Investigation of Inter-Individual Genetic Variability with Physiologically-Based Pharmacokinetic Models and Monte Carlo Analysis

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### REPORT DOCUMENTATION PAGE

**Title:** Investigation of Inter-Individual Genetic Variability with Physiologically-Based Pharmacokinetic Models and Monte Carlo Analysis

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- Joseph Jarvis, Heather Pangburn, Darrin Ott

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**Abstract:**
Genetic variability continues to be a component of interest in assessing the expected impact of chemical exposures on human health. Until the advent of modern “omics” rapid assessment technologies, broad assessment of genetic variation on individualized outcomes was limited to single gene variants. This work enlists genetic information from the DMET™ Plus Array which contains comprehensive and accurate genotyping of specific polymorphisms involved in drug metabolism from the Coriell Personalized Medicine Collaborative. The expected impact of genetic variation in metabolic and transporter processes was assessed in relation to chemicals commonly encountered in the United States Air Force environment. Ten variants in Cytochrome P450, Family 2, Subfamily E, Polypeptide 1 (CYP2E1) were chosen for initial consideration given its in processing volatile organic chemicals. Measured CYP2E1 variation and its expected impact were then incorporated into analyses via a physiologically-based pharmacokinetic (PBPK) model to assess the likely influence on blood time course of isopropanol, acetone and toluene. The PBPK model simulations show that the predictions are influenced by incorporating information on genetic variants and would, therefore, impact predicted exposure estimates. Application of these genome-informed insights will allow a refined estimate of expected exposure response and potentially the prediction of personalized health outcomes.

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- metabolism
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- acetone
- toluene
- polymorphisms
- pilots

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When the work was conducted, Tammie R. Covington and Jeffery M. Gearhart were with FHOF, Heather A. Pangburn was with FHOF and RHDJ and Darrin K. Ott was with FHO. Joseph P. Jarvis was affiliated with Coriell Institute for Medical Research in Camden, New Jersey.
1.0 SUMMARY

Genetic variability continues to be a component of interest in assessing the expected impact of chemical exposures on human health. Until the advent of modern “omics” rapid assessment technologies, broad assessment of genetic variation on individualized outcomes was limited to single gene variants. This work enlists genetic information from the DMET™ Plus Array which contains comprehensive and accurate genotyping of specific polymorphisms involved in drug metabolism measured on approximately 2000 personnel in the Air Force Medical Service Patient-Centered Precision Care Program as implemented by the Coriell Personalized Medicine Collaborative (CPMC). The expected impact of genetic variation in metabolic and transporter processes was assessed in relation to chemicals commonly encountered in the United States Air Force (USAF) environment. Specifically, 10 putatively functional variants in Cytochrome P450, Family 2, Subfamily E, Polypeptide 1 (CYP2E1) were chosen for initial consideration given the role of this locus in processing volatile organic chemicals (VOCs) such as isopropanol, acetone and toluene. Measured CYP2E1 variation and its expected impact were then incorporated into analyses via a physiologically-based pharmacokinetic (PBPK) model to assess the likely influence of genetic variants on blood time course of isopropanol, acetone and toluene. The PBPK model simulations show that the predictions are influenced by incorporating information on genetic variants and would, therefore, impact predicted exposure estimates. Application of these genome-informed insights will allow a refined estimate of expected exposure response and potentially the prediction of personalized health outcomes.
2.0 INTRODUCTION

2.1 Background

Physiologically-based pharmacokinetic (PBPK) models are mathematical descriptions of the absorption, distribution, metabolism and excretion of chemicals in the body and allow for the incorporation of species-specific physiology, chemical-specific characteristics, and the chemical exposures of concern. They typically consist of a series of ordinary differential equations that describe the pharmacokinetics in blood and various tissues. Use of PBPK models allows for the determination of better estimates of the actual chemical dose delivered to a target tissue resulting in a particular response as opposed to estimating a response based on external dose alone [3, 4]. PBPK models alone, however, provide only deterministic estimates of the internal dose that don’t account for even basic individual variations such as body weight or breathing rates. Integrating Monte Carlo analysis with PBPK models allows for the investigation of the impact of individual variations on different exposure scenarios.

The process of combining Monte Carlo analysis with PBPK models has been previously used to investigate the composite effect of physiological variability [5, 6, 7, 8]. These studies used PBPK models and Monte Carlo analysis to investigate the impact of inter-individual variability on PBPK model predictions and the resulting calculations of regulatory safety values for perchloroethylene and methyl mercury. In a similar vein, the previous effort based on High-Performance Aircraft Respiratory Study (HPARS) was expanded to include Monte Carlo analysis to explore the potential variation in estimated pilot exposures due to individual variations in basic physiology [1]. Employing probabilistic methods enabled the use of various distributions to describe each model parameter, and allowed for the prediction of a distribution for exposure concentrations rather than single point estimates. While the distributions from this analysis begin to inform on the potential impact of inter-individual variability, they do not incorporate any information on potential genetic variations that might result in increased susceptibility for a sub-set of the population.

Over the last several decades, a great deal of research has focused on genetic variation in loci that process and transport pharmaceuticals within the body. This work in pharmacogenomics (PGx), as the field is known, has resulted in multiple commercial products geared toward the personalization of treatments that show great promise for minimizing the side effects of therapy, maximizing treatment efficacy, and improving efficiency in healthcare spending. It has also generated a variety of publicly available resources and curated knowledgebases (e.g., PharmGKB) that may be leveraged by work in other areas. For example, the very same loci that process a “voluntary” exposure to a pharmaceutical compound are involved in the body’s response to an “involuntary” chemical exposure in the workplace (e.g., volatile organic compounds (VOCs)). Thus, the rich information, tools, and techniques that have been developed for evaluating PGx genes and variants represent untapped sources of insights that may be deployed in efforts to understand war-fighter risk of negative outcomes following chemical exposures in the United States Air Force (USAF) environment.

There are published studies (e.g., carbon tetrachloride and dichloromethane) demonstrating how genetic polymorphism data may be incorporated into Monte Carlo analysis [9, 10, 11]. In particular, the dichloromethane studies incorporated evaluation of the variability in the
polymorphism affecting metabolism (glutathione-S-transferase theta 1 (GST-T1)) (Table 1) into a Monte Carlo analysis to investigate the predicted variability in tissue dose. The published studies demonstrate that the use of Monte Carlo analysis with PBPK models can be a useful means for examining the potential inter-individual variability due to genetic polymorphisms.

Table 1. Population Distributions of GST-T1 Genotypes from David et al. (2006)*

<table>
<thead>
<tr>
<th>Population</th>
<th>Genotype Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+/+</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.31</td>
</tr>
<tr>
<td>African American</td>
<td>0.28</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.47</td>
</tr>
<tr>
<td>Asian American</td>
<td>0.05</td>
</tr>
<tr>
<td>US Average</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*+” and “-” refer to the wild-type and null alleles, respectively.

2.2 Previous Work

The 711th Human Performance Wing F-22 Physiologic Analysis Team conducted a HPARS to potentially identify the etiology of the reported coughing/respiratory symptoms and mitigate one of the most common health-related complaints of F-22 flight. One unknown component of the proposed induction of coughing/respiratory symptoms that was addressed by HPARS was the collection and analysis of potential atmospheric chemicals in the cockpit air. United States Air Force School of Aerospace Medicine (USAFSAM) Bioenvironmental Engineering performed two types of air sampling: diffusive monitoring of the cockpit and exhaled breath before and after the flight. This study found a positive statistical association between respiratory effects or cough and a short list of known potentially toxic chemicals. Due to the rapid absorption of these volatile organic chemicals into the body via inhalation and often rapid clearance from the blood stream and organs shortly after cessation of exposure, an existing published PBPK model was utilized to predict the concentration range of probable inhalation exposures that could account for the post-flight exhaled breath concentrations.

The work presented here builds upon previous work [1] conducted using the existing published PBPK model of Clewell et al. [2], describing the pharmacokinetics from exposure to isopropanol and its metabolite, acetone, in conjunction with the HPARS data. The published model has flow-limited compartments for brain, fat, liver, skin and the remaining rapidly and slowly perfused tissues, plus first-order urinary excretion from blood. Due to the hydrophilic nature of isopropanol and acetone, Clewell et al. [2] assumed that some absorption in the upper respiratory tract could occur during inhalation, with subsequent desorption during exhalation. Their description of this cyclic phenomenon treats inhalation and exhalation as simultaneous and parallel processes and incorporates the reservoir effect of the mucus layer of the upper respiratory tract on exhaled air concentrations. The structure of the acetone sub-model is the same as that used for isopropanol with the exception of the absorption and desorption of acetone with breathing and urinary excretion from blood. The model provides the capability for
simulating exposure via intravenous injection, intraperitoneal administration, oral gavage, inhalation, and dermal application.

For the purposes of this work, the breathing portion of the metabolite sub-model was modified to include the absorption and desorption of acetone with breathing and to allow for simultaneous inhalation exposure to isopropanol and acetone; additional routes of exposure were not added to the metabolite sub-model as this work was only concerned with inhalation exposure. The metabolite sub-model was also modified to add urinary excretion from the blood compartment. Lastly, the complete model was modified to run in minutes instead of hours for ease in conducting the dose reconstructions. The modified model structure was then used to simulate inhalation exposure to isopropanol, acetone, toluene and cyclohexane by changing the chemical-specific parameters of the model.

For the dose reconstructions, the modified model was run to simulate exposure of various lengths starting at various times during a one hour flight. These simulations also included a 20 minute period following the flight in order to duplicate the actual delay between the end of the flight and the collection of exhaled breath samples. For each combination of length and start of exposure, the model was run and the predicted exhaled air concentration was compared to the measured exhaled breath concentrations from actual high-performance aircraft (HPA) pilots from HPARS. The simulated air concentrations were adjusted until the predicted exhaled air concentration at 80 minutes (one hour flight plus 20 minutes) matched the measured exhaled breath concentration. The estimated doses for all combinations were compiled along with the corresponding maximum blood and brain concentrations for all chemicals.

These reconstructions allowed for the determination of possible exposure distributions across a range of exposure lengths and times, or scenarios, that might be experienced by HPA pilots during flight, but did not account for differences in pharmacokinetics due to genetics that might result in increased susceptibility for a sub-set of the population.

2.3 Objectives

The long term goal of this effort is to produce pilot breathing air exposure guidelines that reduce the likelihood of coughing/respiratory symptoms or other reported symptomology. Incorporation of Monte Carlo analysis with PBPK modeling and information on relevant genetic polymorphisms allows for the investigation of the impact of inter-individual variation on toxic risk. Use of these probabilistic methods will be more informative than the deterministic methods as it enables accounting for inter-individual variability in a given population through the use of various distributions to describe each parameter, and allows for the prediction of distributions of potential exposure concentrations rather than single point estimates (Figure 1).
3.0 METHODS

3.1 CYP2E1 Genetic Variation in an Air Force Population

An inceptive study was conducted focused on 10 single nucleotide polymorphism (SNP) variants in Cytochrome P450, Family 2, Subfamily E, Polypeptide 1 (CYP2E1) that were genotyped using the Affymetrix DMET™ Plus gene chip in approximately 2200 appropriately consented USAF participants in the Coriell Personalized Medicine Collaborative (CPMC) Clinical Utility Study [12]. The CYP2E1 gene was chosen for initial consideration given its role in processing VOCs such as isopropanol, cyclohexane and aliphatic hydrocarbons. Of the 10 variants assayed, nine were bi-allelic. That is, they are known to show only two potential allelic alternatives in the human populations that have been sampled to date (e.g., A or T). One variant is known to show three potential allelic alternatives (G, C, or A) though neither the “A” nor “C” allele was observed with sufficient confidence in the USAF population. One of the bi-allelic SNPs was similarly monomorphic (i.e., showed no variation in the dataset with only the expected “reference” value present).

