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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.

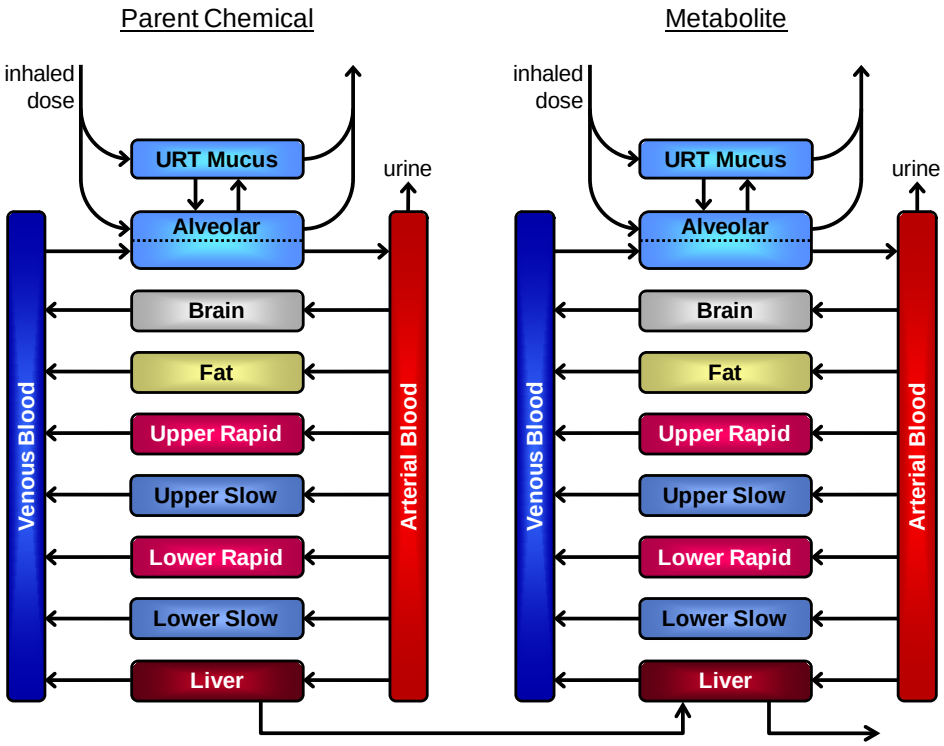

Figure 1. Schematic of Modified PBPK Model for IPA and its Metabolite, Acetone. This schematic shows modifications made to the Clewell *et al*. [1] model in the course of the previous work as well as the modifications made in this work to split the rapidly and slowly perfused compartments into upper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

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

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.

