * CInh(i3)) + (QAlv * (CArt(i3) / PB(i3))) + (kUrt(i3) *
((CMuc(i3) / PMuc(i3)) - (CArt(i3) / PB(i3)))))) &
    & - (kLC * ACh(i3))
3030: CONTINUE
  END

! Amount in Mucous (mg)
  AMuc = INTVC(RAMuc, IAMuc)

! Amount in Arterial Blood (mg)
  AArt = INTVC(RAArt, IAArt)
  AUCCArt = INTVC(CArt, IAUCCArt)

! Amount in Exhaled Air (mg)
  AExh = INTVC(RAExh, IAEExh)

  PROCEDURAL (CMuc, CArt = VALv, VMuc)
  DO 3040 i4=1, NChem
    CMuc(i4) = AMuc(i4) / VMuc ! Concentration of in mucous
(mg/L)
    CArt(i4) = AArt(i4) / VALv ! Concentration of in
arterial blood (mg/L)
3040: CONTINUE
  END
!-----

!-----
  PROCEDURAL (CVen, RAMuc, RAArt, RAExh = QBrn, CBrnBld, QStm, CStmBld, QTL, CTLBld, QCoc,
CCocBld, QFat, CFatBld, QLiv, CLivBld, &
    & QLu, CLuBld, QRap, CRapBld, QSlw, CSlwBld, IVR, QC, kUrt, CInh, CMuc, PMuc, CArt,
PB, QAlv, CVen, RAUrn, QAlv)
DO 3050 i5=1, NChem
! Concentration in Mixed Venous Blood (mg/L)
  CVen(i5) = (QBrn*CBrnBld(i5) + QStm *CStmBld(i5) + QTL*CTLBld(i5) + QCoc*CCocBld(i5) +
QFat*CFatBld(i5) + QLiv*CLivBld(i5) &
    & + QLu*CLuBld(i5) + QRap*CRapBld(i5) + QSlw*CSlwBld(i5) + IVR(i5)) / QC

! Rate of Change in Mucus (mg/hr)
  RAMuc(i5) = (kUrt(i5) * (CInh(i5) - (CMuc(i5) / PMuc(i5)))) - (kUrt(i5) * ((CMuc(i5) /
PMuc(i5)) - (CArt(i5) / PB(i5))))

! Rate of Change in Arterial Blood (mg/hr)
  RAArt(i5) = (QAlv * CInh(i5)) - (kUrt(i5) * (CInh(i5) - (CMuc(i5) / PMuc(i5)))) - (QAlv *
(CArt(i5) / PB(i5))) &
    & + (QC * (CVen(i5) - CArt(i5))) - RAUrn(i5)

! Rate of Change in Exhaled Air (mg/hr)
  RAExh(i5) = (QAlv * (CArt(i5) / PB(i5))) + (kUrt(i5) * ((CMuc(i5) / PMuc(i5)) - (CArt(i5)
/ PB(i5))))
3050: CONTINUE
  END

```

```

!-----
!-----

!-----
!-----
! Brain Remainder Blood and Brain Remainder Tissue

      ABrnBld = INTVC(RABrnBld, IABrnBld)          ! Amount in brain remainder
blood (mg)
      ABrn = INTVC(RABrn, IABrn)                  ! Amount in brain remainder
tissue (mg)
      AUCCBrn = INTVC(CBrn, IAUCBrn)              ! Area under the curve for
the concentration in brain remainder tissue (hr*mg/L)

      PROCEDURAL (CBrnBld, CBrn, CBrnDif, RABrnBld, RABrn = ABrnBld, VBrnBld, ABrn, VBrn, PBrn, QBrn,
CART, PABrn)
DO 3060 i6=1, NChem
      CBrnBld(i6) = ABrnBld(i6) / VBrnBld          ! Concentration in brain
remainder blood (mg/L)
      CBrn(i6) = ABrn(i6) / VBrn                  ! Concentration in brain
remainder tissue (mg/L)
      CBrnDif(i6) = CBrn(i6) / PBrn(i6)           ! Concentration available
for diffusion (mg/L)
      RABrnBld(i6) = (QBrn * (CART(i6) - CBrnBld(i6))) + (PABrn(i6) * (CBrnDif(i6) - CBrnBld(i6)))
                                                    ! Rate of change in brain
remainder blood (mg/hr)
      RABrn(i6) = PABrn(i6) * (CBrnBld(i6) - CBrnDif(i6))
                                                    ! Rate of change in brain
remainder tissue (mg/hr)

3060: CONTINUE
      END
!-----
!-----

!-----
!-----
! Brain Stem and Brain Stem Tissue

      AStmBld = INTVC(RAStmBld, IAStmBld)          ! Amount in brain stem
blood (mg)
      AStm = INTVC(RAStm, IAStm)                  ! Amount in brain stem
tissue (mg)

      PROCEDURAL (CStmBld, CStm, CStmDif, RAStmBld, RAStm = AStmBld, VStmBld, AStm, VStm, PStm, QStm,
CART, PASTm)
DO 3062 i16=1, NChem
      CStmBld(i16) = AStmBld(i16) / VStmBld        ! Concentration in brain
stem blood (mg/L)
      CStm(i16) = AStm(i16) / VStm                ! Concentration in brain
stem tissue (mg/L)
      CStmDif(i16) = CStm(i16) / PStm(i16)        ! Concentration available
for diffusion (mg/L)
      RAStmBld(i16) = (QStm * (CART(i16) - CStmBld(i16))) + (PASTm(i16) * (CStmDif(i16) -
CStmBld(i16)))
                                                    ! Rate of change in brain
stem blood (mg/hr)
      RAStm(i16) = PASTm(i16) * (CStmBld(i16) - CStmDif(i16))
                                                    ! Rate of change in brain
stem tissue (mg/hr)

3062: CONTINUE
      END
!-----
!-----

!-----
!-----
! Brain Temporal Lobe and Brain Temporal Lobe Tissue

```

```

      ATLbld = INTVC(RATLbld, IATLbld)                                ! Amount in brain temporal
lobe blood (mg)
      ATL = INTVC(RATL, IATL)                                        ! Amount in brain temporal
lobe tissue (mg)

      PROCEDURAL (CTLbld, CTL, CTLDif, RATLbld, RATL = ATLbld, VTLbld, ATL, VTL, PTL, QTL, CArt,
PATL)
DO 3064 i17=1, NChem
      CTLbld(i17) = ATLbld(i17) / VTLbld                                ! Concentration in brain
temporal lobe blood (mg/L)
      CTL(i17) = ATL(i17) / VTL                                        ! Concentration in brain
temporal lobe tissue (mg/L)
      CTLDif(i17) = CTL(i17) / PTL(i17)                                ! Concentration available
for diffusion (mg/L)
      RATLbld(i17) = (QTL *(CArt(i17) - CTLbld(i17)))+(PATL(i17) * (CTLDif(i17) - CTLbld(i17)))
                                                                    ! Rate of change in brain
temporal lobe blood (mg/hr)
      RATL(i17) = PATL(i17) * (CTLbld(i17) - CTLDif(i17))            ! Rate of change in brain
tissue (mg/hr)

3064: CONTINUE
      END
!-----
-----

!-----
-----
! Cochlea Tissue Blood and Cochlea Tissue

      ACocbld = INTVC(RACocbld, IACocbld)                                ! Amount in cochlea blood
(mg)
      ACoc = INTVC(RACoc, IACoc)                                        ! Amount in cochlea tissue
(mg)

      PROCEDURAL (CCoCbld, CCoC, CCoCDif, RACoCbld, RACoC = ACocbld, VCoCbld, ACoC, VCoC, PCoC, QCoC,
CArt, PACoC)
DO 3070 i15=1, NChem
      CCocbld(i15) = ACocbld(i15) / VCoCbld                                ! Concentration in cochlea
blood (mg/L)
      CCoc(i15) = ACoc(i15) / VCoC                                    ! Concentration in cochlea
(mg/L)
      CCocDif(i15) = CCoc(i15) / PCoC(i15)                                ! Concentration available
for diffusion (mg/L)
      RACoCbld(i15) = (QCoC *(CArt(i15) - CCocbld(i15)))+(PACoC(i15) * (CCocDif(i15) -
CCocbld(i15)))
                                                                    ! Rate of change in cochlea
blood (mg/hr)
      RACoC(i15) = PACoC(i15) * (CCocbld(i15) - CCocDif(i15))        ! Rate of change in cochlea
(mg/hr)
3070: CONTINUE
      END
!-----
-----

!-----
-----
! Fat Blood and Fat Tissue
      AFatbld = INTVC(RAFatbld, IAFatbld)                                ! Amount in fat blood (mg)
      AFat = INTVC(RAFat, IAFat)                                        ! Amount in fat tissue (mg)

      PROCEDURAL (CFatbld, CFat, CFatDif, RAFatbld, RAFat = AFatbld, VFatbld, AFat, VFat, PFat, QFat,
CArt, PAFat)
DO 3075 i7=1, NChem
      CFatbld(i7) = AFatbld(i7) / VFatbld                                ! Concentration in fat
blood (mg/L)
      CFat(i7) = AFat(i7) / VFat                                        ! Concentration in fat
tissue (mg/L)

```

```

        CFatDif(i7) = CFat(i7) / PFat(i7)                                ! Concentration available
for diffusion (mg/L)
        RAFatBld(i7) = (QFat *(CArt(i7) - CFatBld(i7)))+(PAFat(i7) * (CFatDif(i7) - CFatBld(i7)))
                                                                ! Rate of change in fat
blood (mg/hr)
        RAFat(i7) = PAFat(i7) * (CFatBld(i7) - CFatDif(i7))                ! Rate of change in fat
tissue (mg/hr)
3075: CONTINUE
        END
!-----
!-----

!-----
!-----
! Digestive Tract
! Amount Absorbed (mg)
        AO = INTVC(RAO, IAO)

! Amount Excreted (mg)
        AExc = INTVC(RAExc, IAExc)

! Amount Duodenum (mg)
        ADu = INTVC(RADu, IADu)

! Amount Leaving the Stomach (mg)
! (ASt changed to (INTVC(RASt, IASt)) and is replaced in other equations with (TotDose(i) -
ASt(i)) since ASt
! could not be defined as (TotDose - INTVC(RASt, 0.0)))
        ASt = INTVC(RASt, IASt)

! Rate of Change in Amount Absorbed, Amount Excreted, Amount in Duodenum and Amount Leaving
Stomach (mg/hr)
        PROCEDURAL (RAO, RAExc, RADu, RASt = TotDose)
DO 3080 i8=1, NChem
        RAO(i8) = (kAS(i8) * (TotDose(i8) - ASt(i8))) + (kAD(i8) * ADu(i8))
        RAExc(i8) = kTD(i8) * ADu(i8)
        RADu(i8) = (kTSD(i8) * (TotDose(i8) - ASt(i8))) - (kAD(i8) * ADu(i8)) - (kTD(i8) *
ADu(i8))
        RASt(i8) = (kAS(i8) * (TotDose(i8) - ASt(i8))) + (kTSD(i8) * (TotDose(i8) - ASt(i8)))
3080: CONTINUE
        END
!-----
!-----

!-----
!-----
! Liver Blood and Liver Tissue
        ALivBld = INTVC(RALivBld, IALivBld)                                ! Amount in liver blood (mg)
        ALiv = INTVC(RALiv, IALiv)                                        ! Amount in liver tissue
(mg)

        AMet1 = INTVC(RAMet1, IAMet1)                                    ! Amount metabolized,
saturable (mg)
        AMet2 = INTVC(RAMet2, IAMet2)                                    ! Amount metabolized,
first order (mg)

        PROCEDURAL (CLivBld, CLiv, CLivDif, RALivBld, RAMet1, RAMet2, RALiv = ALivBld, VlivBld, ALiv,
VLiv, PLiv, QLiv, CArt, PALiv, VMax, Km, KF, RAO, Drink)
DO 3090 i9=1, NChem
        CLivBld(i9) = ALivBld(i9) / VlivBld                                ! Concentration in liver
blood (mg/L)
        CLiv(i9) = ALiv(i9) / Vliv                                        ! Concentration in liver
tissue (mg/L)
        CLivDif(i9) = CLiv(i9) / PLiv(i9)                                ! Concentration available
for diffusion (mg/L)
        RALivBld(i9) = (QLiv *(CArt(i9) - CLivBld(i9)))+(PALiv(i9) * (CLivDif(i9) - CLivBld(i9)))
                                                                ! Rate of change in liver
blood (mg/hr)

```

```

        RAMet1(i9) = (VMax(i9) * CLivDif(i9)) / (KM(i9) + CLivDif(i9)) ! Saturable rate of
metabolism in liver (mg/hr)
        RAMet2(i9) = KF(i9) * CLivDif(i9) * VLiv ! First-order rate of
metabolism in liver (mg/hr)
        RALiv(i9) = (PALiv(i9) * (CLivBld(i9) - CLivDif(i9))) - RAMet1(i9) - RAMet2(i9) +
RAO(i9) + Drink(i9)
                                                    ! Rate of change in liver
tissue (mg/hr)
3090: CONTINUE
        END
!-----
!-----

!-----
!-----
! Lung Blood and Lung Tissue
        ALuBld = INTVC(RALuBld, IALuBld) ! Amount in lung blood (mg)
        ALu = INTVC(RALu, IALu) ! Amount in lung tissue (mg)

        AMetLu = INTVC(RAMetLu, IAMetLu) ! Amount metabolized, saturable
(mg)

        PROCEDURAL (CLuBld, CLu, CLuDif, RALuBld, RAMetLu, RALu = ALuBld, VLuBld, ALu, VLu, PLu, QLu,
CART, PALu, VMaxLu, KmLu)
DO 3095 i18=1, NChem
        CLuBld(i18) = ALuBld(i18) / VLuBld ! Concentration in lung
blood (mg/L)
        CLu(i18) = ALu(i18) / VLu ! Concentration in lung
tissue (mg/L)
        CLuDif(i18) = CLu(i18) / PLu(i18) ! Concentration available
for diffusion (mg/L)
        RALuBld(i18) = (QLu * (CART(i18) - CLuBld(i18))) + (PALu(i18) * (CLuDif(i18) - CLuBld(i18)))
! Rate of change in lung
blood (mg/hr)
        RAMetLu(i18) = (VMaxLu(i18) * CLuDif(i18)) / (KMLu(i18) + CLuDif(i18)) ! Saturable rate
of metabolism in lung (mg/hr)
        RALu(i18) = (PALu(i18) * (CLuBld(i18) - CLuDif(i18))) - RAMetLu(i18)
! Rate of change in lung
tissue (mg/hr)
3095: CONTINUE
        END
!-----
!-----

!-----
!-----
! Rapidly Perfused Tissue Blood and Rapidly Perfused Tissue

        ARapBld = INTVC(RARapBld, IARapBld) ! Amount in rapidly
perfused tissue blood (mg)
        ARap = INTVC(RARap, IARap) ! Amount in rapidly
perfused tissue (mg)

        PROCEDURAL (CRapBld, CRap, CRapDif, RARapBld, RARap = ARapBld, VRapBld, ARap, VRap, PRap, QRap,
CART, PARap)
DO 3100 i10=1, NChem
        CRapBld(i10) = ARapBld(i10) / VRapBld ! Concentration in rapidly
perfused tissue blood (mg/L)
        CRap(i10) = ARap(i10) / VRap ! Concentration in rapidly
perfused tissue (mg/L)
        CRapDif(i10) = CRap(i10) / PRap(i10) ! Concentration available
for diffusion (mg/L)
        RARapBld(i10) = (QRap * (CART(i10) - CRapBld(i10))) + (PARap(i10) * (CRapDif(i10) -
CRapBld(i10)))
! Rate of change in rapidly
perfused tissue blood (mg/hr)
        RARap(i10) = PARap(i10) * (CRapBld(i10) - CRapDif(i10)) ! Rate of change in rapidly
perfused tissue (mg/hr)
3100: CONTINUE

```

```

END
!-----
!-----

!-----
!-----
! Slowly Perfused Tissue Blood and Slowly Perfused Tissue

      ASlwBld = INTVC(RASlwBld, IASlwBld)          ! Amount in slowly perfused
tissue blood (mg)
      ASlw = INTVC(RASlw, IASlw)                  ! Amount in slowly perfused
tissue (mg)

      PROCEDURAL (CSlwBld, CSlw, CSlwDif, RASlwBld, RASlw = ASlwBld, VSlwBld, ASlw, VSlw, PSlw, QSlw,
CArt, PASlw)
DO 3120 i12=1, NChem
      CSlwBld(i12) = ASlwBld(i12) / VSlwBld          ! Concentration in slowly
perfused tissue blood (mg/L)
      CSlw(i12) = ASlw(i12) / VSlw                  ! Concentration in slowly
perfused tissue (mg/L)
      CSlwDif(i12) = CSlw(i12) / PSlw(i12)          ! Concentration available
for diffusion (mg/L)
      RASlwBld(i12) = (QSlw *(CArt(i12) - CSlwBld(i12)))+(PASlw(i12) * (CSlwDif(i12) -
CSlwBld(i12)))          ! Rate of change in slowly
perfused tissue blood (mg/hr)
      RASlw(i12) = PASlw(i12) * (CSlwBld(i12) - CSlwDif(i12)) ! Rate of change in slowly
perfused tissue (mg/hr)
3120: CONTINUE
      END
!-----
!-----

!-----
!-----
! Amount in Urine (mg)
      AUrn = INTVC(RAUrn, IAUrn)

! Rate of Excretion (mg/hr)
      PROCEDURAL (RAUrn = ClUr, CArt)
DO 3130 i13=1, NChem
      RAUrn(i13) = ClUr(i13) * CArt(i13)
3130: CONTINUE
      END
!-----
!-----

!----- CHECK MASS BALANCE -----
!-----
! Total Amount Inhaled (mg)
      ATotInh = INTVC(RATotInh, IATotInh)

! Total Amount Injected (mg)
      ATotIV = INTVC(IVR, IATotIV)

! Total Amount Drunk (mg)
      ATotDrink = INTVC(Drink, IATotDrink)

! Calculating Total Brain Concentration (mg/kg), Total Dose (mg), Total Amount in Body (mg) and
Mass Balance (mg)
      PROCEDURAL (CBrnTotBld, CBrnTot, TDose, AmtBody, MassBal, RATotInh = ABrnBld, AStmBld, ATLBld,
VBrnBld, VStmBld, VTLBld, ABrn, AStm, ATL, VBrn, VStm, VTL, &
& QAlv, CInh, ATotInh, ATotIV, TotDose, ATotDrink, AMuc, AArt, ACoc, ACocBld, AFat,
AFatBld, ALiv, ALivBld, ARap, ARapBld, ASlw, ASlwBld, &
& ALu, ALuBld, AExh, AUrn, AMet1, AMet2, AMetLu, AExc, ADu, AST)
DO 3140 i14=1, NChem
      CBrnTotBld(i14) = (ABrnBld(i14) + AStmBld(i14) + ATLBld(i14))/(VBrnBld + VStmBld + VTLBld)
      CBrnTot(i14) = (ABrn(i14) + AStm(i14) + ATL(i14))/(VBrn + VStm + VTL)

```

```

      RATotInh(i14) = QAlv * CInh(i14)
      TDose(i14) = ATotInh(i14) + ATotIV(i14) + TotDose(i14) + ATotDrink(i14)
      AmtBody(i14) = AMuc(i14) + AArt(i14) + ABrn(i14) + ABrnBld(i14) &
                    & + AStm(i14) + AStmBld(i14) + ATL(i14) + ATLBld(i14) &
                    & + ACoc(i14) + ACocBld(i14) + AFat(i14) + AFatBld(i14) + ALiv(i14) +
ALivBld(i14) &
                    & + ARap(i14) + ARapBld(i14) + ASlw(i14) + ASlwBld(i14) + ALu(i14) +
ALuBld(i14) &
                    & + AExh(i14) + AUrn(i14) + AMet1(i14) + AMet2(i14) + AMetLu(i14) + AExc(i14) +
ADu(i14) + ASst(i14)

      MassBal(i14) = TDose(i14) - AmtBody(i14)
3140: CONTINUE
      END

TERMT(T.GT.TStop, 'Simulation Finished')

END          ! End of Derivative
END          ! End of Dynamic
END          ! End of Program

```

APPENDIX C: SCRIPT FILES FOR UTILITIES AND PARAMETER SETTING

The following M files are called within various other M files utilized for this work.

Utility Script Files

Init.m

```
prepare T HOURS MINUTES DAYS CP CMUC CALV CALVPPM CART AUCCART AEXH CEND CENDPPM PEREND PERMIX
prepare CBRN CBRNBLD AUCCBRN CCOC CCOCBLD CFAT CFATBLD CLIV CLIVBLD CLU CLUBLD AMET1 AMET2
prepare CRAP CRAPBLD CSLW CSLWBLD CBRNTOT CBRNTOTBLD CSTM CSTMBLD CTL CTLBLD
prepare CVEN AURN TDOSE AMTBODY MASSBAL CINH
```

```
HVDPRN=0;
WESITG=0;
WEDITG=0;
```

ResetDoses.m

```
% Generic rat parameters

% All cochlea parameters are for paired cochlea.

