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Incorporation of Operational Features of Flight into a Physiologically-Based Pharmacokinetic (PBPK) Model



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14. ABSTRACT Work was previously conducted using physiologically-based pharmacokinetic (PBPk) modeling and Monte Carlo analyses to estimate distributions of exposures that could result in the target exhaled breath measurements from a High-Performance Aircraft Respiratory Study (HPARS). 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 pilots during flight, but did not account for differences in pharmacokinetics due to flight conditions such as altitude and G-forces. The next step, therefore, in this ongoing work was to incorporate descriptions of physiological changes occurring as a result of flight into the existing PBPk model. The work presented here utilizes an updated PBPk model with descriptions for changes in ventilation and cardiac output due to altitude and breathing air oxygen levels as well as changes in tissue blood flows due to G-forces. The resulting PBPk model was then used to reconstruct doses for isopropanol (IPA), acetone, toluene and cyclohexane based on the HPARS in a manner similar to the previous work augmented by the incorporation of physiological changes due to flight. While the predicted ranges were comparable to the previously predicted exposures with respect to STELs, the predicted exposures did show some variation from the previous values, particularly during simulated maneuvers at higher simulated G forces, thus indicating the importance of accounting for the physiological changes during flight. By expanding the current PBPk model paradigm to the physiological changes of HPA flight, a capability has been developed to assess true pilot physiology in a “virtual” context.					
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1.0 SUMMARY

Pilots of high-performance aircraft (HPA) may be exposed to various chemical irritants passing through the onboard oxygen generation system. Work was previously conducted using physiologically-based pharmacokinetic (PBPK) modeling and Monte Carlo analyses to estimate distributions of exposures that could result in the target exhaled breath measurements from a High-Performance Aircraft Respiratory Study (HPARS). 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 pilots during flight, but did not account for differences in pharmacokinetics due to flight conditions such as altitude and G-forces. The next step, therefore, in this ongoing work was to incorporate descriptions of physiological changes occurring as a result of flight into the existing PBPK model. The end goal of this work is to develop a PBPK model for a “virtual” pilot to better assess potential in-flight chemical exposures and produce aircraft cockpit exposure guidelines that will ensure limited probability of contaminated cockpit spaces that might contribute to coughing/respiratory symptoms or can be considered a contributing factor in reported symptomology. The work presented here utilizes an updated PBPK model with descriptions for changes in ventilation and cardiac output due to altitude and breathing air oxygen levels as well as changes in tissue blood flows due to G-forces. The resulting PBPK model was then used to reconstruct doses for isopropanol (IPA), acetone, toluene and cyclohexane based on the HPARS in a manner similar to the previous work augmented by the incorporation of physiological changes due to flight. These reconstructions allowed for the determination of possible exposure ranges experienced by pilots during flight, which were then compared to established short-term exposure limits (STELs). While the predicted ranges were comparable to the previously predicted exposures with respect to STELs, the predicted exposures did show some variation from the previous values, particularly during simulated maneuvers at higher simulated G-forces, thus indicating the importance of accounting for the physiological changes during flight. By expanding the current PBPK model paradigm to the physiological changes of HPA flight, a capability has been developed to assess true pilot physiology in a “virtual” context.

2.0 INTRODUCTION

The 711th Human Performance Wing F-22 Physiologic Analysis Team conducted a High-Performance Aircraft Respiratory Study (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 physiologically-based

pharmacokinetic (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 conducted using the existing published PBPK model of Clewell *et al.* [1], describing the pharmacokinetics from exposure to isopropanol (IPA) 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, and first-order urinary excretion from blood. Due to the high water solubility of IPA and acetone, Clewell *et al.* [1] 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 IPA 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 IPA 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 IPA, 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 flight conditions such as changes in altitude, G-forces. To provide for the most realistic simulations to estimate potential inhaled chemical concentrations by HPA pilots based on the HPARS data, the PBPK model needed to be modified to account for these differences. The long term goal of this effort is to produce aircraft cabin exposure guidelines that will assure limited probability of contaminated cabin spaces which might contribute to coughing/respiratory symptoms and unexplained physiological events (UPEs) or can be considered a contributing factor in reported symptomology.

3.0 MATERIALS AND METHODS

3.1 PBPK Model Structure and Modifications

The version of the PBPK model used in the previous work makes no adjustments for pilot physiology due to changes in altitude or G-forces (*e.g.*, changes in blood flow, ventilation, and pharmacokinetics). The goal of this work was to update the PBPK model with descriptions for changes in ventilation and cardiac output due to altitude and breathing air oxygen levels as well as changes in tissue blood flows due to G-forces. The question, however, was how best to account for these changes. The model could account for these changes by simply incorporating linear equations to change ventilation, cardiac output and tissue blood flows with increases and subsequent decreases in G-forces; more complexly by altering ventilation and flows with pressure changes due to altitude and G-forces; or some version that incorporates both the simple and complex.

The simple approach was implemented first. Because elements of the rapidly and slowly perfused compartments are both above and below the level of the heart and, thus, experience the blood flow changes differently during the application of G-forces, these compartments are split into two compartments to represent an upper and lower compartment for each. Parameters were added to the model so that the fractional splits could be easily adjusted. It was assumed tissue volumes and baseline blood flows would split at the same fraction. Chemical-specific parameters are the same for the two split compartments as for the original compartment. Prior to proceeding further, it was verified that the modified model with the split compartments gives the same results as the version without the split compartments. The schematic for the modified model is shown in Figure 1.

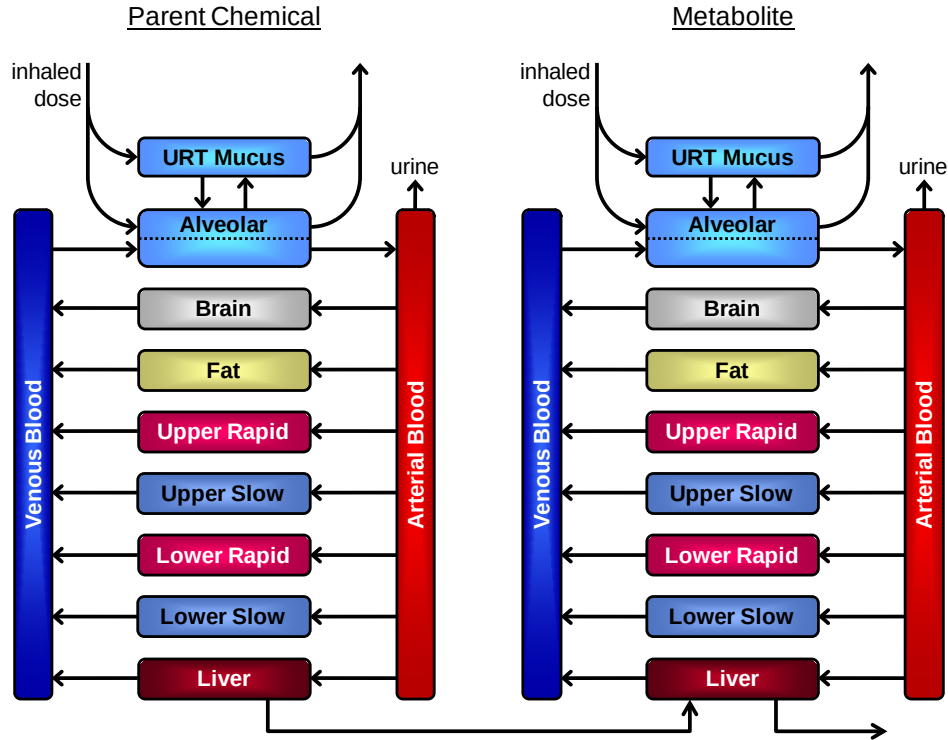


Figure 1. Schematic of Modified PBPK Model for IPA and its Metabolite, Acetone. This schematic shows modifications made to the Clewell *et al.* [1] model in the course of the previous work as well as the modifications made in this work to split the rapidly and slowly perfused compartments into upper and lower compartment for each.

Bomar *et al.* [2] developed a cardiovascular model to predict the arterial and venous pressure changes as a result of changes in breathing rate, acceleration and pressure. They then used this model to predict changes in upright and seated positions at +1 Gz and +4 Gz for various segments of the body. The orientations used for the seated position were chosen to represent the approximate position of a HPA pilot in the cockpit. The work presented here makes the assumption that blood flow to a tissue would change in the same manner as the arterial pressures would change. The arterial pressure data were digitized and the segments were grouped to correspond to the compartments in the modified PBPK model in Figure 1. The segment values were then adjusted by adding the same amount to all of the values such that the values were all now positive. Next, the change between arterial pressure at +4 Gz and +1 Gz was calculated as a fraction of the pressure at +1 Gz. These fractional changes were then averaged for each group and divided by 3 to get an average fractional change per change in Gz. These were then incorporated into equations to describe the change in tissue blood flows with respect to an applied G-force. The resulting equation is

$$Q_{Tissue} = QBase_{Tissue} \times \left(1.0 + (FracChange \times (GForce - 1.0)) \right),$$

where Q_{Tissue} is the adjusted blood flow, $QBase_{Tissue}$ is the baseline blood flow, $FracChange$ is the fractional change in blood flow per change in G-force, and $GForce$ is the applied G-force magnitude. The fractional changes are shown in Table 1. The equation for changes in brain

blood flow are artificially set to not decrease below 2% of the baseline value in order to avoid null or negative blood flow to the brain. As there were not data from Bomar *et al.* [2] for fat, the average of the two slowly perfused compartments is used. In order to maintain mass balance, cardiac output is recalculated as the sum of the adjusted tissue blood flows, and the ventilation rate is recalculated using the ratio of the baseline ventilation rate to the baseline cardiac output and the recalculated cardiac output.

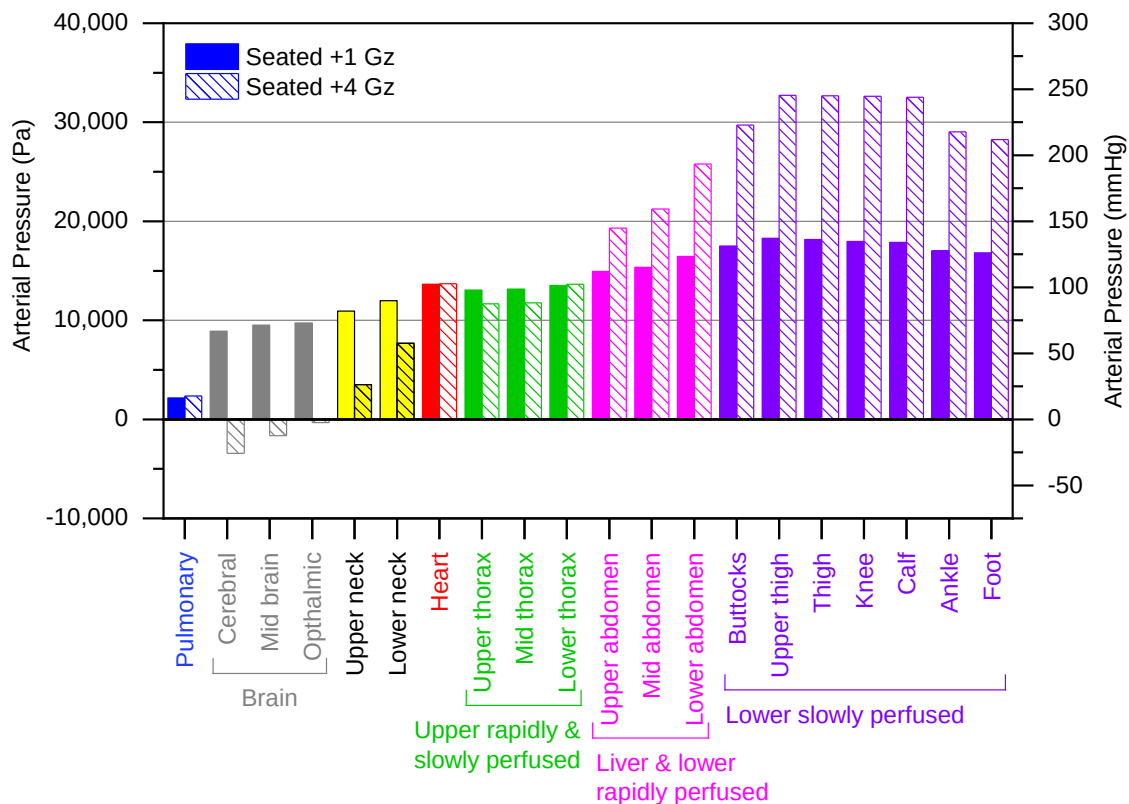


Figure 2. Arterial Pressure Changes. Data were digitized from Figure 6.4 in Bomar *et al.* [2] and represent predicted equilibrium arterial pressure changes for a pilot in a seated position at +1 Gz and +4 Gz. Segments were grouped (colored labels below x-axis) to correspond to compartments in the PBPK model.

Table 1. Fractional Changes in Tissue Blood Flow per Change in G-Force

Parameter	Fractional Change
Brain	-0.1927
Fat	0.07422
Liver	0.08453
Upper rapidly perfused compartment	-0.01297
Lower rapidly perfused compartment	0.08453
Upper slowly perfused compartment	-0.01297
Lower slowly perfused compartment	0.1614

The final modification to the PBPK model was to add coding to change the applied G-force at various times during the simulated one hour flight. This coding currently allows for the specification of up to 100 G-force events (including time at +1 Gz) during the flight with arrays defined for magnitude of each event and the time between events. The time at which the events begin with respect to the start of the simulated flight may also be specified. Data were presented in a figure in Newman [3] for G-force levels experienced during a typical air combat maneuver flight. The peaks and valleys from the figure were digitized. The time frame for the figure was not specified so it was assumed that the flight occurred over the span of one hour. The resulting information was used to populate the model parameters defining the simulated G-force events. Because of the short time frame between events, the model was converted to run in seconds instead of minutes for greater ease in setting the timing parameters.

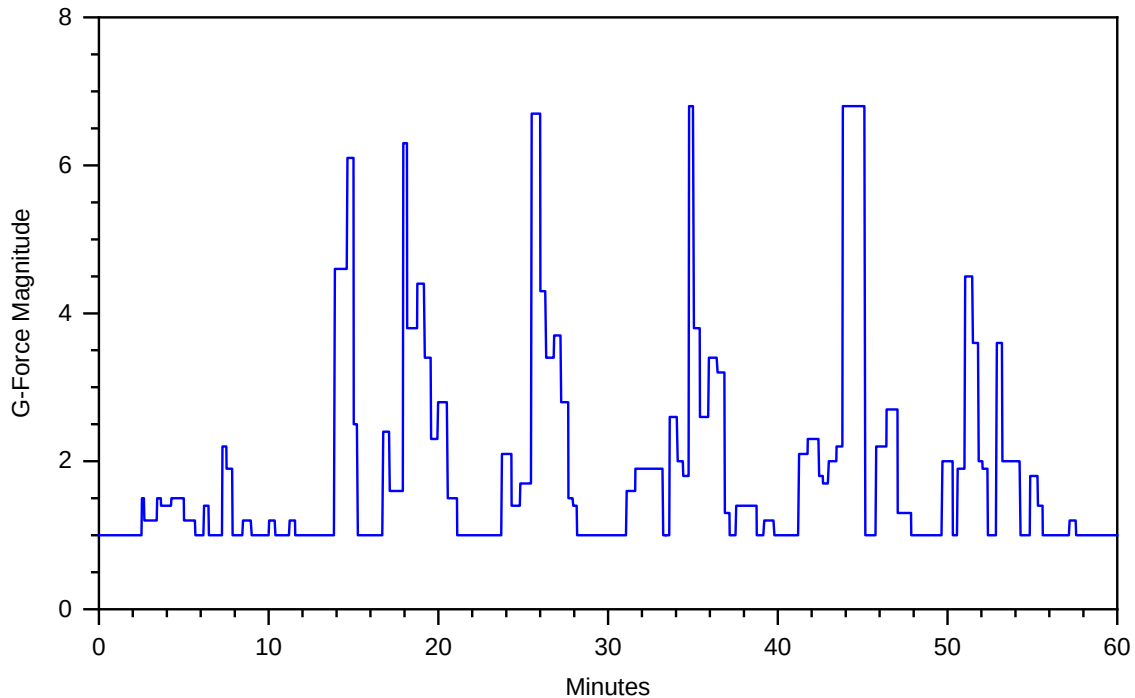


Figure 3. Simulated G-Forces Applied During Simulated Flight. Based on data from Newman [3].

Initial work was begun on implementing a more complex model to adjust physiology based on pressure changes due to altitude and G-forces using the models of Bomar *et al.* [2]. These models include a model for the oxygen delivery system, including both a mask and regulator model and a pulmonary model, and the cardiovascular system.

3.2 Model Parameters

As with the previous modeling work, chemical-specific parameters are from papers describing the PBPK models for each of the chemicals to be simulated [1, 4, 5]. The simulations for dose reconstructions use male body weights taken from an Air Force (AF) biometric database [6] (pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI), physiological parameters averaged across the published models [1, 4, 5], and chemical-specific parameters. These parameters are summarized in Tables 2 and 3. The ventilation rates for the toluene and cyclohexane models are alveolar and have been converted to total ventilation rates in Table 2 by dividing the alveolar rates by two-thirds [7]. The exponential power used for allometric (body weight) scaling is different in the toluene and cyclohexane models than in the IPA model for cardiac output, pulmonary ventilation and maximum metabolic rate; therefore, the values in Tables 2 and 3 have also been adjusted such that the scaled value in the simulations here would be the same as those in the toluene and cyclohexane models for the same body weight. Given that the parameters used for the dose reconstruction simulations are an average of those from the published models, the input value for upper respiratory tract uptake for IPA and acetone are adjusted such that the resulting scaled value used in the simulations would be the

same as was used in the published IPA simulations (*i.e.*, the value from Clewell *et al.* [1] is divided by the ventilation rate from Clewell *et al.* [1] and multiplied by the average ventilation rate used for the dose reconstruction simulations). Parameters included in the IPA model which are not included in the published models for toluene and cyclohexane [4, 5] are 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.* [5] does not include a brain compartment but the modified IPA model used for the dose reconstructions does; therefore, the fractional tissue blood flow and volume from the IPA model [1] are used. The brain/blood partition used for the toluene simulations is calculated from a brain/gas partition from the literature [8] and the blood/air partition [5].

Table 2. Physiological Parameters

Parameter	Dose Reconstructions	IPA / Acetone	Toluene	Cyclohexane
Body weight (kg)	84.14 ^a	70	84.5	79.13
Cardiac output (L/sec/kg ^{0.75})	0.004306	0.003581	0.004	0.005306
Pulmonary ventilation (L/sec/kg ^{0.75})	0.007222	0.007708	0.006	0.007958
Fractional Tissue Blood Flows (fraction of cardiac output)				
Brain	0.123	0.114	0.114 ^b	0.14
Fat	0.05	0.052	0.05	0.05
Liver	0.246	0.227	0.26	0.25
Rapidly perfused compartment	0.352	0.419	0.326	0.31
Slowly perfused compartment	0.229	0.188	0.25	0.25
Fractional Tissue Volumes (fraction of body weight)				
Alveolar blood	0.0079	0.0079	0.0079 ^b	0.0079 ^b
Brain	0.02	0.02	0.02 ^b	0.02
Fat	0.188	0.214	0.19	0.161
Liver	0.026	0.026	0.026	0.026
Rapidly perfused compartment	0.0320	0.036	0.05	0.03
Slowly perfused compartment	0.602	0.536	0.62	0.649

^aAverage male body weight from an AF biometric database [6]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

^bParameter not included in model for this chemical – used IPA/acetone model value

Table 3. Chemical-Specific Parameters

Parameter	IPA	Acetone	Toluene	Cyclohexane
Molecular weight (g/mole)	60.09	58.08	92.1384	84.16
Fractional volume of mucus (fraction of body weight)	0.0001	0.0001	-- ^a	-- ^a
Partition Coefficients (unitless)				
Blood/air	848.0	260.0	15.6	1.3
Mucus/air	848.0	260.0	-- ^a	-- ^a
Brain	1.33	0.69	2.33 ^b	7.62 ^c
Fat	0.32	0.44	65.4 ^c	180.0 ^c
Liver	1.16	0.58	5.36 ^c	7.62 ^c
Rapidly perfused compartment	1.25	0.69	5.36 ^c	7.62 ^c
Slowly perfused compartment	1.3	0.7	1.78 ^c	3.92 ^c
Metabolism Parameters				
Maximum reaction rate (L/sec/kg ^{0.75})	0.0833	0.000972	0.00133	0.00121
Michaelis-Menten affinity constant (mg/L)	10.0	10.0	0.55	0.13
First order rate constant (kg ^{0.75} /sec)	0.0	0.0	0.0	0.0
Uptake and Clearance Parameters (L/sec/kg^{0.75})				
Urinary clearance	1.11×10 ⁻⁶	1.11 ×10 ⁻⁶	-- ^a	-- ^a
Upper respiratory tract uptake	0.00306	0.00306	-- ^a	-- ^a

^aParameter not used for this chemical

^bCalculated using brain/gas partition [8] and the blood/air partition [5].

^cTissue/blood partitions calculated from blood/air partition and tissue/air partition [4, 5]

3.3 Dose Reconstructions

As with the previous work, the PBPK model was parameterized based on published chemical specific values and the model was then exercised to “reconstruct” the potential exposures that could have occurred with IPA, acetone, toluene and cyclohexane. The modified model was run to simulate exposure of various lengths starting at various times during a one hour flight. These simulations also include 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. Table 4 shows the combination of flight lengths and durations simulated. Simulations use chemical-specific parameters from Table 3 and the physiological-parameters from Table 2 designated as dose reconstruction parameters. 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 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.

Table 4. Exposure Scenarios

Length of Exposure	Start of Exposure (from start of flight)
30 seconds	1 minute intervals from 0 to 59 minutes (0, 0.5, 1, 1.5, 2, 2.5, ... 58, 58.5, 59, 59.5)
1 minute	1 minute intervals from 0 to 59 minutes (0, 1, 2, 3, ... 57, 58, 59)
2 minutes	2 minute intervals from 0 to 58 minutes (0, 2, 4, 6, ... 54, 56, 58)
5 minutes	5 minute intervals from 0 to 55 minutes (0, 5, 10, 15, ... 45, 50, 55)
15 minutes	15 minute intervals from 0 to 45 minutes (0, 15, 30, 45)
60 minutes	Once at the start of the flight

3.4 Monte Carlo Analyses

A Monte Carlo analysis was conducted to demonstrate the potential impact in dose estimations for the chemicals due to individual variability for a fixed exposure scenario (a 15 minute exposure starting 15 minutes into the flight). Distributions were defined for both the physiological and chemical-specific parameters (Tables 2, 3 and 5). Standard deviations were calculated from the means and coefficients of variation (CVs). The CVs were based on those used in published analyses [9, 10]. Parameters that were not included in these published analyses were given CVs consistent with similar parameters; metabolic parameters were given CVs of 30% which is less than used by Covington *et al.* [9] but larger than in David *et al.* [10]. Clearance parameters were given CVs of 30% to be consistent with the metabolic parameters. The CV for body weight was calculated based upon data from an AF biometric database [6] (pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI). Bounds for all distributions were calculated as two standard deviations except for body weight for which the maximum and minimum values are from an AF biometric database [6] (pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI). The distributions were sampled to generate 5000 parameter sets and the model was run for each parameter set. For each parameter set, the specific dose was again estimated such that a distribution of estimated doses could be determined.

Table 5. Monte Carlo Settings for Model Parameters
(means for distributions are presented in Tables 2 and 3)

Parameter	Coefficient of Variation (%)	Distribution	Bounds ^a	
			Upper	Lower
Body weight for males (kg)	13.2 ^b	Normal	129.5 ^c	60.24 ^c
Cardiac output (L/sec/kg ^{0.75})	9	Normal		
Ventilation perfusion ratio	14	Log-Normal		
Fractional Tissue Blood Flows (fraction of cardiac output)				
Brain	30	Normal		
Fat	30	Normal		
Liver	35	Normal		
Rapidly perfused compartment	20	Normal		
Slowly perfused compartment	15	Normal		
Fractional Tissue Volumes (fraction of body weight)				
Alveolar blood	30	Normal		
Brain	30	Normal		
Fat	30	Normal		
Liver	5	Normal		
Mucus	10	Normal		
Rapidly perfused compartment	10	Normal		
Slowly perfused compartment	30	Normal		
Partition Coefficients (unitless)				
Blood/air	10	Log-Normal		
Mucus/air	20	Log-Normal		
Brain	20	Log-Normal		
Fat	30	Log-Normal		
Liver	20	Log-Normal		
Rapidly perfused compartment	20	Log-Normal		
Slowly perfused compartment	20	Log-Normal		
Metabolism Parameters				
Maximum reaction rate (L/sec/kg ^{0.75})	30	Log-Normal		
Michaelis-Menten affinity constant (mg/L)	30	Log-Normal		
Uptake and Clearance Parameters				
Urinary clearance (L/sec/kg ^{0.75})	30	Log-Normal		
Upper respiratory tract uptake (L/sec/kg ^{0.75})	30	Log-Normal		

^aValues not shown were calculated as +/- two standard deviations

^bCalculated from mean and standard deviation from AF biometric database [6]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

^cMaximum and minimum values from AF biometric database [6]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

Given that the time or length of the potential exposures is not known, the Monte Carlo analyses were further expanded to randomly select an exposure length and time based upon the lengths and times used for the dose reconstructions (Table 4). The number of options for start times for each exposure length was calculated based on the lengths and exposures in Table 4. So

a 2 minute exposure starting from 0 to 58 minutes at 2 minute intervals would be 30 options. Using a random number generator in EXCEL (the RANDBETWEEN function), a random number between 1 and 6 was selected to represent an exposure length of 30 seconds or 1, 2, 5, 15 or 60 minutes. Then, the RANDBETWEEN function was used to select a random number between 0 and *Options*-1, where *Options* is the total number of options, and was then multiplied by the length to get the actual start time. For example, a random number between 0 and 29 (30 options minus 1) would be chosen for a 2 minute exposure, and would then be multiplied by 2 for the actual start time (e.g., a randomly selected value of 12 would give a start time of 24 minutes). These 5000 pairs of numbers were then saved to a text files that were read by the simulation program during the analysis. Once the dose was fit for the 15 minute exposure starting 15 minutes into the flight, a random exposure length (30 seconds or 1, 2, 5, 15 or 60 minutes) and start time were selected. Start times could be anywhere from 0 to 59.5 minutes after the start of the flight in 30 second intervals, but the exposure had to start long enough before the end of the simulated flight (60 minutes) to be completed by the end of the flight (e.g., a one minute exposure could not be selected with a start time of 59.5 minutes into the flight). The dose necessary to fit the target exhaled breath concentration was again fit for each of the 5000 iterations.

4.0 RESULTS

4.1 PBPK Model Structure and Modifications

The modified model predicts changes in tissue blood flows based upon the simulated G-forces (Figure 3). The cardiac output is updated based on the blood flow changes, and the ventilation rate is updated based on the change in cardiac output using the ventilation perfusion ratio. The resulting changes for ventilation rate, cardiac output, and some of the tissue flows are shown in Figure 4.

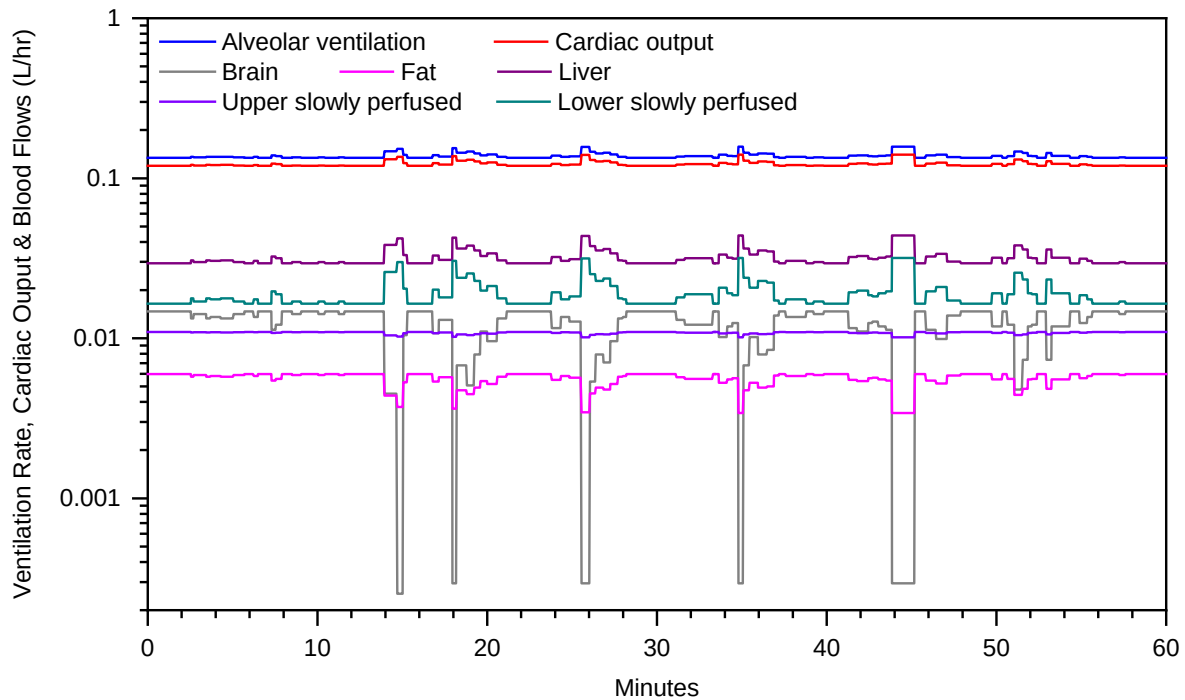


Figure 4. Simulated Changes in Ventilation Rate, Cardiac Output and Selected Blood Flows. This plot shows the predicted physiological changes due to simulation of G-forces applied during flight.