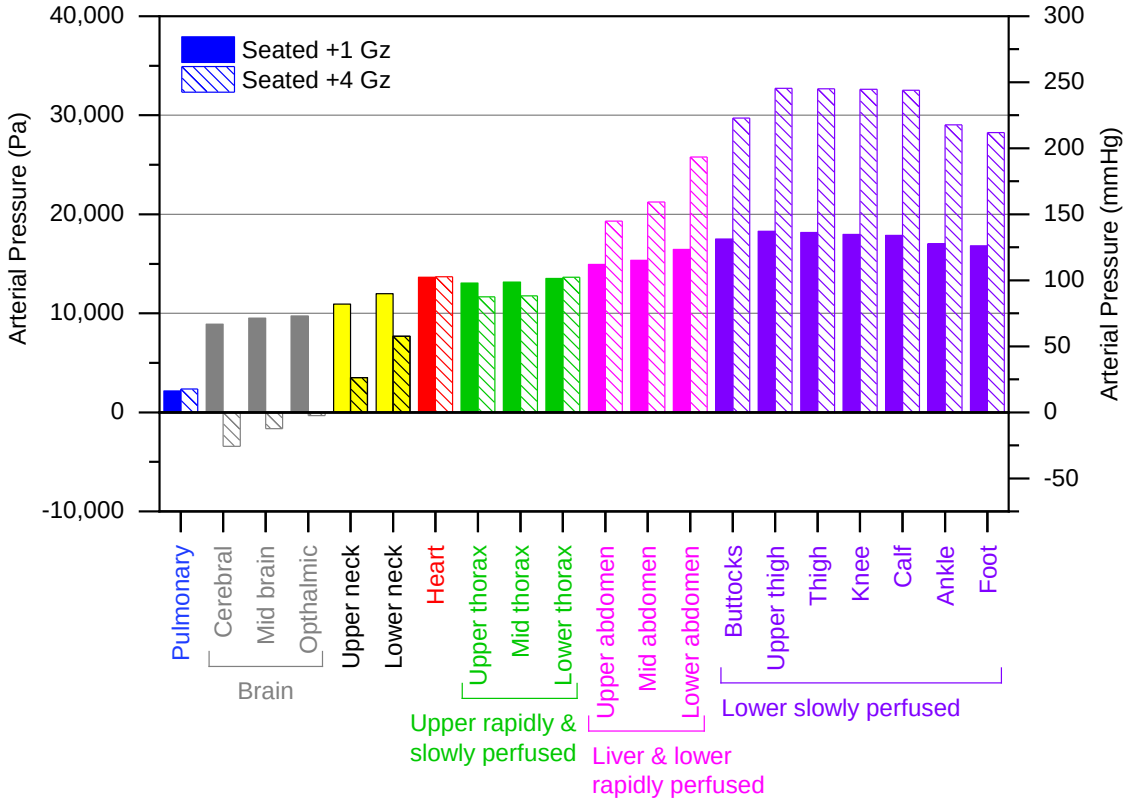

Figure 2. Arterial Pressure Changes. Data were digitized from Figure 6.4 in Bomar *et al*. [2] and represent predicted equilibrium arterial pressure changes for a pilot in a seated position at +1 Gz and +4 Gz. Segments were grouped (colored labels below x-axis) to correspond to compartments in the PBPK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

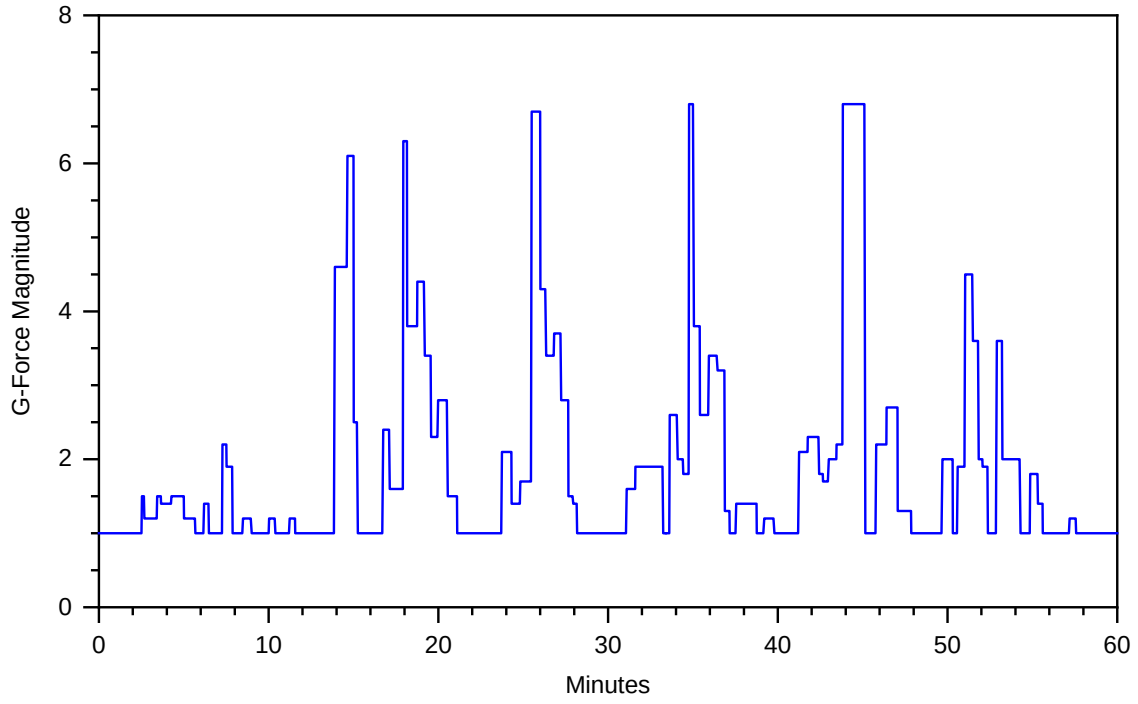

Figure 3. Simulated G-Forces Applied During Simulated Flight. Based on data from Newman [3].