% Values from REF1, unless otherwise stated
BW=0.3;           %REF1 = 0.22, REF8&9 = 0.3
QCC=14.6;
QPC=24.75;

QBRNC=0.013;      %Remainder only; Adds up to 0.02 (REF10)
  QSTMC=0.004;
  QTLC=0.003;      %Calculated using brain volumes & REF2
QCOCC=0.00004;    %REF3
QFATC=0.07;
QLIVC=0.183;
QLUC=0.021
QRAPC=0.536;      %0.557-Lung
QSLWC=0.16996;

VBRNC=0.004;      %Remainder only; 0.006 - VSTMC - VTLC; 0.006 from REF5 Table 3 (0.0057 in
REF10)
  VSTMC=0.001;      %REF5 Table 3
  VTLC=0.001;      %in-house research
VALVC=0.007;
VFATC=0.10;        %0.0625 in REF10
VLIVC=0.034;       %0.0366 in REF10
VLUC=0.005;        %REF10
VMUCC=0.0001;
VRAPC=0.039;       %0.044-Lung
VSLWC=0.65;

% Blood content values for most tissues from REF5
VBRNBLDC=0.03;     %REF4 and REF10
  VSTMBLDC=0.03;    %Assumed same across the brain
  VTLBLDC=0.03;
VCOCBLDC=0.0183;   %Calculated from data in REF7
VFATBLDC=0.0154;   %Not sure of source but close enough to REF10 (0.02)
VLIVBLDC=0.21;     %REF4, REF10
VLUBLDC=0.36;      %REF10
VRAPBLDC=0.2075;
VSLWBLDC=0.0333;

% REF1
% Clewell HJ, III, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME:
% Development of a physiologically based pharmacokinetic model of isopropanol
```

```
% and its metabolite acetone. Toxicol Sci 2001, 63(2):160-172.

% REF2
% Gjedde et al 1980 Rapid simultan determinat of regional blood flow_blood-brain glucose
transfer in brain of rats

% REF3
% Robinson et al. 2013 TR

% REF4
% Sterner et al. 2014 TMB-4 model

% REF5
% Delp et al. 1991

% REF6
% AALAS Learning Library, 2005

% REF7
% Morizono et al 1968 Cochlear blood vol in Gpig measured w Cr51 label RBC (Hearing Loss
reference file)

% REF8
% Merrill et al 2008 Improved predictive model 4 decane kinetics across species.pdf

% REF9
% Robinson and Merrill 2008 Harmonized PBPK mdl 4 nonane as component of jet fuel.pdf

% REF10
% Brown et al. 1997
```

Species Specific Parameter Script Files

Human.m

```
% Human.m
% Human physiological parameters

% All cochlea parameters are for paired cochlea.

% Values from REF2 model unless noted otherwise
BW=70.0;

QCC=12.89; QPC=27.75; %REF2
QBRNC=0.114*0.63; %Remainder only; Total brain=0.114 (REF1) - QSTMC - QTLC
QSTMC=0.114*0.2; %Rat fraction =0.004/0.02=0.2; REF7 0.2
QTLC=0.114*0.17; %Rat fraction =0.003/0.02=0.15; REF6 VOL fraction =171.7/1034=0.17
QCOCC=0.00004; %REF3, rat value
QFATC=0.052; %REF2
QLIVC=0.227; %REF2
QLUC=0.025; %REF1
QRAPC=0.394; %0.419 (REF2) - QLUC
QSLWC=0.188 - QCOCC; %REF2

VALVC=0.0079; VMUCC=0.0001;
VBRNC=0.02*0.81; %Remainder only; Total brain=0.02 (REF1) - QSTMC - QTLC
VSTMC=0.02*0.02; %REF6 fraction =22.14/1034=0.02
VTLC=0.02*0.17; %REF6 fraction =171.7/1034=0.17
VFATC=0.214; %REF2
VLIVC=0.026; %REF2
VLUC=0.0076; %REF1
VRAPC=0.0284; %0.036 (REF2) - VLUC
VSLWC=0.536; %REF2
%VCOCM is calculated in the code based on BW; Assuming rat equation works for humans

% Blood content values
VBRNBLDC=0.04; %REF1
VSTMBLDC=0.04; %Assumed same across the brain
VTBLDC=0.04;
```

```

VCOCBLDC=0.0183; %Calculated from data in REF5 (Gpig value)
VFATBLDC=0.02; %REF1; human value also used for rat
VLIVBLDC=0.11; %REF1
VLUBLDC=0.36; %REF1 rat value
VRAPBLDC=0.17; %mean of all human rapidly perfused tissues reported in REF1
VSLWBLDC=0.04; %mean of all slowly perfused tissues reported excluding fat in REF1

%REF1
% Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. Physiological
% parameter values for physiologically based pharmacokinetic models. Toxicol Ind
% Health. 1997 Jul-Aug;13(4):407-84.

%REF2
% Clewell HJ 3rd, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME.
% Development of a physiologically based pharmacokinetic model of isopropanol and
% its metabolite acetone. Toxicol Sci. 2001 Oct;63(2):160-72.

%REF3
% Robinson et al. 2013 TR

% REF4
% Sterner et al. 2014 TMB-4 model

%REF5
% Morizono et al 1968 Cochlear blood vol in Gpig measured w Cr51 label RBC (Hearing Loss
reference file)

%REF6 *****Volumes shown above expressed in cm3
% Lukies MW, Watanabe Y, Tanaka H, Takahashi H, Ogata S, Omura K, Yoriful S, Tomiyama N, Osaka
University
% Twin Research Group. 2017. Heritability of brain volume on MRI in middle to advanced age: A
twin study
% of Japanese adults. PLoS ONE 12(4): e0175800. https://doi.org/10.1371/journal.pone.0175800

%REF7
% Vanderah TW, Gould DJ. 2016. Blood Supply of the Brain. Chapter 6. In: Nolte's the Human Brain:
An
% Introduction to its Functional Anatomy. Philadelphia PA: Elsevier. pp 126-153.

```

Rattus.m

```

% Generic rat parameters

% All cochlea parameters are for paired cochlea.

% Values from REF1, unless otherwise stated
BW=0.3; %REF1 = 0.22, REF8&9 = 0.3
QCC=14.6;
QPC=24.75;

QBRNC=0.013; %Remainder only; Adds up to 0.02 (REF10)
QSTMC=0.004;
QTLC=0.003; %Calculated using brain volumes & REF2
QCOCC=0.00004; %REF3
QFATC=0.07;
QLIVC=0.183;
QLUC=0.021
QRAPC=0.536; %0.557-Lung
QSLWC=0.16996;

VBRNC=0.004; %Remainder only; 0.006 - VSTMC - VTLC; 0.006 from REF5 Table 3 (0.0057 in
REF10)
VSTMC=0.001; %REF5 Table 3
VTLC=0.001; %in-house research
VALVC=0.007;
VFATC=0.10; %0.0625 in REF10
VLIVC=0.034; %0.0366 in REF10
VLUC=0.005; %REF10
VMUCC=0.0001;
VRAPC=0.039; %0.044-Lung

```

```

VSLWC=0.65;

% Blood content values for most tissues from REF5
VBRNBLDC=0.03;    %REF4 and REF10
  VSTMBLDC=0.03; %Assumed same across the brain
  VTLBLDC=0.03;
VCOCBLDC=0.0183; %Calculated from data in REF7
VFATBLDC=0.0154; %Not sure of source but close enough to REF10 (0.02)
VLIVBLDC=0.21;    %REF4, REF10
VLUBLDC=0.36;     %REF10
VRAPBLDC=0.2075;
VSLWBLDC=0.0333;

% REF1
% Clewell HJ, III, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME:
%   Development of a physiologically based pharmacokinetic model of isopropanol
%   and its metabolite acetone. Toxicol Sci 2001, 63(2):160-172.

% REF2
% Gjedde et al 1980 Rapid simultan determinat of regional blood flow_blood-brain glucose
transfer in brain of rats

% REF3
% Robinson et al. 2013 TR

% REF4
% Sterner et al. 2014 TMB-4 model

% REF5
% Delp et al. 1991

% REF6
% AALAS Learning Library, 2005

% REF7
% Morizono et al 1968 Cochlear blood vol in Gpig measured w Cr51 label RBC (Hearing Loss
reference file)

% REF8
% Merrill et al 2008 Improved predictive model 4 decane kinetics across species.pdf

% REF9
% Robinson and Merrill 2008 Harmonized PBPK mdl 4 nonane as component of jet fuel.pdf

% REF10
% Brown et al. 1997

```

Chemical Specific Parameter Script Files

DecaneRat.m

```

% Sets decane parameters for rat (chemical 5)

MW(5)=142.3;    %4Chem9r4.csl

DS=0.15;        %Per REF2: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

PB(5)=5.0;      %Current study=7.9, REF1=5.0
PLQ(5)=0.0041;  %Saline:air REF3=0.0041
PMUC(5)=0.0041; %Set same as water:air REF4
%   PMUC(5)=1.5;    %Default=PB
% Measured brain PCs indicated less partitioning into stem and temporal lobe than expected
%   based on fat content and nonane measured PCs
PBRN(5)=10.0;   %Current study frontal lobe = 1.75, REF1= 4.8, Fit to Perleberg data
PSTM(5)=(1.56/1.75)*PBRN(5); %Current study = 1.56, Scaled (PBRN*(measured PSTM/measured
frontal lobe))

```

```

    PTL(5)=(1.16/1.75)*PBRN(5);    %Current study = 1.16, Scaled (PBRN*(measured PTL/measured
frontal lobe))
    PCOC(5)=2.15;    %Current study: scaled from measured skull PC using cochlea:skull prediction
ratio
    PFAT(5)=328.0;    %REF1 =328., Current results = 211.71
    PLIV(5)=3.0;    %Fitting to Perleberg data, REF1 = 1.97
    PLU(5)=3.0;    %Set to PRap
    PRAP(5)=3.0;    %REF1=3.0, Current study: kidney = 0.66
    PSLW(5)=0.85;    %REF1=0.85

    VMAXC(5)=0.005;    %REF1=0.4
    KM(5)=0.1;    %REF1=1.5
    KFC(5)=0.0;    %Not expecting first order metabolism for this compound
    VMAXLUC(5)=0.0;    %Assume all metabolism in liver
    KMLU(5)=0.1;    %Set to Km

    CLURC(5)=0.004;    %Urinary clearance, L/hr, REF2 = 0.004, NonaneRat.m=0.4
    KURTC(5)=0.0;    %URT uptake, L/hr, absorption into mucus, 0 = no scrubbing
    %QPC = 24.75
    SCRUB(5)=0.7;    %Fraction of concentration in air that is scrubbed out (not absorbed), 0=no
scrubbing

    %oral dosing parameters from REF1 (not in 4Chem)
    KAD(5)=0.5;
    KAS(5)=2.0;
    KTD(5)=0.25;
    KTSD(5)=3.0;

    % If PA = 1000.0 = flow limited
    PABRN(5)=0.005;    %REF1=0.009
    PASTM(5)=0.005;
    PATL(5)=0.005;
    PACOC(5)=1.0;    %Same as PARAP in REF1
    PAFAT(5)=0.07;    %REF1=0.7
    PALIV(5)=0.15;    %REF1=0.15
    PALU(5)=0.005;    %Set to PARap
    PARAP(5)=0.005;    %REF1= 1.0
    PASLW(5)=0.14;    %REF1 did not use, NonaneRat.m=0.5

    % REF1
    % Merrill et al 2008 Improved predictive model 4 decane kinetics across species.pdf

    % REF2
    % Clewell HJ, III, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME:
    % Development of a physiologically based pharmacokinetic model of isopropanol
    % and its metabolite acetone. Toxicol Sci 2001, 63(2):160-172.

    %REF3
    % Sterner et al 2004 AFRL-HE-WP-TR-2004-0032 Analysis of algorithms predicting blood-
air_tissue-blood PCs fr solvent PCs.pdf

    %REF4
    % Schlosser PM, Asgharian BA, Medinsky M. 2010 Chapter 1.04 Inhalation Exposure and Absorption
of Toxicants.
    % In: McQueen CA (ed). Comprehensive Toxicology. Volume 14. Elsevier e-book

```

EthylbenzeneRat.m

```

    % Sets ethylbenzene parameters for rat (chemical 2)

    MW(2)=106.17;    %Wikipedia

    DS=0.15;    %Per REF2: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

    PB(2)=42.7;    %REF1=42.7, In house study=41.1
    PLQ(2)=1.69;    %Saline:air REF2=1.69
    PMUC(2)=1.69;    %Set same as water:air REF3
    PBRN(2)=1.22;    %In house study frontal lobe = 1.22, REF2 whole brain=0.80
    PSTM(2)=1.93;    %Current study = 1.93

```

```

    PTL(2)=1.44;      %Current study = 1.44
    PCOC(2)=0.44;     %Current study: scaled from measured skull PC using cochlea:skull prediction
ratio
    PFAT(2)=36.4;     %REF1 =1556./42.7=36.4, In-house study=59.62
    PLIV(2)=1.96;     %REF1=83.8/42.7=1.96, Current study: kidney = 3.02
    PLU(2)=1.41;      %Same as PRap
    PRAP(2)=1.41;     %REF1=60.3/42.7=1.41
    PSLW(2)=0.61;     %REF1=26.0/42.7=0.61

    VMAXC(2)=6.39;    %REF1=3.44
    KM(2)=1.04;       %REF1=0.13
    KFC(2)=0.0;       %Not expecting first order metabolism for this compound
    VMAXLUC(2)=0.0;   %Assuming all metabolism in liver
    KMLU(2)=1.04;     %Same as Km

    CLURC(2)=0.04;    %Urinary clearance, L/hr
    KURTC(2)=0.0;     %URT uptake, L/hr, uptake into mucus, 0.0 = no scrubbing
                        %QPC = 24.75
    SCRUB(2)=0.0;     %Fraction of concentration in air that is scrubbed out (not absorbed), 0=no
scrubbing

    %oral dosing parameters from REF1 (not in 4Chem)
    KAD(2)=0.5;
    KAS(2)=2.0;
    KTD(2)=0.25;
    KTSD(2)=3.0;

    % If PA = 10000.0 = flow limited
    PABRN(2)=10000.0;
    PASTM(2)=10000.0;
    PATL(2)=10000.0;
    PACOC(2)=10000.0;
    PAFAT(2)=10000.0;
    PALIV(2)=10000.0;
    PALU(2)=10000.0;
    PARAP(2)=10000.0;
    PASLW(2)=10000.0;

    % REF1
    %Haddad et al 1999 Physiological modeling of the toxicokinetic interactions in a quaternary
mixture
    % of aromatic hydrocarbons. Toxicol Appl Physiol. 161:249-57.

    %REF2
    % Sterner et al 2004 AFRL-HE-WP-TR-2004-0032 Analysis of algorithms predicting blood-
air_tissue-blood PCs fr solvent PCs.pdf

    %REF3
    % Schlosser PM, Asgharian BA, Medinsky M. 2010 Chapter 1.04 Inhalation Exposure and Absorption
of Toxicants.
    % In: McQueen CA (ed). Comprehensive Toxicology. Volume 14. Elsevier e-book

```

NaphHmn.m

```

% Human_Naph.m
% Sets human naphthalene parameters (Chemical 6)

MW(6)=128.1705;  %REF6

%-----PCs-----
%PCs from REF3 (PLU = PRAP)
PB(6)=571.0;
    PLQ(6)=60.0; PMUC(6)=60.0; %Assume LQ=MUC REF7 at 23C, measured
    %Differs from NaDoRT model, assumed = to PB in NaDoRT because Hack had in toluene model

    PFAT(6)=49.0; PLIV(6)=1.6; PLU(6)=3.5; PRAP(6)=3.5; PSLW(6)=3.5;

    %Brain PCs from PRAP to start, PCOC from xylene
    PBRN(6)=3.5; PSTM(6)=3.5; PTL(6)=3.5; PCOC(6)=0.47;

```

```

%PCs from REF8 using tissue data from REF9 (Calc by Robinson)
%PBRN(6)=3.5; PSTM(6)=3.5; PTL(6)=3.5; PCOC(6)=0.47;

%-----PAs-----
%Diffusion limitation default is inactive = 10000.0

PABRN(6)=10000.0;
PASTM(6)=10000.0;
PATL(6)=10000.0;
PACOC(6)=10000.0;
PAFAT(6)=2.0*(BW^0.75); %PA values in NaDoRT model were scaled allometrically
PALIV(6)=10000.0;
PALU(6)=10000.0;
PARAP(6)=10000.0;
PASLW(6) = 2.0*(BW^0.75); %PA values in NaDoRT model were scaled allometrically

%-----Metabolism/urinary clearance parameters-----
% Units are VMaxC (mg/hr/kg^0.75), KM (mg/L), KFC (kg^0.25/hr)
VMAXC(6)=(0.775/(BW^0.75))*BW; %VMAXLIVC in NaDoRT model was not allometrically scaled
% REF4, human microsomes, sum of metabolite VMax values/100
KM(6)=2.94; % 2.94 REF4, diol value (lowest)
KFC(6)=0.0;

VMAXLUC(6)=(0.0035/(BW^0.75))*BW; %VMAXLUC in NaDoRT model was not allometrically scaled
% 0.0035 REF2, lowest value (REF3)
KMLU(6)=8.7; % 8.7 REF2, NHP airways
% weighted average of metabolic pathway Km values, based on paired VMax fraction
of whole

CLURC(6)=0.0; %L/hr/kg^0.75

%-----Upper respiratory-----
KURTC(6)=0.0; SCRUB(6)=0.0; %no scrubbing
DS=0.15; %Per REF5: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

%REF2
% Buckpitt A, Morin D, Murphy S, Edwards P, Van Winkle L. Kinetics of
% naphthalene metabolism in target and non-target tissues of rodents and in nasal
% and airway microsomes from the Rhesus monkey. Toxicol Appl Pharmacol. 2013 Jul
% 15;270(2):97-105.

%REF3
% Campbell JL, Andersen ME, Clewell HJ. A hybrid CFD-PBPK model for naphthalene
% in rat and human with IVIVE for nasal tissue metabolism and cross-species
% dosimetry. Inhal Toxicol. 2014 May;26(6):333-44.

%REF4
% Cho TM, Rose RL, Hodgson E. In vitro metabolism of naphthalene by human liver
% microsomal cytochrome P450 enzymes. Drug Metab Dispos. 2006 Jan;34(1):176-83.

%REF5
% Clewell HJ 3rd, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME.
% Development of a physiologically based pharmacokinetic model of isopropanol and
% its metabolite acetone. Toxicol Sci. 2001 Oct;63(2):160-72.

%REF6
% NIST Chemistry Webbook (https://webbook.nist.gov/cgi/cbook.cgi?Name=naphthalene&Units=SI)

%REF7
% Schwarz FP, Wasik SP. 1977. A fluorescence method for the measurement of the partition
% coefficients of naphthalene, 1-methylnaphthalene, and 1-ethylnaphthalene in water.
% J. Chem. Eng. Data 22(3):270-273.

%REF8
% Ruark CD, Hack CE, Robinson PJ, Mahle DA, Gearhart JM. Predicting passive and
% active tissue:plasma partition coefficients: interindividual and interspecies
% variability. J Pharm Sci. 2014 Jul;103(7):2189-2198.