4.2 Dose Reconstructions

Figure 5 shows a representation of the concept and results for two particular exposure scenarios – a 5 minute exposure starting 10 minutes into the flight and a 15 minute exposure starting 30 minutes into the flight. The example shown is for IPA exposure. The figure indicates both the window of flight time (60 minutes) and the time on the ground following the flight (20 minutes) with shaded bars representing the exposure concentration, length and start time. The red and blue lines are the predicted end-exhaled air concentrations for the given exposure concentrations for the two scenarios. Note the jagged spots in the lines during the exposure period (shaded bars). These are a due to the simulated physiological changes resulting from the simulation of G-forces.

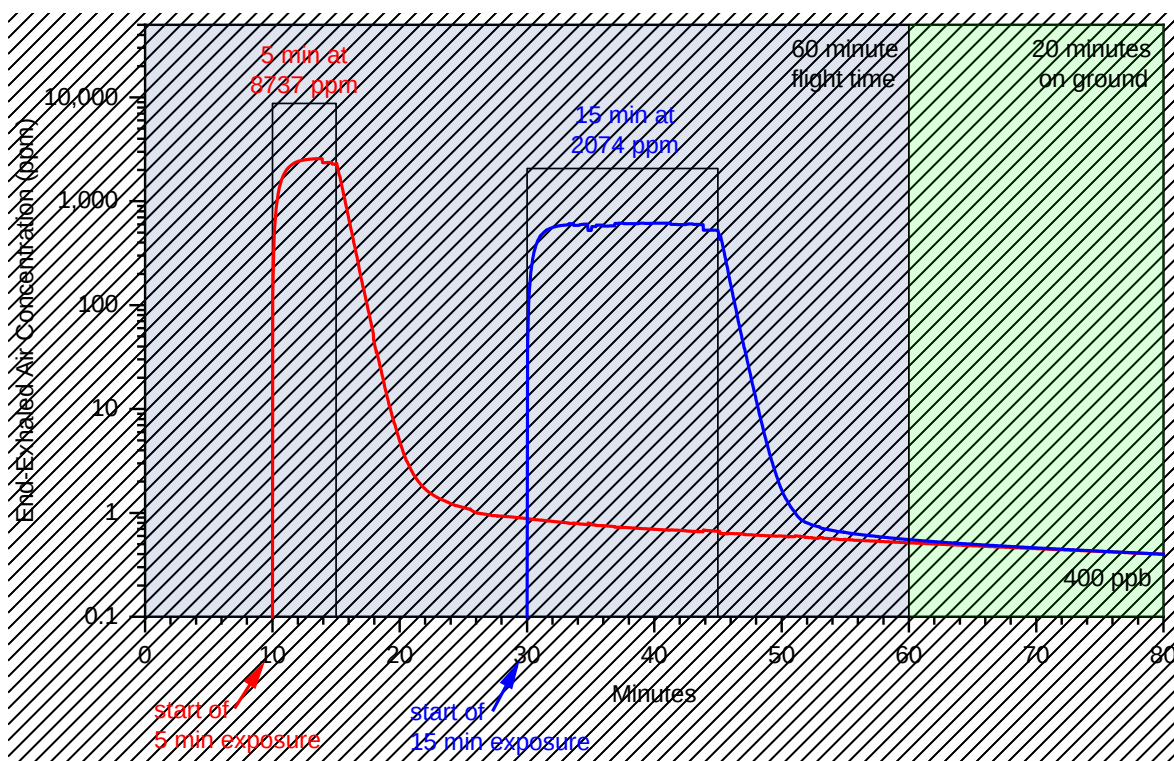


Figure 5. Scenario Used for Dose Reconstructions. This figure represents the scenarios for two of the exposures used for dose reconstruction (a 5 minute exposure occurring 10 minutes into the flight and a 15 minute exposure occurring 30 minutes into the flight). The shaded blue area represents the flight time, and the green shaded area represents the follow-up time on the ground before breath samples were taken. The hatched bars represent the estimated dose for the given exposure scenario, and the red and blue lines represent the predicted exhaled air concentrations for the scenarios.

Estimated doses for the four chemicals along with the corresponding maximum predicted blood and brain concentrations are shown in Figures 6 through 21. For all figures, the light blue line represents the simulated G-forces, and the black-outlined open symbols represent the predicted doses from the previous work when G-forces and the related physiological changes were not simulated. The open symbols correspond to the colored symbols of the same shape. Note that there is some overlap of symbols in the figures and some open symbols may be obscured by the colored symbols.

As with the previous work, the highest doses are estimated for the chemical with the highest target exhaled breath concentration – IPA. Estimated doses for IPA (Figure 6) are again all above the short term exposure limit (STEL) for IPA of 400 ppm and range from a little less than 105,000 ppm to a little less than 600 ppm. Predicted maximum blood concentrations range from approximately 28 mg/L to about 2.5 mg/L (Figure 7); predicted maximum brain concentrations range from about 46 mg/L to a little more than 4 mg/L (Figure 8).

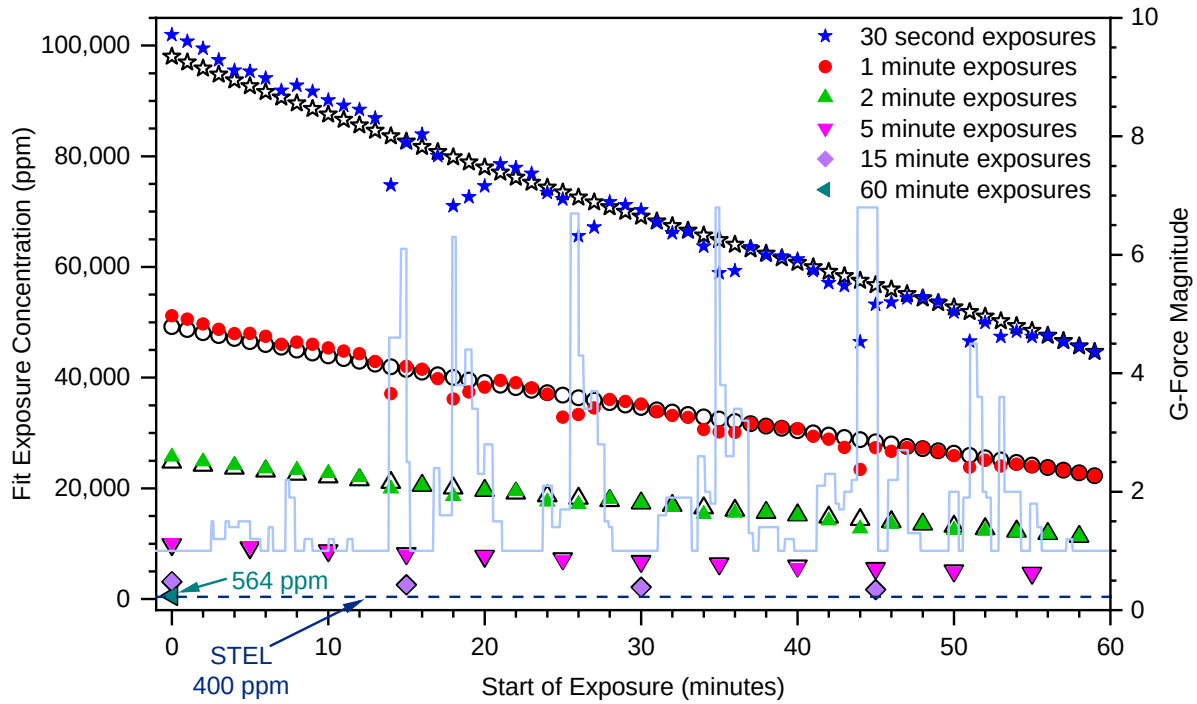


Figure 6. Estimated IPA Exposure Concentrations. Estimated exposure concentrations to predict an IPA exhaled breath target of 400 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

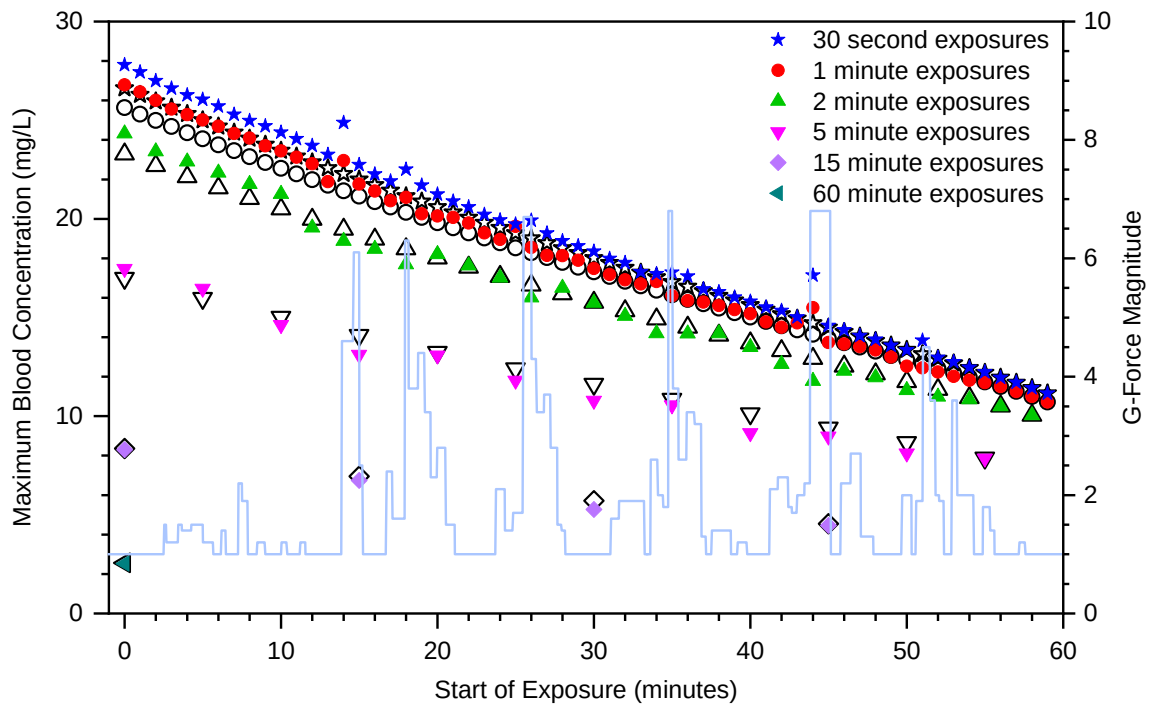


Figure 7. Predicted Maximum IPA Blood Concentrations. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 6.

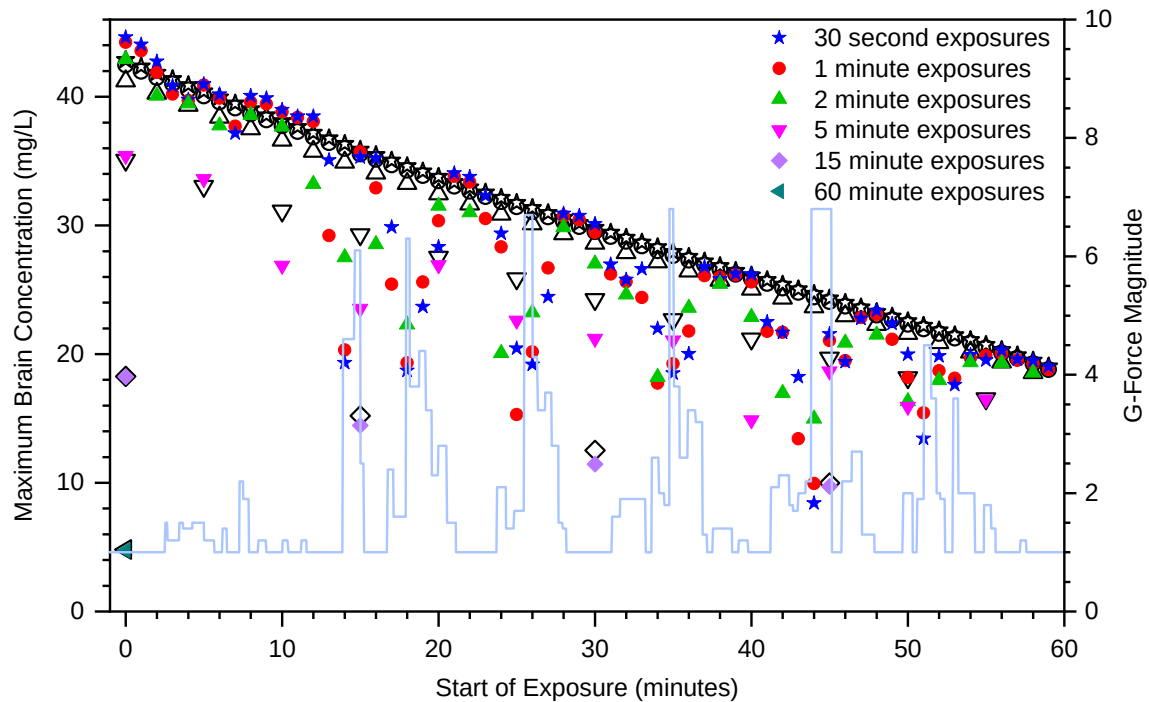


Figure 8. Predicted Maximum IPA Brain Concentrations. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 6.

While the target exhaled breath concentration for acetone is only slightly lower than the target for IPA, the estimated doses (Figure 8) are a factor of about 25 to 30 lower and range from just over 3200 ppm to just under 25 ppm. Estimated doses for exposures lasting two minutes or more are all below the STEL for acetone of 1000 ppm regardless of the start of exposure. The remaining estimated doses are all above the STEL. Predicted maximum blood concentrations for acetone (Figure 16) are within about a factor of 15 or less of the predicted maximums for IPA while predicted maximum brain concentrations (Figure 17) are between a factor of about 30 and 15 less than predicted maximums for IPA.

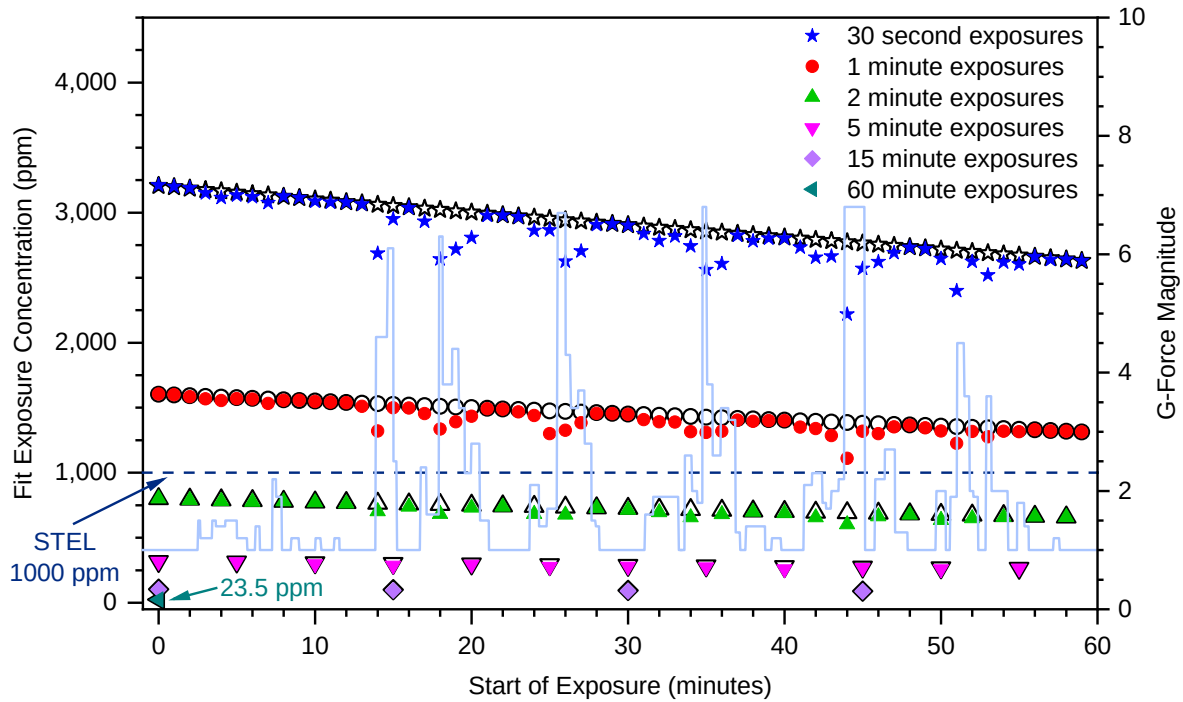


Figure 8. Estimated Acetone Exposure Concentrations. Estimated exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

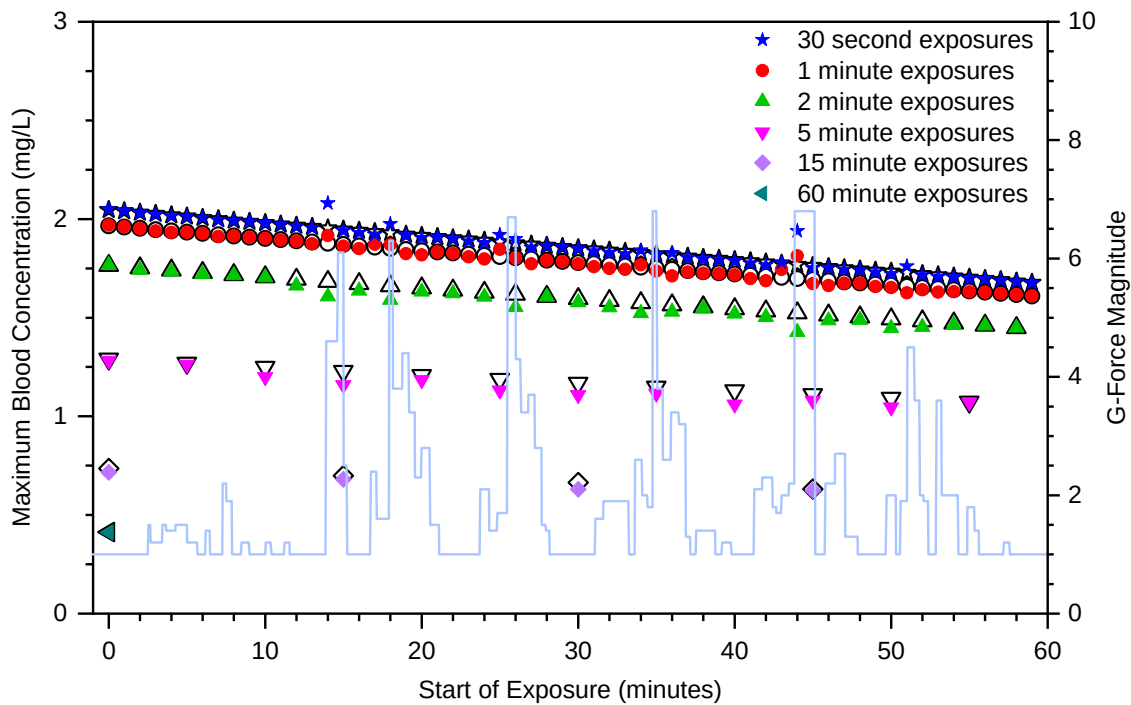


Figure 9. Predicted Maximum Acetone Blood Concentrations. Blood concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 8.

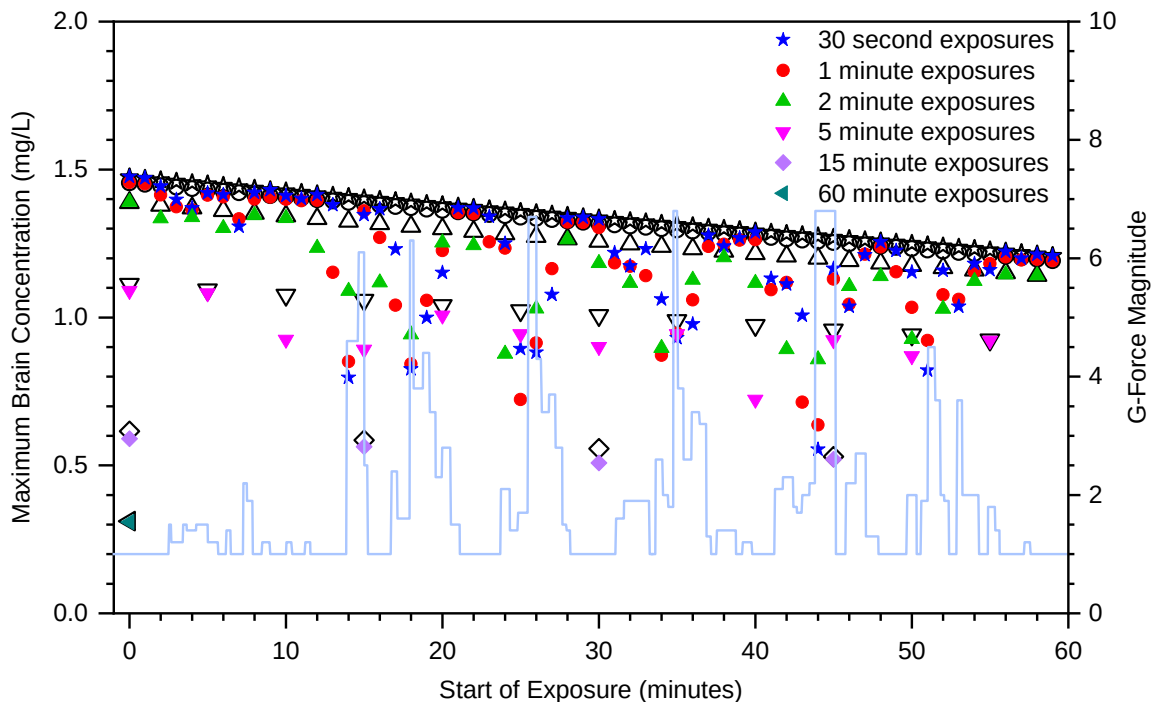


Figure 10. Predicted Maximum Acetone Brain Concentrations. Brain concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 8.

Given that the presence of acetone in exhaled breath could be due from exposure to either acetone or IPA, doses were also estimated for IPA exposure resulting in the acetone target exhaled breath concentration. The range of estimated IPA doses to match the acetone target (Figure 11) are considerably lower (about 4100 ppm to 32 ppm) than the estimated IPA doses to match the IPA target; however, in this case, because the target is for the metabolite rather than the parent chemical, the highest dose for a given exposure length occurs at later start times instead of the early start times as a result of the lag time required for metabolism to occur. Also, the range of doses for a given exposure length do not vary much across the various times for start of exposure. This results in predicted maximum blood and brain concentrations, for both IPA (Figures 12 and 14) and acetone (Figures 13 and 15), that also display little variation for a given exposure length. It is interesting to note that, while the maximum IPA blood concentrations drop below the estimates from the previous work at the higher simulated G-forces, the acetone blood concentrations are above the previous work's estimates. Also, the predicted acetone maximum brain concentrations are not as varied as those for IPA.

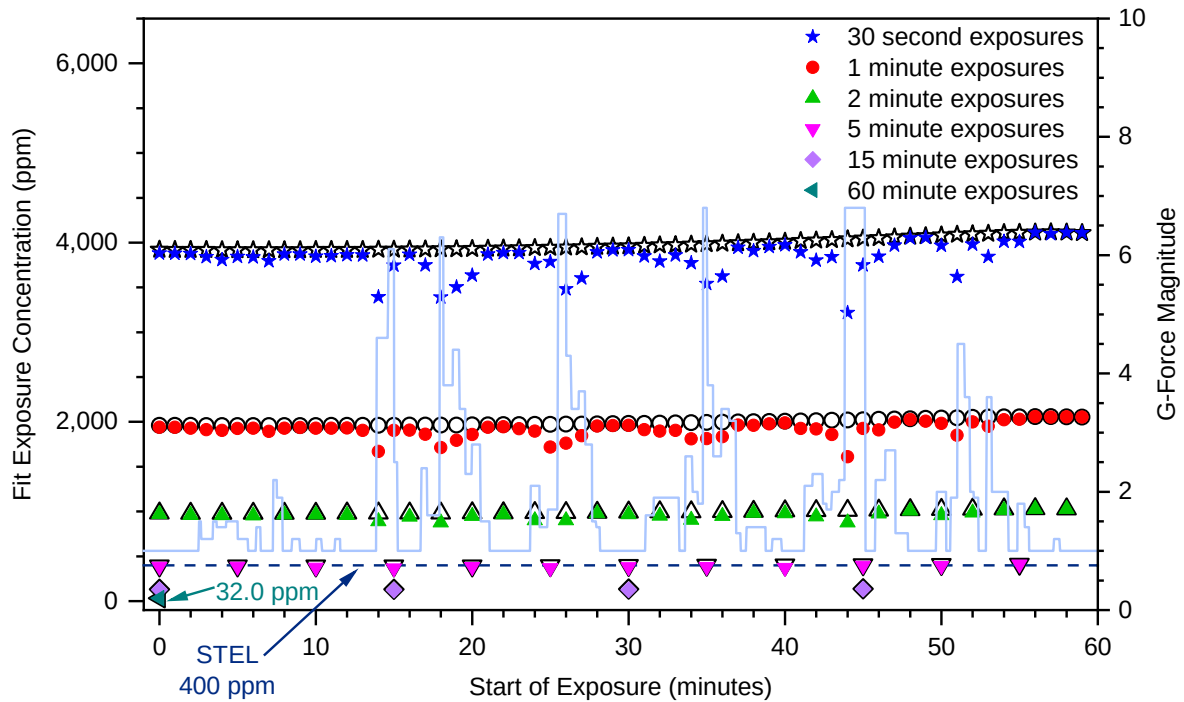


Figure 11. Estimated IPA Exposure Concentrations to Predict Acetone Target. Estimated IPA exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

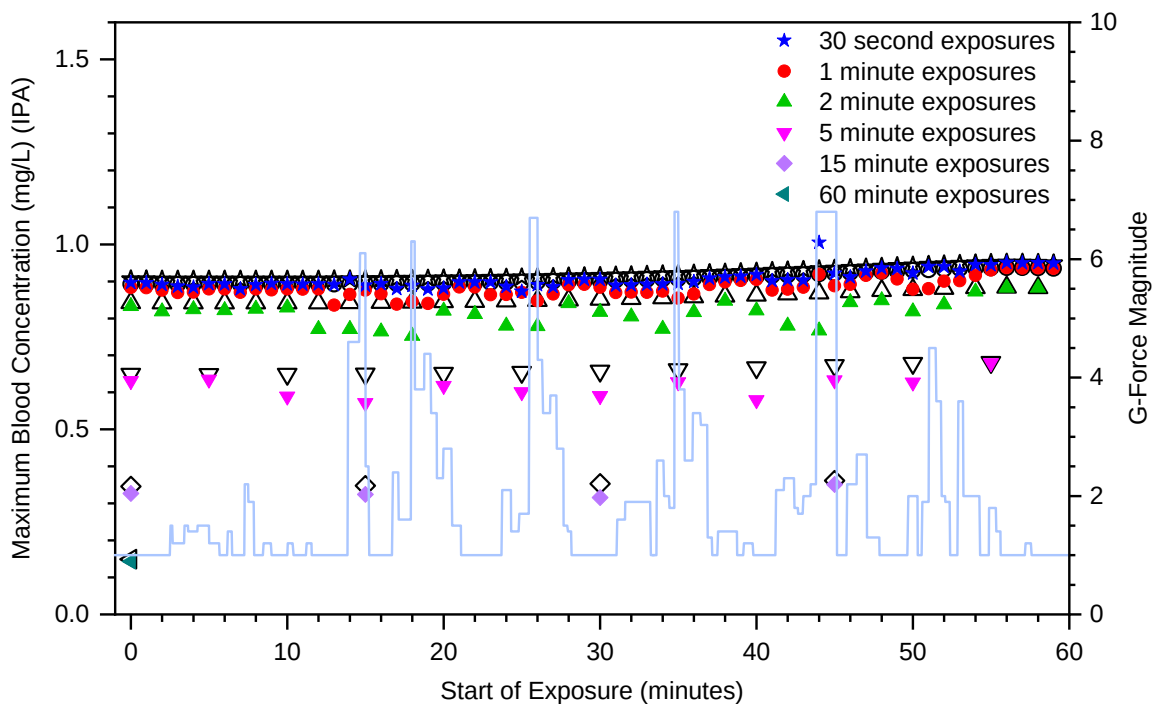


Figure 12. Predicted Maximum IPA Blood Concentrations for Acetone Target. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