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

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

[b]Parameter 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]

[a]Parameter not used for this chemical
[b]Calculated using brain/gas partition [8] and the blood/air partition [5].
[c]Tissue/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 minues	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		

[a]Values not shown were calculated as +/- two standard deviations
[b]Calculated from mean and standard deviation from AF biometric database [6]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI
[c]Maximum 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 ouput using the ventilation perfusion ratio. The resulting changes for ventilation rate, cardiac output, and some of the tissue flows are shown in Figure 4.

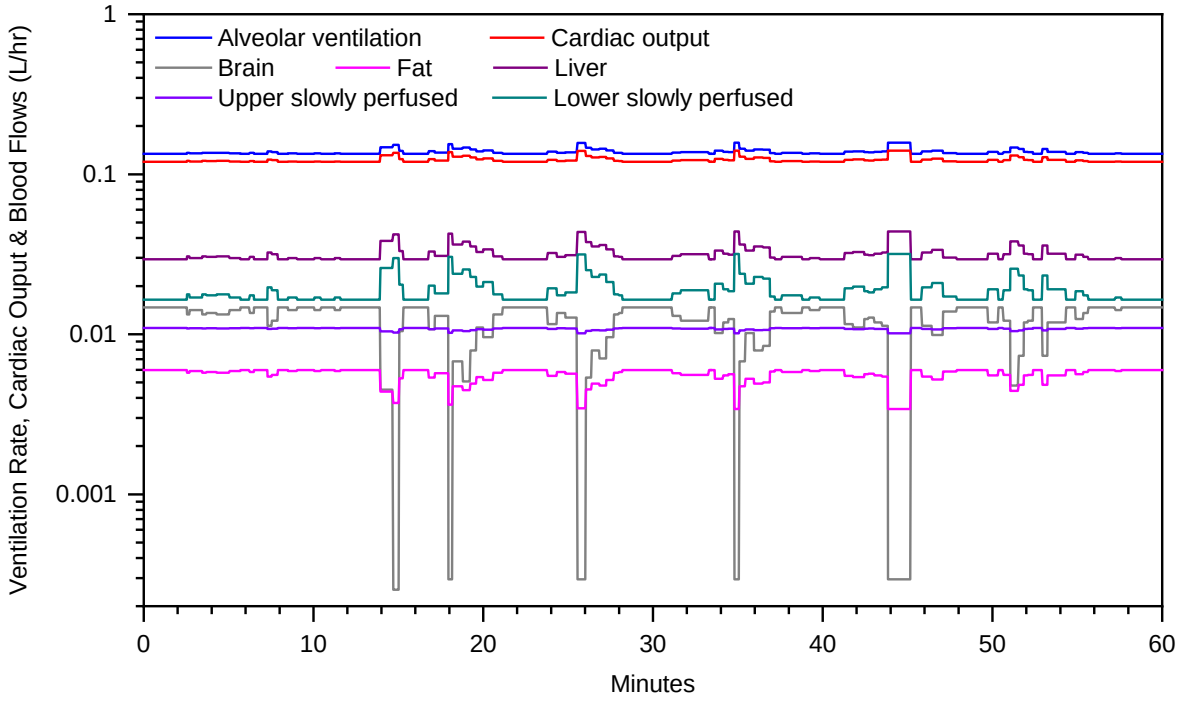

Figure 4. Simulated Changes in Ventilation Rate, Cardiac Outout and Selected Blood Flows. This plot shows the predicted physiological changes due to simulation of G-forces applied during flight.

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.