%REF9
% Sterner 2017 Technical report on JFHL

```

NaphRat.m

```
% Rat_Naph.m
% Sets rat naphthalene parameters (chemical 6)

MW(6)=128.1705; %REF6

%-----PCs-----
%PCs from REF3 (PLU = PRAP)
PB(6)=571.0;
  PLQ(6)=60.0; PMUC(6)=60.0; %Assume LQ=MUC REF7 at 23C, measured
  %Differs from NaDoRT model, assumed = to PB in NaDoRT because Hack had in toluene model
  %Does not appear to affect NTP00_singleihl fits

PFAT(6)=49.0; PLIV(6)=1.6; PLU(6)=3.5; PRAP(6)=3.5; PSLW(6)=3.5;

%Brain PCs from PRAP to start, PCOC from xylene
PBRN(6)=3.5; PSTM(6)=3.5; PTL(6)=3.5; PCOC(6)=0.47;

%PCs from REF8 using tissue data from REF9 (Calc by Robinson)
%PBRN(6)=3.5; PSTM(6)=3.5; PTL(6)=3.5; PCOC(6)=0.47;

%-----PAs-----
%Diffusion limitation default is inactive = 10000.0

PABRN(6)=10000.0;
  PASTM(6)=10000.0;
  PATL(6)=10000.0;
PACOC(6)=10000.0;
PAFAT(6)=0.2*(BW^0.75); %PA values in NaDoRT model were scaled allometrically
PALIV(6)=10000.0;
PALU(6)=10000.0;
PARAP(6)=10000.0;
PASLW(6) = 2.0*(BW^0.75); %PA values in NaDoRT model were scaled allometrically

%-----Metabolism/urinary clearance parameters-----
% Units are VMaxC (mg/hr/kg^0.75), KM (mg/L), KFC (kg^0.25/hr)
VMAXC(6)=(8.28/(BW^0.75))*BW; %VMAXLIVC in NaDORT model was not allometrically scaled
                                % Calc from REF2 with liver:lung ratio from Buckpitt87
KM(6)=2.18; % 2.18 = lung Km
KFC(6)=0.0;

VMAXLUC(6)=(0.45/(BW^0.75))*BW; %VMAXLUC in NaDORT model was not allometrically scaled
                                % REF2, added 2 enzyme values
KMLU(6)=2.18; % 8.7 REF2, weighted average of 2 enzyme values

CLURC(6)=0.0; %L/hr/kg^0.75

%-----Upper respiratory-----
KURTC(6)=0.0; SCRUB(6)=0.0; %no scrubbing
DS=0.15; %Per REF5: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

%REF2
% Buckpitt A, Morin D, Murphy S, Edwards P, Van Winkle L. Kinetics of
% naphthalene metabolism in target and non-target tissues of rodents and in nasal
% and airway microsomes from the Rhesus monkey. Toxicol Appl Pharmacol. 2013 Jul
% 15;270(2):97-105.

%REF3
% Campbell JL, Andersen ME, Clewell HJ. A hybrid CFD-PBPK model for naphthalene
% in rat and human with IVIVE for nasal tissue metabolism and cross-species
% dosimetry. Inhal Toxicol. 2014 May;26(6):333-44.

%REF4
% Cho TM, Rose RL, Hodgson E. In vitro metabolism of naphthalene by human liver
% microsomal cytochrome P450 enzymes. Drug Metab Dispos. 2006 Jan;34(1):176-83.

%REF5
```

```

% Clewell HJ 3rd, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME.
% Development of a physiologically based pharmacokinetic model of isopropanol and
% its metabolite acetone. Toxicol Sci. 2001 Oct;63(2):160-72.

%REF6
% NIST Chemistry Webbook (https://webbook.nist.gov/cgi/cbook.cgi?Name=naphthalene&Units=SI)

%REF7
% Schwarz FP, Wasik SP. 1977. A fluorescence method for the measurement of the partition
% coefficients of naphthalene, 1-methylnaphthalene, and 1-ethylnaphthalene in water.
% J. Chem. Eng. Data 22(3):270-273.

%REF8
% Ruark CD, Hack CE, Robinson PJ, Mahle DA, Gearhart JM. Predicting passive and
% active tissue:plasma partition coefficients: interindividual and interspecies
% variability. J Pharm Sci. 2014 Jul;103(7):2189-2198.

%REF9
% Sterner 2017 Technical report on JFHL

NonaneRat.m

% Sets nonane parameters for rat (chemical 4)
% *****Significant difference between values from different sources

MW(4)=128.0;      %4Chem9r4

DS=0.15;          %Per REF1: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

PB(4)=5.2;        %Current study=5.9, REF5=5.2
PLQ(4)=0.004;     %REF6 decane saline:air PC=0.0041 (Log Kow values are similar so assumed
saline:air PCs are similar)
PMUC(4)=0.004;    %Set same as water:air REF7
PBRN(4)=5.0;      %Current study frontal lobe = 1.70, REF5 = 5.0
PSTM(4)=(2.9/1.7)*PBRN(4); %Current study = 2.9, Scaled (PBRN*(measured PSTM/measured
frontal lobe))
PTL(4)=(2.6/1.7)*PBRN(4); %Current study = 2.6, Scaled (PBRN*(measured PTL/measured
frontal lobe))
PCOC(4)=1.45;     %Current study: scaled from measured skull PC using cochlea:skull prediction
ratio
PFAT(4)=282.0;    %4Chem9r4 = 244.0, REF5 = 282.0, Current results = 145.01,
average[145,282]=214
PLIV(4)=8.0;      %Fitting to data; REF5 found protein binding to be a factor; wonder if this
could concentrate more in liver than PC alone allows; REF5 used decane value
% PLIV(4)=3.5;     %REF4 = 1.51, REF3 = 1.29, 4Chem9r4 (Carraci et al.) = 1.36, REF5 = 3.5
PLU(4)=2.0;       %Same as PRAP=2.0
PRAP(4)=2.0;      %4Chem9r4 = 1.29, REF5=2.0, Current study: kidney = 2.59
PSLW(4)=4.0;      %REF2: muscle = 4.0, , REF5 = 4.0
% PSLW(4)=1.15;    %4Chem9r4 = 1.43
% PSQ(4)=(PSLW(4)+PFAT(4))/2;
PSQ(4)=PFAT(4)*2;

VMAXC(4)=0.1;     %4Chem9r4 = 10.0, REF5=0.0
KM(4)=0.1;        %4Chem9r4 = 0.1, REF5=1.5
KFC(4)=0.0;       %Not expecting first order metabolism for this compound
VMAXLUC(4)=0.0;   %All metab accounted for in liver
KMLU(4)=0.1;     %Same as KM

CLURC(4)=0.4;     %Urinary clearance, L/hr, REF1 = 0.004
KURTC(4)=0.0;     %URT uptake, L/hr, deposition in mucus, model uses minimum value of QPC or
this, 0 = no scrubbing
%QPC = 24.75 default rat
SCRUB(4)=0.4;     %Fraction of concentration in air that is scrubbed out (not absorbed), 0=no
scrubbing

%oral dosing parameters from REF1 (not in 4Chem)
KAD(4)=0.5;
KAS(4)=2.0;
KTD(4)=0.25;

```

```

KTSD(4)=3.0;

% If PA = 10000.0 = flow limited
PABRN(4)=0.5;      %REF5=0.5
  PASTM(4)=0.5;
  PATL(4)=0.5;
PACOC(4)=1.0;      %Same as PARAP
PAFAT(4)=0.5;      %4Chem9r4 = 10.0, REF5=0.8
PALIV(4)=0.07;     %4Chem9r4 = 1.0, REF5=0.07
PALU(4)=1.0;       %Same as PRAP=1.0
PARAP(4)=1.0;      %REF5= 1.0
PASLW(4)=0.5;      %4Chem9r4 = 1.0, REF5=0.5

% REF1
% Clewell HJ, III, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME:
%   Development of a physiologically based pharmacokinetic model of isopropanol
%   and its metabolite acetone. Toxicol Sci 2001, 63(2):160-172.

% REF2
% Robinson, P.J. and Merrill, E.A. 2008. A harmonized physiologically based pharmacokinetic
model
%   for nonane as a component of jet fuel. Wright-Patterson AFB, OH: Air Force Research
Laboratory,
%   Applied Biotechnology Branch. AFRL-RH-WP-TR-2008-0067, ADA502610.

% REF3
% Sterner et al 2006 Analysis of algorithms...

%REF4
% Joshi et al. 2010 PCs 4 nonane_isomers in rat.pdf

%REF5
% Robinson and Merrill 2008 Harmonized PBPK mdl 4 nonane as component of jet fuel.pdf

%REF6
% Sterner et al 2004 AFRL-HE-WP-TR-2004-0032 Analysis of algorithms predicting blood-
air_tissue-blood PCs fr solvent PCs.pdf

%REF7
% Schlosser PM, Asgharian BA, Medinsky M. 2010 Chapter 1.04 Inhalation Exposure and Absorption
of Toxicants.
%   In: McQueen CA (ed). Comprehensive Toxicology. Volume 14. Elsevier e-book

```

TolueneRat.m

```

% Sets toluene parameters for rat (chemical 1)

MW(1)=92.14;      %Wikipedia

DS=0.15;          %Per REF2: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

PB(1)=18.0;       %REF1=REF4=18.0, current study=22.8
  PLQ(1)=1.99;    %Saline:air REF2=1.99
  PMUC(1)=1.99;   %Set same as water:air REF3
PBRN(1)=2.0;      %Current study frontal lobe = 1.26, REF2= 4.22, REF4=2.0
  PSTM(1)=2.87;   %Current study = 1.81, Scaled PBRN*(1.81/1.26)
  PTL(1)=2.13;    %Current study = 1.34, Scaled PBRN*(1.34/1.26)
PCOC(1)=0.54;     %Current study: scaled from measured skull PC using cochlea:skull prediction
ratio
PFAT(1)=56.7;     %REF1 =1021./18.=56.7, Current study: 46.82, REF4=56.7
PLIV(1)=4.64;     %REF1=83.6/18.=4.64, REF4=4.64
PLU(1)=4.64;      %Same as PRap
PRAP(1)=4.64;     %Current study: kidney = 2.37, REF1=83.6/18.=4.64, REF4=4.64

PSLW(1)=1.54;     %REF1=27.7/18.=1.54, REF4=1.54

VMAXC(1)=3.44;    %REF1=3.44, REF4=4.81 except 3.44 for Haddad data
KM(1)=0.13;       %REF1=0.13, REF4=0.55 except 0.13 for Haddad data
KFC(1)=0.0;       %Not expecting first order metabolism for this compound

```

```

VMAXLUC(1)=0.0;    %Assumed all metabolism in liver
KMLU(1)=0.13;      %Same as Km

CLURC(1)=0.004;    %Urinary clearance, L/hr, REF4=0
KURTC(1)=0.0;      %URT uptake, L/hr, uptake into mucus, 0.0 = no scrubbing, REF4=0
SCRUB(1)=0.0;      %Fraction of concentration in air that is scrubbed out (not absorbed), 0=no
scrubbing

%oral dosing parameters from REF1 (not in 4Chem)
KAD(1)=0.5;
KAS(1)=2.0;
KTD(1)=0.25;
KTSD(1)=3.0;

% If PA = 10000.0 = flow limited
PABRN(1)=10000.0;
  PASTM(1)=10000.0;
  PATL(1)=10000.0;
PACOC(1)=10000.0;
PAFAT(1)=10000.0;
PALIV(1)=10000.0;
PALU(1)=10000.0;
PARAP(1)=10000.0;
PASLW(1)=10000.0;

% REF1
%Haddad et al 1999 Physiological modeling of the toxicokinetic interactions in a quaternary
mixture
% of aromatic hydrocarbons. Toxicol Appl Physiol. 161:249-57.

%REF2
% Sterner et al 2004 AFRL-HE-WP-TR-2004-0032 Analysis of algorithms predicting blood-
air_tissue-blood PCs fr solvent PCs.pdf

%REF3
% Schlosser PM, Asgharian BA, Medinsky M. 2010 Chapter 1.04 Inhalation Exposure and Absorption
of Toxicants.
% In: McQueen CA (ed). Comprehensive Toxicology. Volume 14. Elsevier e-book

%REF4
% Hack Toluene model, rat_toluene.m

XyleneRat.m

% Sets xylene parameters for rat (chemical 3)

MW(3)=106.17;      %Wikipedia

DS=0.15;           %Per REF2: acetone = 0.25, isopropanol = 0.15, typical lipophilics = 0.3, csl
default=0.15

PB(3)=46.0;        %REF1=46.0; In house study=42.3
  PLQ(3)=2.03;      %Saline:air REF2 m=1.79, o=2.64, p=1.67, average=2.03
  PMUC(3)=2.03;     %Set same as water:air REF3
PBRN(3)=1.38;      %In house study frontal lobe = 1.38, REF2 whole brain m=1.2, o=1.7, p=1.2
  PSTM(3)=2.29;     %Current study = 2.29
  PTL(3)=1.61;      %Current study = 1.61
PCOC(3)=0.47;      %Current study: scaled from measured skull PC using cochlea:skull prediction
ratio
PFAT(3)=40.4;      %REF1 =1859./46.=40.4, In-house study=70.09
PLIV(3)=1.98;      %REF1=90.9/46.=1.98, Current study: kidney = 2.84
PLU(3)=1.98;       %Same as PRap
PRAP(3)=1.98;      %REF1=90.9/46.=1.98
PSLW(3)=0.91;      %REF1=41.9/46.=0.91

VMAXC(3)=6.49;     %REF1=6.49
KM(3)=0.45;        %REF1=0.45
KFC(3)=0.0;        %Not expecting first order metabolism for this compound
VMAXLUC(3)=0.0;    %Assume all metabolism is in liver
KMLU(3)=0.45;      %Same as Km

```

```

CLURC(3)=0.004;    %Urinary clearance, L/hr
KURTC(3)=0.0;      %URT uptake, L/hr, uptake into mucus, 0.0 = no scrubbing
                  %QPC = 24.75
SCRUB(3)=0.0;      %Fraction of concentration in air that is scrubbed out (not absorbed), 0=no
scrubbing

%oral dosing parameters from REF1 (not in 4Chem)
KAD(3)=0.5;
KAS(3)=2.0;
KTD(3)=0.25;
KTSD(3)=3.0;

% If PA = 10000.0 = flow limited
PABRN(3)=10000.0;
PASTM(3)=10000.0;
PATL(3)=10000.0;
PACOC(3)=10000.0;
PAFAT(3)=10000.0;
PALIV(3)=10000.0;
PALU(3)=10000.0;
PARAP(3)=10000.0;
PASLW(3)=10000.0;

% REF1
%Haddad et al 1999 Physiological modeling of the toxicokinetic interactions in a quaternary
mixture
% of aromatic hydrocarbons. Toxicol Appl Physiol. 161:249-57.

%REF2
% Sterner et al 2004 AFRL-HE-WP-TR-2004-0032 Analysis of algorithms predicting blood-
air_tissue-blood
% PCs fr solvent PCs.pdf

%REF3
% Schlosser PM, Asgharian BA, Medinsky M. 2010 Chapter 1.04 Inhalation Exposure and Absorption
of Toxicants.
% In: McQueen CA (ed). Comprehensive Toxicology. Volume 14. Elsevier e-book

```

APPENDIX D: SCRIPT FILES FOR VALIDATION SIMULATIONS

The following M files are used to generate the simulations for the validation figures in Appendix A. Some lines were too long for the page width and were thus reformatted to fit the page; however, these additional line breaks and space may need to be removed for the M file to run correctly.

Toluene Simulation Script Files

C1_Haddad.m

```
%Haddad, S., Tardif, R., Charest-Tardif, G. and Krishnan, K. 1999. Physiological modeling  
%   of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons.  
%   Toxicol.Appl.Pharmacol. 161(3): 249-257.
```

```
%From Chem4, 4Chem9r5, C3-Haddad.m
```

```
resetdoses  
rattus  
toluenerat
```

```
%T, CVEN  
had50 = [  
4.0      0.472  
4.0      0.546  
4.5      0.210  
4.5      0.281  
4.5      0.354  
5.0      0.093  
5.0      0.136  
5.0      0.182  
5.5      0.083  
5.5      0.133  
5.5      0.108  
6.0      0.045  
6.0      0.059  
6.0      0.072];
```

```
%T, CVEN  
had100 = [  
4.0      0.751  
4.0      1.033  
4.0      1.464  
4.5      0.547  
4.5      0.632  
4.5      0.798  
5.0      0.281  
5.0      0.345  
5.0      0.435  
5.5      0.199  
5.5      0.290  
5.5      0.230  
6.0      0.112  
6.0      0.133  
6.0      0.173];
```

```
%T, CVEN  
had200 = [  
4.0      3.205  
4.0      4.042  
4.0      5.099  
4.5      2.334  
4.5      3.120  
4.5      3.714
```

```

5.0      1.559
5.0      1.856
5.0      2.274
5.5      0.826
5.5      1.352
5.5      1.072
6.0      0.602
6.0      0.716
6.0      0.804];

% Study specific values as found in Hack toluene model, Haddad.m
BW=0.235;
VMAXC(1)=3.44;
KM(1)=0.13;

CONC(1)=50.0, TCHNG=4.0;
TSTOP=8.0;
start @nocallback

plotcven = plot (0, had50(:,1), had50(:,2), '+b', _t, _cven(:,1), '-b');

CONC(1)=100.0;
start @nocallback

plot (plotcven, 1, had100(:,1), had100(:,2), '+k', _t, _cven(:,1), '-k');

CONC(1)=200.0;
start @nocallback

plot (plotcven, 1, had200(:,1), had200(:,2), '+g', _t, _cven(:,1), '-g');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Haddad et al. (1999) Toluene Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"50, 100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood [mg/L]\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"50 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 50 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[4].Title=\"200 ppm\";")
    pltscript(plotcven, "Chart.Series[5].Title=\"Simulation 200 ppm\";")

set @preference=NoBackslashEscapeS

C1_Lam.m

%Lam, C.W., Galen, T.J., Boyd, J.F. and Pierson, D.L. 1990. Mechanism of transport and
distribution
%   of organic solvents in blood. Toxicol.Appl.Pharmacol. 104(1): 117-129.

%From Hack Toluene, Lam.m

%Male Sprague-Dawley rats, BW about 300 g.
% 2-hour whole-body inhalation of 488 +/- 24 ppm toluene.
% n = 5 rats, put in 10 minutes apart.
% 30 L closed chamber with 5 rats, but CONC is maintained at 488 ppm, rather than depleted, so
run as open chamber.
%Data from Plasma+RBC column, Table 1, page 121

resetdoses
rattus

```

```

toluenerat

%T (hr), CVEN (mg/L)
lam = [
2  10.90
2  15.03
2  14.98
2  15.02
2  15.09];

% Study specific values as found in Hack toluene model, Lam.m
BW=0.3;
%VMAXC(1)=3.44;
%KM(1)=0.13;

CONC(1)=488.0, TCHNG=2.0;
TSTOP=4.0;
start @nocallback

plotcven = plot (0, lam(:,1), lam(:,2), '+b', _t, _cven(:,1), '-b');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Lam et al. (1990) Toluene Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"488 ppm Inhalation for 2 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Logarithmic = true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"488 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 488 ppm\";")

set @preference=NoBackslashEscapeS

C1_Romer.m

%Romer, K.G., Federsel, R.J. and Freundt, K.J. 1986. Rise of inhaled toluene, ethyl benzene,
%    m-xylene, or mesitylene in rat blood after treatment with ethanol. Bull Environ Contam
%    Toxicol 37(6): 874-876.