Since each SNP is measured independently on the DMET™ Plus Array, the precise order of allelic variants on the deoxyribonucleic acid (DNA) strand inherited from each parent (i.e., the true state of the two “haplotypes” present collectively known as the “diplotype”) is not known with certainty. Rather, it must be inferred either by matching observations to data from other populations or by one of several mathematical algorithms in a process known as “phasing”. Understanding the phase of variants in each research subject is critical to interpreting their biological significance following chemical exposure. For example, if a subject is heterozygous at two SNPs for alleles that completely eliminate enzyme function, it cannot be determined without phasing if they will have one functional and one non-functional enzyme (that is impacted...
by both variants) or two non-functional enzymes (each being impacted by one of the two null variants). The situation becomes even more complicated with larger numbers of variants at larger numbers of SNPs. In some cases, multiple interpretations of measured genotypes may be equally likely and the various possible phase states may or may not share physiological interpretations (e.g., normal metabolism).

In order to address these complications, a custom diplotyping algorithm based on phase was developed and implemented in the statistical computing language R [13] along with available data (e.g., PharmGKB, CYPalleles). This algorithm helped identify known haplotypes and resolve the independently measured genotype data into as many diplotype calls in the dataset as possible. Due to uncertainty in the cis/trans orientation of multiple heterozygotes, when necessary the algorithm assigns multiple possible metabolizer status categories to some combinations of variants. When there was a conflict, the lowest potential function was taken to represent the status for a given combination of variants. Thus, the output of the algorithm includes an assessment of all potential combinations of haplotypes along with their known/putative functions and inferred physiological categories (e.g., normal metabolism) for each individual. Specific combinations that did not fit known patterns of variation were inspected for evidence of novel haplotypes; several were identified. In all, there is evidence for as many as 21 haplotypes segregating in this population. All identified haplotypes were iteratively added to the algorithm and some level of resolution of diplotype was achieved for 2166 individuals. Eight additional individuals could not be resolved.

Little is known about the functional properties of many of the SNPs measured here with specific respect to VOCs. However, by assigning putative functional characteristics to individual haplotypes, groups of diplotypes were assigned to hypothesized metabolizer status categories (i.e., normal, reduced and very low) for use in exposure modeling. Based on a review of the literature, appropriate analogous values from other work were used to assign putative function. These final physiological groupings were used in the exposure modeling.

3.2 PBPK Model Structure

The PBPK model used for this work is a modification of a previously published PBPK model [2] describing the pharmacokinetics from exposure to isopropanol and its metabolite, acetone, and is described above in Section 2. The model was further modified to remove code for oral, dermal, and intravenous dosing as this work was primarily concerned with inhalation exposure. The modified PBPK model (Figure 2) was then used, with physiological- and chemical-specific parameters from the papers describing the models for isopropanol, acetone, toluene and cyclohexane, to validate endpoints predicted with the modified isopropanol model following exposure to these chemicals. The model is executed using the Gear algorithm in acslX (formerly available from AEgis Technologies Group, Inc., Huntsville, AL).
Figure 2. Schematic of Modified PBPK Model for Isopropanol and its Metabolite, Acetone. This schematic shows the model structure resulting from modifications to the Clewell et al. [2] model.

3.3 PBPK Model Parameters

Chemical-specific parameters were taken from papers describing the PBPK models for isopropanol, acetone, toluene and cyclohexane. The simulations use body weights taken from an Air Force (AF) biometric database [14] (pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI), physiological parameters averaged across the studies, and chemical-specific parameters. These parameters are summarized in Tables 2 and 3. The ventilation rate for the toluene model was alveolar and has been converted to a total ventilation rate in Table 2 by dividing the alveolar rate by two-thirds [15]. The exponential power used for scaling was different in the toluene model than in the isopropanol model for cardiac output, pulmonary ventilation and maximum metabolic rate; therefore, the values in Table 3 have been adjusted such that the scaled value in the simulations here would be the same as those in the toluene model for the same body weight. Parameters included in the isopropanol model (i.e., clearance parameters) which are not included in the published model for toluene [16] were set to values so as to have no effect on the model predictions (e.g., a value of zero for clearance parameters).

The toluene model of Tardif et al. [16] did not include a brain compartment but the modified isopropanol model used for the dose reconstructions does; therefore, parameter values for the brain compartment were taken from other sources: fractional brain blood flow and volume from
the isopropanol model [2] and a brain/gas partition [17] used to calculate the brain/blood partition.

**Table 2. Physiological Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isopropanol / Acetone</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>84.14(^a)</td>
<td>84.14(^a)</td>
</tr>
<tr>
<td>Cardiac output (L/min/kg(^{0.75}))</td>
<td>0.2148</td>
<td>0.24</td>
</tr>
<tr>
<td>Pulmonary ventilation (L/min/kg(^{0.75}))</td>
<td>0.4625</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Fractional Tissue Blood Flows (fraction of cardiac output)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.114(^b)</td>
<td>0.114(^b)</td>
</tr>
<tr>
<td>Fat</td>
<td>0.052</td>
<td>0.05</td>
</tr>
<tr>
<td>Liver</td>
<td>0.227</td>
<td>0.26</td>
</tr>
<tr>
<td>Rapidly perfused compartment</td>
<td>0.419</td>
<td>0.326</td>
</tr>
<tr>
<td>Slowly perfused compartment</td>
<td>0.188</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Fractional Tissue Volumes (fraction of body weight)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar blood</td>
<td>0.0079</td>
<td>0.0079(^b)</td>
</tr>
<tr>
<td>Brain</td>
<td>0.02</td>
<td>0.02(^b)</td>
</tr>
<tr>
<td>Fat</td>
<td>0.214</td>
<td>0.19</td>
</tr>
<tr>
<td>Liver</td>
<td>0.026</td>
<td>0.026</td>
</tr>
<tr>
<td>Mucous</td>
<td>0.0001(^b)</td>
<td>0.0001(^b)</td>
</tr>
<tr>
<td>Rapidly perfused compartment</td>
<td>0.036</td>
<td>0.03</td>
</tr>
<tr>
<td>Slowly perfused compartment</td>
<td>0.536</td>
<td>0.62</td>
</tr>
</tbody>
</table>

\(^a\)Average male body weights from an AF biometric database [14]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

\(^b\)Parameter not included in model for this chemical – used isopropanol/acetone model value
Table 3. Chemical-Specific Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Isopropanol</th>
<th>Acetone</th>
<th>Toluene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mole)</td>
<td>60.09</td>
<td>58.08</td>
<td>92.1384</td>
</tr>
<tr>
<td><strong>Partition Coefficients (unitless)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood/air</td>
<td>848.0</td>
<td>260.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Mucus/air</td>
<td>848.0</td>
<td>260.0</td>
<td>--a</td>
</tr>
<tr>
<td>Brain</td>
<td>1.33</td>
<td>0.69</td>
<td>2.33b</td>
</tr>
<tr>
<td>Fat</td>
<td>0.32</td>
<td>0.44</td>
<td>--a</td>
</tr>
<tr>
<td>Liver</td>
<td>1.16</td>
<td>0.58</td>
<td>5.36c</td>
</tr>
<tr>
<td>Rapidly perfused compartment</td>
<td>1.25</td>
<td>0.69</td>
<td>5.36c</td>
</tr>
<tr>
<td>Slowly perfused compartment</td>
<td>1.3</td>
<td>0.7</td>
<td>1.78c</td>
</tr>
<tr>
<td><strong>Metabolism Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum reaction rate (L/min/kg0.75)</td>
<td>5.0</td>
<td>0.0583</td>
<td>0.08</td>
</tr>
<tr>
<td>Michaelis-Menten affinity constant (mg/L)</td>
<td>10.0</td>
<td>10.0</td>
<td>0.55</td>
</tr>
<tr>
<td>First order rate constant (kg0.75/min)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Endogenous Acetone Parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration of endogenous acetone (mg/L)</td>
<td>0.0</td>
<td>0.0</td>
<td>--a</td>
</tr>
<tr>
<td>Rate of production (mg/min/kg0.75)</td>
<td>0.0</td>
<td>0.0</td>
<td>--a</td>
</tr>
<tr>
<td><strong>Uptake and Clearance Parameters (L/min/kg0.75)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary clearance</td>
<td>6.67×10⁻⁵</td>
<td>6.67×10⁻⁵</td>
<td>--a</td>
</tr>
<tr>
<td>Upper respiratory tract uptake</td>
<td>0.183d</td>
<td>0.183d</td>
<td>--a</td>
</tr>
</tbody>
</table>

aParameter not used for this chemical
bCalculated using brain/gas partition [17] and blood/air partition [16]
cTissue/blood partitions calculated from blood/air partition and tissue/air partition [16]
dThe value for upper respiratory tract uptake was adjusted for the dose reconstruction simulations to maintain the value as the same fraction of pulmonary ventilation as for the validation figures. The adjusted value is 0.172 L/min/kg0.75.

3.4 Simulations for Metabolic Variation

For purposes of demonstrating the impact of different metabolic genotypes, it was assumed that the maximum reaction rate (VMaxC) values from Table 3 would be used for “normal” metabolizers. It was determined that “reduced” and “very low” metabolizers would use one-third and one-tenth, respectively, of the “normal” value based upon the authors’ knowledge and experience with other chemicals (Table 4). Values for the Michaelis-Menten affinity constant (KM) were not altered. For each chemical and each metabolic group, the model was executed to simulate a 1-hour inhalation exposure to the chemical at the chemical’s short-term exposure limit (STEL) and the subsequent kinetics for three hours post-exposure. The STELs are 400, 1000 and 150 ppm for isopropanol, acetone and toluene, respectively.

Monte Carlo analyses were conducted by varying only VMaxC to explore the impact of variation within metabolic groups on the predicted kinetics. The analyses consisted of 10,000 iterations for each chemical for each metabolic group. The distributions for these analyses were defined using the log-space mean and standard deviation (Table 4) and were bounded at two standard
deviations. The log-space mean and standard deviation were based on a coefficient of variation (CV) of 30% to represent a moderate amount of variation.

Table 4. Adjusted VMaxC Values to Represent Genetic Polymorphisms

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Level</th>
<th>KM (mg/L)</th>
<th>VMaxC (mg/hr/kg(^{0.75}))</th>
<th>Natural Space Mean</th>
<th>Log Space Mean</th>
<th>Standard Deviation</th>
<th>Bounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>0.002333</td>
<td>0.009333</td>
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<td>0.128</td>
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<td>-3.667</td>
<td>0.2936</td>
<td>0.01067</td>
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<tr>
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<td>-4.871</td>
<td>0.2936</td>
<td>0.0032</td>
<td>0.0128</td>
</tr>
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</table>

*Corresponds to VMaxC values of 300.0, 3.5 and 4.8 mg/hr/kg\(^{0.75}\) for isopropanol, acetone and toluene, respectively [2, 16]

For further comparison, Monte Carlo analyses were also conducted for a mixed metabolizers group. This group consisted of a mix of normal, reduced and very low metabolizers. The diplotype were grouped by metabolic status (normal, reduced and very low – unknown metabolizers were not included) and the total frequency for each group was calculated. A portion of the simulations conducted for each individual metabolic status group, corresponding to the frequency for each group, were combined for a total of 10,000 iterations there were used for the mixed metabolizers output.