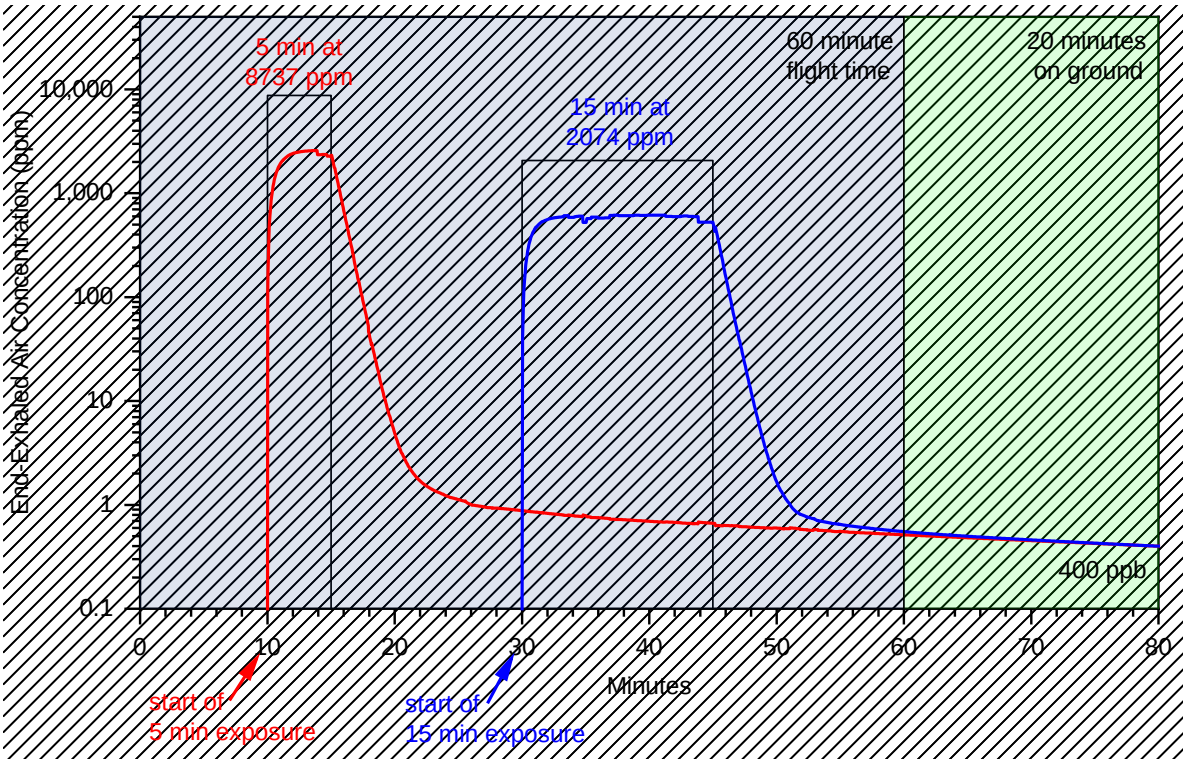

Figure 5. Scenario Used for Dose Reconstructions. This figure represents the scenarios for two of the exposures used for dose reconstruction (a 5 minute exposure occurring 10 minutes into the flight and a 15 minute exposure occurring 30 minutes into the flight). The shaded blue area represents the flight 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).