%From Hack Toluene, romer.m

%Adult female SPF Sprague-Dawley rats
% 200 - 220 g BW
%Groups of 3 rats exposed in a 20 L glass chamber, air flow 1.25 L/min, for 2 hr.
% 20 L closed chamber with 3 rats, but CONC is maintained at 220 ppm, rather than depleted, so
run as open chamber.
%Aromatic conc varied < 5%, delivered via evaporator.
% Sham-treated groups given 5 mL/kg physiological saline.
%Exposure conc monitored via GC using 100 uL air samples.
%Blood (0.02 mL) collected from retro-orbital plexus.
% Blood conc of aromatics determined by GC.

resetdoses
rattus
toluenerat

%Table 1
%meanblood = (56.8e-6 * 92.14 * 1000)=5.23, mol/L conversion to mg/L, MW=92.14
%semblood = (2.1e-6*92.14*1000)=0.19, mol/L conversion to mg/L, MW=92.14
%sem range = 5.04 - 5.43

%T(hr), CVEN(mg/L)
romer = [

```

```

2.0    5.23
2.0    5.04
2.0    5.43];

BW=0.210;
%VMAXC(1)=3.44;
%KM(1)=0.13;

CONC(1)=220.0;
TCHNG=2.0;
TSTOP=3.0;
start @nocallback

plotcven = plot (0, romer(:,1), romer(:,2), '+b', _t, _cven(:,1), '-b');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Romer et al. (1986) Toluene Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"220 ppm Inhalation for 2 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"220 ppm mean value\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 220 ppm\";")

set @preference=NoBackslashEscapeS

```

C1_Tardif.m

```

%Tardif, R., Charest-Tardif, G. and Brodeur, J. 1996. Comparison of the influence
%    of binary mixtures versus a ternary mixture of inhaled aromatic hydrocarbons
%    on their blood kinetics in the rat. Arch Toxicol 70(7): 405-413.

```

```

%Adult male SD rats
% 235-245 g

```

```

resetdoses
rattus
toluenerat

```

```

%T, CVEN from Figure 1, mean followed by +SD then -SD
tar100 = [
4.1 1.14
4.5 0.69
5.0 0.36
5.5 0.23
6.0 0.13
4.1 1.53
4.5 0.82
5.0 0.44
5.5 0.29
6.0 0.19
4.1 0.76
4.5 0.55
5.0 0.27
5.5 0.17
6.0 0.08
];

```

```

%T, CVEN from Figure 2, mean followed by +SD then -SD
tar200 = [
4.1 4.34
4.5 3.17
5.0 1.96

```

```

5.5 1.19
6.0 0.79
4.1 5.29
4.5 3.94
5.0 2.31
5.5 1.42
6.0 0.89
4.1 3.37
4.5 2.47
5.0 1.66
5.5 0.93
6.0 0.64
];

BW=0.240;

CONC(1)=100.0;
TCHNG=4.0;
TSTOP=6.0;
start @nocallback

plotcven = plot (0, tar100(:,1), tar100(:,2), 'b', _t, _cven(:,1), '-b');

CONC(1)=200.0;
start @nocallback

plot (plotcven, 1, tar200(:,1), tar200(:,2), 'k', _t, _cven(:,1), '-k');

set @preference=BackslashEscapes

    pltscript(plotcven, "Chart.Header.Text = \"Tardif et al. (1996) Toluene Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood [mg/L]\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"200 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 200 ppm\";")

set @preference=NoBackslashEscapeS

```

Ethyl Benzene Simulation Script Files

```

%Haddad, S., Tardif, R., Charest-Tardif, G. and Krishnan, K. 1999. Physiological modeling
%   of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons.
%   Toxicol.Appl.Pharmacol. 161(3): 249-257.

resetdoses
rattus
ethylbenzenerat

%T, CVEN (mean, +SD, -SD)
had50 = [
4.1 0.66
4.5 0.46
5.0 0.28
5.5 0.17
6.0 0.13
4.1 0.78
4.5 0.53
5.0 0.32
5.5 0.20

```

```

6.0 0.17
4.1 0.59
4.5 0.33
5.0 0.22
5.5 0.15
6.0 0.09
];

%T, CVEN
had100 = [
4.1 1.52
4.5 1.02
5.0 0.70
5.5 0.45
6.0 0.31
4.1 1.68
4.5 1.15
5.0 0.89
5.5 0.58
6.0 0.36
4.1 1.36
4.5 0.94
5.0 0.57
5.5 0.38
6.0 0.28
];

%T, CVEN
had200 = [
4.1 5.73
4.5 3.79
5.0 2.70
5.5 1.92
6.0 1.36
4.1 6.57
4.5 4.24
5.0 3.02
5.5 2.21
6.0 1.66
4.1 5.05
4.5 3.42
5.0 2.44
5.5 1.72
6.0 1.12
];

BW=0.235;

CONC(2)=50.0, TCHNG=4.0;
TSTOP=8.0;
start @nocallback

plotcven = plot (0, had50(:,1), had50(:,2), '+b', _t, _cven(:,2), '-b');

CONC(2)=100.0;
start @nocallback

plot (plotcven, 1, had100(:,1), had100(:,2), '+k', _t, _cven(:,2), '-k');

CONC(2)=200.0;
start @nocallback

plot (plotcven, 1, had200(:,1), had200(:,2), '+g', _t, _cven(:,2), '-g');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Haddad et al. (1999) Ethylbenzene Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"50, 100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")

```

```
%      pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%      pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
%      pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Ethylbenzene in Venous Blood [mg/L]\";")
%      pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%      pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%      pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
%      pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
%      pltscript(plotcven, "Chart.Series[0].Title=\"50 ppm\";")
%      pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 50 ppm\";")
%      pltscript(plotcven, "Chart.Series[2].Title=\"100 ppm\";")
%      pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 100 ppm\";")
%      pltscript(plotcven, "Chart.Series[4].Title=\"200 ppm\";")
%      pltscript(plotcven, "Chart.Series[5].Title=\"Simulation 200 ppm\";")

set @preference=NoBackslashEscapes
```

C2_Tardif.m

```
%Tardif, R., Charest-Tardif, G. and Brodeur, J. 1996. Comparison of the influence
%      of binary mixtures versus a ternary mixture of inhaled aromatic hydrocarbons
%      on their blood kinetics in the rat. Arch Toxicol 70(7): 405-413.
```

```
%Adult male SD rats
% 235-245 g
```

```
resetdoses
rattus
ethylbenzenerat
```

```
%T, CVEN from Figure 1, mean followed by +SD then -SD
tar100 = [
4.1 1.92
4.5 1.27
5.0 0.86
5.5 0.53
6.0 0.35
4.1 2.11
4.5 1.42
5.0 1.08
5.5 0.66
6.0 0.41
4.1 1.79
4.5 1.14
5.0 0.63
5.5 0.43
6.0 0.29
];
```

```
%T, CVEN from Figure 4, mean followed by +SD then -SD
tar200 = [
4.1 7.67
4.5 4.96
5.0 3.47
5.5 2.50
6.0 1.71
4.1 8.22
4.5 5.51
5.0 3.82
5.5 2.78
6.0 2.01
4.1 6.92
4.5 4.42
5.0 3.25
5.5 2.20
6.0 1.39
];
```

```
BW=0.240;
```

```
CONC(2)=100.0;
```

```

TCHNG=4.0;
TSTOP=6.0;
start @nocallback

plotcven = plot (0, tar100(:,1), tar100(:,2), '+b', _t, _cven(:,2), '-b');

CONC(2)=200.0;
start @nocallback

plot (plotcven, 1, tar200(:,1), tar200(:,2), '+k', _t, _cven(:,2), '-k');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Tardif et al. (1996) Ethylbenzene Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Ethylbenzene in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"200 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 200 ppm\";")

set @preference=NoBackslashEscapeS

```

Xylenes Simulation Script Files

C3_Haddad.m

```

%Haddad, S., Tardif, R., Charest-Tardif, G. and Krishnan, K. 1999. Physiological modeling
% of the toxicokinetic interactions in a quaternary mixture of aromatic hydrocarbons.
% Toxicol.Appl.Pharmacol. 161(3): 249-257.

resetdoses
rattus
xylenerat

%T, CVEN (mean, +SD, -SD)
had50 = [
4.1 0.49
4.5 0.32
5.0 0.24
5.5 0.17
6.0 0.12
4.1 0.55
4.5 0.40
5.0 0.29
5.5 0.21
6.0 0.15
4.1 0.43
4.5 0.23
5.0 0.20
5.5 0.14
6.0 0.09
];

%T, CVEN
had100 = [
4.1 1.20
4.5 0.86
5.0 0.50
5.5 0.37

```

```

6.0 0.24
4.1 1.46
4.5 1.02
5.0 0.62
5.5 0.45
6.0 0.33
4.1 1.10
4.5 0.73
5.0 0.44
5.5 0.33
6.0 0.17
];

%T, CVEN
had200 = [
4.1 6.26
4.5 4.13
5.0 2.83
5.5 1.97
6.0 1.33
4.1 7.60
4.5 5.68
5.0 3.93
5.5 2.83
6.0 1.97
4.1 4.96
4.5 2.80
5.0 1.77
5.5 1.12
6.0 0.71
];

BW=0.235;

CONC(3)=50.0, TCHNG=4.0;
TSTOP=8.0;
start @nocallback

plotcven = plot (0, had50(:,1), had50(:,2), '+b', _t, _cven(:,3), '-b');

CONC(3)=100.0;
start @nocallback

plot (plotcven, 1, had100(:,1), had100(:,2), '+k', _t, _cven(:,3), '-k');

CONC(3)=200.0;
start @nocallback

plot (plotcven, 1, had200(:,1), had200(:,2), '+g', _t, _cven(:,3), '-g');

set @preference=BackslashEscapes

    pltscript(plotcven, "Chart.Header.Text = \"Haddad et al. (1999) m-Xylene Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"50, 100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"m-Xylene in Venous Blood [mg/L]\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"50 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 50 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[4].Title=\"200 ppm\";")
    pltscript(plotcven, "Chart.Series[5].Title=\"Simulation 200 ppm\";")

```

```
set @preference=NoBackslashEscapeS
```

C3_Tardif.m

```
%Tardif, R., Charest-Tardif, G. and Brodeur, J. 1996. Comparison of the influence  
%   of binary mixtures versus a ternary mixture of inhaled aromatic hydrocarbons  
%   on their blood kinetics in the rat. Arch Toxicol 70(7): 405-413.
```

```
%Adult male SD rats  
% 235-245 g
```

```
resetdoses  
rattus  
xylenerat
```

```
%T, CVEN from Figure 1, mean followed by +SD then -SD
```

```
tar100 = [  
4.1 1.26  
4.5 0.86  
5.0 0.51  
5.5 0.37  
6.0 0.24  
4.1 1.44  
4.5 1.01  
5.0 0.62  
5.5 0.43  
6.0 0.30  
4.1 1.09  
4.5 0.71  
5.0 0.43  
5.5 0.31  
6.0 0.15  
];
```

```
%T, CVEN from Figure 3, mean followed by +SD then -SD
```

```
tar200 = [  
4.1 6.32  
4.5 4.26  
5.0 2.83  
5.5 1.99  
6.0 1.37  
4.1 7.80  
4.5 5.74  
5.0 3.95  
5.5 2.83  
6.0 2.04  
4.1 4.89  
4.5 2.83  
5.0 1.75  
5.5 1.12  
6.0 0.74  
];
```

```
BW=0.240;
```

```
CONC(3)=100.0;  
TCHNG=4.0;  
TSTOP=6.0;  
start @nocallback
```

```
plotcven = plot (0, tar100(:,1), tar100(:,2), '+b', _t, _cven(:,3), '-b');
```

```
CONC(3)=200.0;  
start @nocallback
```

```
plot (plotcven, 1, tar200(:,1), tar200(:,2), '+k', _t, _cven(:,3), '-k');
```

```
set @preference=BackslashEscapeS
```

```

    pltscript(plotcven, "Chart.Header.Text = \"Tardif et al. (1996) m-Xylene Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"100, 200 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Xylene in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"200 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 200 ppm\";")

set @preference=NoBackslashEscapeS

```

Nonane Simulation Script Files

C4_inhouse_inhal.m

```

%Robinson, P.J. and Merrill, E.A. 2008. A harmonized physiologically based pharmacokinetic model
%    for nonane as a component of jet fuel. Wright-Patterson AFB, OH: Air Force Research
%    Laboratory, Applied Biotechnology Branch. AFRL-RH-WP-TR-2008-0067, ADA502610.

% From Chem4, 4Chem9r5, C1-In-House-Inhal.m

resetdoses
rattus
nonanerat

%(t, cven, cfat, cliv, cslw)
ihl90d100 = [
    0.5    0.372    NaN    NaN    NaN
    0.5    0.427    NaN    NaN    NaN
    0.5    0.482    NaN    NaN    NaN
    1.0    0.370    NaN    NaN    NaN
    1.0    0.523    NaN    NaN    NaN
    1.0    0.676    NaN    NaN    NaN
    2.0    0.306    NaN    NaN    NaN
    2.0    0.516    NaN    NaN    NaN
    2.0    0.726    NaN    NaN    NaN
    3.0    0.496    NaN    NaN    NaN
    3.0    0.676    NaN    NaN    NaN
    3.0    0.856    NaN    NaN    NaN
    4.0    0.808    13.93    1.44    1.0
    4.0    0.891    27.24    3.83    2.76
    4.0    0.974    40.55    6.22    4.52
    4.08    0.292    NaN    NaN    NaN
    4.08    0.43    NaN    NaN    NaN
    4.08    0.568    NaN    NaN    NaN
    4.16    0.2251    NaN    NaN    NaN
    4.16    0.362    NaN    NaN    NaN
    4.16    0.498    NaN    NaN    NaN
    4.25    0.191    NaN    NaN    NaN
    4.25    0.304    NaN    NaN    NaN
    4.25    0.417    NaN    NaN    NaN
    4.5    0.097    NaN    NaN    NaN
    4.5    0.205    NaN    NaN    NaN
    4.5    0.313    NaN    NaN    NaN
    5.0    0.053    NaN    NaN    NaN
    5.0    0.114    NaN    NaN    NaN
    5.0    0.175    NaN    NaN    NaN
    6.0    0.004    NaN    NaN    NaN
    6.0    0.037    NaN    NaN    NaN
    6.0    0.07    NaN    NaN    NaN
    7.0    0.003    NaN    NaN    NaN

```

```

7.0    0.03    NaN    NaN    NaN
7.0    0.057   NaN    NaN    NaN
8.0    0.0     8.29   0.0    0.0
8.0    0.019   18.65  0.05   0.7
8.0    0.042   29.01  0.22   1.65];

%(t, CV1, CF1, CL1, CS1)
ihl90d500 = [
0.6    1.311   NaN    NaN    NaN
0.6    2.051   NaN    NaN    NaN
0.6    2.791   NaN    NaN    NaN
1.1    1.406   NaN    NaN    NaN
1.1    2.263   NaN    NaN    NaN
1.1    3.12    NaN    NaN    NaN
2.1    2.934   NaN    NaN    NaN
2.1    3.736   NaN    NaN    NaN
2.1    4.538   NaN    NaN    NaN
3.1    2.201   NaN    NaN    NaN
3.1    3.635   NaN    NaN    NaN
3.1    5.069   NaN    NaN    NaN
4.1    3.504   66.01  25.03  11.71
4.1    4.43    131.11  39.63  17.33
4.1    5.356   196.21  54.23  22.95
4.18   3.0     NaN    NaN    NaN
4.18   3.75    NaN    NaN    NaN
4.18   4.5     NaN    NaN    NaN
4.26   1.902   NaN    NaN    NaN
4.26   2.785   NaN    NaN    NaN
4.26   3.668   NaN    NaN    NaN
4.35   1.322   NaN    NaN    NaN
4.35   1.953   NaN    NaN    NaN
4.35   2.584   NaN    NaN    NaN
4.6    1.34    NaN    NaN    NaN
4.6    1.768   NaN    NaN    NaN
4.6    2.196   NaN    NaN    NaN
5.1    0.811   NaN    NaN    NaN
5.1    1.184   NaN    NaN    NaN
5.1    1.557   NaN    NaN    NaN
6.1    0.218   NaN    NaN    NaN
6.1    0.41    NaN    NaN    NaN
6.1    0.602   NaN    NaN    NaN
7.1    0.195   NaN    NaN    NaN
7.1    0.365   NaN    NaN    NaN
7.1    0.535   NaN    NaN    NaN
8.1    0.152   52.64  0.34   0.0
8.1    0.251   82.2   0.48   4.96
8.1    0.35    111.76  0.62   10.08];

%(t, CV1, CF1, CL1, CS1)
ihl90d1000 = [
0.7    1.682   NaN    NaN    NaN
0.7    6.933   NaN    NaN    NaN
0.7    12.184  NaN    NaN    NaN
1.2    3.385   NaN    NaN    NaN
1.2    6.95    NaN    NaN    NaN
1.2    10.515  NaN    NaN    NaN
2.2    9.405   NaN    NaN    NaN
2.2    15.211  NaN    NaN    NaN
2.2    21.017  NaN    NaN    NaN
3.2    7.789   NaN    NaN    NaN
3.2    16.928  NaN    NaN    NaN
3.2    26.067  NaN    NaN    NaN
4.2    4.724    66.86  47.91  23.61
4.2    16.467  360.28  99.9   45.0
4.2    28.21   653.7  151.91  66.39
4.28   6.904   NaN    NaN    NaN
4.28   13.625  NaN    NaN    NaN
4.28   20.346  NaN    NaN    NaN
4.36   2.902   NaN    NaN    NaN
4.36   10.88    NaN    NaN    NaN
4.36   18.858  NaN    NaN    NaN

```

```

4.45    3.02    NaN    NaN    NaN
4.45    9.281    NaN    NaN    NaN
4.45    15.542    NaN    NaN    NaN
4.7     1.649    NaN    NaN    NaN
4.7     5.073    NaN    NaN    NaN
4.7     8.497    NaN    NaN    NaN
5.2     0.888    NaN    NaN    NaN
5.2     4.403    NaN    NaN    NaN
5.2     7.918    NaN    NaN    NaN
6.2     0.638    NaN    NaN    NaN
6.2     2.378    NaN    NaN    NaN
6.2     4.118    NaN    NaN    NaN
7.2     0.514    NaN    NaN    NaN
7.2     1.483    NaN    NaN    NaN
7.2     2.452    NaN    NaN    NaN
8.2     0.247    155.42    2.2    7.07
8.2     0.687    316.26    7.15    21.11
8.2     1.127    477.1    12.1    35.15];

% Study specific setting found in C1-In_house-Inhal.m from 4Chem9r5 model
BW=0.3;

CONC(4)=100.0, TCHNG=4.0;
TSTOP=10;
start @nocallback

plotcven = plot (0, ihl90d100(:,1), ihl90d100(:,2), '+b', _t, _cven(:,4), '-b');
plotcfat = plot (0, ihl90d100(:,1), ihl90d100(:,3), '+b', _t, _cfat(:,4), '-b');
plotcliv = plot (0, ihl90d100(:,1), ihl90d100(:,4), '+b', _t, _cliv(:,4), '-b');
plotcslw = plot (0, ihl90d100(:,1), ihl90d100(:,5), '+b', _t, _cslw(:,4), '-b');

CONC(4)=500.0, TCHNG(4)=4.1;
start @nocallback

plot (plotcven, 1, ihl90d500(:,1), ihl90d500(:,2), '+k', _t, _cven(:,4), '-k');
plot (plotcfat, 1, ihl90d500(:,1), ihl90d500(:,3), '+k', _t, _cfat(:,4), '-k');
plot (plotcliv, 1, ihl90d500(:,1), ihl90d500(:,4), '+k', _t, _cliv(:,4), '-k');
plot (plotcslw, 1, ihl90d500(:,1), ihl90d500(:,5), '+k', _t, _cslw(:,4), '-k');

CONC(4)=1000.0, TCHNG(4)=4.2;
start @nocallback

plot (plotcven, 1, ihl90d500(:,1), ihl90d1000(:,2), '+g', _t, _cven(:,4), '-g');
plot (plotcfat, 1, ihl90d500(:,1), ihl90d1000(:,3), '+g', _t, _cfat(:,4), '-g');
plot (plotcliv, 1, ihl90d500(:,1), ihl90d1000(:,4), '+g', _t, _cliv(:,4), '-g');
plot (plotcslw, 1, ihl90d500(:,1), ihl90d1000(:,5), '+g', _t, _cslw(:,4), '-g');

set @preference=BackslashEscapes

    pltscript(plotcven, "Chart.Header.Text = \"In-House Nonane Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"100, 500, 1000 ppm Inhalation for 4 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Nonane in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 100 ppm\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"500 ppm\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 500 ppm\";")
    pltscript(plotcven, "Chart.Series[4].Title=\"1000 ppm\";")
    pltscript(plotcven, "Chart.Series[5].Title=\"Simulation 1000 ppm\";")

    pltscript(plotcfat, "Chart.Header.Text = \"In-House Nonane Inhalation Study\";")
    pltscript(plotcfat, "Chart.SubHeader.Text = \"100, 500, 1000 ppm Inhalation for 4 Hours\";")
    pltscript(plotcfat, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcfat, "Chart.Axes.Left.Automatic=false;")

```