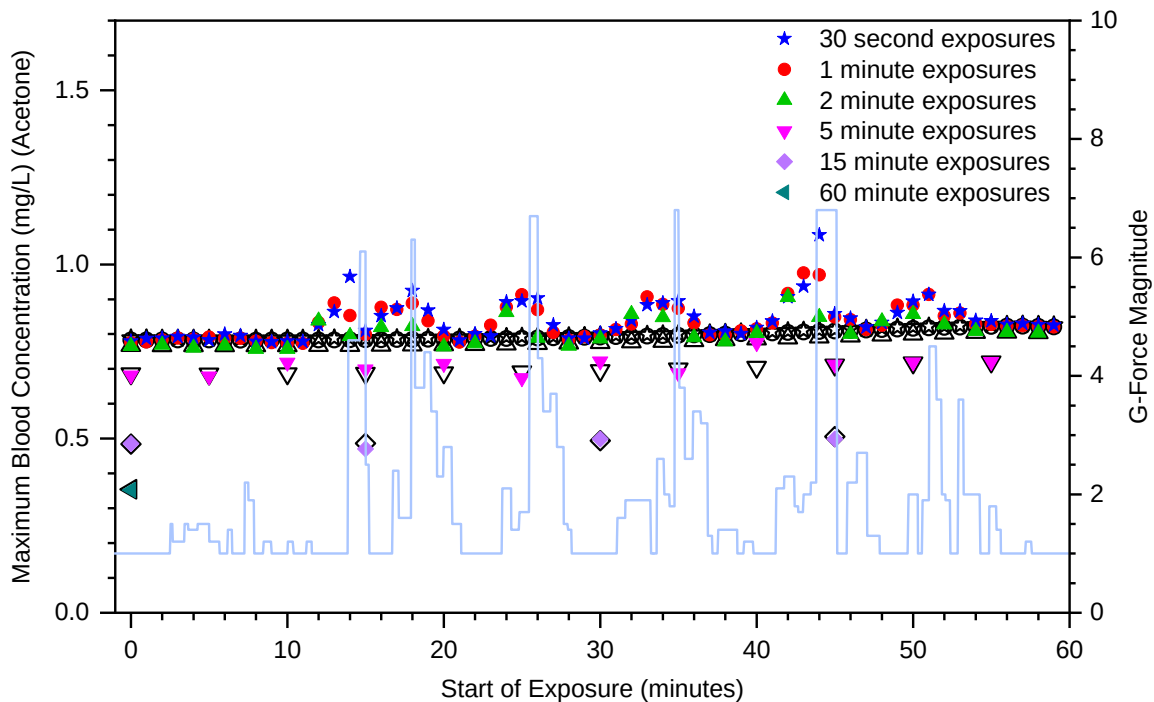


Figure 13. Predicted Maximum Acetone Blood Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

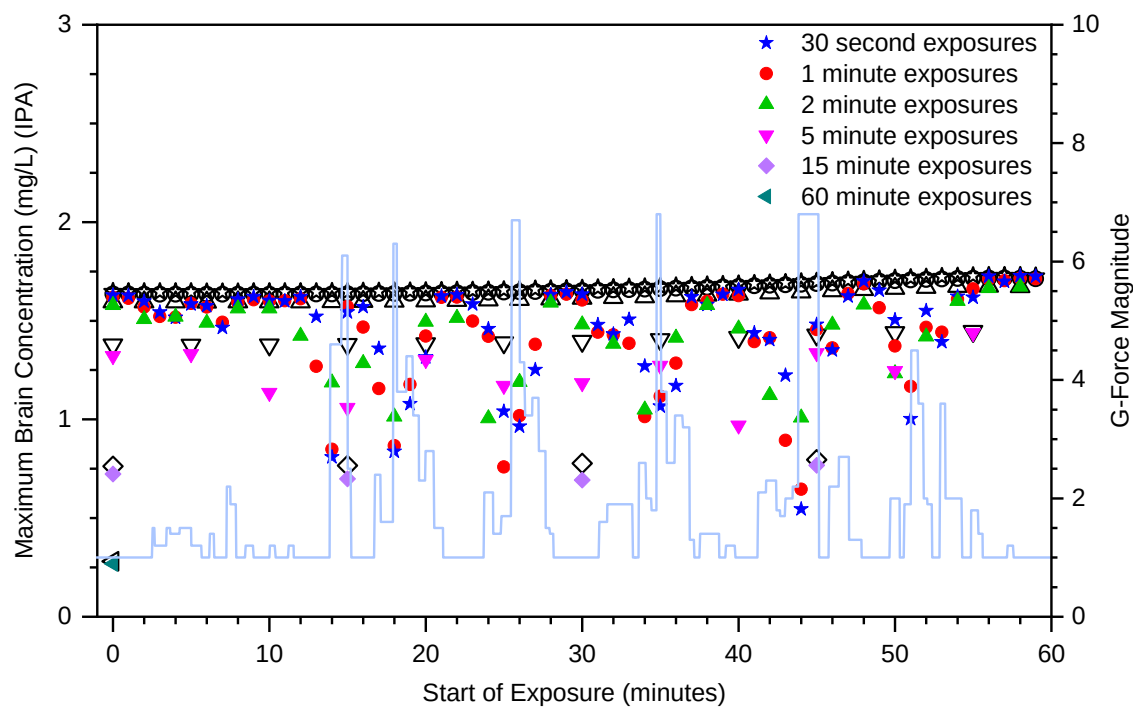


Figure 14. Predicted Maximum IPA Brain Concentrations for Acetone Target. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

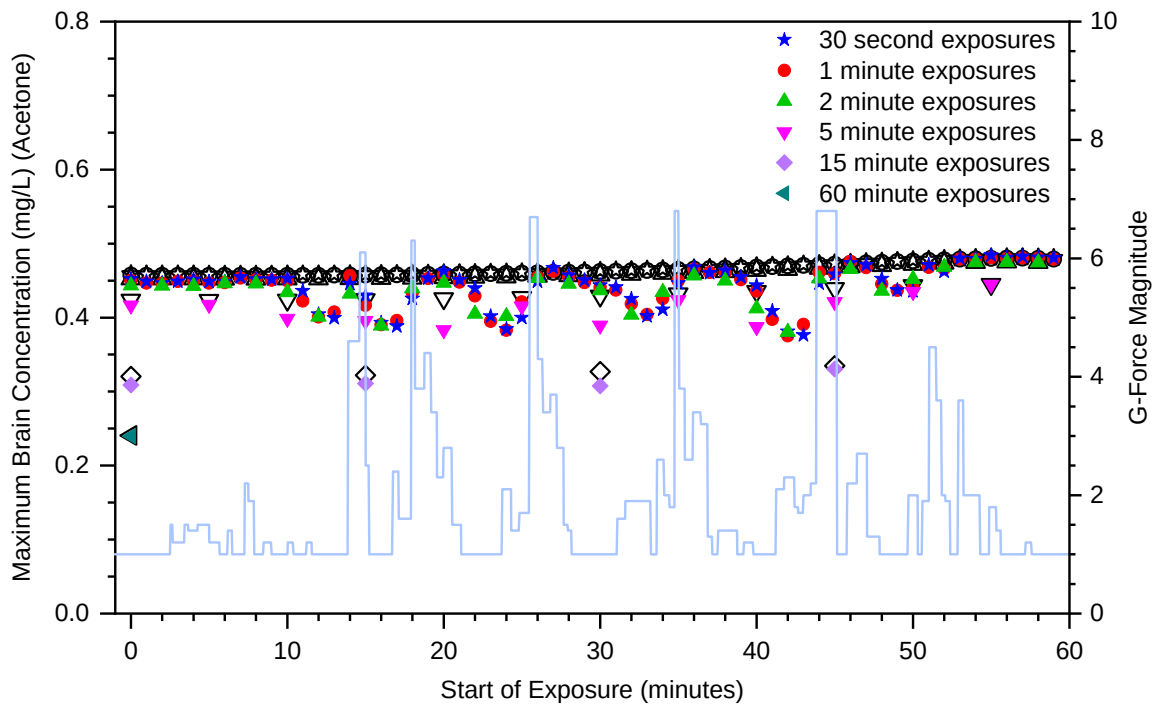


Figure 15. Predicted Maximum Acetone Blood Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

The target exhaled breath concentration for toluene is considerably lower than for IPA and acetone. Toluene estimated doses (Figure 16) are all well below the STEL for toluene of 150 ppm and range from approximately 23 ppm to 0.12 ppm. Predicted maximum blood concentrations range from approximately 0.006 mg/L to about 0.0008 mg/L (Figure 17); predicted maximum brain concentrations are about four times higher than blood concentrations and range from about 0.023 mg/L to 0.003 mg/L (Figure 18).

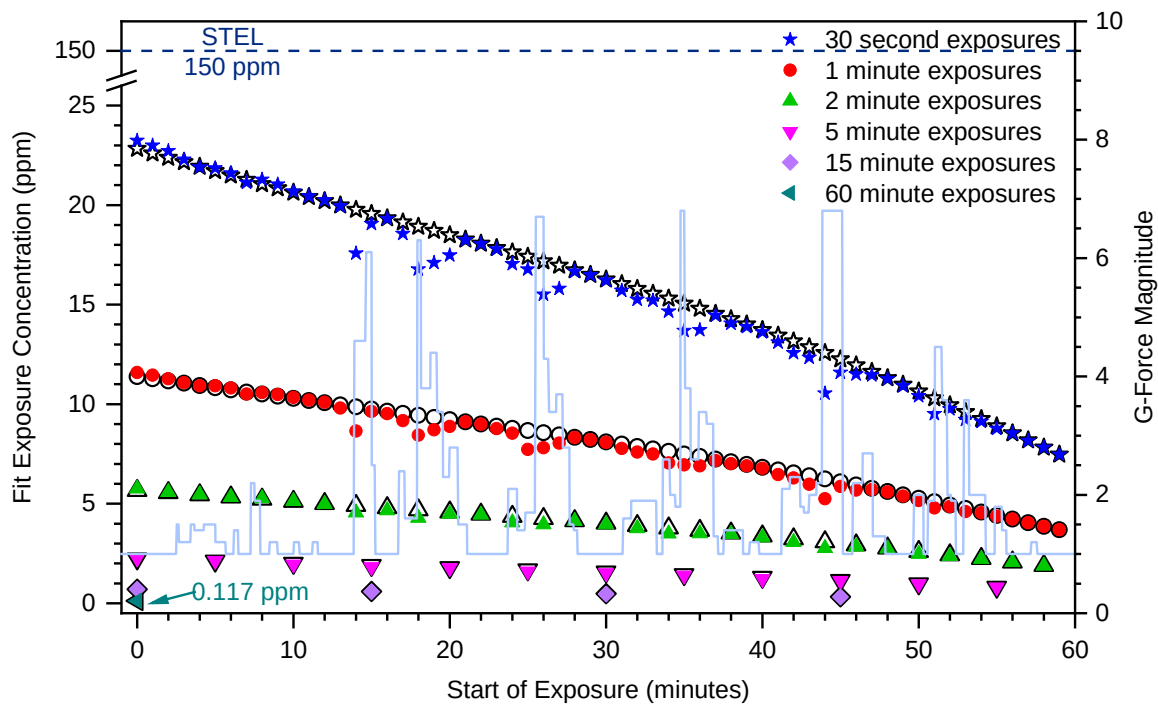


Figure 16. Estimated Toluene Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 6.3 ppb for different exposure scenarios.

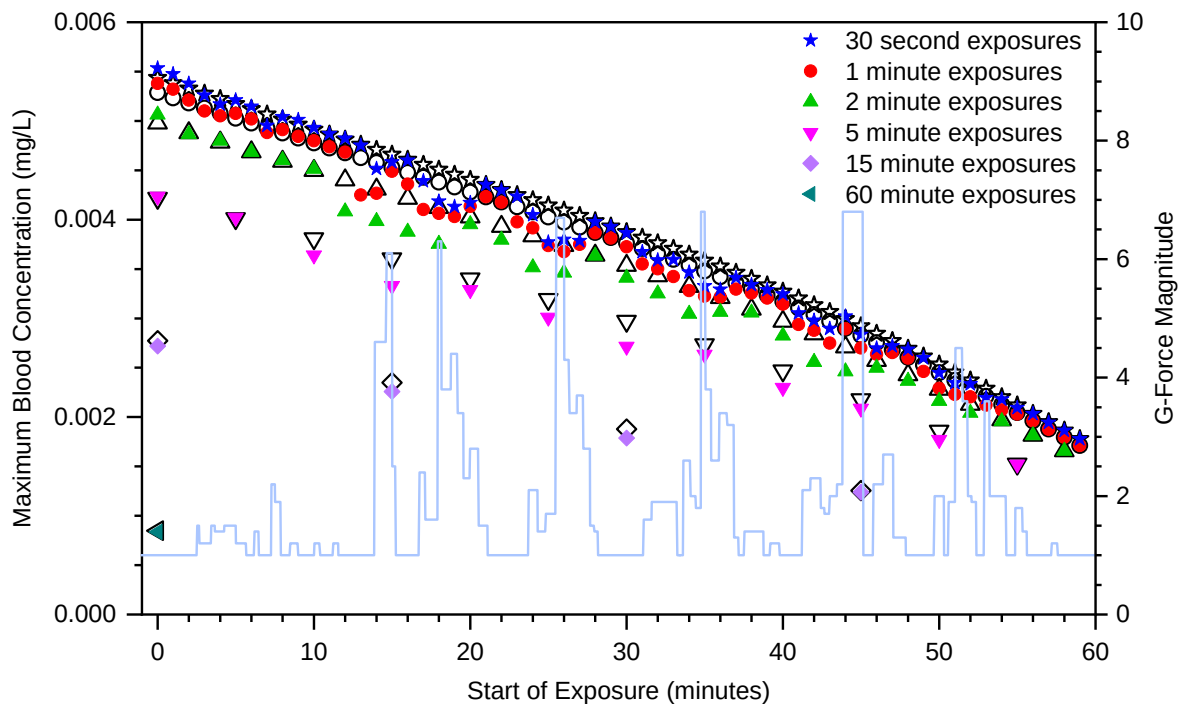


Figure 17. Predicted Maximum Toluene Blood Concentrations. Blood concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 16.

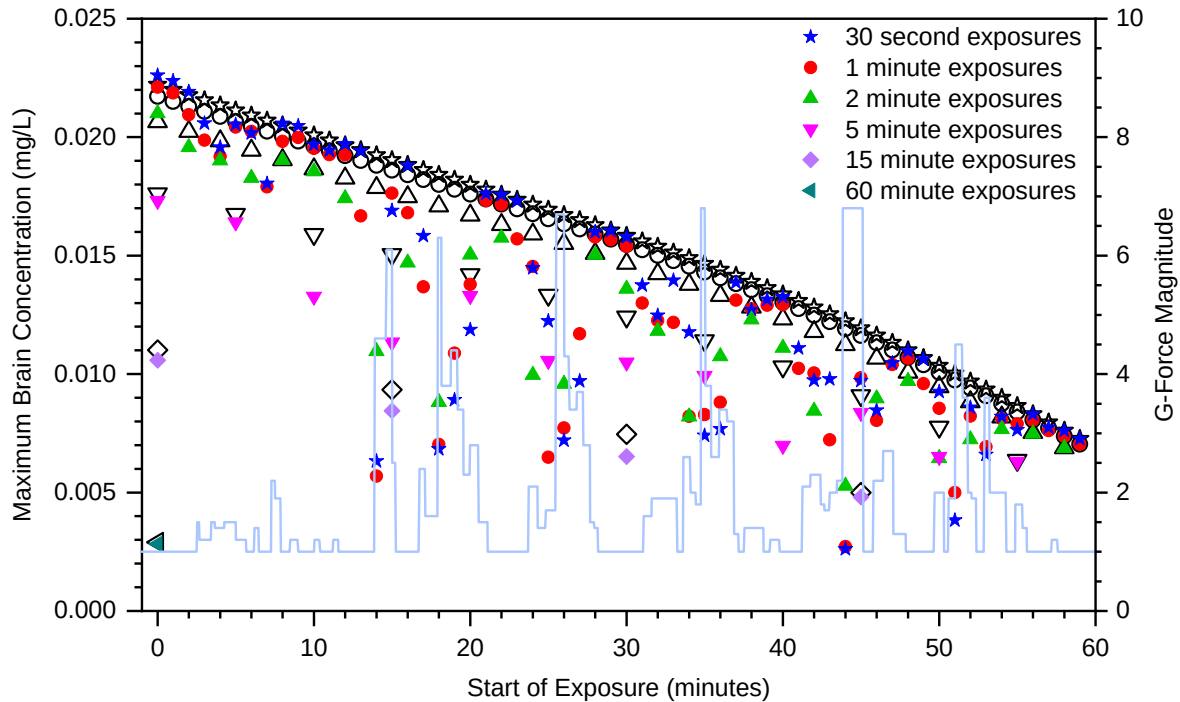


Figure 18. Predicted Maximum Toluene Brain Concentrations. Brain concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 16.

Cyclohexane has the lowest target exhaled breath concentration. A STEL for cyclohexane was not located, but a time-weighted average (TWA) for the OSHA permissible exposure limit (PEL) is 300 ppm. All of the estimated doses for cyclohexane (Figure 19) are well below this OSHA PEL and range from approximately 18 ppm to 0.07 ppm. The lowest values for predicted maximum blood and brain concentrations (Figures 20 and 21) are a factor of 10 lower than the highest predicted values and range from approximately 0.001 mg/L to 0.0001 mg/L for blood and approximately 0.01 mg/L to 0.001 mg/L for brain.

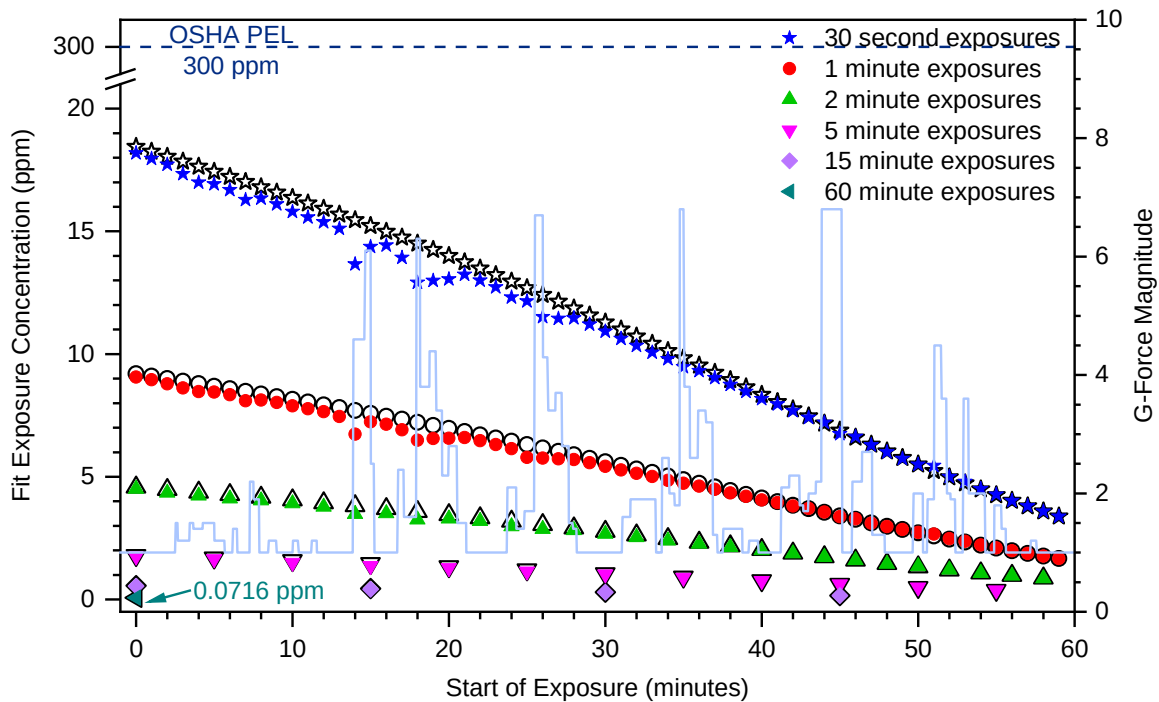


Figure 19. Estimated Cyclohexane Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 5.3 ppb for different exposure scenarios. Dark blue dashed line represents the OSHA PEL.

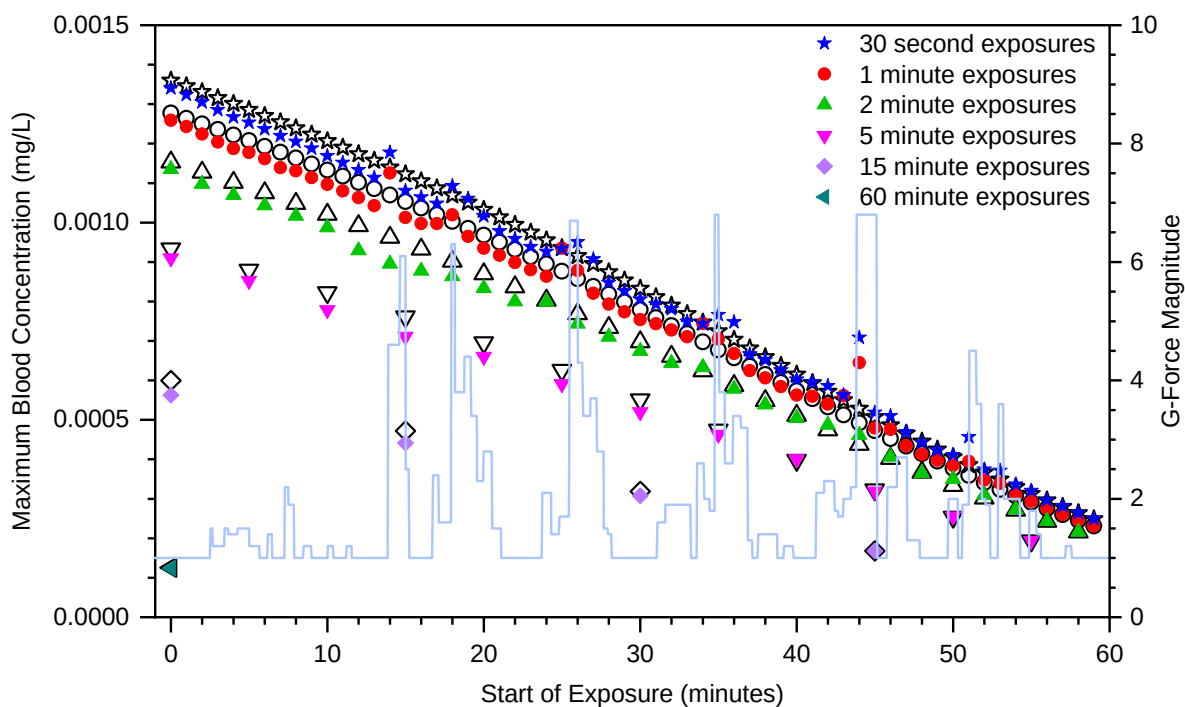


Figure 20. Predicted Maximum Cyclohexane Blood Concentrations. Blood concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 19.

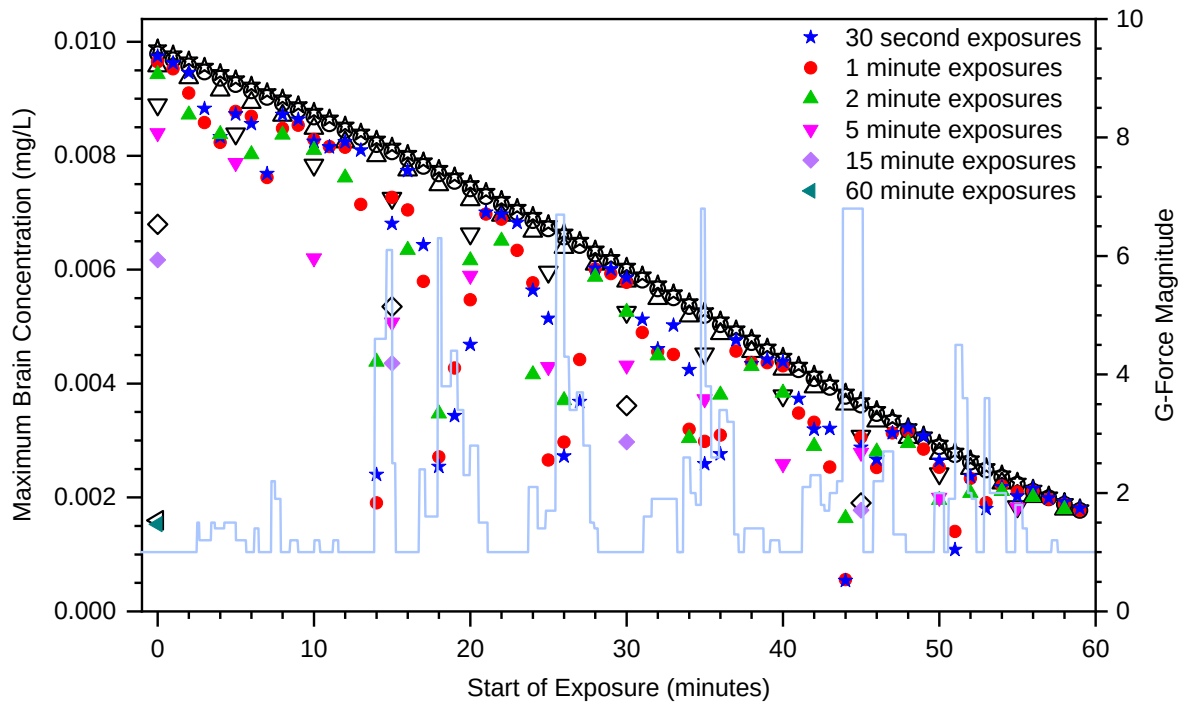


Figure 21. Predicted Maximum Cyclohexane Brain Concentrations. Brain concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 19.

4.3 Monte Carlo Analyses

Results for the Monte Carlo analyses are shown in Figures 22 through 36. For all of the histograms, the blue line represents a log-normal curve fit to the histogram, and the red circle represents the geometric mean. For the remaining figures, the black line represents the predicted exhaled breath concentrations without Monte Carlo (*i.e.*, a single simulation using the mean parameter values), and the red line represents the average for each time point of the 5000 simulations. Also for each time point of the 5000 simulations, the blue area represents two standard deviations, and the green area represents the maximum and minimum prediction.

Figure 22 demonstrates the potential variability in predictions for IPA exhaled air concentration due to inter-individual variation for a 15 minute exposure starting 15 minutes into the flight. The red line, representing the average, is slightly higher during the clearance phase following exposure than the simulation using the mean parameters (black line). As with the scenarios shown in Figure 5, the lines are jagged during the exposure period (15 to 30 minutes). Again, this is due to the simulated physiological changes resulting from the simulation of G-forces. Figure 23 shows the distribution of the exhaled air concentrations as well as the log-normal curve fit to this distribution (blue line) and the geometric mean (red circle). The geometric mean of the distribution (0.407 ppm) is slightly higher than the target exhaled breath concentration of 0.4 ppm (400 ppb), but the highest predicted concentration (2.3 ppm) was almost six times higher than the target.

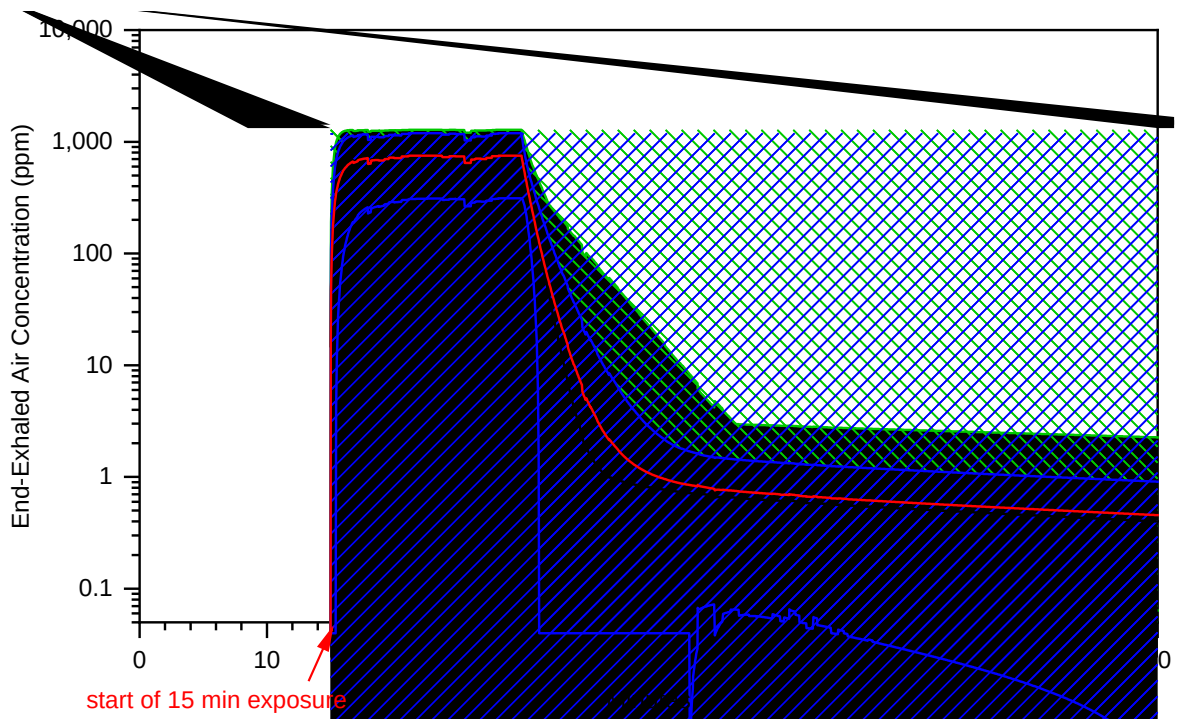


Figure 22. Monte Carlo Results for Exhaled IPA Concentrations for Fixed Exposure. Results are a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

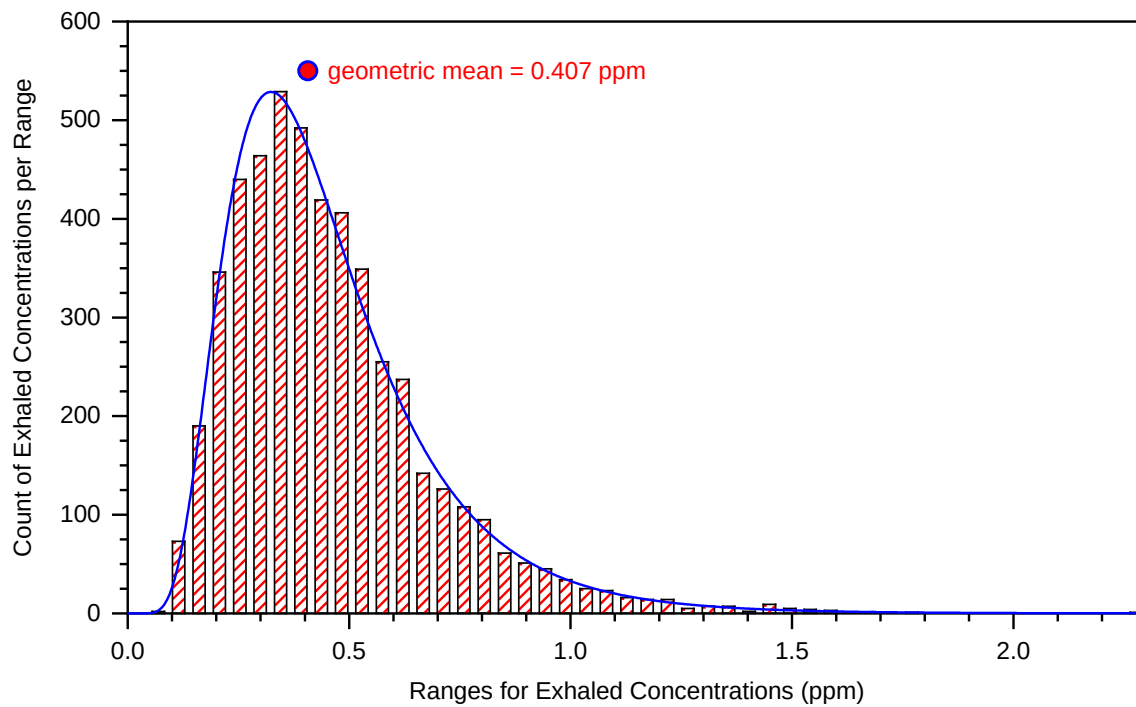


Figure 23. Histogram of Exhaled IPA Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

The Monte Carlo analysis generated 5000 sets of parameters. In addition to compiling the predicted exhaled air concentrations for these parameter sets, the dose needed to match the IPA exhaled breath target of 400 ppb (0.4 ppm) was estimated. Like Figure 22, Figure 24 shows the predicted IPA exhaled air concentrations; the difference is that in Figure 24 the dose for each parameter set has been estimated rather than all sets using the same dose. Again, the red line (average) is slightly higher than the simulation using the mean parameters (black line). Note that for this figure all lines and shaded areas converge to a value of 400 ppb (0.4 ppm) at the end of the follow-up period. The distribution of estimated doses from these simulations is shown in Figure 25 along with the log-normal curve (blue line) and geometric mean (red circle). The geometric mean (2513 ppm) is less than the current point estimate (2558 ppm) and the the point estimate (2601 ppm) and geometric mean (2553 ppm) from the previous work. The highest estimated dose (14,790 ppm), however, is more than a factor of five times higher than the current and previous point estimates, but is less than the highest estimated dose from the previous work (15,742 ppm).