4.0 RESULTS AND DISCUSSION

4.1 Summary of Haplotypes

Haplotypes *1, *4, *5 and *7 were observed in the USAF cohort with *1 being the reference sequence for CYP2E1. The remaining haplotypes involve SNPs at the loci of rs2031920, rs2070672, rs2070673, rs2515641, rs3813867, rs6413419, rs6413420 and rs915909.

The *4 haplotype consists of an allelic variation from G to A at the rs6413419 locus. Three additional variations of the *4 haplotype, referred to as *4_Unk1, *4_Add_A and *4_Add_C in Table 5, were also observed with an allelic variation from T to A at the rs2070673 locus. *4_Unk1 has an additional allelic variation from C to T at the rs2515641 locus, and *4_Add_C has one from G to C at the rs3813867 locus. The activity levels are believed to be normal for *4 and decreased for *4_Add_C but are unknown for *4_Unk1 and *4_Add_A.
Allelic variations from G to C at locus rs3813867 and from C to T at locus rs2031920 define the *5 haplotype with an additional haplotype, referred to as *5_Unk1 in Table 5, having allelic variations from T to A at locus rs2070673 and from C to T at locus rs2515641. Both *5 group haplotypes exhibit a possible decrease in activity [18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28].

There were several haplotypes in the *7 group observed in the USAF cohort with all being characterized by an allelic variation from T to A at the rs2070673 locus. These haplotypes fall into one of three sub-groups: *7A, *7B and *7C. The haplotype referred to as *7A in Table 5 has no additional allelic variations, but *7A_10463 has an additional allelic variation from C to T at locus rs2515641. *7A_6498_10463 has the same variation at locus rs2515641 along with a third allelic variation from C to T at locus rs915909. The *7A haplotypes may have normal activity but the activity is unknown.

There is believed to be an increase in activity when haplotype *7A is combined with an allelic variation from G to T at locus rs6413420; this SNP defines the haplotype referred to as *7B_10463 in Table 5. The haplotype *7B is defined by the allelic variation from T to A at the rs2070673 locus and the allelic variation from G to T at locus rs6413420. These two haplotypes form the *7B sub-group and exhibit a possible increase in activity [18, 29]. It is unclear if the possible increase in activity with *7B is attributed solely to the SNP at locus rs6413420.

The *7C sub-group of haplotypes consists of haplotypes *7C, *7C_10463 and *7C_6498_10463 and are defined by the SNP at locus rs2070673 and an additional allelic variation from A to G at locus rs2070672; all exhibit a possible decrease in activity [30]. *7C_10463 and *7C_6498_10463 have an additional allelic variation at locus rs2515641 from C to T, and *7C_6498_10463 has a third SNP from C to T at locus rs915909. The decreases for the haplotypes in sub-group *7C appear to specifically relate to the rs2070672 SNP. It should be noted that *7C_10463, which is believed to exhibit a decrease in activity, only differs from *7A_10463, which has an unknown activity level, by its SNP at locus rs2070672.

There were two additional haplotypes observed in the USAF cohort; these are labeled CYP2E1_6498 and CYP2E1_10463 in Table 5. Both are believed to exhibit normal activity. Synonymous with SNP I321I, CYP2E1_6498 is defined by an allelic variation from C to T at Rs915909 and CYP2E1_10463 (synonymous with SNP F421F) from C to T at Rs2515641.

### 4.2 Population Genotype and Metabolizer Status

By applying the custom algorithm, visually inspecting results to infer the presence of novel haplotypes (i.e., those not present in the databases used to construct it), and applying appropriate quality control criteria, a total of 21 haplotypes were identified as segregating in the research sample. A total of 12 of these do not appear in standard public databases (e.g., PharmGKB) and may represent novel combinations of variants of particular military interest.

Data from a total of eight individuals could not be resolved, though the overwhelming majority of subjects (N = 2166) could be categorized. This categorization allowed the inference of the potential functional state of the two enzymes produced from the two inherited DNA sequences
based on existing data in PGx resources and the primary literature exploring CYP2E1 variation and VOC exposure specifically.

Table 5. Diplotype Frequencies

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<th>Diplotype</th>
<th>Metabolizer Status</th>
<th>N</th>
<th>Frequency</th>
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<tbody>
<tr>
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<td>*1</td>
<td>Normal</td>
<td>1360</td>
</tr>
<tr>
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<td>CYP2E1_10463</td>
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</tr>
<tr>
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<td>4</td>
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<tr>
<td>*1</td>
<td>4 Add_A or *4</td>
<td>7A</td>
<td>Normal</td>
</tr>
<tr>
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<td>Unk1 or *1</td>
<td>7A_10463 or *7A</td>
<td>CYP2E1_10463</td>
</tr>
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<td>Unk1 or *4</td>
<td>7A_10463 or *7A_10463 or *4 Add_A</td>
</tr>
<tr>
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<td>CYP2E1_6498 or *7A_10463</td>
<td>CYP2E1_6498</td>
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<td>Reduced</td>
<td>97</td>
</tr>
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<td>Reduced</td>
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<td>Reduced</td>
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Figure 3. **Diplotype and Metabolizer Status.** Figure does not show data for unknown metabolizer status.
4.3 PBPK Model Simulations

The frequencies for each metabolizer status group are 73.73%, 12.70%, 0.88% and 12.70% for normal, reduced, very low and unknown metabolic activity. Omitting those with unknown metabolic activity and recalculating the percentages results in 84.45%, 14.54% and 1.01% for normal, reduced and very low.

Figures 4, 6 and 8 show the results of the Monte Carlo analyses for each of the three metabolic groups for isopropanol, acetone and toluene, respectively. The graphs show the mean predicted venous blood and brain concentration at each time point as well as shaded regions representing the mean ± two standard deviations. For all three chemicals, the shaded regions are primarily separate with only slight overlap between the groups for some of the chemicals.

Figure 5, 7 and 9 show comparison of the Monte Carlo analyses for the normal metabolizers with mixed metabolizers. For the mixed metabolizers, 10,000 iterations were conducted with 84.45% of the metabolizers using a VMaxC based on the distribution for normal metabolizers, 14.54% based on the distribution for the reduced metabolizers, and 1.01% based on the distribution for the very low metabolizers. For all three chemicals and both endpoints the shaded region for the normal metabolizers is completely encompassed by the hashed region for the mixed metabolizers.
Figure 4. Isopropanol Monte Carlo Results for Normal, Reduced and Very Low Metabolizers. Simulations are for exposure to 400 ppm isopropanol for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal, reduced and very low metabolizers. Solid lines represent the means and the hashed areas represent ± two standard deviations.
Figure 5. Isopropanol Monte Carlo Results for Normal and Mixed Metabolizers.
Simulations are for exposure to 400 ppm isopropanol for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal and mixed metabolizers. Solid lines represent the means and the hashed and shaded areas represent ± two standard deviations.
Figure 6. Acetone Monte Carlo Results for Normal, Reduced and Very Low Metabolizers. Simulations are for exposure to 1000 ppm acetone for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal, reduced and very low metabolizers. Solid lines represent the means and the hashed areas represent ± two standard deviations.
Figure 7. Acetone Monte Carlo Results for Normal and Mixed Metabolizers. Simulations are for exposure to 1000 ppm acetone for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal and mixed metabolizers. Solid lines represent the means and the hashed and shaded areas represent ± two standard deviations.
Figure 8. Toluene Monte Carlo Results for Normal, Reduced and Very Low Metabolizers. Simulations are for exposure to 150 ppm toluene for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal, reduced and very low metabolizers. Solid lines represent the means and the hashed areas represent ± two standard deviations.
Figure 9. Toluene Monte Carlo Results for Normal and Mixed Metabolizers. Simulations are for exposure to 150 ppm toluene for one hour. Results show predicted venous blood (A) and brain (B) concentrations for normal and mixed metabolizers. Solid lines represent the means and the hashed and shaded areas represent ± two standard deviations.
5.0 CONCLUSIONS

These results demonstrate that incorporation of information on genetic variants impacts PBPK model predictions and, therefore, would impact predicted exposure estimates. The variety of resources originally developed to support PGx research thus show potential value for improving models of environmental exposure to xenobiotics in multiple environments. Improved models, in turn, will allow a refined estimate of expected exposure response and the potential for predicting personalized health outcomes. Application of such genome-informed insights may also ultimately provide an approach to sensibly and systematically set exposure guidelines that account for key biological variation in members of the exposed population. Future work incorporating a metabolic pathway approach, for example by including Cytochrome P450, Family 1, Subfamily A, Polypeptide 2 (CYP1A2) and Cytochrome P450, Family 3, Subfamily A, Polypeptide 4 (CYP3A4) in simulations, may provide additional insights. Such increasingly comprehensive genomic profiles are likely to produce additionally comprehensive assessments of the key genetic variation involved in the inactivation of potentially toxic chemicals absorbed during deployment or normal training in military populations and, thus, account for true biological variability. Therefore, in the future, a larger chemical inventory and more diverse metabolic processes need to be addressed to expand the applicability of this analysis and correlate the end results to a broader group of individuals while delivering individualized risk.
6.0 REFERENCES


APPENDIX A – acsIX Model Code

PROGRAM: GenVar_Phase1.CSL
! Simplified version of BrExp.csl

! THIS VERSION RUNS IN MINUTES INSTEAD OF HOURS !!!

INITIAL

! Physiological Parameters
CONSTANT         BW = 84.14    ! Body weight (kg)
CONSTANT         QCC = 0.2148   ! Cardiac output (L/min/kg^0.75)
CONSTANT         QPC = 0.4625   ! Total pulmonary ventilation (L/min/kg^0.75)

! Fractional Blood Flows (fraction of cardiac output)
CONSTANT       QBrnC = 0.114    ! Brain
CONSTANT       QFatC = 0.052    ! Fat
CONSTANT       QLivC = 0.227    ! Liver
CONSTANT       QRapC = 0.419    ! Rapidly perfused
CONSTANT       QSlwC = 0.188    ! Slowly perfused (includes skin)

! Fractional Tissue Volumes (fraction of body weight)
CONSTANT       VA1vc = 0.0079   ! Alveolar blood
CONSTANT       VBrnC = 0.02     ! Brain
CONSTANT       VFatC = 0.214    ! Fat
CONSTANT       VLivC = 0.026    ! Liver
CONSTANT       VMucC = 0.0001   ! Mucous
CONSTANT       VRapC = 0.036    ! Rapidly perfused
CONSTANT       VSlwC = 0.536    ! Slowly perfused (includes skin)
CONSTANT      VBodyC = 0.84     ! Sum of mean fractional volumes

! Inhalation Exposure Parameters
CONSTANT       TChng = 0.0      ! Length of inhalation exposure (min)

! Dose Timing Parameters
CONSTANT     StrtExp = 0.0      ! Time to start exposure (min)
CONSTANT      ExpEnd = 1.0      ! Time to stop all exposures (min)
CONSTANT     DoseInt = 0.0      ! Interval to repeat dosing (min)

! Simulation Control Parameters
CONSTANT       TStop = 1440.0
CINTERVAL       CINT = 0.6

! ----------------- PARENT CHEMICAL PARAMETERS ----------------------
! Molecular Weights
CONSTANT          MW = 60.09    ! Parent

! Tissue/Blood Partition Coefficients
CONSTANT         PB = 848.0    ! Blood/air
CONSTANT         PMuc = 848.0   ! Mucous/air
CONSTANT         PBrn = 1.33   ! Brain
CONSTANT         PPat = 0.32   ! Fat
CONSTANT         PLiv = 1.16   ! Liver
CONSTANT         PRap = 1.25   ! Rapidly perfused tissue
CONSTANT         PSlw = 1.30   ! Slowly perfused tissue