```

%   pltscript(plotcfat, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcfat, "Chart.Axes.Left.Title.Text=\\"Nonane in Fat [mg/L]\\";")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcfat, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
pltscript(plotcfat, "Chart.Series[0].Title=\\"100 ppm\\";")
pltscript(plotcfat, "Chart.Series[1].Title=\\"Simulation 100 ppm\\";")
pltscript(plotcfat, "Chart.Series[2].Title=\\"500 ppm\\";")
pltscript(plotcfat, "Chart.Series[3].Title=\\"Simulation 500 ppm\\";")
pltscript(plotcfat, "Chart.Series[4].Title=\\"1000 ppm\\";")
pltscript(plotcfat, "Chart.Series[5].Title=\\"Simulation 1000 ppm\\";")

pltscript(plotcliv, "Chart.Header.Text = \\"In-House Nonane Inhalation Study\\";")
pltscript(plotcliv, "Chart.SubHeader.Text = \\"100, 500, 1000 ppm Inhalation for 4 Hours\\";")
pltscript(plotcliv, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcliv, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcliv, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcliv, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcliv, "Chart.Axes.Left.Title.Text=\\"Nonane in Liver [mg/L]\\";")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcliv, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
pltscript(plotcliv, "Chart.Series[0].Title=\\"100 ppm\\";")
pltscript(plotcliv, "Chart.Series[1].Title=\\"Simulation 100 ppm\\";")
pltscript(plotcliv, "Chart.Series[2].Title=\\"500 ppm\\";")
pltscript(plotcliv, "Chart.Series[3].Title=\\"Simulation 500 ppm\\";")
pltscript(plotcliv, "Chart.Series[4].Title=\\"1000 ppm\\";")
pltscript(plotcliv, "Chart.Series[5].Title=\\"Simulation 1000 ppm\\";")

pltscript(plotcslw, "Chart.Header.Text = \\"In-House Nonane Inhalation Study\\";")
pltscript(plotcslw, "Chart.SubHeader.Text = \\"100, 500, 1000 ppm Inhalation for 4 Hours\\";")
pltscript(plotcslw, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcslw, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcslw, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcslw, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcslw, "Chart.Axes.Left.Title.Text=\\"Nonane in Slowly Perfused Tissues [mg/L]\\";")
%   pltscript(plotcslw, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcslw, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcslw, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcslw, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
pltscript(plotcslw, "Chart.Series[0].Title=\\"100 ppm\\";")
pltscript(plotcslw, "Chart.Series[1].Title=\\"Simulation 100 ppm\\";")
pltscript(plotcslw, "Chart.Series[2].Title=\\"500 ppm\\";")
pltscript(plotcslw, "Chart.Series[3].Title=\\"Simulation 500 ppm\\";")
pltscript(plotcslw, "Chart.Series[4].Title=\\"1000 ppm\\";")
pltscript(plotcslw, "Chart.Series[5].Title=\\"Simulation 1000 ppm\\";")

```

```
set @preference=NoBackslashEscapeS
```

C4_Lof99.m

```

%Lof, A., Lam, H.R., Gullstrand, E., Ostergaard, G. and Ladefoged, O. 1999. Distribution of
%   dearomatised white spirit in brain, blood, and fat tissue after repeated exposure of
%   rats. Pharmacol.Toxicol. 85(2): 92-97.

```

```

% Rats dosed with 400 and 800 ppm white spirits; 3.6% n-nonane = 14.4 and 28.8 ppm nonane,
%   respectively

```

```

resetdoses
rattus
nonanerat

```

```

%(T, CVen, CBrnTot, CFat)
lof99lo = [
102.  0.1      0.73  27.26
102.  0.14     1.17  32.

```

```

102.  0.06      0.29  22.52
270.  0.09      0.65  32.5
270.  0.15      0.85  39.7
270.  0.03      0.45  25.3
438.  0.1       0.54  29.06
438.  0.13      0.62  34.41
438.  0.07      0.46  23.71
440.  0.03      0.24  33.85
440.  0.04      0.27  41.22
440.  0.02      0.21  26.48
442.  0.02      0.19  29.75
442.  0.03      0.24  35.48
442.  0.01      0.14  24.02
444.  0.02      0.14  28.54
444.  0.03      0.18  32.46
444.  0.01      0.1   24.62
462.  0.01      0.18  23.75
462.  0.01      0.24  24.58
462.  0.01      0.12  22.92];

%(T, CVen, CBrnTot, CFat)
lof99hi = [
102.  0.26      1.2   69.82
102.  0.41      1.58  81.94
102.  0.11      0.82  57.7
270.  0.21      1.31  90.39
270.  0.31      1.54  111.72
270.  0.11      1.08  69.06
438.  0.32      1.27  99.51
438.  0.44      1.4   127.56
438.  0.2       1.14  71.46
440.  0.06      0.32  88.96
440.  0.08      0.4   101.56
440.  0.04      0.24  76.36
442.  0.03      0.34  74.76
442.  0.04      0.51  82.
442.  0.02      0.17  67.52
444.  0.02      0.2   69.3
444.  0.03      0.23  75.36
444.  0.01      0.17  63.24
462.  0.02      0.18  50.07
462.  0.02      0.25  58.5
462.  0.02      0.11  41.64];

% Default BW from 4Chem9r5 model; No study specific given
BW=0.3;

CONC(4)=14.4;
TCHNG=6.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=504.0;
CINT=0.1;
TSTOP=525.0; %not sure why it was 529 before - this is the next interval of 25 higher than last
dosing
start @nocallback

plotcven = plot (0, lof99lo(:,1), lof99lo(:,2), '+b', _t, _cven(:,4), '-b');
plotcbrntot = plot (0, lof99lo(:,1), lof99lo(:,3), '+b', _t, _cbrntot(:,4), '-b');
plotcfat = plot (0, lof99lo(:,1), lof99lo(:,4), '+b', _t, _cfat(:,4), '-b');

CONC(4)=28.8;
start @nocallback

plot (plotcven, 1, lof99hi(:,1), lof99hi(:,2), '+k', _t, _cven(:,4), '-k');
plot (plotcbrntot, 1, lof99hi(:,1), lof99hi(:,3), '+k', _t, _cbrntot(:,4), '-k');
plot (plotcfat, 1, lof99hi(:,1), lof99hi(:,4), '+k', _t, _cfat(:,4), '-k');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"14.4 and 28.8 ppm for 6 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")

```

```

%   pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Nonane in Venous Blood [mg/L]\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcven, "Chart.Series[0].Title=\"14.4 ppm\";")
pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 14.4 ppm\";")
pltscript(plotcven, "Chart.Series[2].Title=\"28.8 ppm\";")
pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 28.8 ppm\";")

pltscript(plotcbrntot, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
pltscript(plotcbrntot, "Chart.SubHeader.Text = \"14.4 and 28.8 ppm for 6 Hours\";")
pltscript(plotcbrntot, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcbrntot, "Chart.Axes.Left.Title.Text=\"Nonane in Total Brain [mg/L]\";")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcbrntot, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcbrntot, "Chart.Series[0].Title=\"14.4 ppm\";")
pltscript(plotcbrntot, "Chart.Series[1].Title=\"Simulation 14.4 ppm\";")
pltscript(plotcbrntot, "Chart.Series[2].Title=\"28.8 ppm\";")
pltscript(plotcbrntot, "Chart.Series[3].Title=\"Simulation 28.8 ppm\";")

pltscript(plotcfat, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
pltscript(plotcfat, "Chart.SubHeader.Text = \"14.4 and 28.8 ppm for 6 Hours\";")
pltscript(plotcfat, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcfat, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcfat, "Chart.Axes.Left.Title.Text=\"Nonane in Fat [mg/L]\";")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcfat, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcfat, "Chart.Series[0].Title=\"14.4 ppm\";")
pltscript(plotcfat, "Chart.Series[1].Title=\"Simulation 14.4 ppm\";")
pltscript(plotcfat, "Chart.Series[2].Title=\"28.8 ppm\";")
pltscript(plotcfat, "Chart.Series[3].Title=\"Simulation 28.8 ppm\";")

set @preference=NoBackslashEscapeS

```

C4_Zahlsen90.m

```

%Zahlsen, K., Nilsen, A.M., Eide, I. and Nilsen, O.G. 1990. Accumulation and distribution of
%   aliphatic (n-nonane), aromatic (1,2,4-trimethylbenzene) and naphthenic
%   (1,2,4-trimethylcyclohexane) hydrocarbons in the rat after repeated inhalation. Pharmacol.
%   Toxicol. 67(5): 436-440.

```

```

%   Adapted from Chem4, 4Chem9r5, C1-Zahlsen90.m

```

```

resetdoses
rattus
nonanerat

```

```

%(T, CVen, CBrnTot)
zahl90 = [
12.      21.8      179.
60.      17.3      153.
156.     15.4      153.
228.     11.5      132.
348.     10.2      123.];

```

```

% At the start, the animals weighed 150-200 g; Assumed 200 g overall due to growth
BW=0.2;

CONC(4)=1025.2; %Target was 1000 ppm, measured on 5 days, average 1025.2 ppm
TCHNG=12.0; DOSEINT=24.0; DAYSWK=7.0; TMAX=360.0; %TMAX=336.0 depending on how you read it
CINT=0.1;
TSTOP=360.0;

start @nocallback

plotcven = plot (0, zahl90(:,1), zahl90(:,2), 'b', _t, _cven(:,4), '-b');
plotcbrntot = plot (0, zahl90(:,1), zahl90(:,3), 'b', _t, _cbrntot(:,4), '-b');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Zahlsen et al. (1990) Nonane Inhalation Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"1000 ppm for 12 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Nonane in Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"1000 ppm\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 1000 ppm\";")

    pltscript(plotcbrntot, "Chart.Header.Text = \"Zahlsen et al. (1990) Nonane Inhalation
Study\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Text = \"1000 ppm for 12 Hours\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Minimum=0.0;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Title.Text=\"Nonane in Total Brain [mg/L]\";")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcbrntot, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcbrntot, "Chart.Series[0].Title=\"1000 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[1].Title=\"Simulation 1000 ppm\";")

set @preference=NoBackslashEscapeS

```

Decane Simulation Script Files

C5_Lof99.m

```

%Lof, A., Lam, H.R., Gullstrand, E., Ostergaard, G. and Ladefoged, O. 1999. Distribution of
%    dearomatised white spirit in brain, blood, and fat tissue after repeated exposure of
%    rats. Pharmacol.Toxicol. 85(2): 92-97.

%    Adapted from Chem4, 4Chem9r5, C4-Lof99.m

% Rats dosed with 400 and 800 ppm white spirits; 16.6% n-decane = 106.4 and 212 ppm decane,
% respectively

resetdoses
rattus
decanerat

%(T, CVen, CBrnTot, CFat)
%Additional data are present in the original cmd file, but commented out
lof99lo = [
102.    0.7    3.35    150.3
102.    0.86   4.99    178.94
102.    0.54   1.71    121.66

```

```

270.    0.88    2.64    182.8
270.    1.1    3.27    222.1
270.    0.66    2.01    143.5
438.    0.7    2.34    172.1
438.    0.81    2.89    198.4
438.    0.59    1.79    145.8
440.    0.3    1.24    202.8
440.    0.35    1.34    256.19
440.    0.25    1.14    149.41
442.    0.24    0.78    190.8
442.    0.29    0.93    218.12
442.    0.19    0.63    163.48
444.    0.21    0.54    191.7
444.    0.25    0.72    228.18
444.    0.17    0.36    155.22
462.    0.13    0.45    166.5
462.    0.16    0.88    187.19
462.    0.1    0.02    145.81];

%(T, CVen, CBrnTot, CFat)
lof99hi = [
102.    2.09    6.08    440.2
102.    2.78    7.62    493.34
102.    1.4    4.54    387.06
270.    1.73    6.24    537.7
270.    2.12    6.96    642.8
270.    1.34    5.52    432.6
438.    2.21    5.95    590.5
438.    2.75    7.19    770.5
438.    1.67    4.71    410.5
440.    0.57    2.91    547.3
440.    0.64    3.24    616.49
440.    0.5    2.58    478.11
442.    0.44    1.96    511.9
442.    0.48    2.8    571.78
442.    0.4    1.12    452.02
444.    0.36    1.14    489.6
444.    0.42    1.37    534.2
444.    0.3    0.91    445.
462.    0.16    0.57    426.
462.    0.18    0.97    462.76
462.    0.14    0.17    389.24];

% Default BW from 4Chem9r5 model; No study specific given
BW=0.3;

CONC(5)=106.4;
TCHNG=6.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=504.0;
CINT=0.1;
TSTOP=525.0; %not sure why it was 529 before - this is the next interval of 25 higher than last
dosing
start @nocallback

plotcven = plot (0, lof99lo(:,1), lof99lo(:,2), '+b', _t, _cven(:,5), '-b');
plotcbrntot = plot (0, lof99lo(:,1), lof99lo(:,3), '+b', _t, _cbrntot(:,5), '-b');
plotcfat = plot (0, lof99lo(:,1), lof99lo(:,4), '+b', _t, _cfat(:,5), '-b');

CONC(5)=212.0;
start @nocallback

plot (plotcven, 1, lof99hi(:,1), lof99hi(:,2), '+k', _t, _cven(:,5), '-k');
plot (plotcbrntot, 1, lof99hi(:,1), lof99hi(:,3), '+k', _t, _cbrntot(:,5), '-k');
plot (plotcfat, 1, lof99hi(:,1), lof99hi(:,4), '+k', _t, _cfat(:,5), '-k');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"106.4 and 212 ppm for 6 Hours\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")

```

```

%   pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Decane in Venous Blood [mg/L]\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcven, "Chart.Series[0].Title=\"106.4 ppm\";")
pltscript(plotcven, "Chart.Series[1].Title=\"Simulation 106.4 ppm\";")
pltscript(plotcven, "Chart.Series[2].Title=\"212 ppm\";")
pltscript(plotcven, "Chart.Series[3].Title=\"Simulation 212 ppm\";")

pltscript(plotcbrntot, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
pltscript(plotcbrntot, "Chart.SubHeader.Text = \"106.4 and 212 ppm for 6 Hours\";")
pltscript(plotcbrntot, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcbrntot, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcbrntot, "Chart.Axes.Left.Title.Text=\"Decane in Total Brain [mg/L]\";")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcbrntot, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcbrntot, "Chart.Series[0].Title=\"106.4 ppm\";")
pltscript(plotcbrntot, "Chart.Series[1].Title=\"Simulation 106.4 ppm\";")
pltscript(plotcbrntot, "Chart.Series[2].Title=\"212 ppm\";")
pltscript(plotcbrntot, "Chart.Series[3].Title=\"Simulation 212 ppm\";")

pltscript(plotcfat, "Chart.Header.Text = \"Lof et al. (1999) White Spirits Inhalation
Study\";")
pltscript(plotcfat, "Chart.SubHeader.Text = \"106.4 and 212 ppm for 6 Hours\";")
pltscript(plotcfat, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcfat, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plotcfat, "Chart.Axes.Left.Title.Text=\"Decane in Fat [mg/L]\";")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcfat, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcfat, "Chart.Series[0].Title=\"106.4 ppm\";")
pltscript(plotcfat, "Chart.Series[1].Title=\"Simulation 106.4 ppm\";")
pltscript(plotcfat, "Chart.Series[2].Title=\"212 ppm\";")
pltscript(plotcfat, "Chart.Series[3].Title=\"Simulation 212 ppm\";")

set @preference=NoBackslashEscapeS

```

C5_Perleberg04.m

```

%Perleberg, U.R., Keys, D.A. and Fisher, J.W. 2004. Development of a physiologically
%   based pharmacokinetic model for decane, a constituent of Jet Propellant-8.
%   Inhal.Toxicol. 16(11-12): 771-783.

```

```

%   Adapted from Chem4, 4Chem9r5, C4-Perleberg04.m

```

```

resetdoses
rattus
decanerat

```

```

%(1-T, 2-CART, 3-CLiv, 4-CBrnTot, 5-CRap, 6-CFat, 7-conc-bone-marrow, 8-conc-skin)
perl1200 = [
4.08  4.34   33.74  120.38  11.09  104.91  260.89  8.18
4.08  4.79   37.96  131.21  13.08  122.68  315.37  9.83
4.08  3.89   29.52  109.55  9.10   87.15   206.42  6.53
4.50  0.63   17.48  94.85   11.02  60.51   195.57  8.72
4.50  0.82   23.02  108.64  13.91  81.42   272.81  10.82
4.50  0.44   11.94  81.07   8.12   39.60   118.33  6.622
5.00  0.58   5.17   73.29   5.84   112.89  NaN     24.12
5.00  0.72   6.15   75.55   7.44   142.72  NaN     37.15

```

```

5.00 0.45 4.18 71.04 4.23 83.05 NaN 11.09
6.00 0.26 1.16 45.37 4.97 88.52 158.30 10.43
6.00 0.32 1.64 48.94 6.32 107.13 200.46 13.81
6.00 0.20 0.69 41.80 3.62 69.91 116.14 7.050
8.00 0.15 0.55 14.76 3.23 94.43 NaN 8.363
8.00 0.19 0.74 15.76 3.76 118.91 NaN 13.45
8.00 0.10 0.37 13.76 2.71 69.94 NaN 3.277
10.00 NaN NaN 6.90 3.82 101.23 57.139 20.98
10.00 NaN NaN 7.77 5.48 123.56 66.751 29.04
10.00 NaN NaN 6.02 2.17 78.89 47.528 12.93
16.00 NaN NaN 2.09 2.85 74.96 6.140 0.861
16.00 NaN NaN 2.28 4.15 83.96 6.911 1.463
16.00 NaN NaN 1.90 1.55 65.96 5.370 0.259
28.00 NaN NaN 0.36 2.45 55.34 1.348 1.004
28.00 NaN NaN 0.45 3.66 64.11 1.672 1.572
28.00 NaN NaN 0.27 1.24 46.57 1.025 0.435];

%(1-T, 2-Cart, 3-CLiv, 4-CBrnTot, 5-CRap, 6-CFat, 7-conc-bone-marrow, 8-conc-skin)
perl781 = [
4.00 2.68 34.8 61.1 12.1 51.1 109.64 NaN
4.00 3.58 45.1 65.9 16.7 72.3 163.83 NaN
4.00 1.78 24.5 56.2 7.42 29.7 55.469 NaN];

%(1-T, 2-Cart, 3-CLiv, 4-CBrnTot, 5-CRap, 6-CFat, 7-conc-bone-marrow, 8-conc-skin)
perl273 = [
4.00 0.49 4.39 18.3 2.14 14.3 52.479 1.45
4.00 0.65 5.30 21.1 2.76 23.3 66.393 1.45
4.00 0.34 3.49 16.1 1.53 5.34 38.565 0.79];

BW=0.211;

% Note: the above m file indicates that Dr. Merrill may have used a PAFAT=0.06 for this study
only, but the m file used 0.7 anyway (DecaneRat)
%PFAT=0.06;

CONC(5)=1200.0;
TCHNG=4.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=24.0;
CINT=0.1;
TSTOP=30.0;
start @nocallback

plotcart = plot (0, perl1200(:,1), perl1200(:,2), '+b', _t, _cart(:,5), '-b');
plotcliv = plot (0, perl1200(:,1), perl1200(:,3), '+b', _t, _cliv(:,5), '-b');
plotcbrntot = plot (0, perl1200(:,1), perl1200(:,4), '+b', _t, _cbrntot(:,5), '-b');
plotcrap = plot (0, perl1200(:,1), perl1200(:,5), '+b', _t, _crap(:,5), '-b');
plotcfat = plot (0, perl1200(:,1), perl1200(:,6), '+b', _t, _cfat(:,5), '-b');

CONC(5)=781.0;
TSTOP=5.0;
start @nocallback

plot (plotcart, 1, perl781(:,1), perl781(:,2), '+k', _t, _cart(:,5), '-k');
plot (plotcliv, 1, perl781(:,1), perl781(:,3), '+k', _t, _cliv(:,5), '-k');
plot (plotcbrntot, 1, perl781(:,1), perl781(:,4), '+k', _t, _cbrntot(:,5), '-k');
plot (plotcrap, 1, perl781(:,1), perl781(:,5), '+k', _t, _crap(:,5), '-k');
plot (plotcfat, 1, perl781(:,1), perl781(:,6), '+k', _t, _cfat(:,5), '-k');