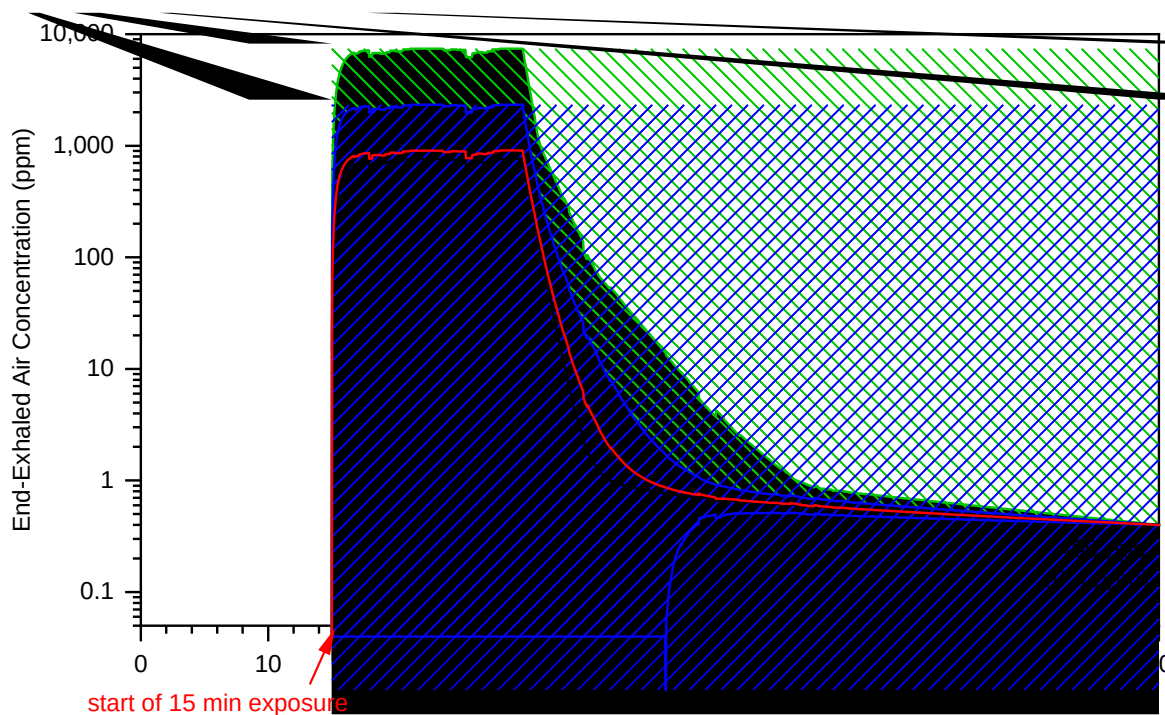


Figure 24. Monte Carlo Results for Exhaled IPA Concentrations from Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

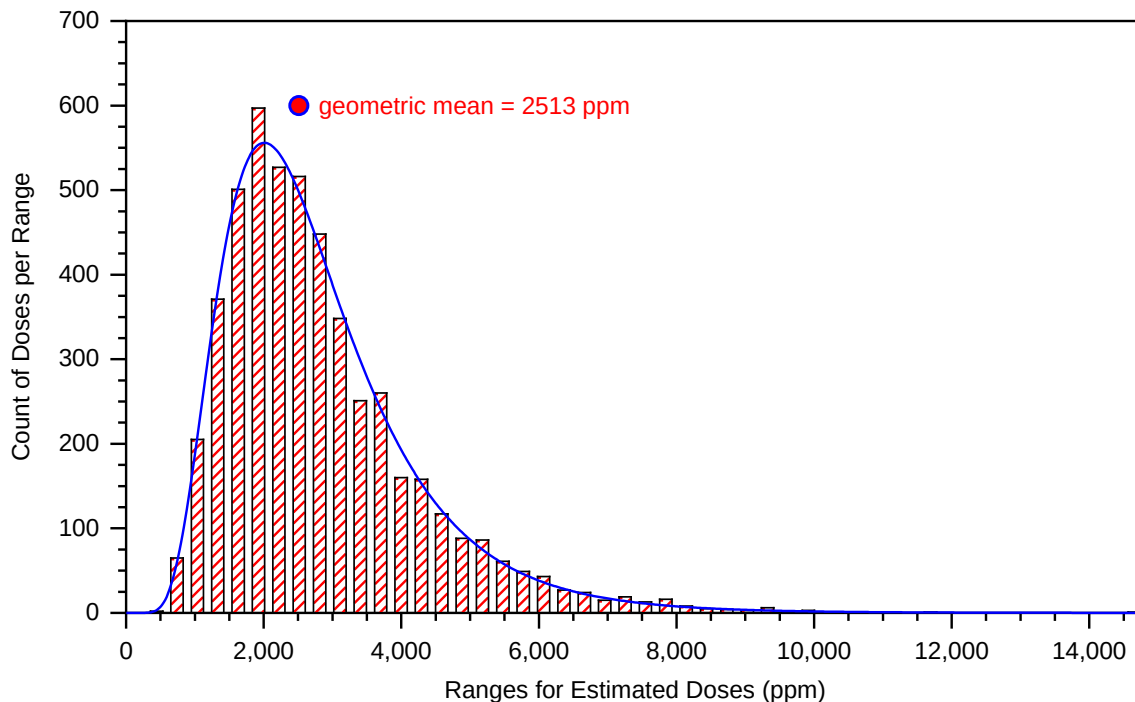


Figure 25. Histogram of Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

Figures 26 and 27 show the distributions of exhaled air concentrations and estimated doses, respectively, from simulations for acetone. In contrast to the IPA results, the geometric mean of the exhaled air distribution (0.345 ppm) is slightly lower than the target exhaled breath concentration of 0.354 ppm (354 ppb), but the highest predicted concentration (0.958 ppm) is more than twice the target. The geometric mean for the estimated doses (97.8 ppm) is slightly more than the current point estimate (95.4 ppm) but slightly less than the previous point estimate (99.8 ppm) and geometric mean (101 ppm). The highest estimated dose (385 ppm) is about four times higher than the current and previous point estimates but is less than the previously estimated highest dose (412 ppm).

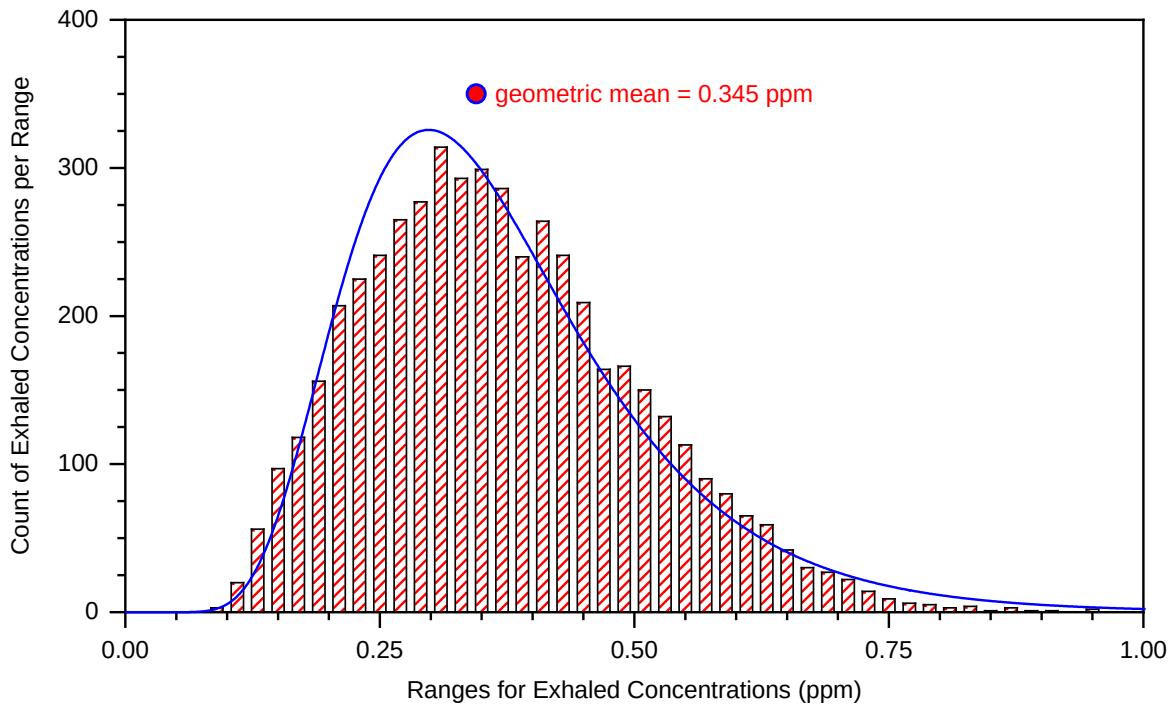


Figure 26. Histogram of Exhaled Acetone Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

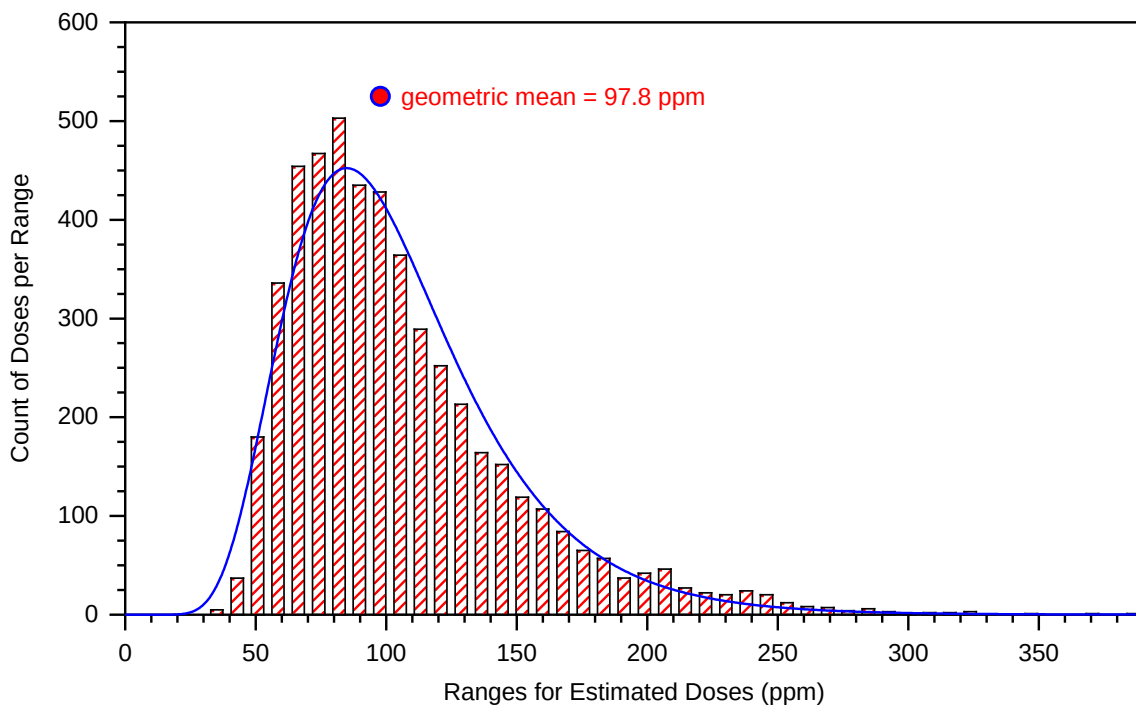


Figure 27. Histogram of Estimated Acetone Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

The distributions of exhaled air concentrations and estimated doses from simulations for toluene are shown in Figures 28 and 29, respectively. The geometric mean of the exhaled air distribution (0.0065 ppm) is slightly higher than the target exhaled breath concentration of 0.0063 ppm (6.3 ppb), and the highest predicted concentration (0.0153 ppm) is more than twice the target. The geometric mean of the estimated doses (0.554 ppm) is less than both the current (0.575 ppm) and the previous point estimate (0.599 ppm) and geometric mean (0.576 ppm), but the highest estimated dose (1.50 ppm), like the highest predicted exhaled air concentration, is more than twice the current and previous point estimates. It is also slightly higher than the previous estimated highest dose (1.47 ppm).

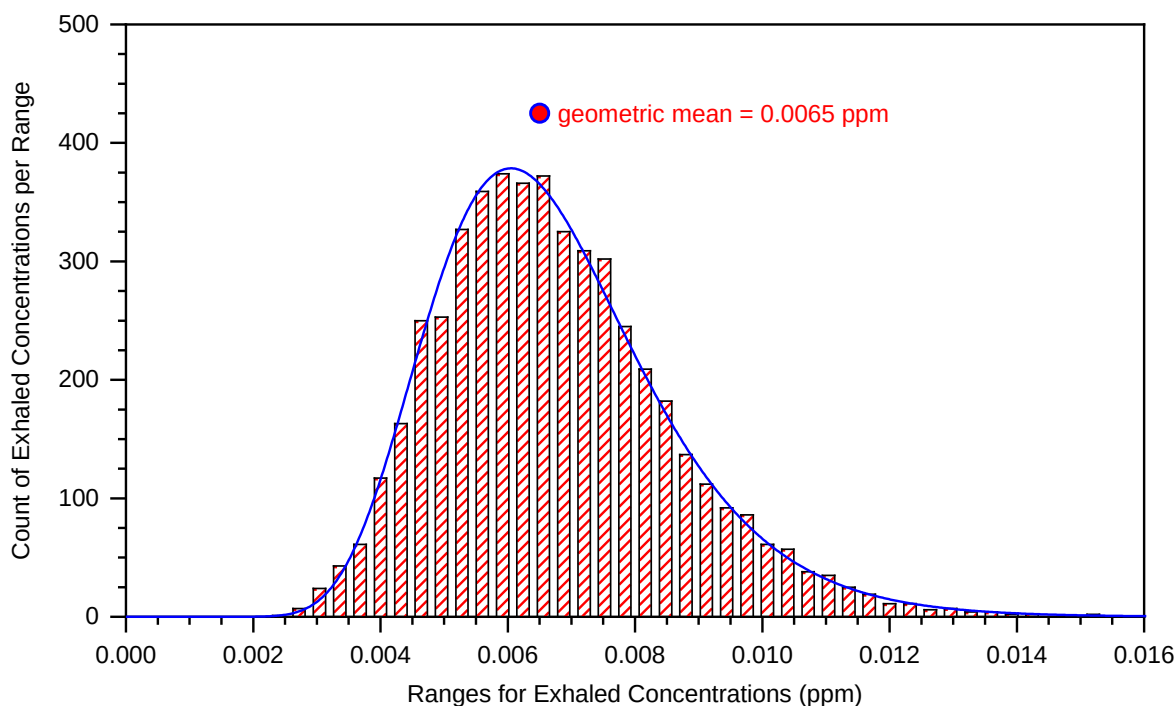


Figure 28. Histogram of Exhaled Toluene Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating toluene exposure of 15 minutes starting 15 minutes into the flight.

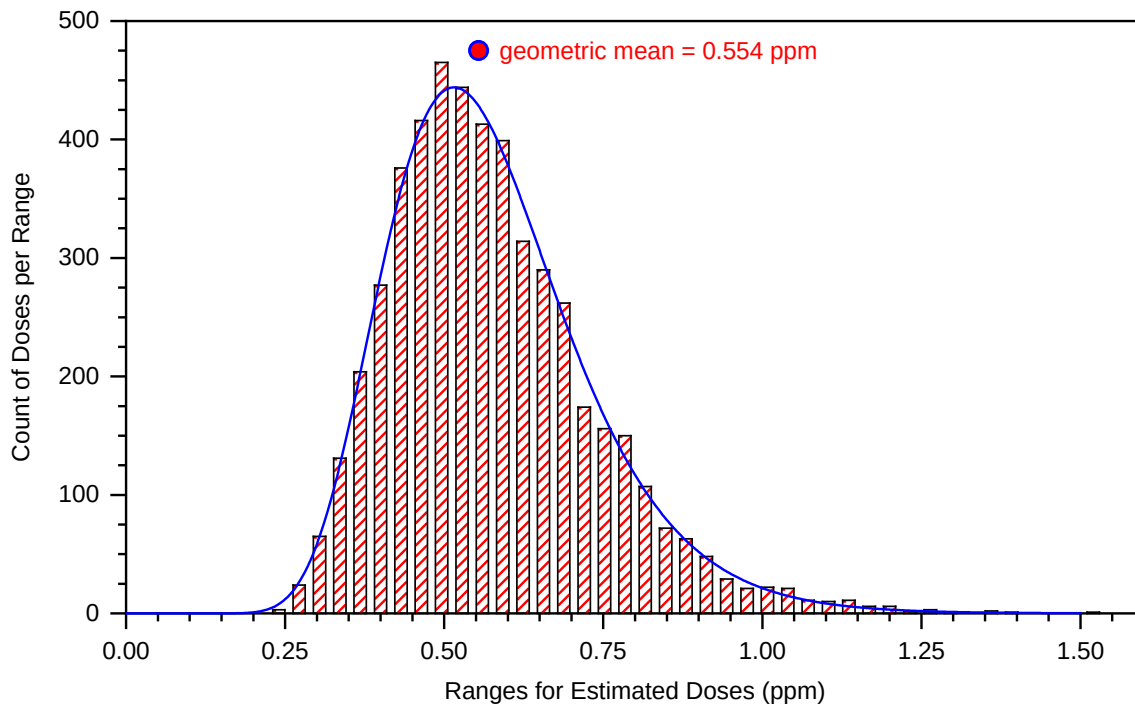


Figure 29. Histogram of Estimated Toluene Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating toluene exposure of 15 minutes starting 15 minutes into the flight.

Distributions for the cyclohexane simulations are shown in Figures 30 and 31. The geometric mean of the exhaled air distribution (0.0055 ppm) is slightly higher than the target exhaled breath concentration of 0.0053 ppm (5.3 ppb), and the highest predicted concentration (0.0132 ppm) is more than twice the target. The geometric mean for the estimated doses (0.405 ppm) is less than the current (0.420 ppm) and previous (0.446 ppm) point estimates and the previous geometric mean (0.431 ppm), but the highest estimated dose (1.14 ppm) is more than twice the current and previous point estimates. The dose is, however, still lower than the previously estimated highest dose (1.20 ppm).

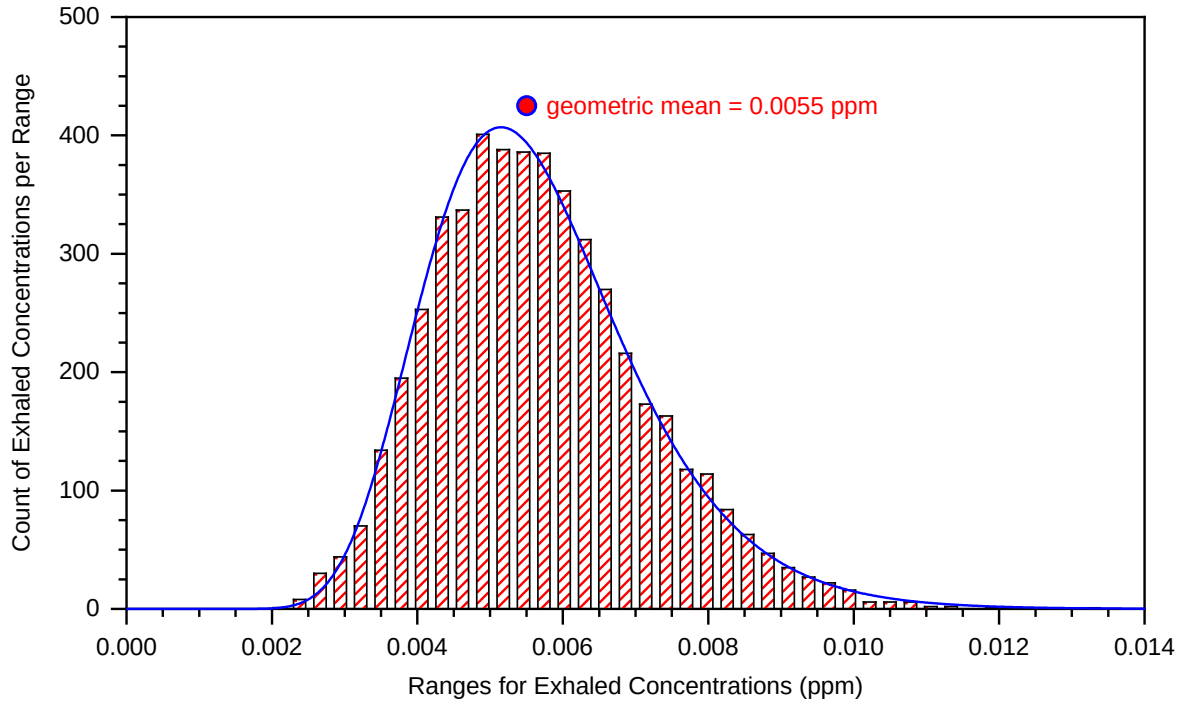


Figure 30. Histogram of Exhaled Cyclohexane Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating cyclohexane exposure of 15 minutes starting 15 minutes into the flight.

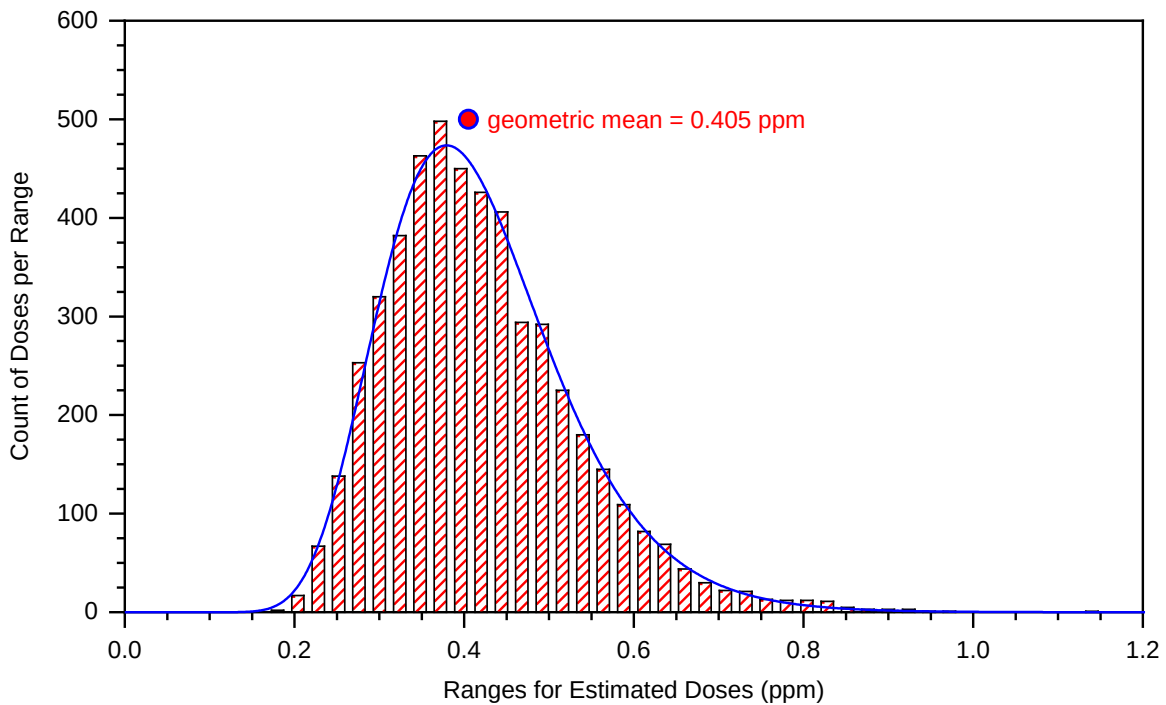


Figure 31. Histogram of Estimated Cyclohexane Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating cyclohexane exposure of 15 minutes starting 15 minutes into the flight.

Figure 32 shows the predicted IPA exhaled air concentrations for the IPA simulations with randomly selected exposure lengths and start times. As in Figure 24, the dose for each parameter set has been estimated and all lines and shaded areas converge to a value of 400 ppb (0.4 ppm) at the end of the follow-up period. The distribution of estimated doses from these simulations is shown in Figure 33. Corresponding histograms for estimated doses for acetone, toluene and cyclohexane are shown in Figures 34 through 36.

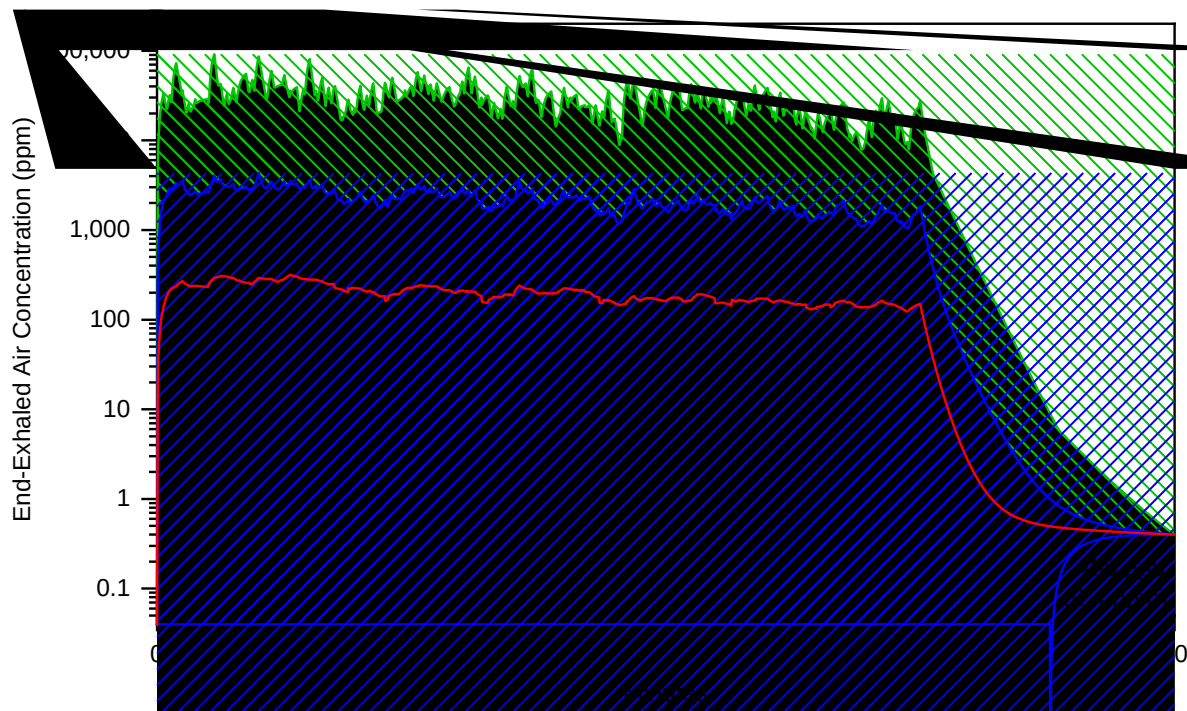


Figure 32. Monte Carlo Results for Exhaled IPA Concentrations from Estimated IPA Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating IPA exposure of random lengths and start times.