! Metabolism Parameters
CONSTANT       VMaxC = 5.0        ! Maximum reaction rate (mg/min/kg^0.75)
CONSTANT          KM = 10.0       ! Michaelis-Menten (mg/L)
CONSTANT         KFC = 0.0        ! First order rate constant (kg^0.25/min)

! Uptake and Clearance Parameters
CONSTANT       ClUrC = 6.67e-5   ! Urinary clearance (L/min/kg^0.75)
CONSTANT       kUrtC = 0.1833   ! URT uptake (L/min/kg^0.75)

! Endogenous Parent Production when Dosed with Parent
CONSTANT       CEndo = 0.0      ! Concentration of metabolite (mg/L)
CONSTANT       REndoC = 0.0     ! Rate of production of metabolite (mg/min/kg^0.75)

! Inhalation Exposure Parameters
CONSTANT       Conc = 0.0      ! Inhaled concentration (ppm) of parent
METABOLITE CHEMICAL PARAMETERS

Molecular Weight
CONSTANT MW_Met = 58.08
Stoch = MW_Met / MW

Tissue/Blood Partition Coefficients
CONSTANT PB_Met = 260.0  ! Blood/air
CONSTANT PMuc_Met = 260.0  ! Mucous/air
CONSTANT PBrn_Met = 0.69  ! Brain
CONSTANT PFat_Met = 0.44  ! Fat
CONSTANT PLiv_Met = 0.58  ! Liver
CONSTANT PRap_Met = 0.69  ! Rapidly perfused tissue
CONSTANT PSlw_Met = 0.70  ! Slowly perfused tissue

Metabolism Parameters
CONSTANT VMax_MetC = 0.05833  ! Maximum reaction rate (mg/min)
CONSTANT KM_Met = 10.0  ! Michaelis-Menten (mg/L)
CONSTANT KF_MetC = 0.0  ! First order rate constant (/min)

Uptake and Clearance Parameters
CONSTANT ClUr_MetC = 6.67e-5  ! Urinary clearance (L/min)
CONSTANT kUrt_MetC = 0.1833  ! URT uptake (L/min) for metabolite

Endogenous Metabolite Production when Dosed with Parent
CONSTANT CEndo_Met = 0.5  ! Concentration of metabolite (mg/L)
CONSTANT REndo_MetC = 0.00345  ! Rate of production of metabolite (mg/min)

Inhalation Exposure Parameters
CONSTANT Conc_Met = 0.0  ! Inhaled concentration (ppm) of metabolite

PARAMETER SCALING

Scaled Pulmonary Ventilation Rate (L/min)
QP = QPC * (BW**0.75)
QA.lv = 0.67 * QP

Scaled Blood Flows (L/min)
QCN = QCC * (BW**0.75)
QAdjus = QBrn + QFatC + QLiv + VRap + QSlwC
QBrn = (QBrnC / QAdjus) * QCN  ! Brain
QFat = (QFatC / QAdjus) * QCN  ! Fat
QLiv = (QLivC / QAdjus) * QCN  ! Liver
QRap = (QRapC / QAdjus) * QCN  ! Rapidly perfused tissues
QSlw = (QSlwC / QAdjus) * QCN  ! Slowly perfused tissues
QC = QBrn + QFat + QLiv + QRap + QSlw

Scaled Tissue Volumes (L)
VTotC = VAlv + VBrnC + VFatC + VLivC + VMucC + VRapC + VSlwC
VAdjus = VBodyC / VTotC
VAlv = (VAlvC * VAdjus) * BW  ! Arterial blood
VBrn = (VBrnC * VAdjus) * BW  ! Brain
VFat = (VFatC * VAdjus) * BW  ! Fat
VLiv = (VLivC * VAdjus) * BW  ! Liver
VMuc = (VMucC * VAdjus) * BW  ! Mucous
VRap = (VRapC * VAdjus) * BW  ! Rapidly perfused tissues
VSlw = (VSlwC * VAdjus) * BW  ! Slowly perfused tissues
VTot = VAlv + VBrn + VFat + VLiv + VMuc + VRap + VSlw

Scaled Metabolism Parameters
VMax = VMaxC * (BW**0.75)
KF = KFC / (BW**0.25)
REndo = REndoC * (BW**0.75)
VMax_Met = VMax_MetC * (BW**0.75)
KF_Met = KF_MetC / (BW**0.25)
REndo_Met = REndo_MetC * (BW**0.75)

Scaled Clearance Rates
ClUr = ClUrC * (BW**0.75)
kUrt = (min((kUrtC * (BW**0.75)), QA.lv))
ClUr_Met = ClUr_MetC * (BW**0.75)
kUrt_Met = (min((kUrt_MetC * (BW**0.75)), QA.lv))
! Initial Amounts of Endogenous Parent (mg) when Dosed with Parent
IAArt = CEndo * VAlv
IABrn = CEndo * VBrn * PBrn
IAFat = CEndo * VFat * PFat
IALiv = CEndo * VLiv * PLiv
IARap = CEndo * VRap * PRap
IASlw = CEndo * VSlw * PSlw
InitTot = IAArt + IABrn + IAFat + IALiv + IARap + IASlw

! Initial Amounts of Endogenous Metabolite (mg) when Dosed with Parent
IAArt_Met = CEndo_Met * VAlv
IABrn_Met = CEndo_Met * VBrn * PBrn_Met
IAFat_Met = CEndo_Met * VFat * PFat_Met
IALiv_Met = CEndo_Met * VLiv * PLiv_Met
IARap_Met = CEndo_Met * VRap * PRap_Met
IASlw_Met = CEndo_Met * VSlw * PSlw_Met
InitTot_Met = IAArt_Met + IABrn_Met + IAFat_Met + IALiv_Met + IARap_Met + IASlw_Met

! Initialize Starting Values
CIZone = 0.0
CIZone_Met = 0.0
PerEnd = 0.0
PerEnd_Met = 0.0

SCHEDULE DoseOn .AT. StrtExp
END               ! End of Initial

DYNAMIC
ALGORITHM  IALG = 2             ! Gear stiff method

DISCRETE DoseOn    ! Start dosing
SCHEDULE DoseOn .AT. T + DoseInt
SCHEDULE DoseOff .AT. T + TChng

IF ((T.LT.ExpEnd) .AND. (Conc.GT.0.0)) CIZone = 1.0
IF ((T.LT.ExpEnd) .AND. (Conc_Met.GT.0.0)) CIZone_Met = 1.0
END

DISCRETE DoseOff
CIZone = 0.0
CIZone_Met = 0.0
END

DERIVATIVE
Hours = T / 60.0
Minutes = T
Days = Hours / 24.0

! ------------------- PARENT PBPK MODEL -------------------

! Amount in Inhaled Air
CInh = ((Conc * MW) / 24450.0) * CIZone
CP = (CInh * 24450.0) / MW

! Amount in Mucous
RAMuc = kUrt * (CInh - (CMuc / PMuc) + CAlv - (CMuc / PMuc))
AMuc = INTEG(RAMuc, 0.0)
CMuc = AMuc / VMuc

! Amount Exhaled (mg)
RAExh = ((QAlv - kUrt) * CAlv) + (kUrt * (CMuc / PMuc))
AExh = INTEG(RAExh, 0.0)

! Concentration in End-Exhaled Air (mg/L)
CEnd = RAExh / QAlv
CEndPPM = CEnd * (24450.0 / MW)
IF (Conc.GT.0.0) PerEnd = (CEnd / ((Conc * MW) / 24450.0)) * 100.0

! Initialize Starting Values
CIZone = 0.0
CIZone_Met = 0.0
PerEnd = 0.0
PerEnd_Met = 0.0

SCHEDULE DoseOn .AT. StrtExp
END               ! End of Initial

DYNAMIC
ALGORITHM  IALG = 2             ! Gear stiff method

DISCRETE DoseOn    ! Start dosing
SCHEDULE DoseOn .AT. T + DoseInt
SCHEDULE DoseOff .AT. T + TChng

IF ((T.LT.ExpEnd) .AND. (Conc.GT.0.0)) CIZone = 1.0
IF ((T.LT.ExpEnd) .AND. (Conc_Met.GT.0.0)) CIZone_Met = 1.0
END

DISCRETE DoseOff
CIZone = 0.0
CIZone_Met = 0.0
END

DERIVATIVE
Hours = T / 60.0
Minutes = T
Days = Hours / 24.0

! ------------------- PARENT PBPK MODEL -------------------

! Amount in Inhaled Air
CInh = ((Conc * MW) / 24450.0) * CIZone
CP = (CInh * 24450.0) / MW

! Amount in Mucous
RAMuc = kUrt * (CInh - (CMuc / PMuc) + CAlv - (CMuc / PMuc))
AMuc = INTEG(RAMuc, 0.0)
CMuc = AMuc / VMuc

! Amount Exhaled (mg)
RAExh = ((QAlv - kUrt) * CAlv) + (kUrt * (CMuc / PMuc))
AExh = INTEG(RAExh, 0.0)

! Concentration in End-Exhaled Air (mg/L)
CEnd = RAExh / QAlv
CEndPPM = CEnd * (24450.0 / MW)
IF (Conc.GT.0.0) PerEnd = (CEnd / ((Conc * MW) / 24450.0)) * 100.0
! Amount in Arterial Blood (mg)
$$\text{RAArt} = ((QAlv - kUrt) \cdot CInh) - ((QAlv - kUrt) \cdot CAlv) + (kUrt \cdot ((CMuc/PMuc) - CAlv)) \&$$
$$+ (QC \cdot (CVen - CArt)) - \text{RAUrn}$$
$$\text{AArt} = \text{INTEG(RAArt, IAArt)}$$
$$\text{CArt} = AArt / VAlv$$
$$\text{CAlv} = \text{CArt} / PB$$
$$\text{CAlvPPM} = \text{CAlv} \cdot (24450.0 / MW)$$
$$\text{AUCCArt} = \text{INTEG(CArt, 0.0)}$$

! Amount in Urine (mg)
$$\text{RAUrn} = \text{ClUr} \cdot \text{CArt}$$
$$\text{AUrn} = \text{INTEG(RAUrn, 0.0)}$$

! Amount in Brain (mg)
$$\text{RABrn} = QBrn \cdot (\text{CArt} - CVBrn)$$
$$\text{ABrn} = \text{INTEG(RABrn, IABrn)}$$
$$\text{CBrn} = \text{ABrn} / VBrn$$
$$\text{CVBrn} = \text{CBrn} / PBrn$$
$$\text{AUCCBrn} = \text{INTEG(CBrn, 0.0)}$$

! Amount in Fat (mg)
$$\text{RAFat} = QFat \cdot (\text{CArt} - CVFat)$$
$$\text{AFat} = \text{INTEG(RAFat, IAFat)}$$
$$\text{CFat} = \text{AFat} / VFat$$
$$\text{CVFat} = \text{CFat} / PFat$$

! Amount in Liver (mg)
$$\text{RALiv} = (QLiv \cdot (\text{CArt} - CVLiv)) + \text{REndo} - \text{RAMet}$$
$$\text{ALiv} = \text{INTEG(RALiv, IALiv)}$$
$$\text{CLiv} = \text{ALiv} / VLiv$$
$$\text{CVLiv} = \text{CLiv} / PLiv$$

! Amount of Endogenous Metabolite Produced when Dosing with Metabolite
$$\text{AEndo} = \text{INTEG(REndo, 0.0)}$$

! Amount Metabolised in Liver -- Saturable and 1st Order (mg)
$$\text{RAMet} = ((VMax \cdot CVLiv) / (KM + CVLiv)) + (KF \cdot CVLiv \cdot VLiv)$$
$$\text{AMet} = \text{INTEG(RAMet, 0.0)}$$