CONC(5)=273.0;
start @nocallback

plot (plotcart, 1, perl273(:,1), perl273(:,2), '+g', _t, _cart(:,5), '-g');
plot (plotcliv, 1, perl273(:,1), perl273(:,3), '+g', _t, _cliv(:,5), '-g');
plot (plotcbrntot, 1, perl273(:,1), perl273(:,4), '+g', _t, _cbrntot(:,5), '-g');
plot (plotcrap, 1, perl273(:,1), perl273(:,5), '+g', _t, _crap(:,5), '-g');
plot (plotcfat, 1, perl273(:,1), perl273(:,6), '+g', _t, _cfat(:,5), '-g');

set @preference=BackslashEscapeS

pltscript(plotcart, "Chart.Header.Text = \"Perleberg et al. (2004) n-Decane Inhalation
Study\";")
pltscript(plotcart, "Chart.SubHeader.Text = \"273, 781 or 1200 ppm for 4 Hours\";")

```

```

    pltscript(plotcart, "Chart.SubHeader.Visible=true;")
    pltscript(plotcart, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcart, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcart, "Chart.Axes.Left.Maximum=100.0;")
    pltscript(plotcart, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcart, "Chart.Axes.Left.Title.Text=\"Decane in Arterial Blood [mg/L]\";")
%   pltscript(plotcart, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcart, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcart, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcart, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcart, "Chart.Series[0].Title=\"1200 ppm\";")
    pltscript(plotcart, "Chart.Series[1].Title=\"Simulation 1200 ppm\";")
    pltscript(plotcart, "Chart.Series[2].Title=\"781 ppm\";")
    pltscript(plotcart, "Chart.Series[3].Title=\"Simulation 781 ppm\";")
    pltscript(plotcart, "Chart.Series[4].Title=\"273 ppm\";")
    pltscript(plotcart, "Chart.Series[5].Title=\"Simulation 273 ppm\";")

    pltscript(plotcliv, "Chart.Header.Text = \"Perleberg et al. (2004) n-Decane Inhalation
Study\";")
    pltscript(plotcliv, "Chart.SubHeader.Text = \"273, 781 or 1200 ppm for 4 Hours\";")
    pltscript(plotcliv, "Chart.SubHeader.Visible=true;")
    pltscript(plotcliv, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcliv, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcliv, "Chart.Axes.Left.Maximum=100.0;")
    pltscript(plotcliv, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcliv, "Chart.Axes.Left.Title.Text=\"Decane in Liver [mg/L]\";")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcliv, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcliv, "Chart.Series[0].Title=\"1200 ppm\";")
    pltscript(plotcliv, "Chart.Series[1].Title=\"Simulation 1200 ppm\";")
    pltscript(plotcliv, "Chart.Series[2].Title=\"781 ppm\";")
    pltscript(plotcliv, "Chart.Series[3].Title=\"Simulation 781 ppm\";")
    pltscript(plotcliv, "Chart.Series[4].Title=\"273 ppm\";")
    pltscript(plotcliv, "Chart.Series[5].Title=\"Simulation 273 ppm\";")

    pltscript(plotcbrntot, "Chart.Header.Text = \"Perleberg et al. (2004) n-Decane Inhalation
Study\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Text = \"273, 781 or 1200 ppm for 4 Hours\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Visible=true;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Maximum=200.0;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Title.Text=\"Decane in Total Brain [mg/L]\";")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcbrntot, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcbrntot, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcbrntot, "Chart.Series[0].Title=\"1200 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[1].Title=\"Simulation 1200 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[2].Title=\"781 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[3].Title=\"Simulation 781 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[4].Title=\"273 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[5].Title=\"Simulation 273 ppm\";")

    pltscript(plotcrap, "Chart.Header.Text = \"Perleberg et al. (2004) n-Decane Inhalation
Study\";")
    pltscript(plotcrap, "Chart.SubHeader.Text = \"273, 781 or 1200 ppm for 4 Hours\";")
    pltscript(plotcrap, "Chart.SubHeader.Visible=true;")
    pltscript(plotcrap, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcrap, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcrap, "Chart.Axes.Left.Maximum=100.0;")
    pltscript(plotcrap, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcrap, "Chart.Axes.Left.Title.Text=\"Decane in Rapidly Perfused Tissues
[mg/L]\";")
%   pltscript(plotcrap, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcrap, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcrap, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcrap, "Chart.Axes.Bottom.Title.Text=\"Hours\";")

```

```

    pltscript(plotcrap, "Chart.Series[0].Title=\"1200 ppm\";")
    pltscript(plotcrap, "Chart.Series[1].Title=\"Simulation 1200 ppm\";")
    pltscript(plotcrap, "Chart.Series[2].Title=\"781 ppm\";")
    pltscript(plotcrap, "Chart.Series[3].Title=\"Simulation 781 ppm\";")
    pltscript(plotcrap, "Chart.Series[4].Title=\"273 ppm\";")
    pltscript(plotcrap, "Chart.Series[5].Title=\"Simulation 273 ppm\";")

    pltscript(plotcfat, "Chart.Header.Text = \"Perleberg et al. (2004) n-Decane Inhalation Study\";")
    pltscript(plotcfat, "Chart.SubHeader.Text = \"273, 781 or 1200 ppm for 4 Hours\";")
    pltscript(plotcfat, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcfat, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Maximum=2.0;")
    pltscript(plotcfat, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcfat, "Chart.Axes.Left.Title.Text=\"Decane in Fat [mg/L]\";")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcfat, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcfat, "Chart.Series[0].Title=\"1200 ppm\";")
    pltscript(plotcfat, "Chart.Series[1].Title=\"Simulation 1200 ppm\";")
    pltscript(plotcfat, "Chart.Series[2].Title=\"781 ppm\";")
    pltscript(plotcfat, "Chart.Series[3].Title=\"Simulation 781 ppm\";")
    pltscript(plotcfat, "Chart.Series[4].Title=\"273 ppm\";")
    pltscript(plotcfat, "Chart.Series[5].Title=\"Simulation 273 ppm\";")

set @preference=NoBackslashEscapeS

```

C5_Zahlsen92.m

```

%Zahlsen, K., Eide, I., Nilsen, A.M. and Nilsen, O.G. 1992. Inhalation kinetics of C6
%   to C10 aliphatic, aromatic and naphthenic hydrocarbons in rat after repeated
%   exposures. Pharmacol.Toxicol. 71(2): 144-149.

```

```

% Adapted from Chem4, 4Chem9r5, C4-Zahlsen92.m

```

```

resetdoses
rattus
decanerat

```

```

%(1-T, 2-Cart, 3-CBrnTot, 4-CLiv, 5-CRap, 6-CFat)
zahl = [
12.0  0.83957 12.73585  5.49278  4.76705 119.6743
12.0  0.93918 13.71772  6.95847  5.53547 167.2025
12.0  0.73996 11.75398  4.02709  3.99863  72.1461
36.0  0.91072  8.28186  6.48888  8.09687 188.4052
36.0  1.01033 10.08907  7.31422  9.07874 208.0426
36.0  0.81111  6.47465  5.66354  7.115   168.7678
60.0  0.96764  8.56646  6.53157 11.05671 175.029
60.0  1.03879 10.37367  7.08654 14.9415 183.9939
60.0  0.89649  6.75925  5.9766  7.17192 166.0641
72.0  0.01423  0.24191  NaN     0.24191 131.6275
72.0  0.02846  0.25614  NaN     0.32729 145.9998
72.0  0.001    0.22768  NaN     0.15653 117.2552];

```

```

BW=0.175;
SCRUB(5)=0.4;

```

```

CONC(5)=100.0;
TCHNG=12.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=72.0;
CINT=0.1;
TSTOP=80.0;
start @nocallback

```

```

plotcart = plot (0, zahl(:,1), zahl(:,2), '+b', _t, _cart(:,5), '-b');
plotcbrntot = plot (0, zahl(:,1), zahl(:,3), '+b', _t, _cbrntot(:,5), '-b');
plotcliv = plot (0, zahl(:,1), zahl(:,4), '+b', _t, _cliv(:,5), '-b');
plotcrap = plot (0, zahl(:,1), zahl(:,5), '+b', _t, _crap(:,5), '-b');
plotcfat = plot (0, zahl(:,1), zahl(:,6), '+b', _t, _cfat(:,5), '-b');

```

set @preference=BackslashEscapes

```
    pltscript(plotcart, "Chart.Header.Text = \"Zahlsen et al. (1992) n-Decane Inhalation
Study\";")
    pltscript(plotcart, "Chart.SubHeader.Text = \"100 ppm for 12 Hours\";")
    pltscript(plotcart, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcart, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcart, "Chart.Axes.Left.Minimum=0.01;")
%    pltscript(plotcart, "Chart.Axes.Left.Maximum=100.0;")
%    pltscript(plotcart, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcart, "Chart.Axes.Left.Title.Text=\"Decane in Arterial Blood [mg/L]\";")
%    pltscript(plotcart, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcart, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcart, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcart, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcart, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcart, "Chart.Series[1].Title=\"Simulation 100 ppm\";")

    pltscript(plotcbrntot, "Chart.Header.Text = \"Zahlsen et al. (1992) n-Decane Inhalation
Study\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Text = \"100 ppm for 12 Hours\";")
    pltscript(plotcbrntot, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Automatic=false;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Minimum=0.01;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Maximum=200.0;")
%    pltscript(plotcbrntot, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcbrntot, "Chart.Axes.Left.Title.Text=\"Decane in Total Brain [mg/L]\";")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcbrntot, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcbrntot, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcbrntot, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcbrntot, "Chart.Series[1].Title=\"Simulation 100 ppm\";")

    pltscript(plotcliv, "Chart.Header.Text = \"Zahlsen et al. (1992) n-Decane Inhalation
Study\";")
    pltscript(plotcliv, "Chart.SubHeader.Text = \"100 ppm for 12 Hours\";")
    pltscript(plotcliv, "Chart.SubHeader.Visible=true;")
    pltscript(plotcliv, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcliv, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcliv, "Chart.Axes.Left.Maximum=100.0;")
    pltscript(plotcliv, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcliv, "Chart.Axes.Left.Title.Text=\"Decane in Liver [mg/L]\";")
%    pltscript(plotcliv, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcliv, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcliv, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcliv, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcliv, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcliv, "Chart.Series[1].Title=\"Simulation 100 ppm\";")

    pltscript(plotcrap, "Chart.Header.Text = \"Zahlsen et al. (1992) n-Decane Inhalation
Study\";")
    pltscript(plotcrap, "Chart.SubHeader.Text = \"100 ppm for 12 Hours\";")
    pltscript(plotcrap, "Chart.SubHeader.Visible=true;")
    pltscript(plotcrap, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcrap, "Chart.Axes.Left.Minimum=0.01;")
    pltscript(plotcrap, "Chart.Axes.Left.Maximum=100.0;")
    pltscript(plotcrap, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcrap, "Chart.Axes.Left.Title.Text=\"Decane in Kidney (Rapidly Perfused Tissues)
[mg/L]\";")
%    pltscript(plotcrap, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcrap, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcrap, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcrap, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcrap, "Chart.Series[0].Title=\"100 ppm\";")
    pltscript(plotcrap, "Chart.Series[1].Title=\"Simulation 100 ppm\";")

    pltscript(plotcfat, "Chart.Header.Text = \"Zahlsen et al. (1992) n-Decane Inhalation
Study\";")
    pltscript(plotcfat, "Chart.SubHeader.Text = \"100 ppm for 12 Hours\";")
```

```

    pltscript(plotcfat, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcfat, "Chart.Axes.Left.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Left.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Maximum=2.0;")
%   pltscript(plotcfat, "Chart.Axes.Left.Logarithmic = true;")
pltscript(plotcfat, "Chart.Axes.Left.Title.Text=\"Decane in Fat [mg/L]\";")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcfat, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcfat, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcfat, "Chart.Series[0].Title=\"100 ppm\";")
pltscript(plotcfat, "Chart.Series[1].Title=\"Simulation 100 ppm\";")

```

```
set @preference=NoBackslashEscapeS
```

Naphthalene Simulation Script Files

C6_Egeghy_hmn_hiconc.m

```

% C6_Egeghy_hmn_hiconc.m

% Egeghy PP, Hauf-Cabalo L, Gibson R, Rappaport SM. Benzene and naphthalene in
%   air and breath as indicators of exposure to jet fuel. Occup Environ Med. 2003
%   Dec;60(12):969-76.

% Human data using median plus upper and lower quartile breath values versus median exposure
% concentration

% Assuming 70 kg std human

% Breath concentrations
%   T to B: median, lower and upper quartile values for times:
%   pre-expos at testing ctr, immediately after 4 hour shift, post-expos at testing ctr

% High exposure group only %first reading is really at -0.57 hours
breath = [
0.00    0.0000006
4.00    0.0000060
4.00    0.0000026
4.00    0.0000161
4.56    0.00000183
4.56    0.0000009
4.56    0.0000040];

    resetdoses
    human
    naphhmn

BW=70.0;

TCHNG=4.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=24.0;
% HIGH EXPOSURE
CONC(6)=0.093;
TSTOP=6.0;

start @NoCallback

    plotcven = plot (0, _t, _cven(:,6), '-b');
    plotcinh = plot(0, _t, _cinh(:,6), '-b');
    plotexh = plot (0, _t, _cend(:,6), '-b', breath(:,1), breath(:,2),'+b');

start @NoCallback

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Egeghy et al. 2003 Human Exposure to Jet Fuel\";")
%   pltscript(plotcven, "Chart.Axes.Left.LogarithmicBase=10;")
%   pltscript(plotcven, "Chart.Axes.Left.Logarithmic=true;")
%   pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")

```

```

% pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Left.Maximum=0.01;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Naphthalene Venous Concentration (mg/L)\";")
% pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcven, "Chart.Series[0].Title=\"High Exposure\";")

pltscript(plotcinh, "Chart.Header.Text = \"Egeghy et al. 2003 Human Exposure to Jet Fuel\";")
%pltscript(plotcinh, "Chart.Axes.Left.LogarithmicBase=10;")
%pltscript(plotcinh, "Chart.Axes.Left.Logarithmic=true;")
%pltscript(plotcinh, "Chart.Axes.Left.Automatic=false;")
%pltscript(plotcinh, "Chart.Axes.Left.Minimum=0.0;")
%pltscript(plotcinh, "Chart.Axes.Left.Maximum=0.05;")
pltscript(plotcinh, "Chart.Axes.Left.Title.Text=\"Naphthalene Concentration in Inhaled Air (mg/L)\";")
% pltscript(plotcinh, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcinh, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcinh, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcinh, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcinh, "Chart.Series[0].Title=\"High Exposure\";")

pltscript(plotexh, "Chart.Header.Text = \"Egeghy et al. 2003 Human Exposure to Jet Fuel\";")
%pltscript(plotexh, "Chart.Axes.Left.LogarithmicBase=10;")
%pltscript(plotexh, "Chart.Axes.Left.Logarithmic=true;")
%pltscript(plotexh, "Chart.Axes.Left.Automatic=false;")
%pltscript(plotexh, "Chart.Axes.Left.Minimum=0.00000001;")
%pltscript(plotexh, "Chart.Axes.Left.Maximum=0.0001;")
pltscript(plotexh, "Chart.Axes.Left.Title.Text=\"Naphthalene Concentration in Exhaled Air (mg/L)\";")
% pltscript(plotexh, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotexh, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotexh, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotexh, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotexh, "Chart.Series[0].Title=\"High Exposure Prediction\";")
pltscript(plotexh, "Chart.Series[1].Title=\"High Exposure Data\";")

set @preference=NoBackslashEscapeS

C6_NTP00_rat_repeatihl_2wk.m

% C6_NTP00_rat_repeatihl_2wk.m

% NTP. 2000. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene
% (CAS NO. 91-20-3) in F344/N Rats. National Toxicology Program, Research Triangle Park NC. NTP
TR 500.
%
% Sprague-Dawley rats, n = 3 males (data for female rats available too; if n=1 or 2, no SE info)
% 10, 30, or 60 ppm
% 6 hr/d, 5 d/wk, 2 week timepoint
% Chambers were allowed to empty for 12 min to reduce the concentration enough to remove the
rats
% Therefore TChng = 6.1
% (adding 6 min of full exposure to average out 12 minutes of exposure decrease from full to
10%)
% BW data from 1 and 4 weeks used to calculate a rough 2 (or 2.5) wk BW of 0.169 kg

resetdoses
rattus
naphrat

% Increased VMaxC values due to metabolic upregulation
% Km = KmLu = 2.18

% Time, CVen for 10, 30, 60 ppm after day 12 exposures ended
% Values, top to bottom, are series of average, -SE, +SE in mg/L

blood = [
270.10 0.331 1.540 3.730

```

```

270.10 0.299 1.473 3.525
270.10 0.363 1.607 3.935
270.60 0.192 0.765 1.640
270.60 0.177 0.724 1.590
270.60 0.207 0.806 1.690
271.10 0.118 NaN NaN
271.10 0.111 NaN NaN
271.10 0.125 NaN NaN
271.60 NaN 0.210 0.544
271.60 NaN 0.190 0.488
271.60 NaN 0.230 0.600
272.10 0.045 NaN NaN
275.10 0.015 0.047 NaN
275.10 0.011 0.043 NaN
275.10 0.019 0.051 NaN
276.10 NaN NaN 0.069
276.10 NaN NaN 0.066
276.10 NaN NaN 0.072
278.10 NaN 0.020 NaN
278.10 NaN 0.016 NaN
278.10 NaN 0.024 NaN
282.10 NaN 0.007 0.022
282.10 NaN 0.007 0.019
282.10 NaN 0.007 0.025
286.10 NaN NaN 0.008
286.10 NaN NaN 0.006
286.10 NaN NaN 0.010];

BW=0.169; %Study specific rat
VMAXC(6)=((8.28/(BW^0.75))*BW)*1.4;
VMAXLUC(6)=((0.45/(BW^0.75))*BW)*1.12;
%These do not equal the upregulated VMax values in NaDoRT but are similar

TCHNG=6.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=270.0;

CONC(6)=10.0;

TSTART=0.0;
TSTOP=290.0;

start @NoCallback

    plotcven = plot (0, blood(:,1), blood(:,2), '+b', _t, _cven(:,6), '-b');
    plotcvenlo = plot (0, blood(:,1), blood(:,2), '+b', _t, _cven(:,6), '-b');

CONC(6)=30.0;
start @NoCallBack

    plot (plotcven, 1, blood(:,1), blood(:,3), '+g', _t, _cven(:,6), '-g');

CONC(6)=60.0;
start @NoCallBack

    plot (plotcven, 1, blood(:,1), blood(:,4), '+m', _t, _cven(:,6), '-m');

set @preference=BackslashEscapes

% pltscript(plotcven, "Chart.Header.Text = \"NTP (2000) Naphthalene Inhalation Exposure in Rats
at 2 Wks\";")
% pltscript(plotcven, "Chart.Axes.Left.LogarithmicBase=10;")
% pltscript(plotcven, "Chart.Axes.Left.Logarithmic=true;")
% pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Left.Minimum=0.01;")
% pltscript(plotcven, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcven, "Chart.Series[0].Title=\"10 ppm\";")

```

```

pltscript(plotcven, "Chart.Series[1].Title=\"10 ppm Prediction\";")
pltscript(plotcven, "Chart.Series[2].Title=\"30 ppm\";")
pltscript(plotcven, "Chart.Series[3].Title=\"30 ppm Prediction\";")
pltscript(plotcven, "Chart.Series[4].Title=\"60 ppm\";")
pltscript(plotcven, "Chart.Series[5].Title=\"60 ppm Prediction\";")

% pltscript(plotcvenlo, "Chart.Header.Text = \"NTP (2000) Naphthalene Inhalation Exposure in Rats
at 2 Wks\";")
% pltscript(plotcvenlo, "Chart.Axes.Left.LogarithmicBase=10;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Logarithmic=true;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Automatic=false;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Minimum=0.01;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Maximum=100.0;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Maximum=15.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcvenlo, "Chart.Series[0].Title=\"10 ppm\";")
pltscript(plotcvenlo, "Chart.Series[1].Title=\"10 ppm Prediction\";")

set @preference=NoBackslashEscapeS

```

C6_NTP00_rat_singleihl.m

```

% C6_NTP00_rat_singleihl.m

% NTP. 2000. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene
% (CAS NO. 91-20-3) in F344/N Rats. National Toxicology Program, Research Triangle Park NC. NTP
TR 500.
%
% Sprague-Dawley rats, n = 3 males (data for female rats available too)
% 10, 30, or 60 ppm
% 6 hr single exposure
% Chambers were allowed to empty for 12 min to reduce the concentration enough to remove the
rats
% Therefore TChng = 6.1
% (adding 6 min of full exposure to average out 12 minutes of exposure decrease from full to
10%)
% Male BW data from Table D5 = 125 g

resetdoses
rattus
naphrat

% Time, CVen for 10, 30, 60 ppm single dose after 6.1 hours of exposure
% Values, top to bottom, are series of average, -SE, +SE in mg/L
blood = [
6.10 0.463 1.387 5.360
6.10 0.497 1.439 6.026
6.10 0.429 1.335 4.694
6.60 0.308 0.911 3.193
6.60 0.317 0.962 3.529
6.60 0.299 0.860 2.857
7.10 0.171 0.661 2.227
7.10 0.179 0.720 2.615
7.10 0.163 0.602 1.839
7.60 0.094 0.476 1.143
7.60 0.103 0.494 1.399
7.60 0.085 0.458 0.887
8.10 0.100 0.239 0.838
8.10 0.111 0.267 0.987
8.10 0.089 0.211 0.689
10.1 0.051 0.138 0.380
10.1 0.053 0.145 0.422
10.1 0.049 0.131 0.338
12.1 0.029 0.071 0.252
12.1 0.030 0.072 0.261
12.1 0.028 0.070 0.243
14.1 0.014 0.060 0.174

```