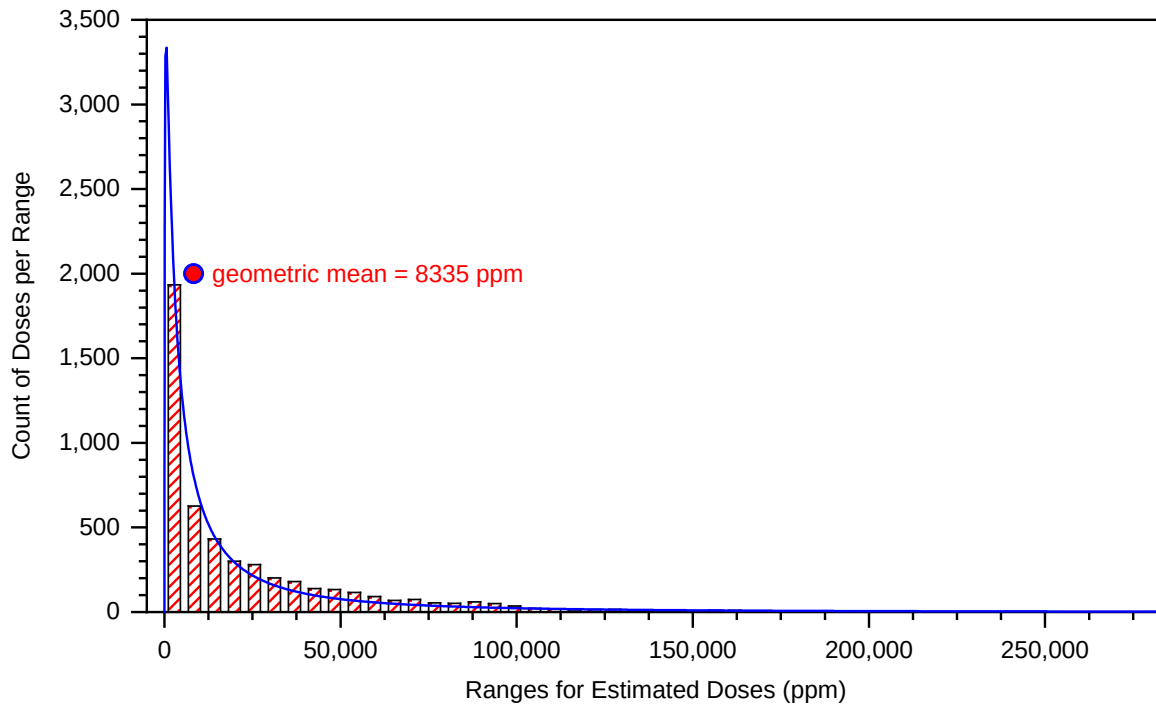


Figure 33. Histogram of Estimated IPA Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating IPA exposure of random lengths and start times.

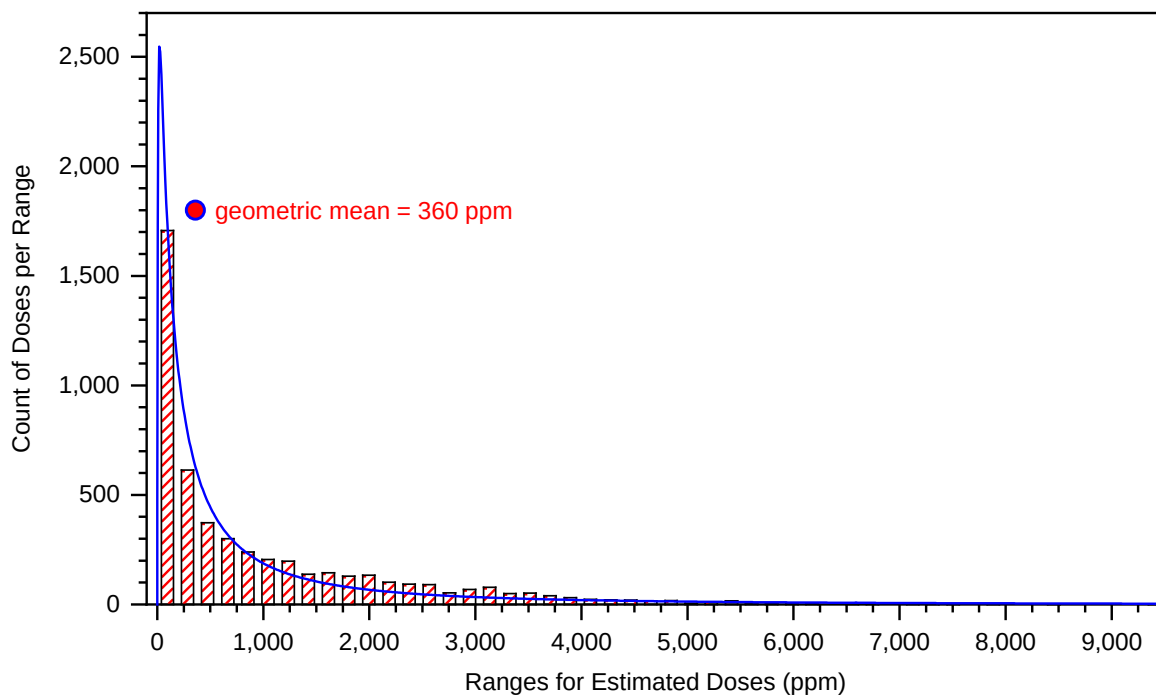


Figure 34. Histogram of Estimated Acetone Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating acetone exposure of random lengths and start times.

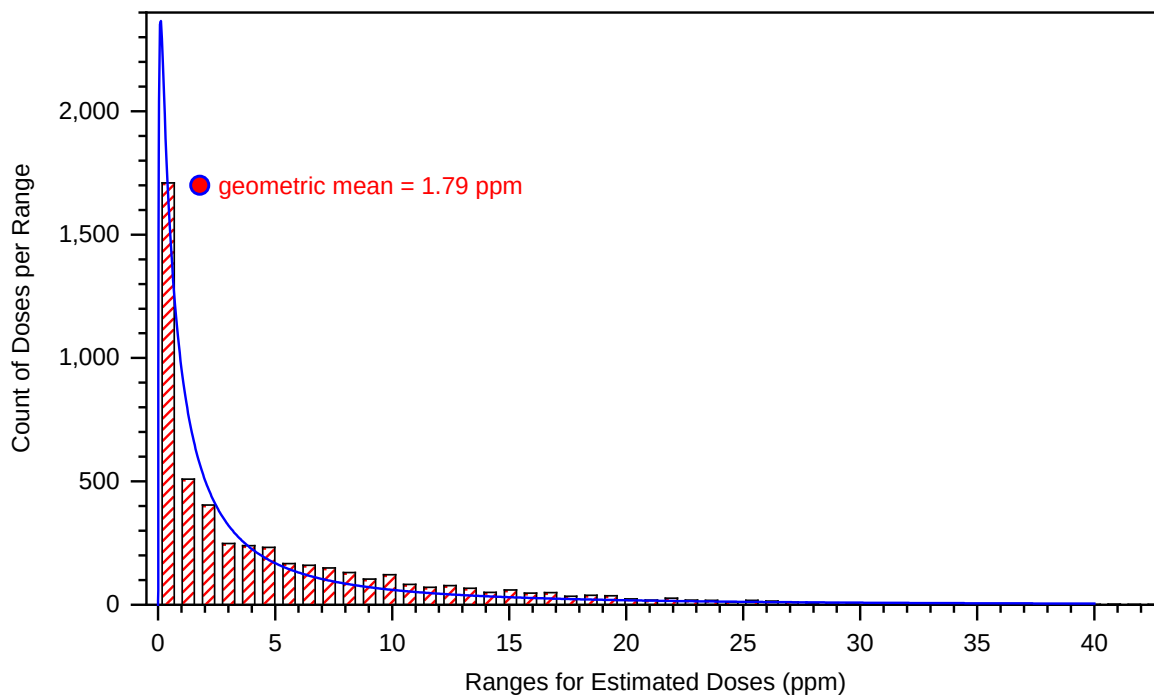


Figure 35. Histogram of Estimated Toluene Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating toluene exposure of random lengths and start times.

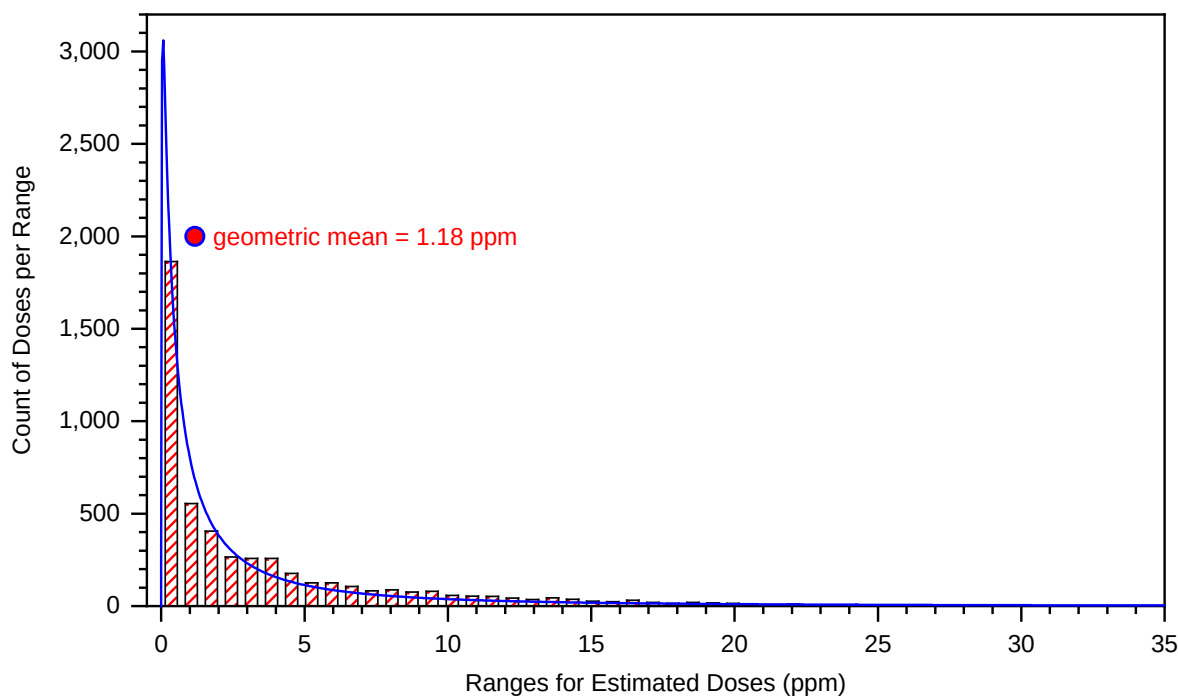


Figure 36. Histogram of Estimated Cyclohexane Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating cyclohexane exposure of random lengths and start times.

5.0 DISCUSSION

An updated PBPK model and pilot exhaled breath exposures from HPARS were used to update previous estimates of potential cockpit exposures. Estimated exposure concentrations derived using linear equations to account for in-flight physiology changes, while consistent with the previously estimated exposures, were generally lower or higher than the previously predicted exposures, particularly for exposures during a maneuver. More specifically, estimated exposures for scenarios occurring during a maneuver pulling G-forces at the upper end of the simulated range were lower than the corresponding concentrations estimated previously which did not account for in-flight physiology changes. Simulated maneuvers of longer length or exerting more G-forces could have an even larger impact. The Monte Carlo analyses results demonstrate how these exposure estimates could vary even more due to inter-individual differences in pharmacokinetics, and it is expected that incorporation of more complex methods of accounting for physiology changes will have more of an effect on predicted exposure concentrations.

This work demonstrated the importance of accounting for in-flight physiology changes in predicting in-flight exposures. As IPA, acetone, toluene and cyclohexane are each known to be respiratory and central nervous system toxicants at the concentrations estimated to have occurred in this study, the range and magnitude of these estimated doses, which are more reflective of pilot physiology during flight, may be used to better correlate the exposures to the reported respiratory pilot symptoms and prioritize which chemicals should be examined further. By expanding the current PBPK model paradigm to the physiological changes of HPA flight, a capability is being developed to assess true pilot physiology in a “virtual” context which will help produce aircraft cabin exposure guidelines to ensure limited probability of contaminated cabin spaces that might contribute to coughing/respiratory symptoms or can be considered a contributing factor in reported symptomology.

6.0 REFERENCES

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APPENDIX A

acslX Model Code

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PROGRAM: OpFeat.CSL
! BrExp.csl with units changed and code added to address changes due to altitude and G forces

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

INITIAL

  INTEGER I
  DIMENSION GForceC(100), NextMove(100)

! Physiological Parameters
  CONSTANT      BW = 70.0           ! Body weight (kg)
  CONSTANT      QCC = 0.004306      ! Cardiac output (L/sec/kg^0.75)
  CONSTANT      VPR = 1.6774       ! Alveolar ventilation-perfusion ratio

! 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      VALvC = 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 (sec)

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

! Simulated G-Force Parameters
  CONSTANT      FracRap = 0.5        ! Fractional split for rapidly perfused compartments
  ! (fraction to upper)
  CONSTANT      FracSlw = 0.4        ! Fractional split for slowly perfused compartments
  ! (fraction to upper)
  CONSTANT      GForceC = 100*1.0    ! G-forces applied (between 1.0 and 7.0)
  CONSTANT      NextMove = 100*5000.0 ! Time between maneuvers (sec)
  CONSTANT      TGForce = 5000.0    ! Time G-force maneuvers start (sec)

! Simulation Control Parameters
  CONSTANT      TStop = 4800.0
  CINTERVAL     CINT = 0.1

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

! Dead Space Volume (fraction)
  CONSTANT      DS = 0.15

! Tissue/Blood Partition Coefficients
  CONSTANT      PB = 848.0          ! Blood/air
  CONSTANT      PMuc = 848.0        ! Mucous/air
  CONSTANT      PBrn = 1.33         ! Brain

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CONSTANT      PFat = 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 = 0.08333      ! Maximum reaction rate (mg/sec/kg^0.75)
CONSTANT      KM = 10.0            ! Michaelis-Menten (mg/L)
CONSTANT      KFC = 0.0            ! First order rate constant (kg^0.25/sec)

! Uptake and Clearance Parameters
CONSTANT      ClUrC = 1.11e-6      ! Urinary clearance (L/sec/kg^0.75)
CONSTANT      kUrtC = 0.003056     ! URT uptake (L/sec/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/sec/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

! Dead Space Volume (fraction)
CONSTANT      DS_Met = 0.15

! 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 = 0.0009722 ! Maximum reaction rate (mg/sec)
CONSTANT      KM_Met = 10.0          ! Michaelis-Menten (mg/L)
CONSTANT      KF_MetC = 0.0          ! First order rate constant (/sec)

! Uptake and Clearance Parameters
CONSTANT      ClUr_MetC = 1.11e-6    ! Urinary clearance (L/sec)
CONSTANT      kUrt_MetC = 0.003056   ! URT uptake (L/sec) for metabolite

! Endogenous Metabolite Production when Dosed with Parent
CONSTANT      CEndo_Met = 0.5         ! Concentration of metabolite (mg/L)
CONSTANT      REndo_MetC = 0.0000575 ! Rate of production of metabolite (mg/sec)

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

! ----- PARAMETER SCALING -----
! Scaled Pulmonary Ventilation Rate (L/sec)
QPC = QCC * VPR
QAlvBase = 0.67 * (QPC * (BW**0.75))

! Scaled Blood Flows (L/sec)
QCBase = QCC * (BW**0.75)
QAdjus = QBrnC + QFatC + QLivC + QRapC + QSlwC

QBrn = (QBrnC / QAdjus) * QCBase      ! Brain
QFat = (QFatC / QAdjus) * QCBase      ! Fat
QLiv = (QLivC / QAdjus) * QCBase      ! Liver
QRap1 = (QRapC / QAdjus) * QCBase * FracRap ! Rapidly perfused tissues #1 (upper)
QRap2 = (QRapC / QAdjus) * QCBase * (1.0 - FracRap) ! Rapidly perfused tissues #2 (lower)
QSlw1 = (QSlwC / QAdjus) * QCBase * FracSlw ! Slowly perfused tissues #1 (upper)

```

```

        QSlw2 = (QSlwC / QAdjus) * QCBase * (1.0 - FracSlw) ! Slowly perfused tissues #2 (lower)
        QCBase = QBrn + QFat + QLiv + QRap1 + QRap2 + QSlw1 + QSlw2

! Scaled Tissue Volumes (L)
        VTotC = VALvC + 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
        VRap1 = (VRapC * VAdjus) * BW * FracRap ! Rapidly perfused tissues #1 (upper)
        VRap2 = (VRapC * VAdjus) * BW * (1.0 - FracRap) ! Rapidly perfused tissues #2 (lower)
        VSlw1 = (VSlwC * VAdjus) * BW * FracSlw ! Slowly perfused tissues #1 (upper)
        VSlw2 = (VSlwC * VAdjus) * BW * (1.0 - FracSlw) ! Slowly perfused tissues #2 (lower)
        VTot = VALv + VBrn + VFat + VLiv + VMuc + VRap1 + VRap2 + VSlw1 + VSlw2

! 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)), QAlvBase))
        ClUr_Met = ClUr_MetC * (BW**0.75)
        kUrt_Met = (min((kUrt_MetC * (BW**0.75)), QAlvBase))

! 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
        IARap1 = CEndo * VRap1 * PRap
        IARap2 = CEndo * VRap2 * PRap
        IASlw1 = CEndo * VSlw1 * PSlw
        IASlw2 = CEndo * VSlw2 * PSlw
        InitTot = IAArt + IABrn + IAFat + IALiv + IARap1 + IARap2 + IASlw1 + IASlw2

! 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
        IARap1_Met = CEndo_Met * VRap1 * PRap_Met
        IARap2_Met = CEndo_Met * VRap2 * PRap_Met
        IASlw1_Met = CEndo_Met * VSlw1 * PSlw_Met
        IASlw2_Met = CEndo_Met * VSlw2 * PSlw_Met
        InitTot_Met = IAArt_Met + IABrn_Met + IAFat_Met + IALiv_Met + IARap1_Met + IARap2_Met +
        IASlw1_Met + IASlw2_Met

! Initialize Starting Values
        I = 1
        GForce = 1.0
        CIZone = 0.0
        CIZone_Met = 0.0
        PerEnd = 0.0
        PerEnd_Met = 0.0
        PerMix = 0.0
        PerMix_Met = 0.0

        SCHEDULE DoseOn .AT. StrtExp
        SCHEDULE GForceOn .AT. TGForce

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 GForceOn  ! Start G-force maneuver
  SCHEDULE GForceOn .AT. T + NextMove(I)

  GForce = GForceC(I)
  I = I + 1
END

DISCRETE DoseOff
  CIZone = 0.0
  CIZone_Met = 0.0
END

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

! Change blood flows with G forces
PROCEDURAL (QBrn = QCBase, QAdjus, GForce)
  QBrn = ((QBrnC / QAdjus) * QCBase) * (1.0 - (0.1927 * (GForce - 1.0)))
  IF (QBrn .LE. 0.0) QBrn = (QBrnC * 0.02) * QCBase
END

! Change blood flows with G-force (baseline value * (1 - (fractional change * increase in G-force
!   from 1)))
  QFat = ((QFatC / QAdjus) * QCBase) * (1.0 - (0.07422 * (GForce - 1.0)))
  QLiv = ((QLivC / QAdjus) * QCBase) * (1.0 - (-0.08453 * (GForce - 1.0)))
  QRap1 = ((QRapC / QAdjus) * QCBase * FracRap) * (1.0 - (0.01297 * (GForce - 1.0)))
  QRap2 = ((QRapC / QAdjus) * QCBase * (1.0 - FracRap)) * (1.0 - (-0.08453 * (GForce - 1.0)))
  QSlw1 = ((QSlwC / QAdjus) * QCBase * FracSlw) * (1.0 - (0.01297 * (GForce - 1.0)))
  QSlw2 = ((QSlwC / QAdjus) * QCBase * (1.0 - FracSlw)) * (1.0 - (-0.1614 * (GForce - 1.0)))

! Cardiac Output (L/sec)
  QC = QBrn + QFat + QLiv + QRap1 + QRap2 + QSlw1 + QSlw2

! Alveolar Ventilation (L/sec)
  QAlv = QAlvBase * (QC / QCBase)

! ----- 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

! Concentration in Mixed Exhaled Air (mg/L)
  CMix = ((1.0 - DS) * CEnd) + (DS * CInh)
  CMixPPM = CMix * (24450.0 / MW)
  IF (Conc.GT.0.0) PerMix = (CMix / ((Conc * MW) / 24450.0)) * 100.0

! Amount in Arterial Blood (mg)
  RAArt = ((QAlv - kUrt) * CInh) - ((QAlv - kUrt) * CALv) + (kUrt * ((CMuc / PMuc) - CALv)) &
    & + (QC * (CVen - CArt)) - RAUrn
  AArt = INTEG(RAArt, IAArt)
  CArt = AArt / VAlv
  CALv = CArt / PB
  CALvPPM = CALv * (24450.0 / MW)
  AUCCArt = INTEG(CArt, 0.0)

! Amount in Urine (mg)
  RAUrn = ClUr * CArt
  AUrn = INTEG(RAUrn, 0.0)

! Amount in Brain (mg)
  RABrn = QBrn * (CArt - CVBrn)
  ABrn = INTEG(RABrn, IABrn)
  CBrn = ABrn / VBrn
  CVBrn = CBrn / PBrn
  AUCCBrn = INTEG(CBrn, 0.0)

! Amount in Fat (mg)
  RAFat = QFat * (CArt - CVFat)
  AFat = INTEG(RAFat, IAFat)
  CFat = AFat / VFat
  CVFat = CFat / PFat

! Amount in Liver (mg)
  RALiv = (QLiv * (CArt - CVLiv)) + REndo - RAMet
  ALiv = INTEG(RALiv, IALiv)
  CLiv = ALiv / VLiv
  CVLiv = CLiv / PLiv

! Amount of Endogenous Metabolite Produced when Dosing with Metabolite
  AEndo = INTEG(REndo, 0.0)

! Amount Metabolised in Liver -- Saturable and 1st Order (mg)
  RAMet = ((VMax * CVLiv) / (KM + CVLiv)) + (KF * CVLiv * VLiv)
  AMet = INTEG(RAMet, 0.0)

! Amount in Rapidly Perfused Tissue #1 (upper) (mg)
  RARap1 = QRap1 * (CArt - CVRap1)
  ARap1 = INTEG(RARap1, IARap1)
  CRap1 = ARap1 / VRap1
  CVRap1 = CRap1 / PRap

! Amount in Rapidly Perfused Tissue #2 (lower) (mg)
  RARap2 = QRap2 * (CArt - CVRap2)
  ARap2 = INTEG(RARap2, IARap2)
  CRap2 = ARap2 / VRap2
  CVRap2 = CRap2 / PRap

! Amount in Slowly Perfused Tissue #1 (upper) (mg)
  RASlw1 = QSlw1 * (CArt - CVSlw1)
  ASlw1 = INTEG(RASlw1, IASlw1)
  CSlw1 = ASlw1 / VSlw1
  CVSlw1 = CSlw1 / PSlw

```

```

! Amount in Slowly Perfused Tissue #2 (lower) (mg)
  RASlw2 = QSlw2 * (CArt - CVSlw2)
  ASlw2 = INTEG(RASlw2, IASlw2)
  CSlw2 = ASlw2 / VSlw2
  CVSlw2 = CSlw2 / PSlw

! Concentration in Mixed Venous Blood (mg/L)
  CVen = (QBrn*CVBrn + QFat*CVFat + QLiv*CVLiv + QRap1*CVRap1 + QRap2*CVRap2 &
    & + QSlw1*CVSlw1 + QSlw2*CVSlw2) / QC

! ----- METABOLITE PBPK MODEL -----
! Amount in Inhaled Air
  Cinh_Met = ((Conc_Met * MW_Met) / 24450.0) * CIZone_Met
  CP_Met = (Cinh_Met * 24450.0) / MW_Met

! Amount in Mucous
  RAMuc_Met = kUrt_Met * (Cinh_Met - (CMuc_Met / PMuc_Met) + CALv_Met - (CMuc_Met / PMuc_Met))
  AMuc_Met = INTEG(RAMuc_Met, 0.0)
  CMuc_Met = AMuc_Met / VMuc

! Amount Exhaled (mg)
  RAExh_Met = ((QAlv - kUrt_Met) * CALv_Met) + (kUrt_Met * (CMuc_Met / PMuc_Met))
  AExh_Met = 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

! Concentration in Mixed Exhaled Air (mg/L)
  CMix_Met = ((1.0 - DS_Met) * CEnd_Met) + (DS_Met * Cinh_Met)
  CMixPPM_Met = CMix_Met * (24450.0 / MW_Met)
  IF (Conc_Met.GT.0.0) PerMix_Met = (CMix_Met / ((Conc_Met * MW) / 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

! Amount in Fat (mg)
  RAFat_Met = QFat * (CArt_Met - CVFat_Met)
  AFat_Met = INTEG(RAFat_Met, IAFat_Met)
  CFat_Met = AFat_Met / VFat
  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)
  CLiv_Met = ALiv_Met / VLiv
  CVLiv_Met = CLiv_Met / PLiv_Met

! 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 #1 (upper) (mg)
RARap1_Met = QRap1 * (CArt_Met - CVRap1_Met)
ARap1_Met = INTEG(RARap1_Met, IARap1_Met)
CRap1_Met = ARap1_Met / VRap1
CVRap1_Met = CRap1_Met / PRap_Met

! Amount in Rapidly Perfused Tissue #2 (lower) (mg)
RARap2_Met = QRap2 * (CArt_Met - CVRap2_Met)
ARap2_Met = INTEG(RARap2_Met, IARap2_Met)
CRap2_Met = ARap2_Met / VRap2
CVRap2_Met = CRap2_Met / PRap_Met

! Amount in Slowly Perfused Tissue #1 (upper) (mg)
RASlw1_Met = QSlw1 * (CArt_Met - CVSlw1_Met)
ASlw1_Met = INTEG(RASlw1_Met, IASlw1_Met)
CSlw1_Met = ASlw1_Met / VSlw1
CVSlw1_Met = CSlw1_Met / PSlw_Met

! Amount in Slowly Perfused Tissue #2 (lower) (mg)
RASlw2_Met = QSlw2 * (CArt_Met - CVSlw2_Met)
ASlw2_Met = INTEG(RASlw2_Met, IASlw2_Met)
CSlw2_Met = ASlw2_Met / VSlw2
CVSlw2_Met = CSlw2_Met / PSlw_Met

! Concentration in Mixed Venous Blood (mg/L)
CVen_Met = (QBrn*CVBrn_Met + QFat*CVFat_Met + QLiv*CVLiv_Met + QRap1*CVRap1_Met &
& + QRap2*CVRap2_Met + QSlw1*CVSlw1_Met + QSlw2*CVSlw2_Met) / QC

! ----- CHECK MASS BALANCE -----
TDose = INTEG((QAlv*CIinh), 0.0)
Parent = AMuc + AArt + ABrn + AFat + ALiv + ARap1 + ARap2 + ASlw1 + ASlw2 + AExh + AUrn &
& + AMet - InitTot - AEndo
Metabolite = AMuc_Met + AArt_Met + ABrn_Met + AFat_Met + ALiv_Met + ARap1_Met + ARap2_Met &
& + ASlw1_Met + ASlw2_Met + AExh_Met &
& + AUrn_Met + AMet_Met - InitTot_Met - AEndo_Met
MassBal = TDose - Parent
MetBal = INTEG((QAlv*CIinh_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 to fit 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;
DS=0.25;
PB=260.0; PMUC=260.0; PBRN=0.69; PFAT=0.44; PLIV=0.58; PRAP=0.69; PSLW=0.7;
VMAXC=3.5/60.0/60.0; KM=10.0; KFC=0.0;
CLURC=0.004/60.0/60.0; KURTC=(11.0/27.75)*QPC;
CENDO=0.5; RENDOC=0.207/60.0/60.0;

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;
```

Cyclohexane.m

```
% Sets human cyclohexane parameters from Table 1 in Hissink et al. (2009)
% Adjusted VMaxC value from (5.4/60.0) to (4.34/60.0) so that IPA model scaling by BW to the 0.75
% gets same value as Hissink who uses 0.7
% DS is only used for CMix and PerMix
```

```
MW=84.16;
DS=0.25;
PB=1.3; PMUC=1.0; PBRN=9.9/PB; PFAT=234.0/PB; PLIV=9.9/PB; PRAP=9.9/PB; PSLW=5.1/PB;
VMAXC=4.34/60.0/60.0; KM=0.13; KFC=0.0;
CLURC=0.0; KURTC=0.0;
CENDO=0.0; RENDOC=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_Male_Acetone.m
```