! Amount in Rapidly Perfused Tissue (mg)
$$\text{RARap} = QRap \cdot (\text{CArt} - CVRap)$$
$$\text{ARap} = \text{INTEG(RARap, IARap)}$$
$$\text{CRap} = \text{ARap} / VRap$$
$$\text{CVRap} = \text{CRap} / PRap$$

! Amount in Slowly Perfused Tissue (mg)
$$\text{RASlw} = QSlw \cdot (\text{CArt} - CVSlw)$$
$$\text{ASlw} = \text{INTEG(RASlw, IASlw)}$$
$$\text{CSlw} = \text{ASlw} / VSlw$$
$$\text{CVSlw} = \text{CSlw} / PSlw$$

! Concentration in Mixed Venous Blood (mg/L)
$$\text{CVen} = (QBrn*CVBrn + QFat*CVFat + QLiv*CVLiv + QRap*CVRap + QSlw*CVSlw) / QC$$
$$\text{AUCCVen} = \text{INTEG(CVen, 0.0)}$$

! ----------------- ACETONE PBPK MODEL-------------------------------

! Amount In Inhaled Air
$$\text{CInh\_Met} = ((\text{Conc\_Met} \cdot MW\_Met) / 24450.0) \cdot CIZone\_Met$$
$$\text{CP\_Met} = (\text{CInh\_Met} * 24450.0) / MW\_Met$$

! Amount in Mucous
$$\text{RAMuc\_Met} = kUrt\_Met \cdot (\text{CInh\_Met} - (\text{CMuc\_Met} / PMuc\_Met) + \text{CALv\_Met} - (\text{CMuc\_Met} / PMuc\_Met))$$
$$\text{AMuc\_Met} = \text{INTEG(RAMuc\_Met, 0.0)}$$
$$\text{CMuc\_Met} = \text{AMuc\_Met} / VMuc$$

! Amount Exhaled (mg)
$$\text{RAExh\_Met} = ((QAlv - kUrt\_Met) \cdot \text{CALv\_Met}) + (kUrt\_Met \cdot (\text{CMuc\_Met} / PMuc\_Met))$$
$$\text{AExh\_Met} = \text{INTEG(RAExh\_Met, 0.0)}$$
! Concentration in End-Exhaled Air (mg/L)
CEnd_Met = RAExh_Met / QAlv
CEndPPM_Met = CEnd_Met * (24450.0 / MW_Met)
IF (Conc_Met.GT.0.0) PerEnd_Met = (CEnd_Met / ((Conc_Met * MW_Met) / 24450.0)) * 100.0

! Amount in Arterial Blood (mg)
RAArt_Met = ((QAlv - kUrt_Met) * CInh_Met) - ((QAlv - kUrt_Met) * CAlv_Met) &
& + (kUrt_Met * (CMuc_Met / PMuc_Met - CAlv_Met)) + (QC * (CVen_Met - CArt_Met)) &
& - RAUrn_Met
AArt_Met = INTEG(RAArt_Met, IAArt_Met)
CArt_Met = AArt_Met / VAlv
CAlv_Met = CArt_Met / PB_Met
CAlvPPM_Met = CAlv_Met * (24450.0 / MW_Met)
AUCCArt_Met = INTEG(CArt_Met, 0.0)

! Amount in Urine (mg)
RAUrn_Met = ClUr_Met * CArt_Met
AUrn_Met = INTEG(RAUrn_Met, 0.0)

! Amount in Brain (mg)
RABrn_Met = QBrn * (CArt_Met - CVBrn_Met)
ABrn_Met = INTEG(RABrn_Met, IABrn_Met)
CBrn_Met = ABrn_Met / VBrn
CVBrn_Met = CBrn_Met / PBrn_Met
AUCCBrn_Met = INTEG(CBrn_Met, 0.0)

! Amount in Fat (mg)
RAFat_Met = QFat * (CArt_Met - CVFat_Met)
AFat_Met = INTEG(RAFat_Met, IAFat_Met)
CVFat_Met = CFat_Met / PFat_Met

! Amount in Liver (mg)
RALiv_Met = (QLiv * (CArt_Met - CVLiv_Met)) + (Stoch * RAMet) + REndo_Met = RAMet_Met
ALiv_Met = INTEG(RALiv_Met, IALiv_Met)
CVLiv_Met = CLiv_Met / PLiv_Met
AUCCLiv_Met = INTEG(CLViv_Met, 0.0)

! Amount of Endogenous Metabolite Produced when Dosing with Parent
AEndo_Met = INTEG(REndo_Met, 0.0)

! Amount Metabolised in Liver -- Saturable and 1st Order (mg)
RAMet_Met = ((VMax_Met * CVLiv_Met) / (KM_Met + CVLiv_Met)) + (KF_Met * CVLiv_Met * VLiv)
AMet_Met = INTEG(RAMet_Met, 0.0)

! Amount in Rapidly Perfused Tissue (mg)
RARap_Met = QRap * (CArt_Met - CVRap_Met)
ARap_Met = INTEG(RARap_Met, IARap_Met)
CRap_Met = ARap_Met / VRap
CVRap_Met = CRap_Met / PRap_Met

! Amount in Slowly Perfused Tissue (mg)
RASlw_Met = QSlw * (CArt_Met - CVSlw_Met)
ASlw_Met = INTEG(RASlw_Met, IASlw_Met)
CVSlw_Met = CSLw_Met / VSlw
CSlw_Met = ASlw_Met / PSlw_Met

! Concentration in Mixed Venous Blood (mg/L)
CVen_Met = (QBrn*CVBrn_Met + QFat*CVFat_Met + QLiv*CVLiv_Met + QRap*CVRap_Met &
& + QSlw*CVSlw_Met) / QC
AUCCVen_Met = INTEG(CVen_Met, 0.0)

! ----------------- CHECK MASS BALANCE ------------------------------
TDose = INTEG((QAlv*CInh), 0.0)
Parent = AMuc + AArt + ABrn + AFat + ALiv + ARap + ASlw + AEExh + AUrn + AMet - InitTot &
& - AEndo
Metabolite = AMuc_Met + AArt_Met + ABrn_Met + AFat_Met + ALiv_Met + ARap_Met + ASlw_Met &
& + AEExh_Met &
& + AUrn_Met + AMet_Met - InitTot_Met - AEndo_Met
MassBal = TDose - Parent
MetBal = INTEG((QAlv*CInh_Met), 0.0) + (AMet * Stoch) - Metabolite
TERMT(T.GE.TStop, 'Simulation Finished')
END ! End of Derivative
END ! End of Dynamic
END ! End of Program
APPENDIX B – Utility M Files for Simulations

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

Acetone.m
% Sets human acetone parameters
% kUrtC set to keep original value of kUrtC the same fraction of QPC as from the original IPA paper (i.e., 11.0/27.75)

MW=58.08;
Pb=260.0; PmuC=260.0; PbRn=0.69; PfAT=0.44; Pliv=0.58; PrAP=0.69; Pslw=0.7;
VMAXC=3.5/60.0; Km=10.0; Kfc=0.0;
ClURC=0.004/60.0; KURTC=(11.0/27.75)*QPC;
Cendo=0.5; Rendo=0.207/60.0;

MW_MET=1.0;
Pb_MET=1.0; Pb_MUC=1.0; PbRn_MET=1.0; PfAT_MET=1.0; Pliv_MET=1.0; PrAP_MET=1.0; Pslw_MET=1.0;
VMAX_METC=0.0; Km_MET=1.0; Kf_METC=0.0;
ClUR_METC=0.0; KURT_METC=0.0;
Cendo_MET=0.5; Rendo_METC=0.207/60.0;

IPA.m
% Sets human isopropanol parameters
% kUrtC set to keep original value of kUrtC the same fraction of QPC as from the original IPA paper (i.e., 11.0/27.75)

MW=60.09;
Pb=848.0; PmuC=848.0; PbRn=1.33; PfAT=0.32; Pliv=1.16; PrAP=1.25; Pslw=1.3;
VMAXC=300.0/60.0; Km=10.0; Kfc=0.0;
ClURC=0.004/60.0; KURTC=(11.0/27.75)*QPC;
Cendo=0.0; Rendo=0.0;

MW_MET=58.08;
Pb_MET=260.0; PmuC_MET=260.0; PbRn_MET=0.69; PfAT_MET=0.44; Pliv_MET=0.58; PrAP_MET=0.69;
Pslw_MET=0.7;
VMAX_METC=3.5/60.0; Km_MET=10.0; Kf_METC=0.0;
ClUR_METC=0.004/60.0; KURT_METC=(11.0/27.75)*QPC;
Cendo_MET=0.5; Rendo_METC=0.207/60.0;

Toluene.m
% MW (molecular weight) is from NIST Chemistry Webbook
% PbRN from Eric's toluene model (tissue/gas value of 36.4 as given in Fiserova-Bergerova et al. (1984))
% Remaining parameters are from Tardif et al. (1997, 1995)

MW=92.1384;
Ds=0.15;
Pb=15.6; PmuC=1.0; PbRN=36.4/PB; PfAT=1021.0/PB; Pliv=83.6/PB; PrAP=83.6/PB; Pslw=27.7/PB;
VMAXC=4.8/60.0; Km=0.55; Kfc=0.0;
ClURC=0.0; KURTC=0.0;
Cendo=0.0; Rendo=0.0;

MW_MET=1.0;
Ds_MET=0.5;
Pb_MET=1.0; Pb_MUC=1.0; PbRN_MET=1.0; PfAT_MET=1.0; Pliv_MET=1.0; PrAP_MET=1.0; Pslw_MET=1.0;
VMAX_METC=0.0; Km_MET=1.0; Kf_METC=0.0;
ClUR_METC=0.0; KURT_METC=0.0;
Cendo_MET=0.0; Rendo_METC=0.0;
Distrib_Acetone.m
% Called through MC_Anal.m in MC_by_Group.m

if (Group == 'Normal ')
    % VMAXC of 0.05833 mg/min/kg^0.75 (3.5 mg/hr/kg^0.75)
    VMAXC = 0 + 1 * lognrnd(-2.8847, 0.29356, 0.023333, 0.093333);
else
    if (Group == 'Reduced')
        % VMAXC of 0.0194445 mg/min/kg^0.75 (1/3 of normal) (1.6667 mg/hr/kg^0.75)
        VMAXC = 0 + 1 * lognrnd(-3.9833, 0.29356, 0.0077776, 0.0311104);
    else
        if (Group == 'VeryLow')
            % VMAXC of 0.005833 mg/min/kg^0.75 (1/10 of normal) (0.35 mg/hr/kg^0.75)
            VMAXC = 0 + 1 * lognrnd(-5.1873, 0.29356, 0.0023333, 0.0093333);
        end
    end
end

Distrib_IPA.m
% Called through MC_Anal.m in MC_by_Group.m

if (Group == 'Normal ')
    % VMAXC of 5.0 mg/min/kg^0.75 (300.0 mg/hr/kg^0.75)
    VMAXC = 0 + 1 * lognrnd(1.5663, 0.29356, 2.0, 8.0);
else
    if (Group == 'Reduced')
        % VMAXC of 1.666666667 mg/min/kg^0.75 (1/3 of normal) (100.0 mg/hr/kg^0.75)
        VMAXC = 0 + 1 * lognrnd(0.4678, 0.29356, 0.66668, 2.66672);
    else
        if (Group == 'VeryLow')
            % VMAXC of 0.5 mg/min/kg^0.75 (1/10 of normal) (30.0 mg/hr/kg^0.75)
            VMAXC = 0 + 1 * lognrnd(-0.7362, 0.29356, 0.2, 0.8);
        end
    end
end