```

14.1    0.017    0.063    0.197
14.1    0.011    0.057    0.151];

BW=0.125; %Study specific rat

TCHNG=6.0; DOSEINT=24.0; DAYSWK=5.0; TMAX=24.0;

CONC(6)=10.0;
  VMAXC(6)=( (8.28/(BW^0.75))*BW);
  VMAXLUC(6)=( (0.45/(BW^0.75))*BW);

TSTART=0.0;
TSTOP=24.0;
start @NoCallback

  plotcven = plot (0, blood(:,1), blood(:,2), '+b', _t, _cven(:,6), '-b');
  plotcvenlo = plot (0, blood(:,1), blood(:,2), '+b', _t, _cven(:,6), '-b');

CONC(6)=30.0;
start @NoCallback

  plot (plotcven, 1, blood(:,1), blood(:,3), '+g', _t, _cven(:,6), '-g');

CONC(6)=60.0;
start @NoCallback

  plot (plotcven, 1, blood(:,1), blood(:,4), '+m', _t, _cven(:,6), '-m');

set @preference=BackslashEscapeS

% pltscript(plotcven, "Chart.Header.Text = \"NTP (2000) Naphthalene Single Inhalation Exposure in
Male Rats\";")
% pltscript(plotcven, "Chart.Axes.Left.LogarithmicBase=10;")
% pltscript(plotcven, "Chart.Axes.Left.Logarithmic=true;")
% pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Left.Minimum=0.01;")
% pltscript(plotcven, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcven, "Chart.Series[0].Title=\"10 ppm\";")
pltscript(plotcven, "Chart.Series[1].Title=\"10 ppm Prediction\";")
pltscript(plotcven, "Chart.Series[2].Title=\"30 ppm\";")
pltscript(plotcven, "Chart.Series[3].Title=\"30 ppm Prediction\";")
pltscript(plotcven, "Chart.Series[4].Title=\"60 ppm\";")
pltscript(plotcven, "Chart.Series[5].Title=\"60 ppm Prediction\";")

% pltscript(plotcvenlo, "Chart.Header.Text = \"NTP (2000) Naphthalene Single Inhalation Exposure
in Male Rats\";")
% pltscript(plotcvenlo, "Chart.Axes.Left.LogarithmicBase=10;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Logarithmic=true;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Automatic=false;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Minimum=0.01;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plotcvenlo, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Maximum=15.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcvenlo, "Chart.Series[0].Title=\"10 ppm\";")
pltscript(plotcvenlo, "Chart.Series[1].Title=\"10 ppm Prediction\";")

set @preference=NoBackslashEscapeS

C6_RTI96_rat_iv.m

% C6_RTI96_rat_iv.m
% Simulates data from RTI 1996

```

```
% SE and individual data are available
% Data used in publications by Quick and Shuler (1999),
% Willems et al. (2001), Campbell et al. (2014).
```

```
resetdoses
rattus
naphrat
```

```
%male rats, 1, 3 and 10 mg/kg, time and mean cvenbldna
```

```
male=[
0.03 1.980 3.580 9.330
0.03 3.080 8.280 11.030
0.03 0.880 0.000 7.630
0.08 0.668 2.310 5.050
0.08 0.707 4.610 6.150
0.08 0.629 0.010 3.950
0.17 0.322 2.120 2.700
0.17 0.337 3.920 2.830
0.17 0.307 0.320 2.570
0.33 0.106 0.720 0.787
0.33 0.128 1.250 0.897
0.33 0.084 0.190 0.677
0.67 0.039 0.245 0.447
0.67 0.059 0.312 0.487
0.67 0.019 0.178 0.407
1.00 0.338 0.158 0.186
1.00 0.341 0.180 0.210
1.00 0.335 0.136 0.162
2.00 0.017 0.123 0.086
2.00 NaN 0.220 0.093
2.00 NaN 0.026 0.078
4.00 0.014 0.053 0.048
4.00 NaN 0.101 0.058
4.00 NaN 0.005 0.038
6.00 0.011 0.091 0.036
6.00 NaN NaN 0.039
6.00 NaN NaN 0.032
8.00 0.007 0.021 0.014
8.00 NaN NaN 0.018
8.00 NaN NaN 0.010];
```

```
%female rats, 1, 3 or 10 mg/kg, time and mean cvenbldna
```

```
fem=[
0.03 1.030 4.140 10.200
0.03 1.930 6.440 12.300
0.03 0.130 1.840 8.100
0.08 0.457 2.100 6.130
0.08 0.827 2.850 9.530
0.08 0.087 1.350 2.730
0.17 0.209 1.780 2.220
0.17 0.409 2.880 2.640
0.17 0.009 0.680 1.800
0.33 0.057 0.457 0.860
0.33 0.112 0.535 1.090
0.33 0.002 0.379 0.630
0.67 0.029 0.179 0.333
0.67 0.046 0.251 0.414
0.67 0.012 0.107 0.252
1.00 0.018 0.108 0.211
1.00 0.022 0.139 0.234
1.00 0.013 0.077 0.188
2.00 0.013 0.047 0.092
2.00 0.020 0.058 0.104
2.00 0.005 0.036 0.080
4.00 0.014 0.022 0.061
4.00 0.021 0.032 0.064
4.00 0.007 0.012 0.058
6.00 0.016 0.026 0.050
6.00 0.027 0.028 0.056
6.00 0.005 0.024 0.045
8.00 0.011 0.024 0.029
```

```

8.00    NaN        NaN    0.031
8.00    NaN        NaN    0.027];

% MALE SIMULATIONS
IVDOSE(6)=1.0; %1 mg/kg
BW=0.255;      %male rats
VMAXC(6)=( (8.28/(BW^0.75))*BW);
VMAXLUC(6)=( (0.45/(BW^0.75))*BW);

TINF=0.008, TSTOP=8.0;
start @nocallback

plotcven = plot (0, _t, _cven(:,6), '-b', male(:,1), male(:,2), '+b');
plotcvenlo = plot (0, _t, _cven(:,6), '-b', male(:,1), male(:,2), '+b');

IVDOSE(6)=3.0; %3 mg/kg
start @nocallback

plot (plotcven, 1, _t, _cven(:,6), '-g', male(:,1), male(:,3), '+g');

IVDOSE(6)=10.0; %10 mg/kg
start @nocallback

plot (plotcven, 1, _t, _cven(:,6), '-m', male(:,1), male(:,4), '+m');

%FEMALE SIMULATIONS
BW=0.156;      %female rats
VMAXC(6)=( (8.28/(BW^0.75))*BW);
VMAXLUC(6)=( (0.45/(BW^0.75))*BW);

IVDOSE(6)=1.0; %1 mg/kg
TINF=0.008, TSTOP=8.0;
start @nocallback

plotcvenf = plot (0, _t, _cven(:,6), '-b', fem(:,1), fem(:,2), '+b');
plotcvenflo = plot (0, _t, _cven(:,6), '-b', fem(:,1), fem(:,2), '+b');

IVDOSE(6)=3.0; %3 mg/kg
start @nocallback

plot (plotcvenf, 1, _t, _cven(:,6), '-g', fem(:,1), fem(:,3), '+g');

IVDOSE(6)=10.0; %10 mg/kg
start @nocallback

plot (plotcvenf, 1, _t, _cven(:,6), '-m', fem(:,1), fem(:,4), '+m');

set @preference=BackslashEscapes

% pltscript(plotcven, "Chart.Header.Text = \"RTI 1996 IV Study delivered to NTP - Male Rats\");")
pltscript(plotcven, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plotcven, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
pltscript(plotcven, "Chart.Axes.Left.Minimum=0.001;")
pltscript(plotcven, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\");")
% pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\");")
pltscript(plotcven, "Chart.Series[0].Title=\"1 mg/kg Simulation\");")
pltscript(plotcven, "Chart.Series[1].Title=\"1 mg/kg Data\");")
pltscript(plotcven, "Chart.Series[2].Title=\"3 mg/kg Simulation\");")
pltscript(plotcven, "Chart.Series[3].Title=\"3 mg/kg Data\");")
pltscript(plotcven, "Chart.Series[4].Title=\"10 mg/kg Simulation\");")
pltscript(plotcven, "Chart.Series[5].Title=\"10 mg/kg Data\");")

% pltscript(plotcvenlo, "Chart.Header.Text = \"RTI 1996 IV Study delivered to NTP - Male
Rats\");")
pltscript(plotcvenlo, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plotcvenlo, "Chart.Axes.Left.Logarithmic=true;")

```

```

pltscript(plotcvenlo, "Chart.Axes.Left.Automatic=false;")
pltscript(plotcvenlo, "Chart.Axes.Left.Minimum=0.001;")
pltscript(plotcvenlo, "Chart.Axes.Left.Maximum=100.0;")
% pltscript(plotcvenlo, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Maximum=15.0;")
% pltscript(plotcvenlo, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcvenlo, "Chart.Series[0].Title=\"1 mg/kg Simulation\";")
pltscript(plotcvenlo, "Chart.Series[1].Title=\"1 mg/kg Data\";")

% pltscript(plotcvenf, "Chart.Header.Text = \"RTI 1996 IV Study delivered to NTP - Female
Rats\";")
pltscript(plotcvenf, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plotcvenf, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plotcvenf, "Chart.Axes.Left.Automatic=false;")
pltscript(plotcvenf, "Chart.Axes.Left.Minimum=0.001;")
pltscript(plotcvenf, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plotcvenf, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcvenf, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcvenf, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcvenf, "Chart.Axes.Bottom.Maximum=15.0;")
pltscript(plotcvenf, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcvenf, "Chart.Series[0].Title=\"1 mg/kg Simulation\";")
pltscript(plotcvenf, "Chart.Series[1].Title=\"1 mg/kg Data\";")
pltscript(plotcvenf, "Chart.Series[2].Title=\"3 mg/kg Simulation\";")
pltscript(plotcvenf, "Chart.Series[3].Title=\"3 mg/kg Data\";")
pltscript(plotcvenf, "Chart.Series[4].Title=\"10 mg/kg Simulation\";")
pltscript(plotcvenf, "Chart.Series[5].Title=\"10 mg/kg Data\";")

% pltscript(plotcvenflo, "Chart.Header.Text = \"RTI 1996 IV Study delivered to NTP - Female
Rats\";")
pltscript(plotcvenflo, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plotcvenflo, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plotcvenflo, "Chart.Axes.Left.Automatic=false;")
pltscript(plotcvenflo, "Chart.Axes.Left.Minimum=0.001;")
pltscript(plotcvenflo, "Chart.Axes.Left.Maximum=100.0;")
% pltscript(plotcvenflo, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L)\";")
% pltscript(plotcvenflo, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcvenflo, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcvenflo, "Chart.Axes.Bottom.Maximum=15.0;")
% pltscript(plotcvenflo, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
pltscript(plotcvenflo, "Chart.Series[0].Title=\"1 mg/kg Simulation\";")
pltscript(plotcvenflo, "Chart.Series[1].Title=\"1 mg/kg Data\";")

set @preference=NoBackslashEscapeS

```

APPENDIX E: SCRIPT FILES FOR REPORT FIGURES

The following M files are used to generate the simulations for the Guthrie *et al.* (2014) predictions and the comparisons between JP-8 and Virent SAK:JP-8 mixture exposures. Some lines were too long for the page width and were thus reformatted to fit the page; however, these additional line breaks and space may need to be removed for the M file to run correctly.

Predict_Guthrie14_scaled.m

```
%Simulates 5 key hydrocarbons for Guthrie et al. 2014 exposure to predict rat target tissue concentrations

%Guthrie, O.W., Xu, H., Wong, B.A., McInturf, S.M., Reboulet, J.E., Ortiz, P.A. and Mattie, D.R. 2014.
%   Exposure to low levels of jet-propulsion fuel impairs brainstem encoding of stimulus intensity.
%   J Toxicol Environ Health A 77(5): 261-280.

resetdoses
rattus
toluenerat
ethylbenzenerat
xylenerat
nonanerat
decanerat
naphrat

BW=0.105; %average starting BW in Guthrie et al. 2014

VMAXC(6)=((8.28/(BW^0.75))*BW);
VMAXLUC(6)=((0.45/(BW^0.75))*BW);

%Calculates concentration of each component in POSF 4658, converted from 1000 mg/m3 to ppm, assuming STP
%Weight percent values from tandem gas chromatography analysis by the 2006 Shafer et al. method
%POSF 4658 contains 0.16 percent toluene, 0.11 percent ethylbenzene,
%   0.67 percent xylenes, 1.14 percent nonane, 2.55 percent decane, 0.12% naphthalene
%   File name: JPC5 Fuels Comparison-Reanalysis Version.xlsx

CONC(1)=((0.0016*1000)*24.45)/MW(1);
CONC(2)=((0.0011*1000)*24.45)/MW(2);
CONC(3)=((0.0067*1000)*24.45)/MW(3);
CONC(4)=((0.0114*1000)*24.45)/MW(4);
CONC(5)=((0.0255*1000)*24.45)/MW(5);
CONC(6)=((0.0012*1000)*24.45)/MW(6);

TCHNG=6.0; %Simulates 1 day of 4 week study
TSTOP=12.0;
start @nocallback

plotcven = plot (0, _t, _cven(:,1), '-b', _t, _cven(:,2), '-k');
    plot (plotcven, 1, _t, _cven(:,3), '-r', _t, _cven(:,4), '-g');
    plot (plotcven, 1, _t, _cven(:,5), '-m', _t, _cven(:,6), '-c');
plotccoc = plot (0, _t, _ccoc(:,1), '-b', _t, _ccoc(:,2), '-k');
    plot (plotccoc, 1, _t, _ccoc(:,3), '-r', _t, _ccoc(:,4), '-g');
    plot (plotccoc, 1, _t, _ccoc(:,5), '-m', _t, _ccoc(:,6), '-c');
plotcbrn = plot (0, _t, _cbrn(:,1), '-b', _t, _cbrn(:,2), '-k');
    plot (plotcbrn, 1, _t, _cbrn(:,3), '-r', _t, _cbrn(:,4), '-g');
    plot (plotcbrn, 1, _t, _cbrn(:,5), '-m', _t, _cbrn(:,6), '-c');
plotcstm = plot (0, _t, _cstm(:,1), '-b', _t, _cstm(:,2), '-k');
    plot (plotcstm, 1, _t, _cstm(:,3), '-r', _t, _cstm(:,4), '-g');
    plot (plotcstm, 1, _t, _cstm(:,5), '-m', _t, _cstm(:,6), '-c');
plotctl = plot (0, _t, _ctl(:,1), '-b', _t, _ctl(:,2), '-k');
    plot (plotctl, 1, _t, _ctl(:,3), '-r', _t, _ctl(:,4), '-g');
    plot (plotctl, 1, _t, _ctl(:,5), '-m', _t, _ctl(:,6), '-c');
plotcliv = plot (0, _t, _cliv(:,1), '-b', _t, _cliv(:,2), '-k');
```

```

        plot (plotcliv, 1, _t, _cliv(:,3), '-r', _t, _cliv(:,4), '-g');
        plot (plotcliv, 1, _t, _cliv(:,5), '-m', _t, _cliv(:,6), '-c');
    plotclu = plot (0, _t, _clu(:,1), '-b', _t, _clu(:,2), '-k');
        plot (plotclu, 1, _t, _clu(:,3), '-r', _t, _clu(:,4), '-g');
        plot (plotclu, 1, _t, _clu(:,5), '-m', _t, _clu(:,6), '-c');

set @preference=BackslashEscapes

    pltscript(plotcven, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014)
Exposure\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcven, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Venous Blood [mg/L]\";")
%    pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcven, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotcven, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotcven, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotcven, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotcven, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotcven, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotccoc, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014)
Exposure\";")
    pltscript(plotccoc, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotccoc, "Chart.SubHeader.Visible=true;")
%    pltscript(plotccoc, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotccoc, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotccoc, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotccoc, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotccoc, "Chart.Axes.Left.Title.Text=\"Cochlea [mg/L]\";")
%    pltscript(plotccoc, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotccoc, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotccoc, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotccoc, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotccoc, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotccoc, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotccoc, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotccoc, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotccoc, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotccoc, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotcbrn, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014)
Exposure\";")
    pltscript(plotcbrn, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotcbrn, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcbrn, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcbrn, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcbrn, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcbrn, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotcbrn, "Chart.Axes.Left.Title.Text=\"Remainder of the Brain [mg/L]\";")
%    pltscript(plotcbrn, "Chart.Axes.Bottom.Automatic=false;")
%    pltscript(plotcbrn, "Chart.Axes.Bottom.Minimum=0.0;")
%    pltscript(plotcbrn, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcbrn, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcbrn, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotcbrn, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotcbrn, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotcbrn, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotcbrn, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotcbrn, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotcstm, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014)
Exposure\";")
    pltscript(plotcstm, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")

```

```

    pltscript(plotcstm, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcstm, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcstm, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotcstm, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcstm, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotcstm, "Chart.Axes.Left.Title.Text=\"Brain Stem [mg/L]\";")
%   pltscript(plotcstm, "Chart.Axes.BottomAutomatic=false;")
%   pltscript(plotcstm, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcstm, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcstm, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcstm, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotcstm, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotcstm, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotcstm, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotcstm, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotcstm, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotctl, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014) Exposure\";")
    pltscript(plotctl, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotctl, "Chart.SubHeader.Visible=true;")
%   pltscript(plotctl, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotctl, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotctl, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotctl, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotctl, "Chart.Axes.Left.Title.Text=\"Temporal Lobe [mg/L]\";")
%   pltscript(plotctl, "Chart.Axes.BottomAutomatic=false;")
%   pltscript(plotctl, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotctl, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotctl, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotctl, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotctl, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotctl, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotctl, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotctl, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotctl, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotcliv, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014) Exposure\";")
    pltscript(plotcliv, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotcliv, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcliv, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcliv, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotcliv, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcliv, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotcliv, "Chart.Axes.Left.Title.Text=\"Liver [mg/L]\";")
%   pltscript(plotcliv, "Chart.Axes.BottomAutomatic=false;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcliv, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcliv, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotcliv, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotcliv, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotcliv, "Chart.Series[2].Title=\"Xylene\";")
    pltscript(plotcliv, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotcliv, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotcliv, "Chart.Series[5].Title=\"Naphthalene\";")

    pltscript(plotclu, "Chart.Header.Text = \"Predictions for Guthrie et al. (2014) Exposure\";")
    pltscript(plotclu, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotclu, "Chart.SubHeader.Visible=true;")
%   pltscript(plotclu, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotclu, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotclu, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotclu, "Chart.Axes.Left.Maximum=0.4;")
    pltscript(plotclu, "Chart.Axes.Left.Title.Text=\"Lung [mg/L]\";")
%   pltscript(plotclu, "Chart.Axes.BottomAutomatic=false;")
%   pltscript(plotclu, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotclu, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotclu, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
    pltscript(plotclu, "Chart.Series[0].Title=\"Toluene\";")
    pltscript(plotclu, "Chart.Series[1].Title=\"Ethylbenzene\";")
    pltscript(plotclu, "Chart.Series[2].Title=\"Xylene\";")

```

```

    pltscript(plotclu, "Chart.Series[3].Title=\"Nonane\";")
    pltscript(plotclu, "Chart.Series[4].Title=\"Decane\";")
    pltscript(plotclu, "Chart.Series[5].Title=\"Naphthalene\";")

set @preference=NoBackslashEscapeS

Predict_ratOEL_scaled.m

%Simulates 6 key hydrocarbons at OEL concentration for jet fuels

resetdoses
rattus
toluenerat
ethylbenzenerat
xylenerat
nonanerat
decanerat
naphrat