```
PB = 0 + 1 * lognrnd(5.5557, 0.099751, 208, 312);
PMUC = 0 + 1 * lognrnd(5.5411, 0.19804, 46.901, 93.122);
PBRN = 0 + 1 * lognrnd(-0.39067, 0.19804, 0.414, 0.966);
PFAT = 0 + 1 * lognrnd(-0.86407, 0.29356, 0.176, 0.704);
PLIV = 0 + 1 * lognrnd(-0.56434, 0.19804, 0.348, 0.812);
PRAP = 0 + 1 * lognrnd(-0.39067, 0.19804, 0.414, 0.966);
PSLW = 0 + 1 * lognrnd(-0.37629, 0.19804, 0.42, 0.98);
VMAX = 0 + 1 * lognrnd(-6.979, 0.29356, 0.00038889, 0.0015556);
KM = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLURC = 0 + 1 * lognrnd(-13.7532, 0.29356, 4.4444e-7, 1.77776e-6);
KURTC = 0 + 1 * lognrnd(-5.8990, 0.29356, 0.0011452, 0.0045806);
```

Distrib_Cyclohex.m

% Called through MC_Anal.m in MC_Male_Cyclohex.m

```
PB = 0 + 1 * lognrnd(0.25739, 0.099751, 1.04, 1.56);
PBRN = 0 + 1 * lognrnd(2.0106, 0.19804, 4.5692, 10.662);
PFAT = 0 + 1 * lognrnd(5.1499, 0.29356, 72, 288);
PLIV = 0 + 1 * lognrnd(2.0106, 0.19804, 4.5692, 10.662);
PRAP = 0 + 1 * lognrnd(2.0106, 0.19804, 4.5692, 10.662);
PSLW = 0 + 1 * lognrnd(1.3473, 0.19804, 2.3539, 5.4923);
VMAXC = 0 + 1 * lognrnd(-6.7639, 0.29356, 0.00048224, 0.001929);
KM = 0 + 1 * lognrnd(-2.0833, 0.29356, 0.052, 0.208);
```

Distrib_IPA.m

% Called through MC_Anal.m in MC_Male_IPA.m

```
PB = 0 + 1 * lognrnd(6.7379, 0.099751, 678.4, 1017.6);
PMUC = 0 + 1 * lognrnd(6.7233, 0.19804, 508.8, 1187.2);
PBRN = 0 + 1 * lognrnd(0.26557, 0.19804, 0.798, 1.862);
PFAT = 0 + 1 * lognrnd(-1.1825, 0.29356, 0.128, 0.512);
PLIV = 0 + 1 * lognrnd(0.12881, 0.19804, 0.696, 1.624);
PRAP = 0 + 1 * lognrnd(0.20353, 0.19804, 0.75, 1.75);
PSLW = 0 + 1 * lognrnd(0.24275, 0.19804, 0.78, 1.82);
VMAXC = 0 + 1 * lognrnd(-2.5280, 0.29356, 0.0333332, 0.1333328);
KM = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLURC = 0 + 1 * lognrnd(-13.7532, 0.29356, 4.4444e-7, 1.77776e-6);
KURTC = 0 + 1 * lognrnd(-5.8990, 0.29356, 0.0011452, 0.0045806);

% PB_MET = 0 + 1 * lognrnd(5.5557, 0.099751, 208, 312);
% PMUC_MET = 0 + 1 * lognrnd(5.5411, 0.19804, 46.901, 93.122);
% PBRN_MET = 0 + 1 * lognrnd(-0.39067, 0.19804, 0.414, 0.966);
% PFAT_MET = 0 + 1 * lognrnd(-0.86407, 0.29356, 0.176, 0.704);
% PLIV_MET = 0 + 1 * lognrnd(-0.56434, 0.19804, 0.348, 0.812);
% PRAP_MET = 0 + 1 * lognrnd(-0.39067, 0.19804, 0.414, 0.966);
% PSLW_MET = 0 + 1 * lognrnd(-0.37629, 0.19804, 0.42, 0.98);
% VMAX_METC = 0 + 1 * lognrnd(-6.979, 0.29356, 0.00038889, 0.0015556);
% KM_MET = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
% CLURC_MET = 0 + 1 * lognrnd(-13.7532, 0.29356, 4.4444e-7, 1.77776e-6);
% KURTC_MET = 0 + 1 * lognrnd(-5.8990, 0.29356, 0.0011452, 0.0045806);
```

Distrib_Physio.m

% Called through MC_Anal.m in, MC_Male_Acetone.m, MC_Male_Cyclohex.m, MC_Male_IPA.m,
% MC_Male_Toluene.m, MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and
% MC_Female_Toluene.m

```
if (Gender == 'Male ')
    BW = 0 + 1 * normrnd(84.14, 11.118, 60.237, 129.46);
else
    BW = 0 + 1 * normrnd(67.77, 9.2079, 46.901, 93.122);
end
```

```
QCC = 0 + 1 * normrnd(0.0043056, 0.0003875, 0.0035306, 0.0050806);
VPR = 0 + 1 * lognrnd(0.50754, 0.13932, 1.2077, 2.1471);
QBRNC = 0 + 1 * normrnd(0.123, 0.0369, 0.0492, 0.1968);
QFATC = 0 + 1 * normrnd(0.05, 0.015, 0.02, 0.08);
QLIVC = 0 + 1 * normrnd(0.246, 0.0861, 0.0738, 0.4182);
QRAPC = 0 + 1 * normrnd(0.352, 0.0704, 0.2112, 0.4928);
QSLWC = 0 + 1 * normrnd(0.229, 0.03435, 0.1603, 0.2977);
VALVC = 0 + 1 * normrnd(0.0079, 0.00237, 0.00316, 0.01264);
VBRNC = 0 + 1 * normrnd(0.02, 0.006, 0.008, 0.032);
VFATC = 0 + 1 * normrnd(0.188, 0.0564, 0.0752, 0.3008);
VLIVC = 0 + 1 * normrnd(0.026, 0.0013, 0.0234, 0.0286);
VMUCC = 0 + 1 * normrnd(0.0001, 0.00001, 0.00008, 0.00012);
VRAPC = 0 + 1 * normrnd(0.032, 0.0032, 0.0256, 0.0384);
VSLWC = 0 + 1 * normrnd(0.602, 0.1806, 0.2408, 0.9632);
```

Distrib_Toluene.m

% Called through MC_Anal.m in MC_Male_Toluene.m

```
PB = 0 + 1 * lognrnd(2.7423, 0.099751, 12.48, 18.72);
PBRN = 0 + 1 * lognrnd(0.82767, 0.19804, 1.4, 3.2666);
PFAT = 0 + 1 * lognrnd(4.1382, 0.29356, 26.18, 104.72);
PLIV = 0 + 1 * lognrnd(1.6592, 0.19804, 3.2154, 7.5026);
PRAP = 0 + 1 * lognrnd(1.6592, 0.19804, 3.2154, 7.5026);
PSLW = 0 + 1 * lognrnd(0.55453, 0.19804, 1.0654, 2.4858);
VMAXC = 0 + 1 * lognrnd(-6.6632, 0.29356, 0.00053332, 0.0021333);
KM = 0 + 1 * lognrnd(-0.64093, 0.29356, 0.22, 0.88);
```

Fit_Dose_Alg.m

% Dose fitting algorithm -- uses ratios

```
if TargetParam == 'CendPPM'
    EndPt = CENDPPM;
else
    EndPt = CENDPPM_MET;
end

NumAttempt = 0;
while abs(EndPt-Target) > Tolerance
    if ConcFit == 'Conc'
        CONC = CONC * (Target / EndPt);
    else
        CONC_MET = CONC_MET * (Target / EndPt);
    end

    start @NoCallback
    NumAttempt = NumAttempt + 1;
    TCHNG
    STRTEXP
    CONC
    CONC_MET

    if TargetParam == 'CendPPM'
        CENDPPM
        EndPt = CENDPPM;
    else
        CENDPPM_MET
        EndPt = CENDPPM_MET;
    end

    if NumAttempt > 50
        break;
    end
end
```

Fit_Dose_Alt_Alg.m

% Alternate dose fitting algorithm -- uses interval halving

% Find doses that bound the target endpoint value

```
if TargetParam == 'CENDPPM'
    EndPt = CENDPPM;
else
    EndPt = CENDPPM_MET;
end

if ConcFit == 'Conc'
    CurrentConc = CONC;
else
    CurrentConc = CONC_MET;
end

if (EndPt < Target)
    while EndPt < Target
        PLowConc = CurrentConc;
        CurrentConc = 1.01 * CurrentConc;

        if ConcFit == 'Conc'
            CONC = CurrentConc;
        else
            CONC_MET = CurrentConc;
        end

        start @NoCallback
        if TargetParam == 'CENDPPM'
            EndPt = CENDPPM;
        else
            EndPt = CENDPPM_MET;
        end
    end
    PHighConc = CurrentConc;
else
    while EndPt > Target
        PHighConc = CurrentConc;
        CurrentConc = 0.99 * CurrentConc;

        if ConcFit == 'Conc'
            CONC = CurrentConc;
        else
            CONC_MET = CurrentConc;
        end

        start @NoCallback
        if TargetParam == 'CENDPPM'
            EndPt = CENDPPM;
        else
            EndPt = CENDPPM_MET;
        end
    end
    PLowConc = CurrentConc;
end

if ConcFit == 'Conc'
    CONC = (PHighConc + PLowConc) / 2.0;
    CurrentConc = CONC;
else
    CONC_MET = (PHighConc + PLowConc) / 2.0;
    CurrentConc = CONC_MET;
end

start @NoCallback
TCHNG
STRTEXP
CONC
CONC_MET
```

```

    if TargetParam == 'CENDPPM      '
        CENDPPM
        EndPt = CENDPPM;
    else
        CENDPPM_MET
        EndPt = CENDPPM_MET;
    end

% -----
% Repeat simulations until the dose to match the target endpoint value is found
NumAttempt = 0;
while abs(EndPt-Target) > Tolerance
    if (EndPt < Target)
        PLowConc = CurrentConc;
    else
        PHighConc = CurrentConc;
    end

    if ConcFit == 'Conc      '
        CONC = (PHighConc + PLowConc) / 2.0;
        CurrentConc = CONC;
    else
        CONC_MET = (PHighConc + PLowConc) / 2.0;
        CurrentConc = CONC_MET;
    end

    start @NoCallback
    NumAttempt = NumAttempt + 1;
    TCHNG
    STRTEXP
    CONC
    CONC_MET

    if TargetParam == 'CENDPPM      '
        CENDPPM
        EndPt = CENDPPM;
    else
        CENDPPM_MET
        EndPt = CENDPPM_MET;
    end

    if NumAttempt > 50
        break;
    end
end
end

```

FitAllDoses.m

```
% Called in FitDoses_Acetone_Only_with_Gs.m, FitDoses_Acetone_from_IPA_Only_with_Gs.m,
%   FitDoses_Cyclohexane_with_Gs.m, FitDoses_IPA_with_Gs.m, FitDoses_Toluene_with_Gs.m and
%   FitDoses_IPA_without_Gs.m

% Initialize arrays and counter
fitdoses = []; times = []; cendoutput = []; cendmet_output = []; massbal_th = [];
metbal_th = []; mb_maxmin = [];
MaxI = 0;

% Start iterative loop to fit dose for each value of TChng
for iter = [1 : 6]
    STRTEXP = 0.0;
    TCHNG = TChngList(iter);
    i = 1;
    j = 1 + ((iter-1) * 9);

    while STRTEXP + TCHNG <= EXPEND
        % Run to get initial value for CEndPPM for fitting doses and then fit dose
        start @NoCallback
        Fit_Dose_Alg

        % If dose isn't fit, use alternate methods
        if abs(EndPt-Target) > Tolerance
            Fit_Dose_Alt_Alg
        end

        % If dose still isn't fit, increase tolerance
        if abs(EndPt-Target) > Tolerance
            Tolerance = Tolerance * 10.0;
            Fit_Dose_Alg

            if abs(EndPt-Target) > Tolerance
                Fit_Dose_Alt_Alg
            end

            Tolerance = Tolerance / 10.0;
        end

        disp("Finished Fitting Dose");

        % Check minimum compartment values to check for validity of run
        mins = [];
        mins(:, :) = [mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
            min(_aliv) min(_amet) min(_arap1) min(_arap2) min(_aslw1) min(_aslw2)
            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(_arap1_met) min(_arap2_met) min(_aslw1_met) min(_aslw2_met)
            min(_cven_met)];
        min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
        massbal_th = addcolsj(massbal_th, _massbal, @Justification = 'begin');
        metbal_th = addcolsj(metbal_th, _metbal, @Justification = 'begin');

        % Save final values from each simulation
        fitdoses(i,j) = STRTEXP / 60.0;
        fitdoses(i,j+1) = CONC;
        fitdoses(i,j+2) = CENDPPM;
        fitdoses(i,j+3) = max(_cven);
        fitdoses(i,j+4) = max(_cbrn);
        fitdoses(i,j+5) = CENDPPM_MET;
        fitdoses(i,j+6) = max(_cven_met);
        fitdoses(i,j+7) = max(_cbrn_met);

        if abs(EndPt-Target) > Tolerance
            fitdoses(i,j+8) = 0;
        else
            fitdoses(i,j+8) = 1;
        end
    end
end
```

```

%      Save timecourse for exhaled air concentrations for parent and metabolite
times = addcolsj(times, _minutes, @Justification = 'begin');
cendoutput = addcolsj(cendoutput, _cendppm, @Justification = 'begin');
cendmet_output = addcolsj(cendmet_output, _cendppm_met, @Justification = 'begin');

%      Move to next start time of exposure for a given length of exposure
if TCHngList(iter) == 30.0
    STRTEXP = STRTEXP + (2.0 * TCHNG);
else
    STRTEXP = STRTEXP + TCHNG;
end
i = i + 1;
end

%      Update counter (MaxI) for total number of simulations
if (i > MaxI)
    MaxI = i-1;
end
end

mb_maxmin(1) = max(max(massbal_th));
mb_maxmin(2) = min(min(massbal_th));
mb_maxmin(3) = max(max(metbal_th));
mb_maxmin(4) = min(min(metbal_th));

% Save flight scenario
save _gforce @file='fitdoses_male_Gs_scenario.txt' @format=ascii

% Save cardiac output values and tissue blood flow values
flows = [];
flows = addcolsj(flows, _qalv, @Justification = 'begin');
flows = addcolsj(flows, _qc, @Justification = 'begin');
flows = addcolsj(flows, _qbrn, @Justification = 'begin');
flows = addcolsj(flows, _qfat, @Justification = 'begin');
flows = addcolsj(flows, _qliv, @Justification = 'begin');
flows = addcolsj(flows, _qrap1, @Justification = 'begin');
flows = addcolsj(flows, _qrap2, @Justification = 'begin');
flows = addcolsj(flows, _qslw1, @Justification = 'begin');
flows = addcolsj(flows, _qslw2, @Justification = 'begin');
save flows @file='fitdoses_male_Gs_flows.txt' @format=ascii

```

FitAllDoses_Met.m

```
% Called in FitDoses_Acetone_and_IPA_with_Gs.m

% Initialize arrays and counter
fitdoses = []; massbal_th = []; metbal_th = []; mb_maxmin = [];
MaxI = 0;

% Start iterative loop to fit metabolite dose for each value of TChng
for iter = [1 : 6]
    TCHNG = TChngList(iter);
    i = 1;
    j = 1 + ((iter-1) * 10);

% Start iterative loop to fit acetone dose for each IPA concentration
    for iter2 = [(((iter-1)*8)+1) : 48]
        CONC = ConcList(iter2);
        STRTEXP = 0.0;

        while STRTEXP + TCHNG <= EXPEND
% Run to get initial value for CEndPPM_Met for fitting doses and then fit dose
            start @NoCallback
            Fit_Dose_Alg

% If dose isn't fit, use alternate methods
            if abs(EndPt-Target) > Tolerance
                Fit_Dose_Alt_Alg
            end

% If dose still isn't fit, increase tolerance
            if abs(EndPt-Target) > Tolerance
                Tolerance = Tolerance * 10.0;
                Fit_Dose_Alg

                if abs(EndPt-Target) > Tolerance
                    Fit_Dose_Alt_Alg
                end

                Tolerance = Tolerance / 10.0;
            end

            disp("Finished Fitting Dose");

% Check minimum compartment values to check for validity of run
            mins = [];
            mins(:, :) = [mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
                min(_afat) min(_aliv) min(_amet) min(_arap1) min(_arap2) min(_aslw1)
                min(_aslw2) 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(_arap1_met) min(_arap2_met) min(_aslw1_met)
                min(_aslw2_met) min(_cven_met)];
            min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
            massbal_th = addcolsj(massbal_th, _massbal, @Justification = 'begin');
            metbal_th = addcolsj(metbal_th, _metbal, @Justification = 'begin');

% Save final values from each simulation
            fitdoses(i,j) = STRTEXP / 60.0;
            fitdoses(i,j+1) = CONC;
            fitdoses(i,j+2) = CONC_MET;
            fitdoses(i,j+3) = CENDPPM;
            fitdoses(i,j+4) = max(_cven);
            fitdoses(i,j+5) = max(_cbrn);
            fitdoses(i,j+6) = CENDPPM_MET;
            fitdoses(i,j+7) = max(_cven_met);
            fitdoses(i,j+8) = max(_cbrn_met);

            if abs(EndPt-Target) > Tolerance
                fitdoses(i,j+9) = 0;
            else
                fitdoses(i,j+9) = 1;
            end
        end
    end
end
```

```

%           Move to next start time of exposure for a given length of exposure
if TChngList(iter) == 30.0
    STRTEXP = STRTEXP + (2.0 * TCHNG);
else
    STRTEXP = STRTEXP + TCHNG;
end
%           STRTEXP = STRTEXP + 1.0;
i = i + 1;
end

%           Update counter (MaxI) for total number of simulations
if (i > MaxI)
    MaxI = i-1;
end
end
end

mb_maxmin(1) = max(max(massbal_th));
mb_maxmin(2) = min(min(massbal_th));
mb_maxmin(3) = max(max(metbal_th));
mb_maxmin(4) = min(min(metbal_th));

```

FitDoses Acetone from IPA Only with Gs.m

```

% Breath exposure simulations for Acetone for males with G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
IPA
BW=84.14; CONC=100.0; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
CENDO_MET=0.0; RENDO_METC=0.0;
TGFORCE=152.0;
SetGForces

% Define tolerance and target value for endpoint (target for end-exhaled air of 353.706 ppb
% (0.3537 ppm))
Tolerance = 0.00000000001; TargetParam = 'CEndPPM_Met'; Target = 0.3537;
ConcFit = 'Conc    ';

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_acetone_from_ipa_only_Gs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_acetone_from_ipa_only_Gs_mb.txt' @format=ascii

% Save individual time courses for CEndPPM and CEndPPM_Met for each fit dose for each value of
% TChng (for each value of TChng, this writes a column of values for each exposure start time
% -- repeats set of columns for each new TChng)
save times @file='fitdoses_male_acetone_from_ipa_only_Gs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_acetone_from_ipa_only_Gs_cendppm.txt' @format=ascii
save cendmet_output @file='fitdoses_male_acetone_from_ipa_only_Gs_cendppm_met.txt'
@format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_acetone_from_ipa_only_Gs_min_tiss.txt' @format=ascii

```

FitDoses_Acetone_Only_with_Gs.m

```
% Breath exposure simulations for Acetone for males with G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
Acetone
BW=84.14; CONC=100.0; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
CENDO=0.0; RENDOC=0.0;
TGFORCE=152.0;
SetGForces

% Define tolerance and target value for endpoint (target for end-exhaled air of 353.706 ppb
% (0.3537 ppm))
Tolerance = 0.0000000001; TargetParam = 'CEndPPM'; Target = 0.3537;
ConcFit = 'Conc';

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_acetone_only_Gs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_acetone_only_Gs_mb.txt' @format=ascii

% Save individual time courses for CEndPPM for each fit dose for each value of TChng
% (for each value of TChng, this writes a column of values for each exposure start time -
% repeats set of columns for each new TChng)
save times @file='fitdoses_male_acetone_only_Gs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_acetone_only_Gs_cendppm.txt' @format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_acetone_only_Gs_min_tiss.txt' @format=ascii
```

FitDoses_Cyclohexane_with_Gs.m

```
% Breath exposure simulations for Cyclohexane for males with G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Cyclohexane
BW=84.14; CONC=0.7; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
CENDO_MET=0.0; RENDOC_METC=0.0;
TGFORCE=152.0;
SetGForces

% Define tolerance and target value for endpoint (target for end-exhaled air of 5.314 ppb
% (0.005314 ppm))
Tolerance = 0.00000000000001; TargetParam = 'CEndPPM'; Target = 0.005314;
ConcFit = 'Conc';
```

```

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_cyclohex_Gs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_cyclohex_Gs_mb.txt' @format=ascii

% Save individual time courses for CEndPPM for each fit dose for each value of TChng
% (for each value of TChng, this writes a column of values for each exposure start time -
% repeats set of columns for each new TChng)
save times @file='fitdoses_male_cyclohex_Gs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_cyclohex_Gs_cendppm.txt' @format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_cyclohexane_Gs_min_tiss.txt' @format=ascii

```

FitDoses_IPA_with_Gs.m

```

% Breath exposure simulations for IPA for males with G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
IPA
BW=84.14; CONC=100.0; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
CENDO_MET=0.0; RENDO_METC=0.0;
TGFORCE=152.0;
SetGForces

% Define tolerance and target value for endpoint (target for end-exhaled air of 400 ppb
% (0.4 ppm))
Tolerance = 0.0000001; TargetParam = 'CendPPM'; Target = 0.4; ConcFit = 'Conc';

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_ipa_Gs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_ipa_Gs_mb.txt' @format=ascii

% Save individual time courses for CendPPM and CendPPM_Met for each fit dose for each value of
% TChng (for each value of TChng, this writes a column of values for each exposure start time
% -- repeats set of columns for each new TChng)
save times @file='fitdoses_male_ipa_Gs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_ipa_Gs_cendppm.txt' @format=ascii
save cendmet_output @file='fitdoses_male_ipa_Gs_cendppm_met.txt' @format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_male_ipa_Gs_min_tiss.txt' @format=ascii

```

FitDoses_IPA_without_Gs.m

```
% Breath exposure simulations for IPA for males without G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
IPA
BW=84.14; CONC=100.0; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
CENDO_MET=0.0; RENDO_METC=0.0;
TGFORCE=5000.0;

% Define tolerance and target value for endpoint (target for end-exhaled air of 400 ppb
% (0.4 ppm))
Tolerance = 0.0000001; TargetParam = 'CEndPPM'; Target = 0.4; ConcFit = 'Conc';

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_ipa_noGs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_ipa_noGs_mb.txt' @format=ascii

% Save cardiac output values and tissue blood flow values
flows = [];
flows = addcolsj(flows, _qalv, @Justification = 'begin');
flows = addcolsj(flows, _qc, @Justification = 'begin');
flows = addcolsj(flows, _qbrn, @Justification = 'begin');
flows = addcolsj(flows, _qfat, @Justification = 'begin');
flows = addcolsj(flows, _qliv, @Justification = 'begin');
flows = addcolsj(flows, _grap1, @Justification = 'begin');
flows = addcolsj(flows, _grap2, @Justification = 'begin');
flows = addcolsj(flows, _qslw1, @Justification = 'begin');
flows = addcolsj(flows, _qslw2, @Justification = 'begin');
save flows @file='fitdoses_male_ipa_noGs_flows.txt' @format=ascii

% Save individual time courses for CEndPPM and CEndPPM_Met for each fit dose for each value of
% TChng (for each value of TChng, this writes a column of values for each exposure start time
% -- repeats set of columns for each new TChng)
save times @file='fitdoses_male_ipa_noGs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_ipa_noGs_cendppm.txt' @format=ascii
save cendmet_output @file='fitdoses_male_ipa_noGs_cendppm_met.txt' @format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_male_ipa_noGs_min_tiss.txt' @format=ascii
```

FitDoses_Toluene_with_Gs.m

```
% Breath exposure simulations for Toluene for males with G-force scenario

% Calls FitAllDoses.m

% load @format=model @file=OpFeat

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Toluene
BW=84.14; CONC=0.7; TSTOP=4800.0; STRTEXP=0.0; EXPEND=3600.0; DOSEINT=5000.0;
CINT=3.0;
TGFORCE=152.0;
SetGForces

% Define tolerance and target value for endpoint (target for end-exhaled air of 6.265 ppb
% (0.006265 ppm))
Tolerance = 0.0000000001; TargetParam = 'CEndPPM'; Target = 0.006265;
ConcFit = 'Conc';

% Define list of exposure lengths to be simulated
TChngList = [30.0 60.0 120.0 300.0 900.0 3600.0];

% Initialize arrays and counter
min_tiss = [];

FitAllDoses

% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_toluene_Gs.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_toluene_Gs_mb.txt' @format=ascii

% Save individual time courses for CEndPPM for each fit dose for each value of TChng
% (for each value of TChng, this writes a column of values for each exposure start time -
% repeats set of columns for each new TChng)
save times @file='fitdoses_male_toluene_Gs_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_toluene_Gs_cendppm.txt' @format=ascii

% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_toluene_Gs_min_tiss.txt' @format=ascii
```

Human.m

```
BW=70.0; QCC=12.89/60.0/60.0; QPC=27.75/60.0/60.0; VPR=QPC/QCC; 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; VMUCC=0.0001; VRAPC=0.036; VSLWC=0.536;
VBODYC=0.84;
```

HumanPilot.m

```
% Values to use for dose reconstruction
% BW is average from Air Force database (from e-mail from Jeff Hudson)
% Remaining values are average from values from IPA/Acetone, Tardiff et al. 1997 toluene model
% and cyclohexane model

BW=84.14; QCC=15.5/60.0/60.0; QPC=26.0/60.0/60.0; VPR=QPC/QCC; QBRNC=0.123; QFATC=0.05;
QLIVC=0.246; QRAPC=0.352; QSLWC=0.229;
VALVC=0.0079; VBRNC=0.02; VFATC=0.188; VLIVC=0.026; VMUCC=0.0001; VRAPC=0.032; VSLWC=0.602;
VBODYC=0.8760;

%% Female body weight
% BW=67.77;
```

Init.m

prepare @All

HVDPRN=0;
WESITG=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;
DS=0.15;
PB=848.0; PMUC=848.0; PBRN=1.33; PFAT=0.32; PLIV=1.16; PRAP=1.25; PSLW=1.3;
VMAXC=300.0/60.0/60.0; KM=10.0; KFC=0.0;
CLURC=0.004/60.0/60.0; KURTC=(11.0/27.75)*QPC;
CENDO=0.0; RENDOC=0.0;

MW_MET=58.08;
DS_MET=0.25;
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=3.5/60.0/60.0; KM_MET=10.0; KF_METC=0.0;
CLUR_METC=0.004/60.0/60.0; KURT_METC=(11.0/27.75)*QPC;
CENDO_MET=0.5; RENDO_METC=0.207/60.0/60.0;

MC_Anal.m

% MC analysis

% Called in MC_Male_Acetone.m, MC_Male_Cyclohex.m, MC_Male_IPA.m, MC_Male_Toluene.m,
% MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and MC_Female_Toluene.m

% Load exposure start times and lengths for varied exposure
load StrtTimeLst @file=VarExp_StrtTimeLst.dat @format=ascii
load TChngLst @file=VarExp_TChngLst.dat @format=ascii

% Initialize arrays
good_params = []; failed_params = []; fit_doses = []; mb_maxmin_fail = [];
tmp_massbal = []; tmp_massbal_fd = []; massbal_th = []; massbal_fd = [];
massbal_fd_all = []; massbal_fail = [];
tmp_metbal = []; tmp_metbal_fd = []; metbal_th = []; metbal_fd = []; metbal_fd_all = [];
metbal_fail = [];
tmp_cendppm = []; tmp_cendppm_fd = []; cendppm_fin = []; cendppm_th = []; cendppm_fd = [];
cendppm_fd_all = [];
tmp_cendppm_met = []; tmp_cendppm_met_fd = []; cendppm_met_fin = []; cendppm_met_th = [];
cendppm_met_fd = []; cendppm_met_fd_all = [];
min_tiss_th = []; min_tiss_fd = []; min_tiss_fd_all = []; min_tiss_fail = []; mintiss = [];
NumFails = 0;

% Define parameters for number of iterations for Monte Carlo
numIts = 5000; numIts2 = numIts*2; NumSims = 0;

% Start Monte Carlo analysis

```
for iter = [1 : numIts2]
    Distrib_Physio

    if (ChemName == 'Ace ')
        Distrib_Acetone
    else
        if (ChemName == 'Cyc ')
            Distrib_Cyclohex
        else
            if (ChemName == 'IPA ')
                Distrib_IPA
            else
                if (ChemName == 'Tol ')
                    Distrib_Toluene
                Else

```

```

        if (ChemName == 'Both')
            Distrib_IPA_and_Acetone
        end
    end
end
end
end

disp(sprintf("Starting MC Iteration #%d of %d", iter, numIts2));
disp("-----");

% Run parameter set with fixed dose, exposure length and start time for exposure
CONC=StartConc; TCHNG=900.0; STRTEXP=900.0;
start @NoCallback
mins_th = [];
mins_th(:, :) = [mins_th min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
    min(_aliv) min(_amet) min(_arap1) min(_arap2) min(_aslw1) min(_aslw2)
    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(_arap1_met)
    min(_arap2_met) min(_aslw1_met) min(_aslw2_met) min(_cven_met)];
tot_massbal = _massbal;
if (ChemName == 'Both')
    tot_massbal = addcolsj(tot_massbal, _metbal, @Justification = 'begin');
end

if (T >= TSTOP & max(max(tot_massbal)) < 0.00000001 & min(min(tot_massbal)) > -0.00000001 &
    min(min(mins_th)) > -0.00000001)
    tmp_massbal = _massbal;
    tmp_cendppm = _cendppm;
    cendppm_fixed = CENDPPM;
    if (ChemName == 'Both')
        tmp_metbal = _metbal;
        tmp_cendppm_met = _cendppm_met;
        cendppm_met_fixed = CENDPPM_MET;
    end
    MC_FitDose