Distrib_Toluene.m
% Called through MC_Anal.m in MC_by_Group.m

if (Group == 'Normal ')
    % VMAXC of 0.08 mg/min/kg^0.75 (4.8 mg/hr/kg^0.75)
    VMAXC = 0 + 1 * lognrnd(-2.5688, 0.29356, 0.032, 0.128);
else
    if (Group == 'Reduced')
        % VMAXC of 0.026667 mg/min/kg^0.75 (1/3 of normal) (1.6 mg/hr/kg^0.75)
        VMAXC = 0 + 1 * lognrnd(-3.6674, 0.29356, 0.010667, 0.042667);
    else
        if (Group == 'VeryLow')
            % VMAXC of 0.008 mg/min/kg^0.75 (1/10 of normal) (0.48 mg/hr/kg^0.75)
            VMAXC = 0 + 1 * lognrnd(-4.8714, 0.29356, 0.0032, 0.0128);
        end
    end
end
Init.m

prepare T HOURS MINUTES DAYS CART CALV CALVPPM AEIX CEND CENDPPM PEREND AMET CVEN MASSBAL
prepare CART_MET CALVPPM_MET AEIX_MET CENDPPM_MET AMET_MET CVEN_MET METBAL
prepare AMUC AART AURN ABRN AFAT ALIV ARAP ASLW CBRN CFAT CLIV CMUC CRAP CSLW
prepare AMUC_MET AART_MET AURN_MET ABRN_MET AFAT_MET ALIV_MET ARAP_MET ASLW_MET CBRN_MET CFAT_MET
CLIV_MET CMUC_MET CRAP_MET CSLW_MET

HVDPRN=0;
WESITG=0;

ResetDoses.m

TCHNG=0.0;
STRTEXP=0.0; EXPEND=1.0; DOSEINT=1.0;
CINT=0.5;
CONC=0.0;
CONC_MET=0.0;

MC by Group.m
% MC analysis -- 4-hr simulation with 1-hr exposure at the STEL (400 ppm for IPA, 1000 ppm for acetone and 150 ppm for toluene)
% Calls Start_MC_IPA, Start_MC_Acetone, Start_MC_Toluene, MC_Init.m, MC_Anal.m and MC_Sum_Mixed

% IPA ------------------------------------------------------------------------------------------------------------------------------------------------------------
% Normal metabolizers
Start_MC_IPA
Group = 'Normal '; NumMetab = round(PerNorm * NumIts); PMnumMetab = 1; VMAXC=5.0; MC_Init
MC_Anal
load @format=model @file=Revised_IPA_Model

% Reduced metabolizers
Start_MC_IPA
Group = 'Reduced'; PMnumMetab = round(PerNorm * NumIts) + 1; NumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts); VMAXC=1.6667;
MC_Init
MC_Anal
load @format=model @file=Revised_IPA_Model

% Very low metabolizers
Start_MC_IPA
Group = 'VeryLow'; PMnumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts) + 1; NumMetab = round(PerNorm*NumIts) + round(PerReduced*NumIts) + round(PerVeryLow*NumIts); VMAXC=0.5;
MC_Init
MC_Anal
load @format=model @file=Revised_IPA_Model

% Population of normal, reduced and very low metabolizers
Start_MC_IPA
MC_Sum_Mixed
load @format=model @file=Revised_IPA_Model

% Acetone ------------------------------------------------------------------------------------------------------------------------------------------------------------
% Normal metabolizers
Start_MC_Acetone
Group = 'Normal '; PMnumMetab = 1; NumMetab = round(PerNorm * NumIts); VMAXC=0.058333;
MC_Init
MC_Anal
load @format=model @file=Revised_IPA_Model
% Reduced metabolizers
Start_MC_Acetone
Group = 'Reduced'
PNumMetab = round(PerNorm * NumIts) + 1;
NumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts);
VMAXC=0.019445;
MC_Init
MC_Anal
load @format-model @file=Revised_IPA_Model

% Very low metabolizers
Start_MC_Acetone
Group = 'VeryLow'
PNumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts) + 1;
NumMetab = round(PerNorm*NumIts) + round(PerReduced*NumIts) + round(PerVeryLow*NumIts);
VMAXC=0.0058333;
MC_Init
MC_Anal
load @format-model @file=Revised_IPA_Model

% Population of normal, reduced and very low metabolizers
Start_MC_Acetone
MC_Sum_Mixed
load @format-model @file=Revised_IPA_Model

% Toluene

% Normal metabolizers
Start_MC_Toluene
Group = 'Normal'
NumMetab = round(PerNorm * NumIts);
PNumMetab = 1;
VMAXC=0.08;
MC_Init
MC_Anal
load @format-model @file=Revised_IPA_Model

% Reduced metabolizers
Start_MC_Toluene
Group = 'Reduced'
PNumMetab = round(PerNorm * NumIts) + 1;
NumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts);
VMAXC=0.026667;
MC_Init
MC_Anal
load @format-model @file=Revised_IPA_Model

% Very low metabolizers
Start_MC_Toluene
Group = 'VeryLow'
PNumMetab = round(PerNorm * NumIts) + round(PerReduced * NumIts) + 1;
NumMetab = round(PerNorm*NumIts) + round(PerReduced*NumIts) + round(PerVeryLow*NumIts);
VMAXC=0.008;
MC_Init
MC_Anal

% Population of normal, reduced and very low metabolizers
Start_MC_Toluene
MC_Sum_Mixed
load @format-model @file=Revised_IPA_Model
Start_MC_Acetone.m

% Called by MC_by_Group.m

load @format=model @file=GenVar_Phase1

% Set parameters for simulations -- WITHOUT endogenous acetone production
% BW is average from Air Force database (from e-mail from Jeff Hudson)
% Remaining parameters are from IPA published model
Init
ResetDoses
ChemName = 'Ace';
Acetone
BW=84.14; QCC=12.89/60.0; QPC=27.75/60.0; QBRNC=0.114; QFATC=0.052; QLIVC=0.227; QRAPC=0.419;
QSLWC=0.188;
VALVC=0.0079; VBRNC=0.02; VFATC=0.214; VLIVC=0.026; VNMUC=0.0001; VRAPC=0.036; VSLWC=0.536;
VBOYC=0.84;
CONC=1000.0; TCHNG=60.0; TSTOP=240.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=250.0;
CENDO=0.0; RENDOC=0.0;
CINT=0.1;
NumIts = 10000;

% Percent of individuals per metabolic group (omit those with unknown metabolic activity and
% recalculate percentages)
PerNorm = 0.8445;
PerReduced = 0.1454;
PerVeryLow = 0.0101;
cven_mixed = []; cbrn_mixed = [];

Start_MC_IPA.m

% Called by MC_by_Group.m

load @format=model @file=GenVar_Phase1

% Set parameters for simulations -- WITHOUT endogenous acetone production
% BW is average from Air Force database (from e-mail from Jeff Hudson)
% Remaining parameters are from IPA published model
Init
ResetDoses
ChemName = 'IPA';
IPA
BW=84.14; QCC=12.89/60.0; QPC=27.75/60.0; QBRNC=0.114; QFATC=0.052; QLIVC=0.227; QRAPC=0.419;
QSLWC=0.188;
VALVC=0.0079; VBRNC=0.02; VFATC=0.214; VLIVC=0.026; VNMUC=0.0001; VRAPC=0.036; VSLWC=0.536;
VBOYC=0.84;
CONC=400.0; TCHNG=60.0; TSTOP=240.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=250.0;
CENDO_MET=0.0; RENDO_METC=0.0;
CINT=0.1;
NumIts = 10000;

% Percent of individuals per metabolic group (omit those with unknown metabolic activity and
% recalculate percentages)
PerNorm = 0.8445;
PerReduced = 0.1454;
PerVeryLow = 0.0101;
cven_mixed = []; cbrn_mixed = [];
**Start_MC_Toluene.m**

% Called by MC_by_Group.m

        load @format=model @file=GenVar_Phase1

% Set parameters for simulations -- WITHOUT endogenous acetone production
% BW is average from Air Force database (from e-mail from Jeff Hudson)
% QBRn and VBn are values from IPA model -- Tardif model did not have a brain compartment
% Remaining parameters are from Tardif et al. (1997, 1995)
% Adjusted QCC value from (18.0/60.0) to (14.4/60.0) so that IPA model scaling by BW to the 0.75
% gets same value as Tardiff who uses 0.7
% Adjusted QPC value from (18.0/60.0/(2/3)) to (14.4/60.0/(2/3)) so that IPA model scaling by BW
% to the 0.75 gets same value as Tardiff who uses 0.7

Init
ResetDoses
ChemName = 'Tol';
Toluene
BW=84.14; QCC=14.4/60.0; QPC=14.4/60.0/(2/3); QBRN=0.114; QFATC=0.05; QLIVC=0.26;
QRAPC=0.44-QBRN; QSLWC=0.25;
VALVC=0.0079; VBRNC=0.02; VFATC=0.19; VLIVC=0.026; VMUCC=0.0001; VRAFC=0.05-VBRNC; VSLWC=0.62;
VBODYC=0.8940;
CONC=150.0; TCHNG=60.0; TSTOP=240.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=250.0;
CINT=0.1;
NumIts = 10000;

% Percent of individuals per metabolic group (omit those with unknown metabolic activity and
% recalculate percentages)
PerNorm = 0.8445;
PerReduced = 0.1454;
PerVeryLow = 0.0101;

cven_mixed = []; cbrn_mixed = [];

**MC_Init.m**

% Run to get baseline values for MC analysis

% Called in MC_by_Group.m

% Initialize array
    cven_th = []; final = []; massbal_th = [];

% Make first run
    start @NoCallback
    cven_th = _hours;
    cven_th = addcolsj(cven_th, _cven, @Justification = 'begin');
    cven_th = addcolsj(cven_th, _cbrn, @Justification = 'begin');

    if (ChemName == 'IPA')
        cven_th = addcolsj(cven_th, _cven_met, @Justification = 'begin');
        cven_th = addcolsj(cven_th, _cbrn_met, @Justification = 'begin');
    end

    final = [final AUCCVEN];
    final = [final AUCCBRN];

    if (ChemName == 'IPA')
        final = [final AUCCVEN_MET];
        final = [final AUCCBRN_MET];
    end

% Save mass balance to check for validity of run
    massbal_th(1, 1) = max(_massbal);
    massbal_th(2, 1) = min(_massbal);