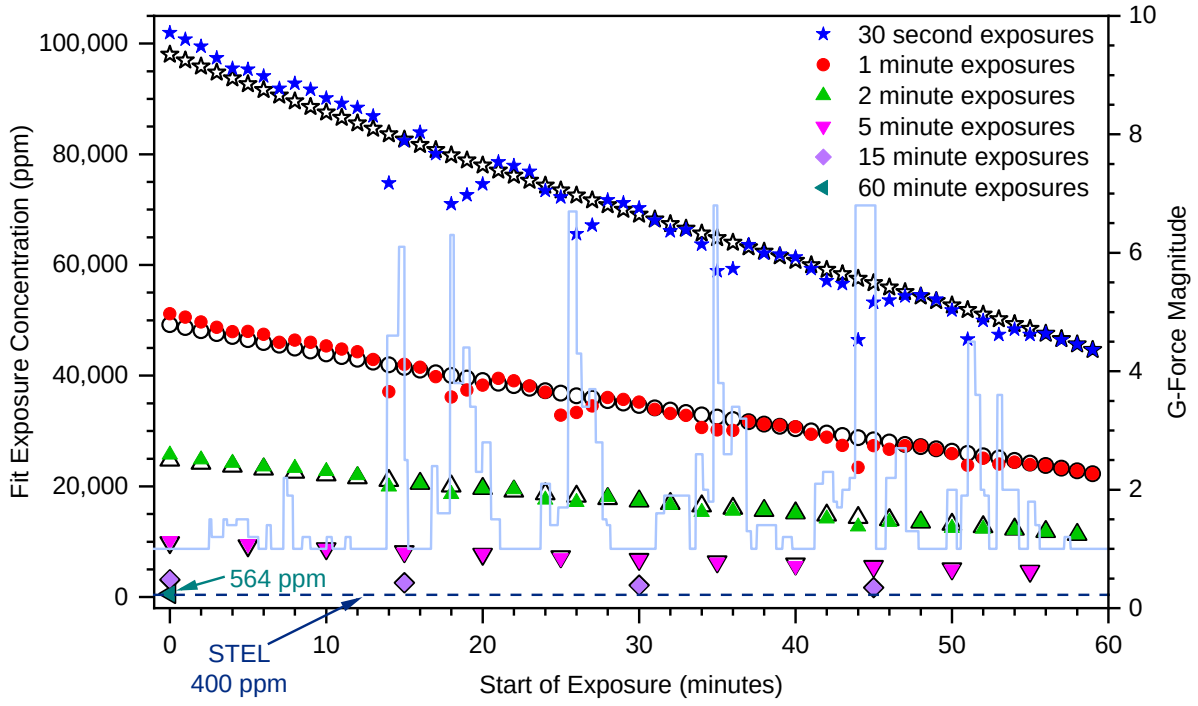

Figure 6. Estimated IPA Exposure Concentrations. Estimated exposure concentrations to predict an IPA exhaled breath target of 400 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