% Check mass balances to make sure simulation is valid
% If simulation is valid, move on to fitting doses for varied exposure length and start
% time for exposure
mins_fd = [];
mins_fd(:, :) = [mins_fd min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn)
    min(_afat) min(_aliv) min(_amet) min(_arap1) min(_arap2) min(_aslw1)
    min(_aslw2) 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(_arap1_met) min(_arap2_met) min(_aslw1_met)
    min(_aslw2_met) min(_cven_met)];
tot_massbal = _metbal;
if (ChemName == 'Both')
    tot_massbal = addcolsj(tot_massbal, _metbal, @Justification = 'begin');
end

if (T >= TSTOP & max(max(tot_massbal)) < 0.00000001 &
    min(min(tot_massbal)) > -0.00000001 & min(min(mins_fd)) > -0.00000001)
    tmp_massbal_fd = _massbal;
    tmp_cendppm_fd = _cendppm;
    conc_fd = CONC;
    cend_fd = CENDPPM;
    if (ChemName == 'Both')
        tmp_metbal_fd = _metbal;
        tmp_cendppm_met_fd = _cendppm_met;
        cend_met_fd = CENDPPM_MET;
    end

    if abs(EndPt-Target) > Tolerance
        conc_fd_fit = 0;
    else
        conc_fd_fit = 1;
    end
end

```

```

%          Fit doses to internal dosemetric for varied exposure length and time
CONC=StartConc; TCHNG=TChngLst(NumSims+1); STRTEXP=StrtTimeLst(NumSims+1);
start @NoCallback
MC_FitDose

%          Check mass balances to make sure simulation is valid
%          If simulation is valid, save parameter set, time course for endpoint values,
%          miniumum tissue values and mass balance values
mins_fd_all = [];
mins_fd_all(:, :) = [mins_fd_all min(_amuc) min(_aexh) min(_aart) min(_aurn)
                    min(_abrn) min(_afat) min(_aliv) min(_amet) min(_arap1)
                    min(_arap2) min(_aslw1) min(_aslw2) 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(_arap1_met)
                    min(_arap2_met) min(_aslw1_met) min(_aslw2_met) min(_cven_met)];
tot_massbal = _metbal;
if (ChemName == 'Both')
    tot_massbal = addcolsj(tot_massbal, _metbal, @Justification = 'begin');
end

if (T >= TSTOP & max(max(tot_massbal)) < 0.00000001 &
    min(min(tot_massbal)) > -0.00000001 & min(min(mins_fd_all)) > -0.00000001)
    MC_SaveGoodRuns

%          If simulation is NOT valid, save failed parameter set, miniumum tissue values and
%          mass balance values
else
    MC_BadParams
end

%          If simulation is NOT valid, save failed parameter set, miniumum tissue values and mass
%          balance values
else
    MC_BadParams
end

%          If simulation is NOT valid, save failed parameter set, miniumum tissue values and mass
%          balance values
else
    MC_BadParams
end

%          If desired number of valid simulations have been completed, exit loop
if (NumSims == numIts)
    break;
end
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(cendppm_th);
i = 1; j = 1;
while i <= ncols
    while j <= nrows
        trans_cendppm_th(i, j) = cendppm_th(j, i);
        trans_cendppm_fd(i, j) = cendppm_fd(j, i);
        trans_cendppm_fd_all(i, j) = cendppm_fd_all(j, i);
        if (ChemName == 'Both')
            trans_cendppm_met_th(i, j) = cendppm_met_th(j, i);
            trans_cendppm_met_fd(i, j) = cendppm_met_fd(j, i);
            trans_cendppm_met_fd_all(i, j) = cendppm_met_fd_all(j, i);
        end
        j = j + 1;
    end
    i = i + 1;
    j = 1;
end

```

```

% Calculate statistics for fixed dose, exposure length and start time for exposure
mean_th = mean(trans_cendppm_th);
twostd_th = 2*std(trans_cendppm_th);
max_th = max(trans_cendppm_th);
min_th = min(trans_cendppm_th);

if (ChemName == 'Both')
    mean_met_th = mean(trans_cendppm_met_th);
    twostd_met_th = 2*std(trans_cendppm_met_th);
    max_met_th = max(trans_cendppm_met_th);
    min_met_th = min(trans_cendppm_met_th);
end

% Calculate statistics for fit dose and fixed exposure length and start time for exposure
mean_fd = mean(trans_cendppm_fd);
twostd_fd = 2*std(trans_cendppm_fd);
max_fd = max(trans_cendppm_fd);
min_fd = min(trans_cendppm_fd);

if (ChemName == 'Both')
    mean_met_fd = mean(trans_cendppm_met_fd);
    twostd_met_fd = 2*std(trans_cendppm_met_fd);
    max_met_fd = max(trans_cendppm_met_fd);
    min_met_fd = min(trans_cendppm_met_fd);
end

% Calculate statistics for fit dose and varied exposure length and start time for exposure
mean_fd_all = mean(trans_cendppm_fd_all);
twostd_fd_all = 2*std(trans_cendppm_fd_all);
max_fd_all = max(trans_cendppm_fd_all);
min_fd_all = min(trans_cendppm_fd_all);

if (ChemName == 'Both')
    mean_met_fd_all = mean(trans_cendppm_met_fd_all);
    twostd_met_fd_all = 2*std(trans_cendppm_met_fd_all);
    max_met_fd_all = max(trans_cendppm_met_fd_all);
    min_met_fd_all = min(trans_cendppm_met_fd_all);
end

% Save statistics to one array to be saved
i = 1;
while i <= nrows
    statscendppm(i,1) = mean_th(i);
    statscendppm(i,2) = twostd_th(i);
    statscendppm(i,3) = max_th(i);
    statscendppm(i,4) = min_th(i);

    statscendppm(i,5) = mean_fd(i);
    statscendppm(i,6) = twostd_fd(i);
    statscendppm(i,7) = max_fd(i);
    statscendppm(i,8) = min_fd(i);

    statscendppm(i,9) = mean_fd_all(i);
    statscendppm(i,10) = twostd_fd_all(i);
    statscendppm(i,11) = max_fd_all(i);
    statscendppm(i,12) = min_fd_all(i);

    if (ChemName == 'Both')
        statscendppm_met(i,1) = mean_met_th(i);
        statscendppm_met(i,2) = twostd_met_th(i);
        statscendppm_met(i,3) = max_met_th(i);
        statscendppm_met(i,4) = min_met_th(i);

        statscendppm_met(i,5) = mean_met_fd(i);
        statscendppm_met(i,6) = twostd_met_fd(i);
        statscendppm_met(i,7) = max_met_fd(i);
        statscendppm_met(i,8) = min_met_fd(i);
    end
end

```

```

        statscendppm_met(i,9) = mean_met_fd_all(i);
        statscendppm_met(i,10) = twostd_met_fd_all(i);
        statscendppm_met(i,11) = max_met_fd_all(i);
        statscendppm_met(i,12) = min_met_fd_all(i);
    end

    i = i + 1;
end

% Transpose matrix of minimum tissue values to calculate minimum across all simulations
[nrows,ncols] = size(min_tiss_th);
i = 1; j = 1;
while i <= ncols
    while j <= nrows
        trans_min_tiss_th(i, j) = min_tiss_th(j, i);
        trans_min_tiss_fd(i, j) = min_tiss_fd(j, i);
        trans_min_tiss_fd_all(i, j) = min_tiss_fd_all(j, i);
        j = j + 1;
    end
    i = i + 1;
    j = 1;
end

% Find minimum for minimum tissue values across all simulations
min_th = min(trans_min_tiss_th);
min_fd = min(trans_min_tiss_fd);
min_fd_all = min(trans_min_tiss_fd_all);

% Save minimums to one array to be saved
i = 1;
while i <= nrows
    min_tiss(i,1) = min_th(i);
    min_tiss(i,2) = min_fd(i);
    min_tiss(i,3) = min_fd_all(i);
    i = i + 1;
end

% Find maximum and minimum for mass balance values
if (ChemName == 'Both')
    mb_maxmin(1) = max(max(massbal_th));
    mb_maxmin(2) = min(min(massbal_th));
    mb_maxmin(3) = max(max(metbal_th));
    mb_maxmin(4) = min(min(metbal_th));

    mb_maxmin(5) = max(max(massbal_fd));
    mb_maxmin(6) = min(min(massbal_fd));
    mb_maxmin(7) = max(max(metbal_fd));
    mb_maxmin(8) = min(min(metbal_fd));

    mb_maxmin(9) = max(max(massbal_fd_all));
    mb_maxmin(10) = min(min(massbal_fd_all));
    mb_maxmin(11) = max(max(metbal_fd_all));
    mb_maxmin(12) = min(min(metbal_fd_all));
else
    mb_maxmin(1) = max(max(massbal_th));
    mb_maxmin(2) = min(min(massbal_th));

    mb_maxmin(3) = max(max(massbal_fd));
    mb_maxmin(4) = min(min(massbal_fd));

    mb_maxmin(5) = max(max(massbal_fd_all));
    mb_maxmin(6) = min(min(massbal_fd_all));
end

```

MC_BadParams.m

```
% To save parameters from failed runs

% Called through MC_Anal.m in, MC_Male_Acetone.m,, MC_Male_Cyclohex.m, MC_Male_IPA.m,
% MC_Male_Toluene.m, MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and
% MC_Female_Toluene.m

params = [];
mins_fail = [];
NumFails = NumFails + 1;

mins_fail(:, :) = [mins_fail min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
min(_aliv) min(_amet) min(_arap1) min(_arap2) min(_aslw1) min(_aslw2)
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(_arap1_met)
min(_arap2_met) min(_aslw1_met) min(_aslw2_met) min(_cven_met)];
min_tiss_fail = addcolsj(min_tiss_fail, mins_fail, @Justification = 'begin');
mins_fail = [];

if (ChemName == 'Both')
    params(:, :) = [params BW QCC VPR QBRNC QFATC QLIVC QRAPC QSLWC VALVC VBRNC VFATC VLIVC VMUCC
VRAPC VSLWC PB PMUC PBRN PFAT PLIV PRAP PSLW VMAXC KM CLURC KURTC PB_MET
PMUC_MET PBRN_MET PFAT_MET PLIV_MET PRAP_MET PSLW_MET VMAX_METC KM_MET
CLUR_METC KURT_METC];
else
    params(:, :) = [params BW QCC VPR QBRNC QFATC QLIVC QRAPC QSLWC VALVC VBRNC VFATC VLIVC VMUCC
VRAPC VSLWC PB PMUC PBRN PFAT PLIV PRAP PSLW VMAXC KM CLURC KURTC];
end

failed_params = addcolsj(failed_params, params, @Justification = 'begin');
params = [];

mb_maxmin_fail(1, NumFails) = max(max(tot_massbal));
mb_maxmin_fail(2, NumFails) = min(min(tot_massbal));
```

MC_FitDose.m

```
% Called through MC_Anal.m in, MC_Male_Acetone.m, MC_Male_Cyclohex.m, MC_Male_IPA.m,
% MC_Male_Toluene.m, MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and
% MC_Female_Toluene.m

% Fit doses to internal dosemetric
Fit_Dose_Alg

% If dose isn't fit, use alternate methods
if abs(EndPt-Target) > Tolerance
    Fit_Dose_Alt_Alg
end

% If dose still isn't fit, increase tolerance
if abs(EndPt-Target) > Tolerance
    Tolerance = Tolerance * 10.0;
    Fit_Dose_Alg

    if abs(EndPt-Target) > Tolerance
        Fit_Dose_Alt_Alg
    end

    Tolerance = Tolerance / 10.0;
end

disp("Finished Fitting Dose");
```

MC_Init.m

```
% Run to get baseline values for MC analysis

% Called in MC_Male_Acetone.m, MC_Male_Cyclohex.m, MC_Male_IPA.m, MC_Male_Toluene.m,
%   MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and MC_Female_Toluene.m

% Initialize array
mb_maxmin = [];

% Make first run at fixed dose for fixed exposure scenario of 15 minute exposure 15 minutes into
%   flight
start @NoCallback
baseline = _minutes;
baseline = addcolsj(baseline, _cendppm, @Justification = 'begin');
if (ChemName == 'Both')
    baseline = addcolsj(baseline, _cendppm_met, @Justification = 'begin');
end

% Save mass balance to check for validity of run
mb_maxmin(1) = max(_massbal);
mb_maxmin(2) = min(_massbal);
if (ChemName == 'Both')
    mb_maxmin(3) = max(_metbal);
    mb_maxmin(4) = min(_metbal);
end
```

MC_Male_Acetone_with_Gs.m

```
% MC analysis for Acetone exposure -- males -- fixed and varied exposure with G-force scenario
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=OpFeat

% Concentration for starting point with fitting
StartConc = 95.39559313;

% Define gender and chemical being simulated
Gender = 'Male '; ChemName = 'Ace ';

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
Acetone
BW=84.14; CONC=StartConc; TCHNG=900.0; TSTOP=4800.0; STRTEXP=900.0; EXPEND=3600.0;
DOSEINT=5000.0;
CEND0=0.0; RENDOC=0.0;
TGFORCE=152.0;
SetGForces
CINT=3.0;

MC_Init

save baseline @file='mc_male_acetone_Gs_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_acetone_Gs_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000000001; TargetParam = 'CEndPPM '; Target = 0.3537;
ConcFit = 'Conc ';

% Initialize random seed
seedrnd(507434805, 350827437);

MC_Anal
```

```
% Save parameters sets generated from Monte Carlo
save good_params @file='mc_male_acetone_Gs_good_params.txt' @format=ascii
save failed_params @file='mc_male_acetone_Gs_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_acetone_Gs_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_acetone_Gs_mb_fail.txt' @format=ascii

% Save statistics for the time course data
save statscendppm @file='mc_male_acetone_Gs_fit_statscend.txt' @format=ascii

% Save final value for fixed dose and fixed scenario runs
save cendppm_fin @file='mc_male_acetone_Gs_cendppm.txt' @format=ascii

% Save the fit doses
save fit_doses @file='mc_male_acetone_Gs_fit_doses.txt' @format=ascii

% Save the minimum tissue values
save min_tiss @file='mc_male_acetone_Gs_mintiss.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_acetone_Gs_mb.txt' @format=ascii

zznumbins = sqrt(250);
```

MC Male Cyclohexane with Gs.m

```
% MC analysis for Cyclohexane exposure -- males -- fixed and varied exposure with G-force
% scenario (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=OpFeat

% Concentration for starting point with fitting
StartConc = 0.419611314;

% Define gender and chemical being simulated
Gender = 'Male '; ChemName = 'Cyc ';

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Cyclohexane
BW=84.14; CONC=StartConc; TCHNG=900.0; TSTOP=4800.0; STRTEXP=900.0; EXPEND=3600.0;
DOSEINT=5000.0;
TGFORCE=152.0;
SetGForces
CINT=3.0;

MC_Init

save baseline @file='mc_male_cyclohex_Gs_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_cyclohex_Gs_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.000000000001; TargetParam = 'CEndPPM '; Target = 0.005314;
ConcFit = 'Conc ';

% Initialize random seed
seedrnd(553579145, 907965080);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_male_cyclohex_Gs_good_params.txt' @format=ascii
save failed_params @file='mc_male_cyclohex_Gs_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_cyclohex_Gs_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_cyclohex_Gs_mb_fail.txt' @format=ascii

% Save statistics for the time course data
```

```

save statscendppm @file='mc_male_cyclohex_Gs_fit_statscend.txt' @format=ascii

% Save final value for fixed dose and fixed scenario runs
save cendppm_fin @file='mc_male_cyclohex_Gs_cendppm.txt' @format=ascii

% Save the fit doses
save fit_doses @file='mc_male_cyclohex_Gs_fit_doses.txt' @format=ascii

% Save the minimum tissue values
save min_tiss @file='mc_male_cyclohex_Gs_mintiss.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_cyclohex_Gs_mb.txt' @format=ascii

zznumbins = sqrt(250);

MC Male IPA with Gs.m
% MC analysis for IPA exposure -- males -- fixed and varied exposure with G-force scenario
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=OpFeat

% Concentration for starting point with fitting
StartConc = 2557.952065;

% Define gender and chemical being simulated
Gender = 'Male '; ChemName = 'IPA ';

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
IPA
BW=84.14; CONC=StartConc; TCHNG=900.0; TSTOP=4800.0; STRTEXP=900.0; EXPEND=3600.0;
DOSEINT=5000.0;
CENDO_MET=0.0; RENDO_METC=0.0;
TGFORCE=152.0;
SetGForces
CINT=3.0;

MC_Init

save baseline @file='mc_male_ipa_Gs_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_ipa_Gs_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000001; TargetParam = 'CEndPPM '; Target = 0.4; ConcFit = 'Conc ';

% Initialize random seed
seedrnd(969960349, 890917552);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_male_ipa_Gs_good_params.txt' @format=ascii
save failed_params @file='mc_male_ipa_Gs_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_ipa_Gs_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_ipa_Gs_mb_fail.txt' @format=ascii

% Save statistics for the time course data
save statscendppm @file='mc_male_ipa_Gs_fit_statscend.txt' @format=ascii

% Save final value for fixed dose and fixed scenario runs
save cendppm_fin @file='mc_male_ipa_Gs_cendppm.txt' @format=ascii

```

```

% Save the fit doses
save fit_doses @file='mc_male_ipa_Gs_fit_doses.txt' @format=ascii

% Save the minimum tissue values
save min_tiss @file='mc_male_ipa_Gs_mintiss.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_ipa_Gs_mb.txt' @format=ascii

zznumbins = sqrt(250);

MC_Male_IPA_without_Gs.m
% MC analysis for IPA exposure -- males -- fixed and varied exposure without G-force scenario
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=OpFeat

% Concentration for starting point with fitting
StartConc = 2601.056442;

% Define gender and chemical being simulated
Gender = 'Male '; ChemName = 'IPA ';

% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
Init
ResetDoses
HumanPilot
IPA
BW=84.14; CONC=StartConc; TCHNG=900.0; TSTOP=4800.0; STRTEXP=900.0; EXPEND=3600.0;
DOSEINT=5000.0;
CENDO_MET=0.0; RENDO_METC=0.0;
TGFORCE=5000.0;
CINT=3.0;

MC_Init

save baseline @file='mc_male_ipa_noGs_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_ipa_noGs_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000001; TargetParam = 'CendPPM '; Target = 0.4; ConcFit = 'Conc ';

% Initialize random seed
seedrnd(969960349, 890917552);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_male_ipa_noGs_good_params.txt' @format=ascii
save failed_params @file='mc_male_ipa_noGs_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_ipa_noGs_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_ipa_noGs_mb_fail.txt' @format=ascii

% Save statistics for the time course data
save statscendppm @file='mc_male_ipa_noGs_fit_statscend.txt' @format=ascii

% Save final value for fixed dose and fixed scenario runs
save cendppm_fin @file='mc_male_ipa_noGs_cendppm.txt' @format=ascii

% Save the fit doses
save fit_doses @file='mc_male_ipa_noGs_fit_doses.txt' @format=ascii

% Save the minimum tissue values
save min_tiss @file='mc_male_ipa_noGs_mintiss.txt' @format=ascii

```

```

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_ipa_noGs_mb.txt' @format=ascii

zznumbins = sqrt(250);

MC_Male_Toluene_with_Gs.m
% MC analysis for Toluene exposure -- males -- fixed and varied exposure with G-force scenario
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=OpFeat

% Concentration for starting point with fitting
StartConc = 0.575276698;

% Define gender and chemical being simulated
Gender = 'Male '; ChemName = 'Tol ';

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Toluene
BW=84.14; CONC=StartConc; TCHNG=900.0; TSTOP=4800.0; STRTEXP=900.0; EXPEND=3600.0;
DOSEINT=5000.0;
TGFORCE=152.0;
SetGForces
CINT=3.0;

MC_Init

save baseline @file='mc_male_toluene_Gs_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_toluene_Gs_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000000001; TargetParam = 'CEndPPM '; Target = 0.006265;
ConcFit = 'Conc ';

% Initialize random seed
seedrnd(708099566, 863559432);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_male_toluene_Gs_good_params.txt' @format=ascii
save failed_params @file='mc_male_toluene_Gs_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_toluene_Gs_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_toluene_Gs_mb_fail.txt' @format=ascii

% Save statistics for the time course data
save statscendppm @file='mc_male_toluene_Gs_fit_statscend.txt' @format=ascii

% Save final value for fixed dose and fixed scenario runs
save cendppm_fin @file='mc_male_toluene_Gs_cendppm.txt' @format=ascii

% Save the fit doses
save fit_doses @file='mc_male_toluene_Gs_fit_doses.txt' @format=ascii

% Save the minimum tissue values
save min_tiss @file='mc_male_toluene_Gs_mintiss.txt' @format=ascii

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_toluene_Gs_mb.txt' @format=ascii

zznumbins = sqrt(250);

```

MC_SaveGoodRuns.m

```
% Called through MC_Anal.m in, MC_Male_Acetone.m, MC_Male_Cyclohex.m, MC_Male_IPA.m,
% MC_Male_Toluene.m, MC_Female_Acetone.m, MC_Female_Cyclohex.m, MC_Female_IPA.m and
% MC_Female_Toluene.m

params = [];
NumSims = NumSims + 1;

min_tiss_th = addcolsj(min_tiss_th, mins_th, @Justification = 'begin');
min_tiss_fd = addcolsj(min_tiss_fd, mins_fd, @Justification = 'begin');
min_tiss_fd_all = addcolsj(min_tiss_fd_all, mins_fd_all, @Justification = 'begin');

massbal_th = addcolsj(massbal_th, tmp_massbal, @Justification = 'begin');
massbal_fd = addcolsj(massbal_fd, tmp_massbal_fd, @Justification = 'begin');
massbal_fd_all = addcolsj(massbal_fd_all, _massbal, @Justification = 'begin');

cendppm_th = addcolsj(cendppm_th, tmp_cendppm, @Justification = 'begin');
cendppm_fd = addcolsj(cendppm_fd, tmp_cendppm_fd, @Justification = 'begin');
cendppm_fd_all = addcolsj(cendppm_fd_all, _cendppm, @Justification = 'begin');
cendppm_fin(NumSims,1) = cendppm_fixed;

fit_doses(NumSims,1) = conc_fd;
fit_doses(NumSims,2) = cend_fd;

if (ChemName == 'Both')
    params(:, :) = [params BW QCC VPR QBRNC QFATC QLIVC QRAPC QSLWC VALVC VBRNC VFATC VLIVC VMUCC
                    VRAPC VSLWC PB PMUC PBRN PFAT PLIV PRAP PSLW VMAXC KM CLURC KURTC PB_MET
                    PMUC_MET PBRN_MET PFAT_MET PLIV_MET PRAP_MET PSLW_MET VMAX_METC KM_MET
                    CLUR_METC KURT_METC];
    metbal_th = addcolsj(metbal_th, tmp_metbal, @Justification = 'begin');
    metbal_fd = addcolsj(metbal_fd, tmp_metbal_fd, @Justification = 'begin');
    metbal_fd_all = addcolsj(metbal_fd_all, _metbal, @Justification = 'begin');
    cendppm_met_th = addcolsj(cendppm_met_th, tmp_cendppm_met, @Justification = 'begin');
    cendppm_met_fd = addcolsj(cendppm_met_fd, tmp_cendppm_met_fd, @Justification = 'begin');
    cendppm_met_fd_all = addcolsj(cendppm_met_fd_all, _cendppm_met, @Justification = 'begin');
    cendppm_fin(NumSims,2) = cendppm_met_fixed;

    fit_doses(NumSims,3) = cend_met_fd;
    fit_doses(NumSims,4) = conc_fd_fit;
    fit_doses(NumSims,5) = CONC;
    fit_doses(NumSims,6) = CENDPPM;
    fit_doses(NumSims,7) = CENDPPM_MET;
    if abs(EndPt-Target) > Tolerance
        fit_doses(NumSims,8) = 0;
    else
        fit_doses(NumSims,8) = 1;
    end
else
    params(:, :) = [params BW QCC VPR QBRNC QFATC QLIVC QRAPC QSLWC VALVC VBRNC VFATC VLIVC VMUCC
                    VRAPC VSLWC PB PMUC PBRN PFAT PLIV PRAP PSLW VMAXC KM CLURC KURTC];
    fit_doses(NumSims,3) = conc_fd_fit;
    fit_doses(NumSims,4) = CONC;
    fit_doses(NumSims,5) = CENDPPM;
    if abs(EndPt-Target) > Tolerance
        fit_doses(NumSims,6) = 0;
    else
        fit_doses(NumSims,6) = 1;
    end
end

good_params = addcolsj(good_params, params, @Justification = 'begin');
params = [];

disp(sprintf("Finished MC Simulation #%d of %d", NumSims, numIts));
disp("-----");
```

ResetDoses.m

```
TCHNG=0.0;  
STRTEXP=0.0; EXPEND=1.0; DOSEINT=10000.0;  
CINT=30.0;  
ADJQCP=0; TEXER=0.0; LEXER=1.0; EXERINC=1.0; RAMPUP=0.0; RAMPDN=0.0;  
ADJCONC=0; CONCUP=1.0; CONC=0.0;  
CONC_MET=0.0;  
TGFORCE=5000.0;
```

Run_All_FitDoses.m

```
% load @format=model @file=OpFeat
```

```
FitDoses_IPA_without_Gs  
FitDoses_IPA_with_Gs  
FitDoses_Acetone_Only_with_Gs  
FitDoses_Acetone_from_IPA_Only_with_Gs  
FitDoses_Toluene_with_Gs  
FitDoses_Cyclohexane_with_Gs  
FitDoses_Acetone_and_IPA_with_Gs
```

SetGForces.m

```
% Set parameters for simulating G forces
```

```
GFORCEC(1)=1.5; GFORCEC(2)=1.2; GFORCEC(3)=1.5; GFORCEC(4)=1.4; GFORCEC(5)=1.5; GFORCEC(6)=1.2;  
GFORCEC(7)=1.0; GFORCEC(8)=1.4; GFORCEC(9)=1.0; GFORCEC(10)=2.2;  
GFORCEC(11)=1.9; GFORCEC(12)=1.0; GFORCEC(13)=1.2; GFORCEC(14)=1.0; GFORCEC(15)=1.2;  
GFORCEC(16)=1.0; GFORCEC(17)=1.2; GFORCEC(18)=1.0; GFORCEC(19)=4.6; GFORCEC(20)=6.1;  
GFORCEC(21)=2.5; GFORCEC(22)=1.0; GFORCEC(23)=2.4; GFORCEC(24)=1.6; GFORCEC(25)=6.3;  
GFORCEC(26)=3.8; GFORCEC(27)=4.4; GFORCEC(28)=3.4; GFORCEC(29)=2.3; GFORCEC(30)=2.8;  
GFORCEC(31)=1.5; GFORCEC(32)=1.0; GFORCEC(33)=2.1; GFORCEC(34)=1.4; GFORCEC(35)=1.7;  
GFORCEC(36)=6.7; GFORCEC(37)=4.3; GFORCEC(38)=3.4; GFORCEC(39)=3.7; GFORCEC(40)=2.8;  
GFORCEC(41)=1.5; GFORCEC(42)=1.4; GFORCEC(43)=1.0; GFORCEC(44)=1.6; GFORCEC(45)=1.9;  
GFORCEC(46)=1.0; GFORCEC(47)=2.6; GFORCEC(48)=2.0; GFORCEC(49)=1.8; GFORCEC(50)=6.8;  
GFORCEC(51)=3.8; GFORCEC(52)=2.6; GFORCEC(53)=3.4; GFORCEC(54)=3.2; GFORCEC(55)=1.3;  
GFORCEC(56)=1.0; GFORCEC(57)=1.4; GFORCEC(58)=1.0; GFORCEC(59)=1.2; GFORCEC(60)=1.0;  
GFORCEC(61)=2.1; GFORCEC(62)=2.3; GFORCEC(63)=1.8; GFORCEC(64)=1.7; GFORCEC(65)=2.0;  
GFORCEC(66)=2.2; GFORCEC(67)=6.8; GFORCEC(68)=1.0; GFORCEC(69)=2.2; GFORCEC(70)=2.7;  
GFORCEC(71)=1.3; GFORCEC(72)=1.0; GFORCEC(73)=2.0; GFORCEC(74)=1.0; GFORCEC(75)=1.9;  
GFORCEC(76)=4.5; GFORCEC(77)=3.6; GFORCEC(78)=2.0; GFORCEC(79)=1.9; GFORCEC(80)=1.0;  
GFORCEC(81)=3.6; GFORCEC(82)=2.0; GFORCEC(83)=1.0; GFORCEC(84)=1.8; GFORCEC(85)=1.4;  
GFORCEC(86)=1.0; GFORCEC(87)=1.2; GFORCEC(88)=1.0; GFORCEC(89)=1.0; GFORCEC(90)=1.0;  
GFORCEC(91)=1.0; GFORCEC(92)=1.0; GFORCEC(93)=1.0; GFORCEC(94)=1.0; GFORCEC(95)=1.0;  
GFORCEC(96)=1.0; GFORCEC(97)=1.0; GFORCEC(98)=1.0; GFORCEC(99)=1.0; GFORCEC(100)=1.0;  
  