    SaveInitOutput
    cven_th = []; final = []; massbal_th = [];
SaveInitOutput.m

% Save output to text files
% Contents of files based on file names where
% * = "ipa", "acetone" or "toluene", and
% ** = "normal", "reduced" or "verylow"
% mc_*_**_baseline.txt - time course output for endpoints
% mc_*_**_baseline_final.txt - final endpoint values
% mc_*_**_baseline_mb.txt - minimum and maximum mass balance values

if (ChemName == 'IPA')
    if (Group == 'Normal ')
        save cven_th @file='mc_ipa_normal_baseline.txt' @format=ascii
        save final @file='mc_ipa_normal_baseline_final.txt' @format=ascii
        save massbal_th @file='mc_ipa_normal_baseline_mb.txt' @format=ascii
    else
        if (Group == 'Reduced')
            save cven_th @file='mc_ipa_reduced_baseline.txt' @format=ascii
            save final @file='mc_ipa_reduced_baseline_final.txt' @format=ascii
            save massbal_th @file='mc_ipa_reduced_baseline_mb.txt' @format=ascii
        else
            if (Group == 'VeryLow')
                save cven_th @file='mc_ipa_verylow_baseline.txt' @format=ascii
                save final @file='mc_ipa_verylow_baseline_final.txt' @format=ascii
                save massbal_th @file='mc_ipa_verylow_baseline_mb.txt' @format=ascii
            end
        end
    end
else
    if (ChemName == 'Ace')
        if (Group == 'Normal ')
            save cven_th @file='mc_acetone_normal_baseline.txt' @format=ascii
            save final @file='mc_acetone_normal_baseline_final.txt' @format=ascii
            save massbal_th @file='mc_acetone_normal_baseline_mb.txt' @format=ascii
        else
            if (Group == 'Reduced')
                save cven_th @file='mc_acetone_reduced_baseline.txt' @format=ascii
                save final @file='mc_acetone_reduced_baseline_final.txt' @format=ascii
                save massbal_th @file='mc_acetone_reduced_baseline_mb.txt' @format=ascii
            else
                if (Group == 'VeryLow')
                    save cven_th @file='mc_acetone_verylow_baseline.txt' @format=ascii
                    save final @file='mc_acetone_verylow_baseline_final.txt' @format=ascii
                    save massbal_th @file='mc_acetone_verylow_baseline_mb.txt' @format=ascii
                end
            end
        end
    else
        if (ChemName == 'Tol')
            if (Group == 'Normal ')
                save cven_th @file='mc_toluene_normal_baseline.txt' @format=ascii
                save final @file='mc_toluene_normal_baseline_final.txt' @format=ascii
                save massbal_th @file='mc_toluene_normal_baseline_mb.txt' @format=ascii
            else
                if (Group == 'Reduced')
                    save cven_th @file='mc_toluene_reduced_baseline.txt' @format=ascii
                    save final @file='mc_toluene_reduced_baseline_final.txt' @format=ascii
                    save massbal_th @file='mc_toluene_reduced_baseline_mb.txt' @format=ascii
                else
                    if (Group == 'VeryLow')
                        save cven_th @file='mc_toluene_verylow_baseline.txt' @format=ascii
                        save final @file='mc_toluene_verylow_baseline_final.txt' @format=ascii
                        save massbal_th @file='mc_toluene_verylow_baseline_mb.txt' @format=ascii
                    end
                end
            end
        end
    end
end
end
end
MC_Anal.m

% MC analysis for genetic variability Phase 1 work

% Called in MC_by_Group.m

final = [];  good_params = [];  min_tiss_th = [];  massbal_th = [];  cven_th = [];  cbrn_th = [];
failed_params = [];  mb_maxmin_fail = [];  min_tiss_fail = [];
NumFails = 0;

% Define parameters for number of iterations for Monte Carlo
NumIts2 = NumIts*2;  NumSims = 0;

% Initialize random seed
seedrnd(969960349, 890917552);

% Start Monte Carlo analysis
for iter = [1 : NumIts2]
    if (ChemName == 'IPA')
        Distrib_IPA
    else
        if (ChemName == 'Ace')
            Distrib_Acetone
        else
            if (ChemName == 'Tol')
                Distrib_Toluene
            end
        end
    end
end

disp(sprintf("Starting MC Iteration #\%d of \%d", iter, NumIts2));
disp("-----------------------------");
start @NoCallback
mins_th = [];
if (ChemName == 'IPA')
    mins_th(:, :) = [mins_th min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
                    min(_afat) min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)
                    min(_amuc_met) min(_aexh_met) min(_aart_met) min(_aurn_met)
                    min(_abrn_met) min(_afat_met) min(_aliv_met) min(_amet_met)
                    min(_arap_met) min(_aslw_met) min(_cven_met)];
else
    mins_th(:, :) = [mins_th min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
                    min(_afat) min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)];
end

% Check mass balances to make sure simulation is valid
% If simulation is valid, move on to next iteration
if (T >= TSTOP & max(_massbal) < 0.00000001 & min(_massbal) > -0.00000001 & min(min(mins_th)) >= 0.0)
    NumSims = NumSims + 1;
disp(sprintf("Finished MC Simulation #\%d of \%d", NumSims, NumIts));
disp("-----------------------------");
params = [];
min_tiss_th = addcolsj(min_tiss_th, mins_th, @Justification = 'begin');
massbal_th = addcolsj(massbal_th, _massbal, @Justification = 'begin');
cven_th = addcolsj(cven_th, _cven, @Justification = 'begin');
cbrn_th = addcolsj(cbrn_th, _cbrn, @Justification = 'begin');
params(:, :) = (params VMAXC);
good_params = addcolsj(good_params, params, @Justification = 'begin');
params = [];
mins_th = [];
end

% If simulation is NOT valid, save failed parameter set, minimum tissue values and mass
% balance values
else
    NumFails = NumFails + 1;
    mins_fail = [];
    params = [];
end
if (ChemName == 'IPA')
    mins_fail(:, :) = [mins_fail min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
    min(_afat) min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)
    min(_amuc_met) min(_aexh_met) min(_aart_met) min(_aurn_met)
    min(_abrn_met) min(_afat_met) min(_aliv_met) min(_amet_met)
    min(_arap_met) min(_aslw_met) min(_cven_met)];
else
    mins_fail(:, :) = [mins_fail min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
    min(_afat) min(_aliv) min(_amet) min(_arap) min(_aslw)
    min(_cven)];
end

min_tiss_fail = adaddclosj(min_tiss_fail, mins_fail, @Justification = 'begin');
params(:, :) = [params VMAXC];
failed_params = adaddclosj(failed_params, params, @Justification = 'begin');
mb_maxmin_fail(1, NumFails) = max(max(_massbal));
params = []; mins_fail = []; mins_th = [];
end

if desired number of valid simulations have been completed, exit loop
if (NumSims == NumIts)
    break;
end

disp(sprintf("Ran %d simulations to get output for %d simulations", iter, NumIts));

% Save a percentage of iterations to array for mixed population calculations
for iter = [PNumMetab : NumMetab]
    i = iter;
    vmaxc_mixed(i, 1) = good_params(1, i);
end
PNumMetab = NumMetab + 1;

for iter = [PNumMetab : NumIts]
    i = iter;
    vmaxc_mixed(i, 1) = 0.0;
end

if (Group == 'Normal ')
    save vmaxc_mixed @file='mc_normal_vmaxc_mixed.txt' @format=ascii
else
    if (Group == 'Reduced')
        save vmaxc_mixed @file='mc_reduced_vmaxc_mixed.txt' @format=ascii
    else
        if (Group == 'VeryLow')
            save vmaxc_mixed @file='mc_verylow_vmaxc_mixed.txt' @format=ascii
        end
    end
end
vmaxc_mixed = [];

% Transpose matrix of time courses for endpoint to calculate statistics
[nrows, ncols] = size(cven_th);
i = 1; j = 1;
while i <= ncols
    while j <= nrows
        trans_cven_th(i, j) = cven_th(j, i);
        trans_cbrn_th(i, j) = cbrn_th(j, i);
        j = j + 1;
    end
    i = i + 1;
    j = 1;
end
cven_th = []; cbrn_th = [];
% Calculate statistics for fixed dose, exposure length and start time for exposure
mean_cven_th = mean(trans_cven_th);
std_cven_th = std(trans_cven_th);
max_cven_th = max(trans_cven_th);
min_cven_th = min(trans_cven_th);
mean_cbrn_th = mean(trans_cbrn_th);
std_cbrn_th = std(trans_cbrn_th);
max_cbrn_th = max(trans_cbrn_th);
min_cbrn_th = min(trans_cbrn_th);
trans_cven_th = [];
trans_cbrn_th = [];

% Save statistics to one array to be saved
i = 1;
while i <= nrows
    stats(i,1) = mean_cven_th(i);
    stats(i,2) = std_cven_th(i);
    stats(i,3) = mean_cven_th(i) + (2 * std_cven_th(i));
    stats(i,4) = mean_cven_th(i) - (2 * std_cven_th(i));
    stats(i,5) = max_cven_th(i);
    stats(i,6) = min_cven_th(i);
    stats(i,7) = mean_cbrn_th(i);
    stats(i,8) = std_cbrn_th(i);
    stats(i,9) = mean_cbrn_th(i) + (2 * std_cbrn_th(i));
    stats(i,10) = mean_cbrn_th(i) - (2 * std_cbrn_th(i));
    stats(i,11) = max_cbrn_th(i);
    stats(i,12) = min_cbrn_th(i);
    i = i + 1;
end
mean_cven_th = [];
std_cven_th = [];
max_cven_th = [];
min_cven_th = [];
mean_cbrn_th = [];
std_cbrn_th = [];
max_cbrn_th = [];
min_cbrn_th = [];

% Transpose matrix of minimum tissue values to calculate minimum across all simulations

% Find minimum for minimum tissue values across all simulations
min_th = min(trans_min_tiss_th);
trans_min_tiss_th = [];

% Save minimums to one array to be saved
i = 1;
while i <= nrows
    min_tiss(i,1) = min_th(i);
    i = i + 1;
end
min_th = [];

% Find maximum and minimum for mass balance values
mb_maxmin(1, 1) = max(max(massbal_th));
mb_maxmin(2, 1) = min(min(massbal_th));
massbal_th = [];

zznumbins = sqrt(250);
% Save output to text files
% Contents of files based on file names where
% * = "ipa", "acetone" or "toluene", and
% ** = "normal", "reduced" or "verylow"

% mc_***_good_params.txt = parameters from "good" simulations
% mc_***_failed_params.txt = parameters from failed simulations
% mc_***_mintiss_fail.txt = minimum tissue values from failed simulations
% mc_***_mb_fail.txt = mass balance values from failed simulations
% mc_***_stats.txt = statistics for endpoints
% mc_***_mb.txt = minimum and maximum mass balance values