BW=0.25;

VMAXC(6)=((8.28/(BW^0.75))*BW);
VMAXLUC(6)=((0.45/(BW^0.75))*BW);

%Calculates concentration of each component in POSF 4658, converted from 200 mg/m3 to ppm,
assuming STP
%Weight percent values from tandem gas chromatography analysis by the 2006 Shafer et al. method
%POSF 4658 contains 0.16 percent toluene, 0.11 percent ethylbenzene,
% 0.67 percent xylenes, 1.14 percent nonane, 2.55 percent decane, 0.12% naphthalene
% File name: JPC5 Fuels Comparison-Reanalysis Version.xlsx

CONC(1)=((0.0016*200.0)*24.45)/MW(1);
CONC(2)=((0.0011*200.0)*24.45)/MW(2);
CONC(3)=((0.0067*200.0)*24.45)/MW(3);
CONC(4)=((0.0114*200.0)*24.45)/MW(4);
CONC(5)=((0.0255*200.0)*24.45)/MW(5);
CONC(6)=((0.0012*200.0)*24.45)/MW(6);

TCHNG=8.0; %Simulates 8 hour work day
TSTOP=12.0;
start @nocallback

plotcven = plot (0, _t, _cven(:,1), '-b', _t, _cven(:,2), '-k');
    plot (plotcven, 1, _t, _cven(:,3), '-r', _t, _cven(:,4), '-g');
    plot (plotcven, 1, _t, _cven(:,5), '-m', _t, _cven(:,6), '-c');
plotccoc = plot (0, _t, _ccoc(:,1), '-b', _t, _ccoc(:,2), '-k');
    plot (plotccoc, 1, _t, _ccoc(:,3), '-r', _t, _ccoc(:,4), '-g');
    plot (plotccoc, 1, _t, _ccoc(:,5), '-m', _t, _ccoc(:,6), '-c');
plotcbrn = plot (0, _t, _cbrn(:,1), '-b', _t, _cbrn(:,2), '-k');
    plot (plotcbrn, 1, _t, _cbrn(:,3), '-r', _t, _cbrn(:,4), '-g');
    plot (plotcbrn, 1, _t, _cbrn(:,5), '-m', _t, _cbrn(:,6), '-c');
plotcstm = plot (0, _t, _cstm(:,1), '-b', _t, _cstm(:,2), '-k');
    plot (plotcstm, 1, _t, _cstm(:,3), '-r', _t, _cstm(:,4), '-g');
    plot (plotcstm, 1, _t, _cstm(:,5), '-m', _t, _cstm(:,6), '-c');
plotctl = plot (0, _t, _ctl(:,1), '-b', _t, _ctl(:,2), '-k');
    plot (plotctl, 1, _t, _ctl(:,3), '-r', _t, _ctl(:,4), '-g');
    plot (plotctl, 1, _t, _ctl(:,5), '-m', _t, _ctl(:,6), '-c');
plotcliv = plot (0, _t, _cliv(:,1), '-b', _t, _cliv(:,2), '-k');
    plot (plotcliv, 1, _t, _cliv(:,3), '-r', _t, _cliv(:,4), '-g');
    plot (plotcliv, 1, _t, _cliv(:,5), '-m', _t, _cliv(:,6), '-c');
plotclu = plot (0, _t, _clu(:,1), '-b', _t, _clu(:,2), '-k');
    plot (plotclu, 1, _t, _clu(:,3), '-r', _t, _clu(:,4), '-g');
    plot (plotclu, 1, _t, _clu(:,5), '-m', _t, _clu(:,6), '-c');

set @preference=BackslashEscapeS

    pltscript(plotcven, "Chart.Header.Text = \"Predictions for OEL Exposure\";")
    pltscript(plotcven, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\";")
    pltscript(plotcven, "Chart.SubHeader.Visible=true;")
%    pltscript(plotcven, "Chart.Axes.Left.Logarithmic = true;")

```

```

    pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcven, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcven, "Chart.Axes.Left.Maximum=0.025;")
    pltscript(plotcven, "Chart.Axes.Left.Title.Text=\\"Venous Blood [mg/L]\\";")
%   pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcven, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
    pltscript(plotcven, "Chart.Series[0].Title=\\"Toluene\\";")
    pltscript(plotcven, "Chart.Series[1].Title=\\"Ethylbenzene\\";")
    pltscript(plotcven, "Chart.Series[2].Title=\\"Xylene\\";")
    pltscript(plotcven, "Chart.Series[3].Title=\\"Nonane\\";")
    pltscript(plotcven, "Chart.Series[4].Title=\\"Decane\\";")
    pltscript(plotcven, "Chart.Series[5].Title=\\"Naphthalene\\";")

    pltscript(plotccoc, "Chart.Header.Text = \\"Predictions for OEL Exposure\\";")
    pltscript(plotccoc, "Chart.SubHeader.Text = \\"5 Key Hydrocarbons in JP-8\\";")
    pltscript(plotccoc, "Chart.SubHeader.Visible=true;")
%   pltscript(plotccoc, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotccoc, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotccoc, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotccoc, "Chart.Axes.Left.Maximum=0.07;")
    pltscript(plotccoc, "Chart.Axes.Left.Title.Text=\\"Cochlea [mg/L]\\";")
%   pltscript(plotccoc, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotccoc, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotccoc, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotccoc, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
    pltscript(plotccoc, "Chart.Series[0].Title=\\"Toluene\\";")
    pltscript(plotccoc, "Chart.Series[1].Title=\\"Ethylbenzene\\";")
    pltscript(plotccoc, "Chart.Series[2].Title=\\"Xylene\\";")
    pltscript(plotccoc, "Chart.Series[3].Title=\\"Nonane\\";")
    pltscript(plotccoc, "Chart.Series[4].Title=\\"Decane\\";")
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    pltscript(plotcbrn, "Chart.Header.Text = \\"Predictions for OEL Exposure\\";")
    pltscript(plotcbrn, "Chart.SubHeader.Text = \\"5 Key Hydrocarbons in JP-8\\";")
    pltscript(plotcbrn, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcbrn, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcbrn, "Chart.Axes.Left.Automatic=false;")
    pltscript(plotcbrn, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcbrn, "Chart.Axes.Left.Maximum=0.07;")
    pltscript(plotcbrn, "Chart.Axes.Left.Title.Text=\\"Remainder of the Brain [mg/L]\\";")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcbrn, "Chart.Axes.Bottom.Title.Text=\\"Hours\\";")
    pltscript(plotcbrn, "Chart.Series[0].Title=\\"Toluene\\";")
    pltscript(plotcbrn, "Chart.Series[1].Title=\\"Ethylbenzene\\";")
    pltscript(plotcbrn, "Chart.Series[2].Title=\\"Xylene\\";")
    pltscript(plotcbrn, "Chart.Series[3].Title=\\"Nonane\\";")
    pltscript(plotcbrn, "Chart.Series[4].Title=\\"Decane\\";")
    pltscript(plotcbrn, "Chart.Series[5].Title=\\"Naphthalene\\";")

    pltscript(plotcstm, "Chart.Header.Text = \\"Predictions for OEL Exposure\\";")
    pltscript(plotcstm, "Chart.SubHeader.Text = \\"5 Key Hydrocarbons in JP-8\\";")
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%   pltscript(plotcstm, "Chart.Axes.Left.Logarithmic = true;")
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    pltscript(plotcstm, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcstm, "Chart.Axes.Left.Maximum=0.07;")
    pltscript(plotcstm, "Chart.Axes.Left.Title.Text=\\"Brain Stem [mg/L]\\";")
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%   pltscript(plotcstm, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcstm, "Chart.Axes.Bottom.Maximum=60.0;")
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    pltscript(plotcstm, "Chart.Series[2].Title=\\"Xylene\\";")
    pltscript(plotcstm, "Chart.Series[3].Title=\\"Nonane\\";")
    pltscript(plotcstm, "Chart.Series[4].Title=\\"Decane\\";")
    pltscript(plotcstm, "Chart.Series[5].Title=\\"Naphthalene\\";")

```

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    pltscript(plotctl, "Chart.Header.Text = \"Predictions for OEL Exposure\");")
    pltscript(plotctl, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\");")
    pltscript(plotctl, "Chart.SubHeader.Visible=true;")
%   pltscript(plotctl, "Chart.Axes.Left.Logarithmic = true;")
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    pltscript(plotctl, "Chart.Series[3].Title=\"Nonane\");")
    pltscript(plotctl, "Chart.Series[4].Title=\"Decane\");")
    pltscript(plotctl, "Chart.Series[5].Title=\"Naphthalene\");")

    pltscript(plotcliv, "Chart.Header.Text = \"Predictions for OEL Exposure\");")
    pltscript(plotcliv, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\");")
    pltscript(plotcliv, "Chart.SubHeader.Visible=true;")
%   pltscript(plotcliv, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotcliv, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotcliv, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotcliv, "Chart.Axes.Left.Maximum=0.025;")
    pltscript(plotcliv, "Chart.Axes.Left.Title.Text=\"Liver [mg/L]\");")
%   pltscript(plotcliv, "Chart.Axes.BottomAutomatic=false;")
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%   pltscript(plotcliv, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotcliv, "Chart.Axes.Bottom.Title.Text=\"Hours\");")
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    pltscript(plotcliv, "Chart.Series[2].Title=\"Xylene\");")
    pltscript(plotcliv, "Chart.Series[3].Title=\"Nonane\");")
    pltscript(plotcliv, "Chart.Series[4].Title=\"Decane\");")
    pltscript(plotcliv, "Chart.Series[5].Title=\"Naphthalene\");")

    pltscript(plotclu, "Chart.Header.Text = \"Predictions for OEL Exposure\");")
    pltscript(plotclu, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in JP-8\");")
    pltscript(plotclu, "Chart.SubHeader.Visible=true;")
%   pltscript(plotclu, "Chart.Axes.Left.Logarithmic = true;")
    pltscript(plotclu, "Chart.Axes.LeftAutomatic=false;")
    pltscript(plotclu, "Chart.Axes.Left.Minimum=0.0;")
    pltscript(plotclu, "Chart.Axes.Left.Maximum=0.025;")
    pltscript(plotclu, "Chart.Axes.Left.Title.Text=\"Lung [mg/L]\");")
%   pltscript(plotclu, "Chart.Axes.BottomAutomatic=false;")
%   pltscript(plotclu, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotclu, "Chart.Axes.Bottom.Maximum=60.0;")
    pltscript(plotclu, "Chart.Axes.Bottom.Title.Text=\"Hours\");")
    pltscript(plotclu, "Chart.Series[0].Title=\"Toluene\");")
    pltscript(plotclu, "Chart.Series[1].Title=\"Ethylbenzene\");")
    pltscript(plotclu, "Chart.Series[2].Title=\"Xylene\");")
    pltscript(plotclu, "Chart.Series[3].Title=\"Nonane\");")
    pltscript(plotclu, "Chart.Series[4].Title=\"Decane\");")
    pltscript(plotclu, "Chart.Series[5].Title=\"Naphthalene\");")

```

```
set @preference=NoBackslashEscapeS
```

Predict_ratOEL_Virent_50_50.m

```
%Simulates 6 key hydrocarbons at OEL concentration for JP-8 and Virent SAK 50:50 blend
```

```

resetdoses
rattus
toluenerat
ethylbenzenerat
xylenerat
nonanerat

```

```

decanerat
naphrat

BW=0.25;

VMAXC(6)=( (8.28/(BW^0.75))*BW);
VMAXLUC(6)=( (0.45/(BW^0.75))*BW);

%Calculates concentration of each component in POSF 4658 and 10326, converted from 200 mg/m3 to
ppm, assuming STP
%Weight percent values from tandem gas chromatography analysis by the 2006 Shafer et al. method
%POSF 4658 contains 0.16 percent toluene, 0.11 percent ethylbenzene,
% 0.67 percent xylenes, 1.14 percent nonane, 2.55 percent decane, 0.12% naphthalene
% File name: JPC5 Fuels Comparison-Reanalysis Version.xlsx
%10326 contains 0.3 % toluene, 0.09% nonane, 0.13% decane, 0.02% naphthalene
% 10326 contains 0.67% C2-benzenes - divided by 4 then assigned 1 part to each component
% ethylbenzene (0.17%), m-, o-, p-xylene (total = 0.05%)
% File name: 10326-Virent SAK -GCxGC w C3-Alkylbenzene speciation.xlsx
%The 50-50 blend averages the concentrations of each compounent

CONC(1)=( (0.0023*200.0)*24.45)/MW(1);
CONC(2)=( (0.0014*200.0)*24.45)/MW(2);
CONC(3)=( (0.0059*200.0)*24.45)/MW(3);
CONC(4)=( (0.0062*200.0)*24.45)/MW(4);
CONC(5)=( (0.0134*200.0)*24.45)/MW(5);
CONC(6)=( (0.0007*200.0)*24.45)/MW(6);

TCHNG=8.0; %Simulates 8 hour work day
TSTOP=12.0;
start @nocallback

plotcven = plot (0, _t, _cven(:,1), '-b', _t, _cven(:,2), '-k');
plot (plotcven, 1, _t, _cven(:,3), '-r', _t, _cven(:,4), '-g');
plot (plotcven, 1, _t, _cven(:,5), '-m', _t, _cven(:,6), '-c');
plotccoc = plot (0, _t, _ccoc(:,1), '-b', _t, _ccoc(:,2), '-k');
plot (plotccoc, 1, _t, _ccoc(:,3), '-r', _t, _ccoc(:,4), '-g');
plot (plotccoc, 1, _t, _ccoc(:,5), '-m', _t, _ccoc(:,6), '-c');
plotcbrn = plot (0, _t, _cbrn(:,1), '-b', _t, _cbrn(:,2), '-k');
plot (plotcbrn, 1, _t, _cbrn(:,3), '-r', _t, _cbrn(:,4), '-g');
plot (plotcbrn, 1, _t, _cbrn(:,5), '-m', _t, _cbrn(:,6), '-c');
plotcstm = plot (0, _t, _cstm(:,1), '-b', _t, _cstm(:,2), '-k');
plot (plotcstm, 1, _t, _cstm(:,3), '-r', _t, _cstm(:,4), '-g');
plot (plotcstm, 1, _t, _cstm(:,5), '-m', _t, _cstm(:,6), '-c');
plotctl = plot (0, _t, _ctl(:,1), '-b', _t, _ctl(:,2), '-k');
plot (plotctl, 1, _t, _ctl(:,3), '-r', _t, _ctl(:,4), '-g');
plot (plotctl, 1, _t, _ctl(:,5), '-m', _t, _ctl(:,6), '-c');
plotcliv = plot (0, _t, _cliv(:,1), '-b', _t, _cliv(:,2), '-k');
plot (plotcliv, 1, _t, _cliv(:,3), '-r', _t, _cliv(:,4), '-g');
plot (plotcliv, 1, _t, _cliv(:,5), '-m', _t, _cliv(:,6), '-c');
plotclu = plot (0, _t, _clu(:,1), '-b', _t, _clu(:,2), '-k');
plot (plotclu, 1, _t, _clu(:,3), '-r', _t, _clu(:,4), '-g');
plot (plotclu, 1, _t, _clu(:,5), '-m', _t, _clu(:,6), '-c');

set @preference=BackslashEscapes

pltscript(plotcven, "Chart.Header.Text = \"Predictions for OEL Exposure\";")
pltscript(plotcven, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in Virent SAK\";")
pltscript(plotcven, "Chart.SubHeader.Visible=true;")
% pltscript(plotcven, "Chart.Axes.Left.Logarithmic = true;")
pltscript(plotcven, "Chart.Axes.Left.Automatic=false;")
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pltscript(plotcven, "Chart.Axes.Left.Title.Text=\"Venous Blood [mg/L]\";")
% pltscript(plotcven, "Chart.Axes.Bottom.Automatic=false;")
% pltscript(plotcven, "Chart.Axes.Bottom.Minimum=0.0;")
% pltscript(plotcven, "Chart.Axes.Bottom.Maximum=60.0;")
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pltscript(plotcven, "Chart.Series[0].Title=\"Toluene\";")
pltscript(plotcven, "Chart.Series[1].Title=\"Ethylbenzene\";")
pltscript(plotcven, "Chart.Series[2].Title=\"Xylene\";")
pltscript(plotcven, "Chart.Series[3].Title=\"Nonane\";")

```

```

pltscript(plotcven, "Chart.Series[4].Title=\"Decane\";")
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pltscript(plotccoc, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in Virent SAK\";")
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%   pltscript(plotccoc, "Chart.Axes.Bottom.Maximum=60.0;")
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pltscript(plotccoc, "Chart.Series[3].Title=\"Nonane\";")
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pltscript(plotccoc, "Chart.Series[5].Title=\"Naphthalene\";")

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pltscript(plotcbrn, "Chart.SubHeader.Text = \"5 Key Hydrocarbons in Virent SAK\";")
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pltscript(plotcbrn, "Chart.Axes.Left.Maximum=0.07;")
pltscript(plotcbrn, "Chart.Axes.Left.Title.Text=\"Remainder of the Brain [mg/L]\";")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Automatic=false;")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Minimum=0.0;")
%   pltscript(plotcbrn, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plotcbrn, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
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pltscript(plotcbrn, "Chart.Series[3].Title=\"Nonane\";")
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pltscript(plotcstm, "Chart.Series[2].Title=\"Xylene\";")
pltscript(plotcstm, "Chart.Series[3].Title=\"Nonane\";")
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pltscript(plotctl, "Chart.Header.Text = \"Predictions for OEL Exposure\";")
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pltscript(plotctl, "Chart.SubHeader.Visible=true;")
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pltscript(plotctl, "Chart.Axes.Left.Maximum=0.07;")
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pltscript(plotcliv, "Chart.Series[3].Title=\"Nonane\";")
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pltscript(plotcliv, "Chart.Series[5].Title=\"Naphthalene\";")

pltscript(plotclu, "Chart.Header.Text = \"Predictions for OEL Exposure\";")
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pltscript(plotclu, "Chart.Axes.Left.Maximum=0.025;")
pltscript(plotclu, "Chart.Axes.Left.Title.Text=\"Lung [mg/L]\";")
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set @preference=NoBackslashEscapeS

```

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

ACGIH	formerly: American Conference of Governmental Industrial Hygienists
AFRL/RQTF	Air Force Research Laboratory Fuels and Energy Branch
AFWAL/POSF	Air Force Wright Aeronautical Laboratories fuel lab
APHC	Army Public Health Center
ASTM	Formerly: American Society for Testing and Materials
<i>BW</i>	body weight
CAS	central auditory system
<i>CLiv</i>	concentration of the parent compound in the liver tissue
<i>CTiss</i>	concentration in the tissue
<i>CVLiv</i>	concentration of the parent compound in the liver capillary bed
<i>CVTiss</i>	venous blood concentration within the tissue
DTIC	Defense Technical Information Center
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
GC x GC	tandem gas chromatography
HJF	Henry M. Jackson Foundation for the Advancement of Military Medicine
IV	Intravenous
JPC-5	Joint Program Committee 5
<i>Km</i>	liver tissue affinity constant
<i>KmLu</i>	lung tissue affinity constant
mg/m	milligrams/meter
NRC	National Research Council
OEL	occupational exposure limit
PA	permeability:area affinity constant
<i>PATiss</i>	permeability:area affinity constant
PBPK	physiologically-based pharmacokinetic
PC	partition coefficient
PCA	principal component analysis
<i>PLiv</i>	liver:blood partition coefficient
<i>PTiss</i>	tissue:blood partition coefficient
<i>QTiss</i>	tissue blood flow
SAK	Synthesized Aromatic Kerosene
<i>Scrub</i>	percent scrubbed by upper respiratory tract
STP	standard temperature and pressure
TLV	threshold limit value
TOX	Toxicology Directorate
TPHCWG	Total Petroleum Hydrocarbon Working Group
TWA	time-weighted average
URT	upper respiratory tract
U.S.	United States
<i>VMax</i>	liver tissue Michaelis Menten maximum velocity, normalized to BW
<i>VMaxC</i>	liver tissue Michaelis Menten maximum velocity constant
<i>VMaxLuC</i>	lung tissue Michaelis Menten maximum velocity constant
<i>VTiss</i>	tissue volume

VT_{issB}

volume of blood in the tissue