NEXTMOVE(1)=9.0; NEXTMOVE(2)=45.0; NEXTMOVE(3)=14.0; NEXTMOVE(4)=36.0; NEXTMOVE(5)=45.0;  
NEXTMOVE(6)=40.0; NEXTMOVE(7)=31.0; NEXTMOVE(8)=17.0; NEXTMOVE(9)=48.0; NEXTMOVE(10)=14.0;  
NEXTMOVE(11)=22.0; NEXTMOVE(12)=36.0; NEXTMOVE(13)=31.0; NEXTMOVE(14)=62.0; NEXTMOVE(15)=22.0;  
NEXTMOVE(16)=50.0; NEXTMOVE(17)=20.0; NEXTMOVE(18)=140.0; NEXTMOVE(19)=45.0; NEXTMOVE(20)=22.0;  
NEXTMOVE(21)=14.0; NEXTMOVE(22)=90.0; NEXTMOVE(23)=23.0; NEXTMOVE(24)=48.0; NEXTMOVE(25)=14.0;  
NEXTMOVE(26)=36.0; NEXTMOVE(27)=26.0; NEXTMOVE(28)=22.0; NEXTMOVE(29)=25.0; NEXTMOVE(30)=34.0;  
NEXTMOVE(31)=34.0; NEXTMOVE(32)=158.0; NEXTMOVE(33)=34.0; NEXTMOVE(34)=31.0; NEXTMOVE(35)=40.0;  
NEXTMOVE(36)=31.0; NEXTMOVE(37)=20.0; NEXTMOVE(38)=28.0; NEXTMOVE(39)=25.0; NEXTMOVE(40)=26.0;  
NEXTMOVE(41)=17.0; NEXTMOVE(42)=14.0; NEXTMOVE(43)=175.0; NEXTMOVE(44)=31.0; NEXTMOVE(45)=98.0;  
NEXTMOVE(46)=23.0; NEXTMOVE(47)=28.0; NEXTMOVE(48)=20.0; NEXTMOVE(49)=20.0; NEXTMOVE(50)=17.0;  
NEXTMOVE(51)=22.0; NEXTMOVE(52)=31.0; NEXTMOVE(53)=31.0; NEXTMOVE(54)=26.0; NEXTMOVE(55)=17.0;  
NEXTMOVE(56)=23.0; NEXTMOVE(57)=73.0; NEXTMOVE(58)=26.0; NEXTMOVE(59)=36.0; NEXTMOVE(60)=87.0;  
NEXTMOVE(61)=31.0; NEXTMOVE(62)=40.0; NEXTMOVE(63)=14.0; NEXTMOVE(64)=20.0; NEXTMOVE(65)=28.0;  
NEXTMOVE(66)=22.0; NEXTMOVE(67)=79.0; NEXTMOVE(68)=39.0; NEXTMOVE(69)=37.0; NEXTMOVE(70)=39.0;  
NEXTMOVE(71)=48.0; NEXTMOVE(72)=110.0; NEXTMOVE(73)=37.0; NEXTMOVE(74)=17.0; NEXTMOVE(75)=26.0;  
NEXTMOVE(76)=28.0; NEXTMOVE(77)=20.0; NEXTMOVE(78)=14.0; NEXTMOVE(79)=19.0; NEXTMOVE(80)=31.0;  
NEXTMOVE(81)=20.0; NEXTMOVE(82)=64.0; NEXTMOVE(83)=34.0; NEXTMOVE(84)=28.0; NEXTMOVE(85)=17.0;  
NEXTMOVE(86)=95.0; NEXTMOVE(87)=23.0; NEXTMOVE(88)=146.0; NEXTMOVE(89)=150.0;  
NEXTMOVE(90)=500.0;  
NEXTMOVE(91)=500.0; NEXTMOVE(92)=500.0; NEXTMOVE(93)=500.0; NEXTMOVE(94)=500.0;  
NEXTMOVE(95)=500.0; NEXTMOVE(96)=500.0; NEXTMOVE(97)=500.0; NEXTMOVE(98)=500.0;  
NEXTMOVE(99)=500.0; NEXTMOVE(100)=500.0;
```

Toluene.m

% MW (molecular weight) is from NIST Chemistry Webbook
% (<http://webbook.nist.gov/cgi/cbook.cgi?Name=toluene&Units=SI>)
% DS value from IPA parameters
% 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) paper or aren't used (so set to 1.0 or 0.0)

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=4.8/60.0/60.0; KM=0.55; KFC=0.0;
CLURC=0.0; KURTC=0.0;
CENDO=0.0; RENDOC=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;

APPENDIX C

Data Files for Simulations

The following data files are called within various M files utilized for this work. The values were randomly generated in an EXCEL spreadsheet. “VarExp_StrtTimeLst.dat” contains the start times for the random exposures and “VarExp_TChngLst.dat” contains the exposure lengths.

VarExp_StrtTimeLst.dat

120	2100	3540	1500	2160	1410	0	900
1800	0	0	1500	600	2040	0	0
0	300	2670	3300	3300	2550	3240	2700
270	3000	3420	300	570	3360	1800	3300
1680	0	840	0	750	1500	0	0
0	2520	0	1800	0	0	2910	0
180	840	1140	0	960	900	0	2700
1560	900	2280	3450	2400	1800	0	900
0	900	1200	2700	0	0	3240	960
840	2700	60	1680	0	1800	900	0
1170	0	1500	0	720	0	0	60
0	1440	1920	0	990	900	2760	1320
900	0	0	1560	960	2430	600	600
0	1080	3360	1800	0	1920	0	2400
1380	2880	2700	3060	0	450	2760	0
780	600	2760	2400	2370	2700	1170	1200
0	780	0	0	2700	1200	900	2100
2400	0	1500	1200	0	3240	2640	0
1680	2040	900	1500	0	0	900	2100
2190	3120	1140	0	2700	0	2700	720
0	1500	360	1200	900	0	1920	0
0	780	2700	0	2100	2760	2340	0
1440	1980	0	1800	0	2640	1620	900
0	30	0	0	1200	0	1200	1800
3000	2700	1200	3030	2700	1800	3240	2640
1560	300	1080	300	0	0	2400	1380
2280	2700	0	0	1800	1440	420	180
0	0	2220	600	3360	600	2940	1800
1920	3240	1800	3360	600	1200	0	360
0	480	0	2700	0	0	1620	900
1200	600	270	2700	1950	1560	1800	0
3000	2400	360	1920	2700	120	2400	3570
2700	1500	1080	2700	900	1830	480	2520
3360	2160	2700	0	2100	0	120	600
2700	900	2700	2100	2640	810	240	0
660	2550	120	3180	390	0	1800	2400
0	300	2760	2880	3240	0	2040	0
3120	840	1800	0	0	960	1320	0
2040	3000	2040	840	0	2340	0	2460
2700	600	0	2700	0	300	0	1080
1860	2940	1800	2280	0	2700	0	0
3240	1890	1080	0	2940	0	300	1230
0	0	3180	960	2670	840	2520	2700
0	0	1920	900	600	3060	1110	2640
2160	3120	3000	2910	1260	2040	1800	1800
2580	2520	2340	0	0	2940	0	2940
0	2400	0	3000	1740	0	2580	2670
0	2280	1200	900	1500	900	0	1770
2520	450	3300	120	3000	2520	1200	0
0	450	0	600	0	0	2100	0
0	600	480	0	900	2700	1500	0
1320	1800	300	1920	2400	1800	0	1320
0	2940	0	2400	0	1320	2100	360
300	0	0	3450	0	0	2640	2700
0	1740	3120	1080	1800	2640	2640	3000
0	630	1800	1740	2280	1200	0	2340
720	1080	0	90	3300	2400	1800	1860
2760	2700	0	840	1620	0	3480	3300
1500	2700	1200	0	2400	480	2400	840

2400	900	900	2400	2550	2640	1500	3090
900	1530	0	810	2970	1920	2400	2730
0	0	0	0	600	1320	0	3000
2400	0	1800	0	900	930	3000	3240
0	1800	2640	600	900	2100	0	0
2760	1200	1530	1800	2580	600	3480	2160
0	1800	2250	0	120	0	3300	3570
1560	0	150	0	0	540	3480	0
900	3420	120	2700	0	1500	660	2040
1800	2730	0	540	0	600	1800	1560
2490	2040	0	3120	3300	0	1260	900
0	960	1200	1800	3120	2160	2790	1980
3360	2700	840	2730	2640	750	2100	1680
1410	1800	1500	180	540	2700	2100	0
1800	0	3540	1800	900	1920	3210	1980
1800	1800	780	1800	1320	2760	1800	0
0	2340	0	2520	3240	0	900	480
2100	1800	0	2520	0	2700	0	1800
0	3390	0	1200	480	0	1680	0
900	1470	360	2520	1200	0	2400	3540
600	0	2640	1200	900	1800	3240	3210
0	3240	2400	2400	1380	720	2400	3120
1500	2340	0	720	0	240	1140	2010
0	1800	2670	2340	0	1200	1560	3300
2280	0	0	1860	1080	1680	300	1800
0	300	2520	0	2700	1800	480	0
0	2700	2760	900	0	900	900	0
1080	1800	750	1200	1800	1680	2820	3300
2640	1800	1200	3000	1200	900	1440	0
990	2700	3120	1260	3300	1350	270	1320
2760	1320	3000	2400	1800	0	2520	1320
1200	2700	3120	1320	3540	3000	2700	900
0	3240	0	0	900	1560	0	1560
450	900	120	3060	1800	150	0	0
0	3180	3300	600	1080	3360	0	0
900	0	2400	1800	2700	0	2370	2400
0	0	0	0	3000	0	2760	1680
0	0	2430	0	2700	600	480	0
2730	300	1080	0	2490	90	2940	780
2100	3420	0	240	600	900	360	900
0	0	0	780	2400	3360	2430	2550
2100	1800	3120	0	1800	2100	2700	1860
1800	1920	960	2700	1440	0	1470	0
600	2190	0	0	2370	1140	1200	570
2700	2700	0	2520	2700	480	1410	600
240	2880	2040	1800	900	1800	1500	0
2040	900	900	810	900	1200	0	1560
2520	780	0	1980	1200	900	2100	0
0	0	570	2400	2700	0	1800	2970
3420	780	120	840	3300	90	3000	2880
2700	0	0	1170	900	1440	2760	0
900	2760	840	3000	3000	0	0	1800
900	0	300	2700	900	120	0	2640
330	0	2700	0	2100	1680	0	0
3270	0	900	420	0	1680	900	0
0	0	3570	1200	900	1500	180	2820
3240	0	2280	2700	1800	1980	480	1200
1440	600	2700	0	2700	2700	0	3060
150	1920	900	1800	3480	0	3240	2400
1800	660	780	960	1320	660	0	0
390	0	900	2100	1800	240	480	0
0	0	0	0	0	360	1440	2700
0	3300	2040	300	0	1140	0	600
3300	3120	120	240	90	2280	3180	0
3000	2700	60	0	3240	2040	2100	60
2760	0	3300	2160	1920	0	0	0
480	3360	0	1620	3300	1680	1290	1680
2280	0	2700	600	900	2340	2040	0
840	3300	1560	2460	0	2100	1200	2640
1800	2040	1500	1920	0	3300	2700	1020
0	0	0	0	2580	0	3150	1920

1470	510	0	3420	900	360	600	870
3000	2760	240	240	1410	2700	2700	900
0	900	0	1800	2700	0	480	2760
300	2160	0	900	1560	0	3510	3240
900	570	1800	2700	900	2040	1800	1800
2880	1800	0	1800	2400	300	2100	240
1320	1380	1440	3420	1590	0	1080	0
450	1440	0	0	0	3030	1500	0
3480	3180	3420	1560	0	0	900	1410
3390	0	1200	840	3360	0	2400	2700
300	2280	1770	2100	2760	900	0	2700
0	2640	3360	120	3000	3360	0	1890
1560	900	3300	2700	1500	600	720	0
3000	900	2400	930	630	2880	1740	1500
1380	0	240	0	2700	480	1800	0
1140	600	1800	1800	2190	3000	180	480
2160	3000	600	840	0	0	3300	0
1440	3360	1620	3420	0	600	3150	1200
1620	960	0	0	0	90	3180	3300
2190	3060	300	2400	300	300	1800	0
0	1680	2400	0	3000	2400	1140	570
0	1140	1770	0	900	0	480	2100
2460	1140	1230	3150	480	3120	1140	1980
2700	2700	900	600	3300	780	1800	0
1500	270	240	240	3540	3300	300	720
2040	2700	0	0	0	1800	900	2100
1860	450	2700	0	900	0	0	0
900	3360	2940	1560	480	1680	3060	0
1410	3360	900	0	0	1500	2520	1080
2400	0	3090	0	0	2700	0	0
2640	0	3360	300	1920	2280	2400	900
300	0	1500	3300	1860	0	900	2580
0	900	900	2220	840	360	2460	0
1800	2400	2280	1140	3120	0	0	0
2640	1920	900	0	2700	0	2400	2310
600	3120	360	2100	2700	450	1380	2700
2700	0	0	0	300	3120	1800	600
420	1800	3540	0	2400	1800	690	1200
840	0	2700	1080	0	3120	690	0
480	2700	1800	900	1680	1560	3300	0
1500	2700	0	3000	0	3300	0	2700
1920	2160	900	180	2400	1530	1710	3120
3300	870	0	0	3300	3120	2640	1290
0	0	1800	2160	360	2700	0	0
3360	3000	0	0	3300	960	3300	3420
900	240	510	1800	2100	0	1500	3300
0	900	0	1440	1740	1920	0	1800
0	240	2760	3300	1800	0	0	0
3360	0	2700	720	2700	0	1800	900
3300	0	2280	3060	1620	240	0	120
2850	900	0	2100	1800	0	1080	0
600	0	0	0	900	0	1680	900
3240	0	1200	1080	0	1920	2160	0
2280	3330	240	540	2520	300	0	2280
2520	90	2340	1500	3180	2580	900	0
1800	600	0	480	1320	1560	1290	2280
1800	1680	2880	2010	1800	0	1020	1500
0	2700	0	2700	0	1800	2550	1800
3240	240	2940	0	2160	1800	120	1500
1800	1560	1830	900	600	360	0	2400
240	2280	0	2700	1920	2700	480	240
720	2520	360	600	1140	0	2070	3180
1800	0	360	120	0	0	3000	2640
600	510	2280	2160	840	1800	0	0
1890	3090	2100	3300	1470	1200	2700	2100
0	420	420	1200	0	660	600	2520
900	0	660	2760	2040	0	3300	1320
1080	3000	2700	600	900	2520	840	0
570	1080	2400	2640	2760	900	0	60
480	600	1860	600	0	3300	900	0
0	0	600	0	1410	1320	0	600

2640	840	240	2100	1440	3300	900	3000
0	2280	2520	300	1710	2580	2700	1080
0	480	3210	2700	3360	2040	900	1800
1920	600	2700	1680	0	0	1920	960
1200	240	0	1530	0	2280	2700	150
300	3240	990	720	2760	0	1740	1500
1320	2340	0	1800	480	1020	360	2700
2700	1140	1800	1560	1800	1500	0	900
1260	2280	600	630	3000	240	2400	660
900	0	300	0	3480	2700	0	150
0	2940	840	0	300	0	3300	960
3000	1800	720	0	2400	0	0	3300
2400	2700	0	420	2820	1980	780	3240
30	0	0	0	0	0	1200	780
0	2640	600	270	360	420	0	0
2130	1620	420	1140	300	3120	2700	2100
1800	720	2670	240	0	2610	0	2700
1860	2850	2700	0	1440	1920	1500	2700
900	1800	180	0	1800	3090	3390	0
1800	150	600	600	2400	1380	1560	210
2100	3180	900	0	900	3060	3000	2880
0	1800	0	0	0	600	0	2700
120	0	900	600	300	1800	2880	0
3300	900	2700	1800	600	600	900	0
600	1920	2820	600	1980	3360	900	1440
3540	3240	330	600	3300	600	3060	720
2700	600	900	150	2820	1920	3360	0
600	3300	720	1800	1890	1200	1320	2640
1800	2400	600	1860	3000	1800	600	0
3000	0	0	0	2400	3360	2520	0
2130	360	300	0	0	1440	0	360
840	1800	2700	0	3240	720	1500	1020
600	2490	0	1800	300	3000	3240	960
1500	3000	2610	2700	120	2700	1800	300
2700	3450	2700	2220	1560	2670	3240	900
0	630	900	2700	900	1920	0	0
2700	600	3510	900	1440	900	0	3300
570	1800	510	0	0	1800	0	300
600	1200	3480	3000	2760	3000	0	120
2100	2700	0	0	360	0	0	0
1800	2880	1080	0	1800	300	1260	1890
0	2760	1290	2790	1860	0	1440	600
1290	3000	0	0	3060	2880	2070	2100
120	0	2610	2820	2400	0	0	1800
1560	0	540	1800	3120	900	2250	1800
60	420	900	840	600	1800	2220	1500
300	0	1800	0	0	2820	0	2040
600	1440	0	600	900	0	3120	0
1800	2640	3300	1080	1230	1200	2460	1950
300	3300	2880	1800	1680	3570	0	3240
900	2040	2700	0	900	840	300	0
960	0	2520	900	0	0	600	630
2700	3000	2700	1200	600	0	2640	1890
1830	3120	2700	2730	240	0	1320	2160
240	0	3270	2520	0	1440	810	2040
0	0	0	2700	600	2700	1650	0
660	720	0	3300	480	3240	1800	2880
720	1800	0	3300	30	1800	90	1800
240	1200	1800	2700	0	0	2700	3540
1170	1800	180	3420	840	1800	0	1680
3300	1950	2370	2280	0	240	1620	720
1080	900	1080	1080	1920	900	1560	360
1530	240	2700	3360	0	600	1800	1380
1980	0	1260	2040	3540	600	2010	60
2310	60	780	1800	1080	0	2010	2880
2580	0	0	1080	1800	1800	0	2700
3270	1800	3180	960	2700	2580	0	1200
0	3480	540	2040	2400	3360	1800	3060
600	0	900	1110	0	3180	3300	900
1140	0	2400	2700	1800	2040	870	2400
480	3000	0	1800	300	0	2880	2760

0	240	2160	0	2700	1590	1200	0
3210	420	2700	1800	0	900	1950	2400
3330	2160	900	0	1800	240	3240	0
0	1350	1140	900	0	1410	1800	2280
0	0	2400	3570	1800	3300	3000	2160
2700	3000	600	0	900	3300	900	2550
0	1680	0	1200	1800	1800	2700	0
1200	2520	2040	600	2700	2700	3300	2400
0	0	1890	600	1800	900	0	0
3000	3060	1200	3090	1500	960	3000	2820
1920	2520	600	2400	2040	2700	0	0
2700	2700	240	270	2400	0	0	0
2010	0	2700	1080	0	2820	360	0
0	1980	2280	2400	2700	2700	480	0
2940	2400	1800	840	900	360	960	1800
3570	2700	0	0	2700	900	600	0
0	3300	0	1500	2400	900	900	1320
2580	1140	1800	0	960	480	2820	900
900	2700	0	60	0	2460	0	120
1800	0	1500	0	1800	480	1800	900
120	1200	1020	0	2760	600	0	900
0	1200	2880	0	240	3330	3360	1200
2670	0	1080	600	0	0	2700	480
2700	0	0	0	900	2880	0	3480
0	1800	1560	2700	0	2400	1800	2100
1680	1800	1800	0	3420	0	2700	3030
900	1800	2640	0	2400	1620	0	540
1020	300	870	1680	780	1800	2700	900
480	1800	3120	840	480	2700	0	2700
1680	840	0	0	3450	0	3000	900
0	900	1080	0	2280	0	120	600
1560	0	2160	2940	1470	1050	2910	1740
1800	900	900	1800	1320	90	2700	0
0	60	2400	1500	1800	1800	1140	2490
2040	0	1680	0	3240	3060	0	0
300	1920	0	0	2520	360	0	3120
2250	0	3000	1800	2700	2400	2100	3480
2520	990	3000	360	3120	0	1800	0
2340	2970	1080	0	3300	2580	0	1380
840	2340	2700	3000	0	0	2700	1800
120	0	2700	2400	3300	3000	2700	3570
3480	0	2700	1800	2820	2520	2340	2400
3480	0	900	2940	2280	2520	1740	2550
960	3480	1410	0	300	1500	0	0
600	2160	0	2400	1320	900	0	2670
360	1500	1680	1800	570	2880	2700	1470
120	2940	0	1680	2400	2400	900	0
1500	3300	1800	2910	1320	0	960	0
480	1800	1800	2940	1680	900	0	1740
1080	2700	3000	1800	540	0	1800	270
3000	0	1800	1800	2400	1500	0	0
3120	2880	2880	0	0	660	0	2730
1500	3300	2040	1440	3300	0	720	360
1260	1800	1110	900	1200	240	2880	600
0	240	0	2520	450	1800	2400	0
0	3000	0	2340	720	1200	810	240
0	750	0	240	3360	120	1800	1890
600	1890	2880	0	0	3120	1680	900
0	0	0	3000	3300	480	0	570
0	900	1800	1800	1800	1500	2400	1800
0	2400	2640	900	3000	300	0	0
0	3000	900	0	2820	2400	2520	2100
720	1200	1800	0	0	30	3000	2460
1800	900	0	2340	1920	2700	0	0
300	0	3540	0	900	600	1200	3420
0	60	2520	0	2010	0	0	3360
2700	3300	1800	330	960	1800	840	3120
3000	0	0	2220	2040	0	0	0
2100	0	2100	2400	3060	1560	0	2700
1200	180	300	720	720	2880	0	120
0	3000	3300	3480	0	0	1440	2160

1200	3570	1260	1800	2580	2040	2040	900
3030	2700	2100	1800	120	0	0	1020
300	3000	2640	1500	0	0	1800	0
780	1800	1200	0	1800	2400	1800	600
0	0	0	300	1920	480	2580	0
3000	1410	900	1080	3000	0	2040	90
2700	2640	0	1860	900	0	120	1200
1800	1560	1560	1680	1620	2400	1800	480
1440	0	2760	2400	3060	480	0	0
3120	0	2100	2730	0	300	0	1350
840	0	0	3300	3210	0	1800	300
3240	0	480	2340	3480	1680	2640	1800
0	0	0	2400	900	0	1200	1140
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0	1860	0	2700	900	0	2820	2400
0	3210	1470	360	0	1500	0	2400
900	3120	1800	2790	0	840	0	300
0	3060	0	0	0	3300	2700	810
3240	900	1800	3420	3300	90	2520	1560
2580	660	480	1560	1200	900	1800	240
1800	1920	1800	0	2760	2130	900	3300
3030	3570	150	2400	2100	1800	0	0
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990	1560	3240	1470	0	0	0	1200
0	2280	2400	1590	1800	2460	1680	360
1680	2910	0	2400	0	0	1800	1500
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2340	3240	900	1800	2700	3360	0	1770
600	1860	2760	0	2520	1800	0	0
2280	900	0	2700	900	2700	0	0
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3240	600	1800	2790	2700	420	420	2820
2040	1980	3000	0	300	0	2640	0
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1560	3360	0	1800	1440	900	1740	2100
660	3480	3000	2880	3540	1800	240	1800
2280	3000	2880	3540	240	600	0	3120
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540	0	1440	0	1200	2820	900	1800
3240	2100	0	0	1200	810	1470	0
1800	900	2070	180	3000	2580	0	2700
1980	0	2520	3360	1980	2520	900	900
3000	3120	0	3000	0	3480	900	2700
2760	840	240	900	3000	60	2520	420
900	900	480	1200	3300	540	2760	3000
2100	1800	3510	0	300	2400	0	1260
660	2880	0	2700	2700	480	3030	3240
2520	0	2640	720	0	240	390	3060
2400	2490	840	600	900	720	2400	600
960	1800	120	1500	1800	1200	2700	0
2520	3180	0	3300	300	1980	2220	2070
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3360	2100	0	2700	0	2610	0	3570
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840	1560	900	2970	1740	3540	0	2520
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3300	1620	3000	2520	600	2040	3000	2160
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2790	900	0	3450	3510	840	2310	900
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1680	0	2700	900	360	300	780	2700
2220	2340	0	2700	3300	0	0	600
2160	600	2880	3480	1350	0	840	900
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1920	1320	900	1800	3240	240	2700	240
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2880	330	1260	3300	960	0	3000	2700
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3480	2880	480	1800	2400	1800	600	1860
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780	1800	3000	0	3480	1500	0	2700
630	3000	1050	900	3390	0	600	1680
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3300	570	900	0	1320	0	2490	2940
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900	3000	240	2100	1800	2160	3390	3570
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1260	900	1440	1080	30	0	3420	1800
2700	0	600	0	2820	1800	1500	1800
2700	1200	2280	0	600	1080	0	0
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3480	0	600	2220	900	60	1110	0
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120	30	1500	1200	1080	2700	0	2100
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750	1560	1500	2400	60	1260	1560	780
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1500	600	2700	630	1920	420	2100	0
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1200	0	0	2700	2760	360	0	240
480	60	1140	3300	270	1800	2940	3240
2400	0	3300	690	600	1200	3240	1200
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900	2730	840	2400	1200	2580	2400	960
1800	360	600	660	2100	2700	3300	2700
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1800	2880	2700	1680	2580	540	1500	900
1500	300	0	960	2700	2700	0	2550

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1800	2640	1500	300	2520	2730	3390	0
840	0	1680	0	0	1200	1200	1800
3120	900	360	900	3300	3540	600	2640
600	930	960	3120	0	0	900	300
2940	2520	2520	1500	3360	2520	600	1920
780	1050	1500	0	1560	1800	0	0
1800	2100	0	1380	3480	2700	1680	2700
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1980	1440	1200	1680	0	2700	1800	2520
2640	3240	1920	0	0	2700	720	2700
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600	0	0	900	1800	900	900	2700
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2700	1830	3300	1320	3330	900	0	0
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2100	1800	3390	480	2100	1080	0	720
1800	1680	2400	2700	0	0	1800	450
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0	3000	3000	390	1200	900	720	0
1890	180	480	1200	0	900	0	0
2160	1800	1680	1800	0	240	360	3000
2700	0	870	960	480	1680	900	0
1920	1980	3360	1440	360	0	60	0
1950	1800	0	0	900	2700	1980	1260
3540	360	2820	1800	0	2130	2700	300
2640	1320	900	0	1800	0	0	1800
1500	600	2100	0	1650	1620	1650	2640
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2700	0	3000	3000	600	1800	2700	300
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900	600	1950	0	1320	0	1800	3120
2100	2700	0	1890	3300	2700	2790	0
2640	0	0	2520	1920	1800	900	1500
840	1620	630	2700	0	2700	0	750
600	2520	600	2430	0	1620	0	2550
2700	300	3000	180	900	2220	960	1500
2700	420	1140	0	900	1860	900	360
1800	0	2700	1800	3000	960	2040	900
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3360	2700	3120	0	2880	1680	900	2640
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3480	0	1380	0	900	2100	2880	2760
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690	0	0	2400	1380	600	1200	2700
300	180	1200	0	1200	1800	0	0
3240	3000	2670	0	900	2700	3480	1710
0	900	600	1680	2100	1680	2880	300
960	0	3420	300	420	2490	810	1230
720	0	0	1440	1080	1800	0	0
0	1740	0	30	0	1980	1350	1800
0	900	1920	0	2280	2040	0	3150
480	2700	1500	1170	900	0	240	1920
2400	960	480	2880	900	540	540	1200
1800	1200	3000	3540	720	1680	2460	0
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600	1800	90	900	0	600	720	0
1200	2220	1680	1800	0	300	2880	2700
1800	2160	2700	2760	600	1320	660	2700
2100	0	900	0	1500	1200	0	2340
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1200	2160	2100	1800	1860	600	0	2400
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2580	300	0	3360	2700	870	840	2700
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2400	1560	0	1200	900	0	180	0
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2820	840	2760	2400	1800	900	2700	1860
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2640	0	2700	3360	1800	0	0	0
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1440	2700	720	2700	1800	2100	0	0
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2700	1680	840	900	1500	1200	900	0
1680	2910	2820	780	900	3420	0	2520
2220	1440	1500	300	1260	900	0	900
1800	2700	2100	3360	0	1650	0	1590
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VarExp_TChngLst.dat

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3600	3600	900	300	300	900	300
900	900	900	300	120	300	300
30	60	30	60	60	120	60
900	3600	30	3600	30	900	60
120	300	30	30	900	60	120
120	30	60	3600	30	900	900
60	60	300	60	900	300	300
300	900	30	3600	30	300	60
120	30	300	900	120	3600	120
60	3600	300	60	900	900	
3600	120	300	30	120	3600	
900	300	300	30	3600	3600	
30	30	3600	120	60	900	
3600	60	30	60	30	120	
120	30	900	900	300	120	
300	300	60	3600	300	30	
120	900	900	900	120	300	
120	3600	900	3600	3600	900	
300	3600	60	3600	300	30	
300	60	30	60	30	900	
900	120	120	300	30	3600	
120	900	300	3600	900	3600	
30	900	30	30	60	60	
30	120	30	60	300	900	
60	3600	900	3600	300	300	
300	900	60	120	3600	30	
30	300	300	60	30	3600	
120	30	30	120	300	900	
120	60	300	30	900	30	
900	60	300	3600	3600	3600	
60	3600	900	30	120	30	
300	300	900	30	30	3600	
900	60	900	300	900	120	
30	3600	900	3600	3600	120	
30	120	900	120	60	120	
900	120	900	30	120	60	
120	300	30	120	60	120	
900	3600	300	300	30	60	
60	60	300	3600	60	120	
300	900	30	120	300	30	
30	900	30	30	300	900	
300	30	60	300	30		

LIST OF ABBREVIATIONS AND ACRONYMS

AF	Air Force
CV	coefficient of variation
HPA	high performance aircraft
HPARS	High Performance Aircraft Respiratory Study
IPA	isopropanol
OSHA	Occupational Safety and Health Administration
PBPK	physiologically-based pharmacokinetic
PEL	permissible exposure limit
STEL	short term exposure limit
TWA	time-weighted average
UPE	unexplained physiological events
USAFSAM	United States Air Force School of Aerospace Medicine