if (ChemName == 'IPA')
    if (Group == 'Normal ')
        save good_params @file='mc_ipa_normal_good_params.txt' @format=ascii
        save failed_params @file='mc_ipa_normal_failed_params.txt' @format=ascii
        save min_tiss_fail @file='mc_ipa_normal_mintiss_fail.txt' @format=ascii
        save mb_maxmin_fail @file='mc_ipa_normal_mb_fail.txt' @format=ascii
        save stats @file='mc_ipa_normal_stats.txt' @format=ascii
        save min_tiss @file='mc_ipa_normal_mintiss.txt' @format=ascii
        save mb_maxmin @file='mc_ipa_normal_mb.txt' @format=ascii
    else
        if (Group == 'Reduced')
            save good_params @file='mc_ipa_reduced_good_params.txt' @format=ascii
            save failed_params @file='mc_ipa_reduced_failed_params.txt' @format=ascii
            save min_tiss_fail @file='mc_ipa_reduced_mintiss_fail.txt' @format=ascii
            save mb_maxmin_fail @file='mc_ipa_reduced_mb_fail.txt' @format=ascii
            save stats @file='mc_ipa_reduced_stats.txt' @format=ascii
            save min_tiss @file='mc_ipa_reduced_mintiss.txt' @format=ascii
            save mb_maxmin @file='mc_ipa_reduced_mb.txt' @format=ascii
        else
            if (Group == 'VeryLow')
                save good_params @file='mc_ipa_verylow_good_params.txt' @format=ascii
                save failed_params @file='mc_ipa_verylow_failed_params.txt' @format=ascii
                save min_tiss_fail @file='mc_ipa_verylow_mintiss_fail.txt' @format=ascii
                save mb_maxmin_fail @file='mc_ipa_verylow_mb_fail.txt' @format=ascii
                save stats @file='mc_ipa_verylow_stats.txt' @format=ascii
                save min_tiss @file='mc_ipa_verylow_mintiss.txt' @format=ascii
                save mb_maxmin @file='mc_ipa_verylow_mb.txt' @format=ascii
            end
        end
    else
        if (ChemName == 'Ace')
            if (Group == 'Normal ')
                save good_params @file='mc_acetone_normal_good_params.txt' @format=ascii
                save failed_params @file='mc_acetone_normal_failed_params.txt' @format=ascii
                save min_tiss_fail @file='mc_acetone_normal_mintiss_fail.txt' @format=ascii
                save mb_maxmin_fail @file='mc_acetone_normal_mb_fail.txt' @format=ascii
                save stats @file='mc_acetone_normal_stats.txt' @format=ascii
                save min_tiss @file='mc_acetone_normal_mintiss.txt' @format=ascii
                save mb_maxmin @file='mc_acetone_normal_mb.txt' @format=ascii
            else
                if (Group == 'Reduced')
                    save good_params @file='mc_acetone_reduced_good_params.txt' @format=ascii
                    save failed_params @file='mc_acetone_reduced_failed_params.txt' @format=ascii
                    save min_tiss_fail @file='mc_acetone_reduced_mintiss_fail.txt' @format=ascii
                    save mb_maxmin_fail @file='mc_acetone_reduced_mb_fail.txt' @format=ascii
                    save stats @file='mc_acetone_reduced_stats.txt' @format=ascii
                    save min_tiss @file='mc_acetone_reduced_mintiss.txt' @format=ascii
                    save mb_maxmin @file='mc_acetone_reduced_mb.txt' @format=ascii
        end
end
end
else
    if (ChemName == 'Ace')
        if (Group == 'Normal ')
            save good_params @file='mc_acetone_normal_good_params.txt' @format=ascii
            save failed_params @file='mc_acetone_normal_failed_params.txt' @format=ascii
            save min_tiss_fail @file='mc_acetone_normal_mintiss_fail.txt' @format=ascii
            save mb_maxmin_fail @file='mc_acetone_normal_mb_fail.txt' @format=ascii
            save stats @file='mc_acetone_normal_stats.txt' @format=ascii
            save min_tiss @file='mc_acetone_normal_mintiss.txt' @format=ascii
            save mb_maxmin @file='mc_acetone_normal_mb.txt' @format=ascii
        else
            if (Group == 'Reduced')
                save good_params @file='mc_acetone_reduced_good_params.txt' @format=ascii
                save failed_params @file='mc_acetone_reduced_failed_params.txt' @format=ascii
                save min_tiss_fail @file='mc_acetone_reduced_mintiss_fail.txt' @format=ascii
                save mb_maxmin_fail @file='mc_acetone_reduced_mb_fail.txt' @format=ascii
                save stats @file='mc_acetone_reduced_stats.txt' @format=ascii
                save min_tiss @file='mc_acetone_reduced_mintiss.txt' @format=ascii
                save mb_maxmin @file='mc_acetone_reduced_mb.txt' @format=ascii
end
end
end
else
  if (Group == 'VeryLow')
    save good_params @file='mc_acetone_verylow_good_params.txt' @format=ascii
    save failed_params @file='mc_acetone_verylow_failed_params.txt' @format=ascii
    save min_tiss_fail @file='mc_acetone_verylow_mintiss_fail.txt' @format=ascii
    save mb_maxmin_fail @file='mc_acetone_verylow_mb_fail.txt' @format=ascii
    save min_tiss @file='mc_acetone_verylow_mintiss.txt' @format=ascii
    save mb_maxmin @file='mc_acetone_verylow_mb.txt' @format=ascii
  end
  end
end
else
  if (ChemName == 'Tol')
    if (Group == 'Normal ')
      save good_params @file='mc_toluene_normal_good_params.txt' @format=ascii
      save failed_params @file='mc_toluene_normal_failed_params.txt' @format=ascii
      save min_tiss_fail @file='mc_toluene_normal_mintiss_fail.txt' @format=ascii
      save mb_maxmin_fail @file='mc_toluene_normal_mb_fail.txt' @format=ascii
      save min_tiss @file='mc_toluene_normal_mintiss.txt' @format=ascii
      save mb_maxmin @file='mc_toluene_normal_mb.txt' @format=ascii
    else
      if (Group == 'Reduced')
        save good_params @file='mc_toluene_reduced_good_params.txt' @format=ascii
        save failed_params @file='mc_toluene_reduced_bad_params.txt' @format=ascii
        save min_tiss_fail @file='mc_toluene_reduced_mintiss_fail.txt' @format=ascii
        save mb_maxmin_fail @file='mc_toluene_reduced_mb_fail.txt' @format=ascii
        save min_tiss @file='mc_toluene_reduced_mintiss.txt' @format=ascii
        save mb_maxmin @file='mc_toluene_reduced_mb.txt' @format=ascii
      else
        if (Group == 'VeryLow')
          save good_params @file='mc_toluene_verylow_good_params.txt' @format=ascii
          save failed_params @file='mc_toluene_verylow_bad_params.txt' @format=ascii
          save min_tiss_fail @file='mc_toluene_verylow_mintiss_fail.txt' @format=ascii
          save mb_maxmin_fail @file='mc_toluene_verylow_mb_fail.txt' @format=ascii
          save min_tiss @file='mc_toluene_verylow_mintiss.txt' @format=ascii
          save mb_maxmin @file='mc_toluene_verylow_mb.txt' @format=ascii
        end
      end
    end
  end
end
end
end
good_params = []; failed_params = []; mb_maxmin_fail = []; min_tiss_fail = []; stats = [];
min_tiss = []; mb_maxmin = [];
MC_Sum_Mixed.m

% MC analysis summary for genetic variability Phase 1 work

% Called in MC_Anal.m

% Parameters are from Crystal Ball results using 500 bins for LHS
load NormalParams @file=mc_normal_vmaxc_mixed.txt @format=ascii
load ReducedParams @file=mc_reduced_vmaxc_mixed.txt @format=ascii
load VeryLowParams @file=mc_verylow_vmaxc_mixed.txt @format=ascii

good_params = []; massbal_th = []; cven_th = []; cbrn_th = [];

% Start Monte Carlo analysis
for iter = [1 : NumIts]

VMAXC = NormalParams(iter,1) + ReducedParams(iter,1) +VeryLowParams(iter,1);
disp(sprintf("Starting Iteration #%d", iter));
start @NoCallback
mins_th = [];
good_params(iter, 1) = VMAXC;
massbal_th = addcols(massbal_th, massbal, @Justification = 'begin');
cven_th = addcols(cven_th, _cven, @Justification = 'begin');
cbrn_th = addcols(cbrn_th, _cbrn, @Justification = 'begin');
end

disp(sprintf("Ran %d simulations to get output for %d simulations", iter, NumIts));

% Transpose matrix of time courses for endpoint to calculate statistics
[nrows, ncols] = size(cven_th);
i = 1; j = 1;
while i <= ncols
    while j <= nrows
        trans_cven_th(i, j) = cven_th(j, i);
        trans_cbrn_th(i, j) = cbrn_th(j, i);
        j = j + 1;
    end
    i = i + 1;
end

cven_th = []; cbrn_th = [];

% Calculate statistics for fixed dose, exposure length and start time for exposure
mean_cven_th = mean(trans_cven_th);
std_cven_th = std(trans_cven_th);
max_cven_th = max(trans_cven_th);
min_cven_th = min(trans_cven_th);
mean_cbrn_th = mean(trans_cbrn_th);
std_cbrn_th = std(trans_cbrn_th);
max_cbrn_th = max(trans_cbrn_th);
min_cbrn_th = min(trans_cbrn_th);
trans_cven_th = []; trans_cbrn_th = [];

% Save statistics to one array to be saved
i = 1;
while i <= nrows
    stats(i,1) = mean_cven_th(i);
    stats(i,2) = std_cven_th(i);
    stats(i,3) = mean_cven_th(i) + (2 * std_cven_th(i));
    stats(i,4) = mean_cven_th(i) - (2 * std_cven_th(i));
    stats(i,5) = max_cven_th(i);
    stats(i,6) = min_cven_th(i);
    stats(i,7) = mean_cbrn_th(i);
    stats(i,8) = std_cbrn_th(i);
    stats(i,9) = mean_cbrn_th(i) + (2 * std_cbrn_th(i));
    stats(i,10) = mean_cbrn_th(i) - (2 * std_cbrn_th(i));
    stats(i,11) = max_cbrn_th(i);
    stats(i,12) = min_cbrn_th(i);
    i = i + 1;
end
mean_cven_th = [];  std_cven_th = [];  max_cven_th = [];  min_cven_th = [];
mean_cbrn_th = [];  std_cbrn_th = [];  max_cbrn_th = [];  min_cbrn_th = [];

% Find maximum and minimum for mass balance values
mb_maxmin(1, 1) = max(max(massbal_th));
mb_maxmin(2, 1) = min(min(massbal_th));
massbal_th = [];

% Save output to text files
% Contents of files based on file names where
%   * = "ipa", "acetone" or "toluene", and
%     mc_*_mixed_good_params.txt = parameters from "good" simulations
%     mc_*_mixed_stats.txt = statistics for endpoints
%     mc_*_mixed_mb.txt = minimum and maximum mass balance values
if (ChemName == 'IPA')
save good_params @file='mc_ipa_mixed_vmaxc.txt' @format=ascii
save stats @file='mc_ipa_mixed_stats.txt' @format=ascii
save mb_maxmin @file='mc_ipa_mixed_mb.txt' @format=ascii
else
  if (ChemName == 'Ace')
    save good_params @file='mc_acetone_mixed_vmaxc.txt' @format=ascii
    save stats @file='mc_acetone_mixed_stats.txt' @format=ascii
    save mb_maxmin @file='mc_acetone_mixed_mb.txt' @format=ascii
  else
    if (ChemName == 'Tol')
      save good_params @file='mc_toluene_mixed_vmaxc.txt' @format=ascii
      save stats @file='mc_toluene_mixed_stats.txt' @format=ascii
      save mb_maxmin @file='mc_toluene_mixed_mb.txt' @format=ascii
  end
end

good_params = [];  stats = [];  mb_maxmin = [];
zznumbins = sqrt(250);
LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Abbreviation/Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Air Force</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>CPMC</td>
<td>Coriell Personalized Medicine Collaborative</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Cytochrome P450, Family 1, Subfamily A, Polypeptide 2</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Cytochrome P450, Family 2, Subfamily E, Polypeptide 1</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Cytochrome P450, Family 3, Subfamily A, Polypeptide 4</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>GST-T1</td>
<td>glutathione-S-transferase theta 1</td>
</tr>
<tr>
<td>HPA</td>
<td>high performance aircraft</td>
</tr>
<tr>
<td>HPARS</td>
<td>High Performance Aircraft Respiratory Study</td>
</tr>
<tr>
<td>VMaxC</td>
<td>maximum reaction rate</td>
</tr>
<tr>
<td>KM</td>
<td>Michaelis-Menten affinity constant</td>
</tr>
<tr>
<td>PGx</td>
<td>pharmacogenomics</td>
</tr>
<tr>
<td>PBPK</td>
<td>physiologically-based pharmacokinetic</td>
</tr>
<tr>
<td>RSAAC</td>
<td>Research Studies and Analysis Council</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>STEL</td>
<td>short-term exposure limit</td>
</tr>
<tr>
<td>USAF</td>
<td>United States Air Force</td>
</tr>
<tr>
<td>USAFSAM</td>
<td>United States Air Force School of Aerospace Medicine</td>
</tr>
<tr>
<td>VOC</td>
<td>volatile organic chemical</td>
</tr>
</tbody>
</table>