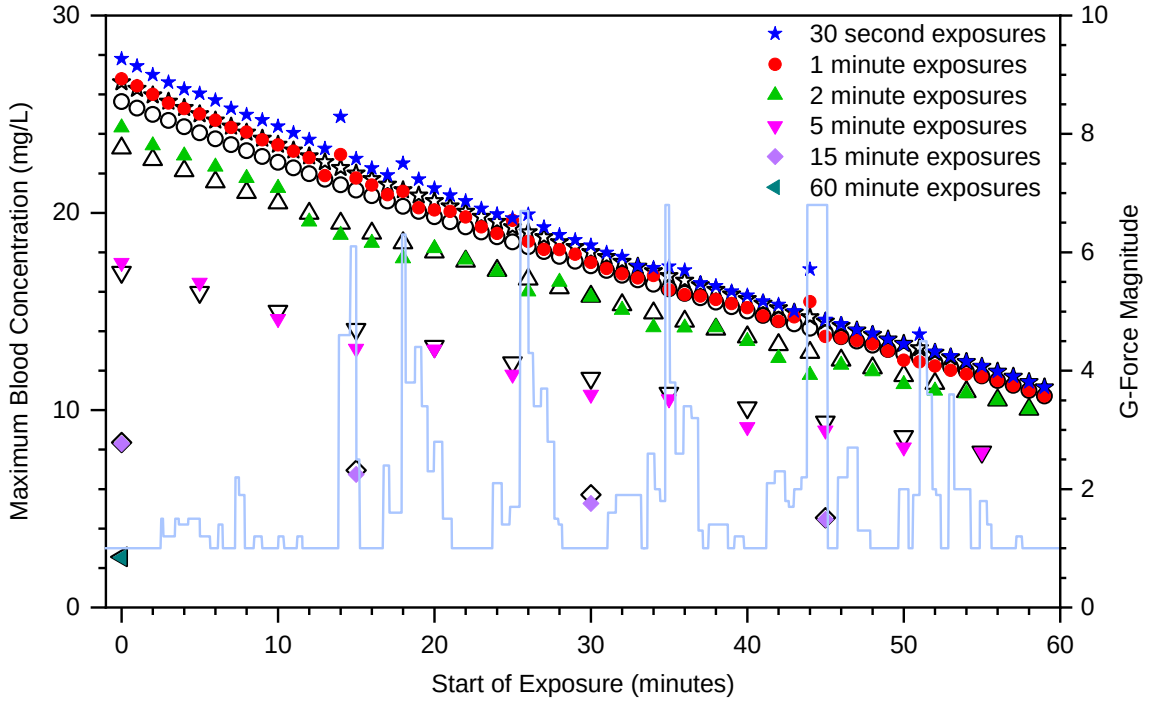

Figure 7. Predicted Maximum IPA Blood Concentrations. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 6.

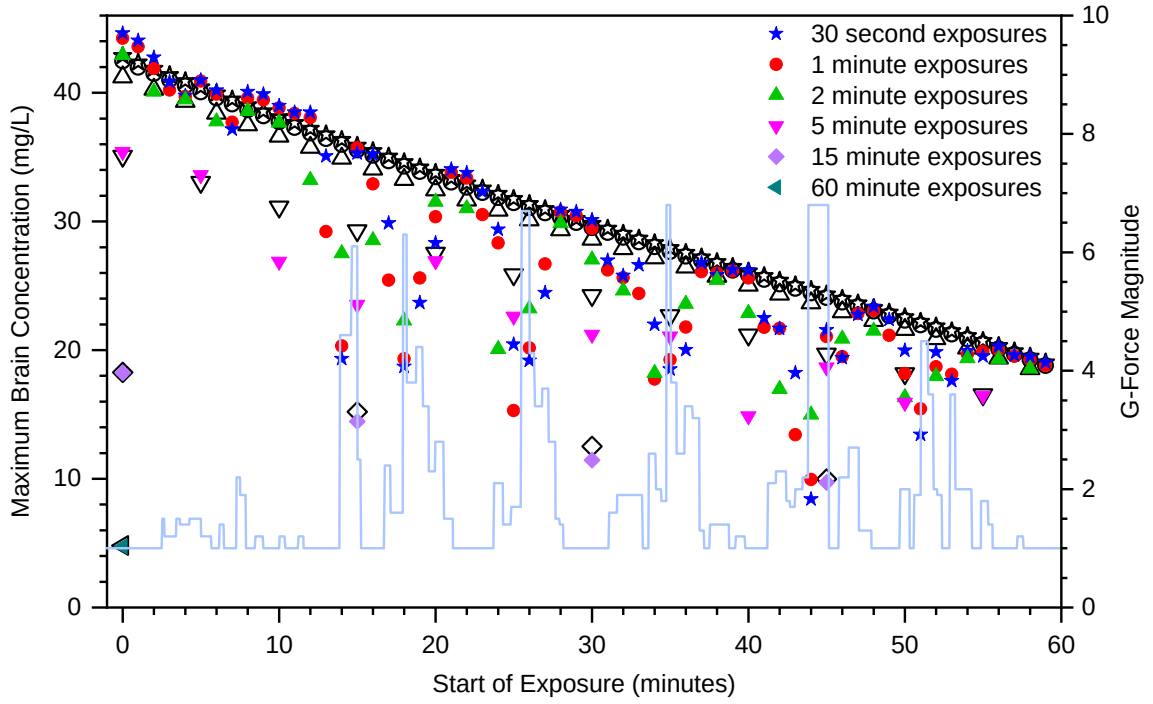

Figure 8. Predicted Maximum IPA Brain Concentrations. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 6.

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 withing 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.

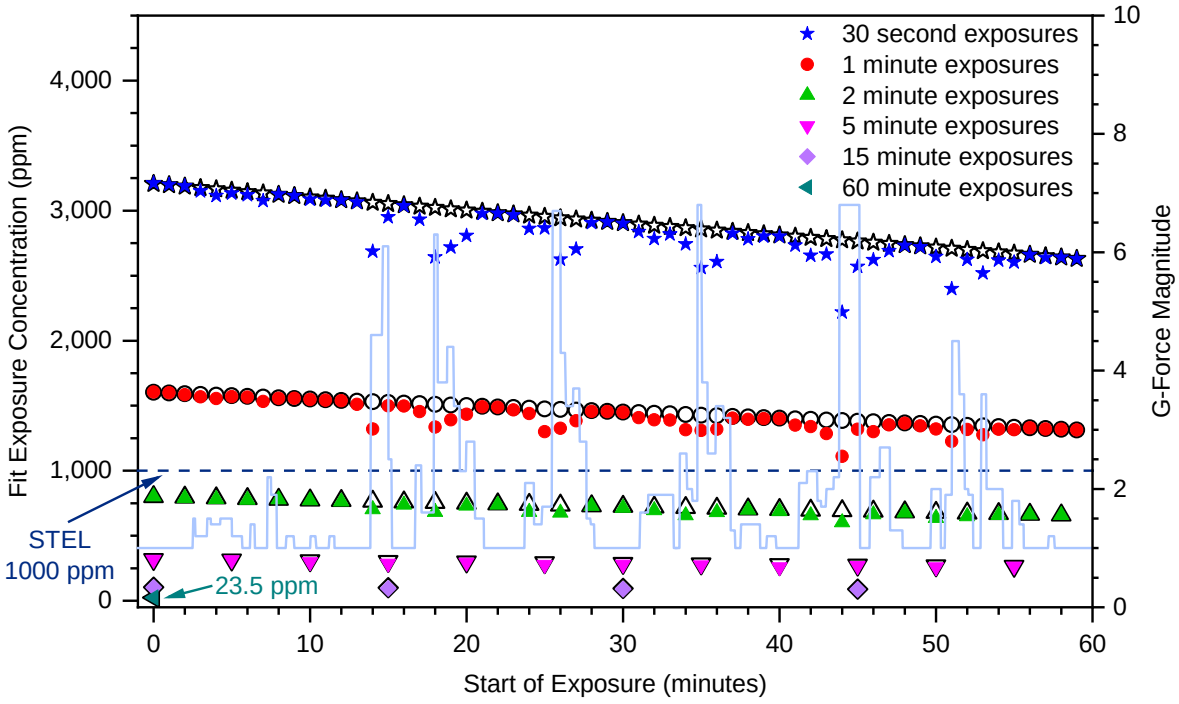

Figure 8. Estimated Acetone Exposure Concentrations. Estimated exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

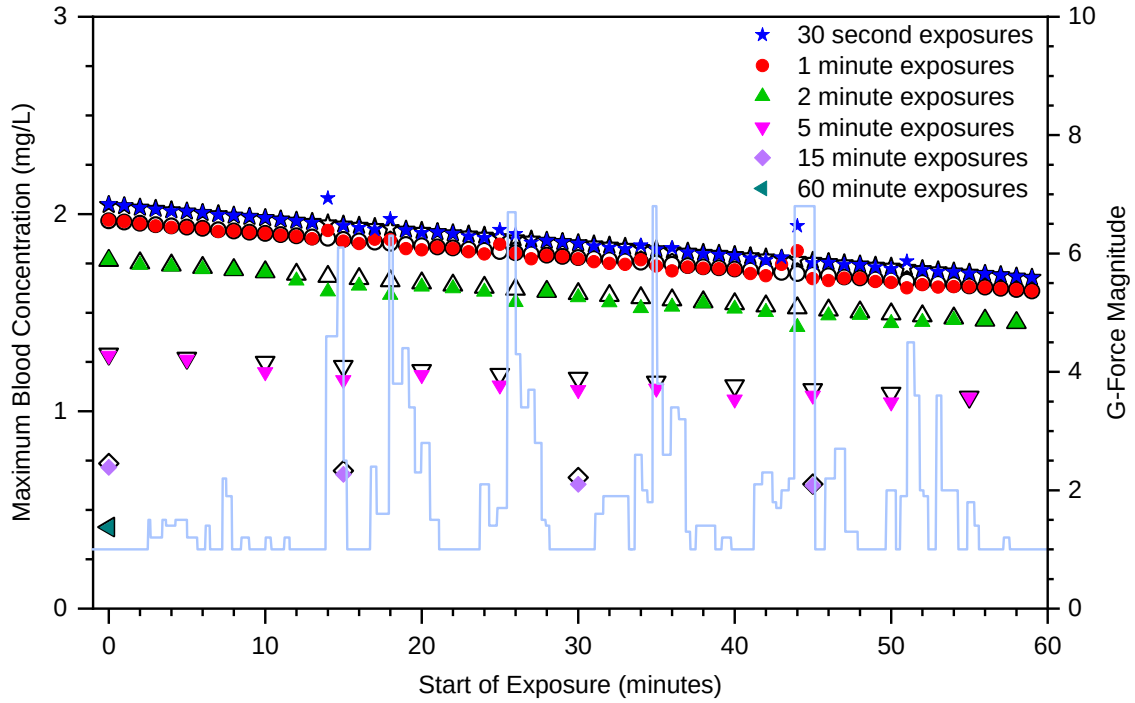

Figure 9. Predicted Maximum Acetone Blood Concentrations. Blood concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 8.

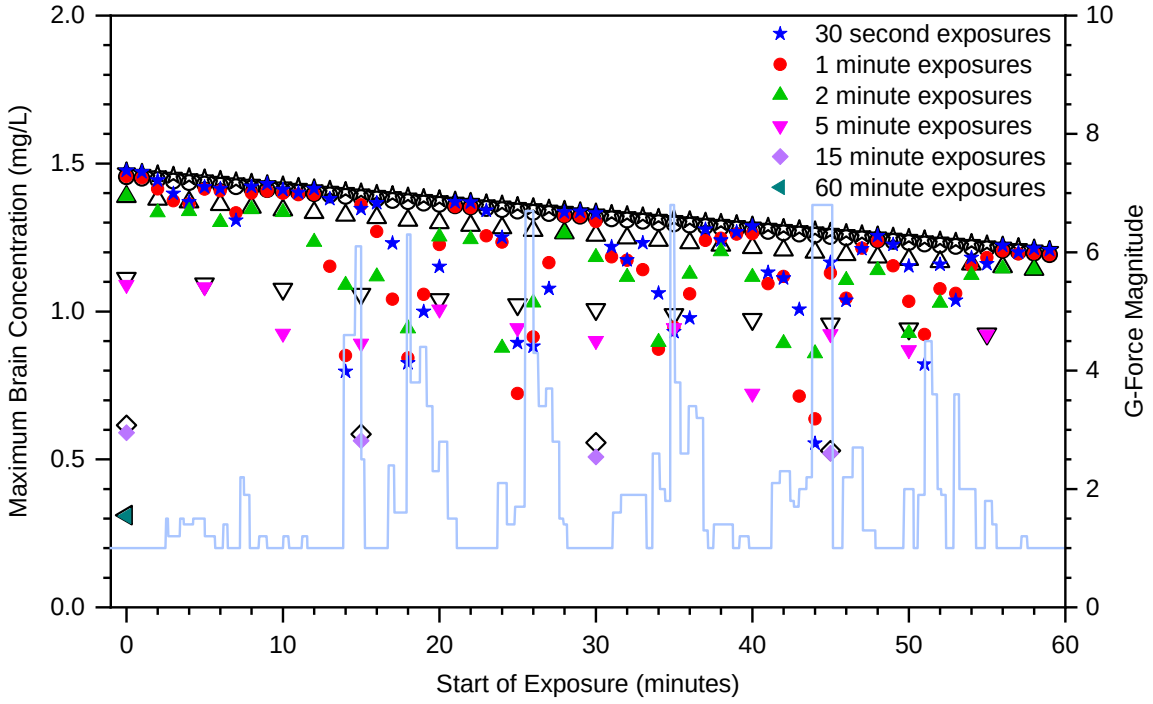

Figure 10. Predicted Maximum Acetone Brain Concentrations. Brain concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 8.

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.

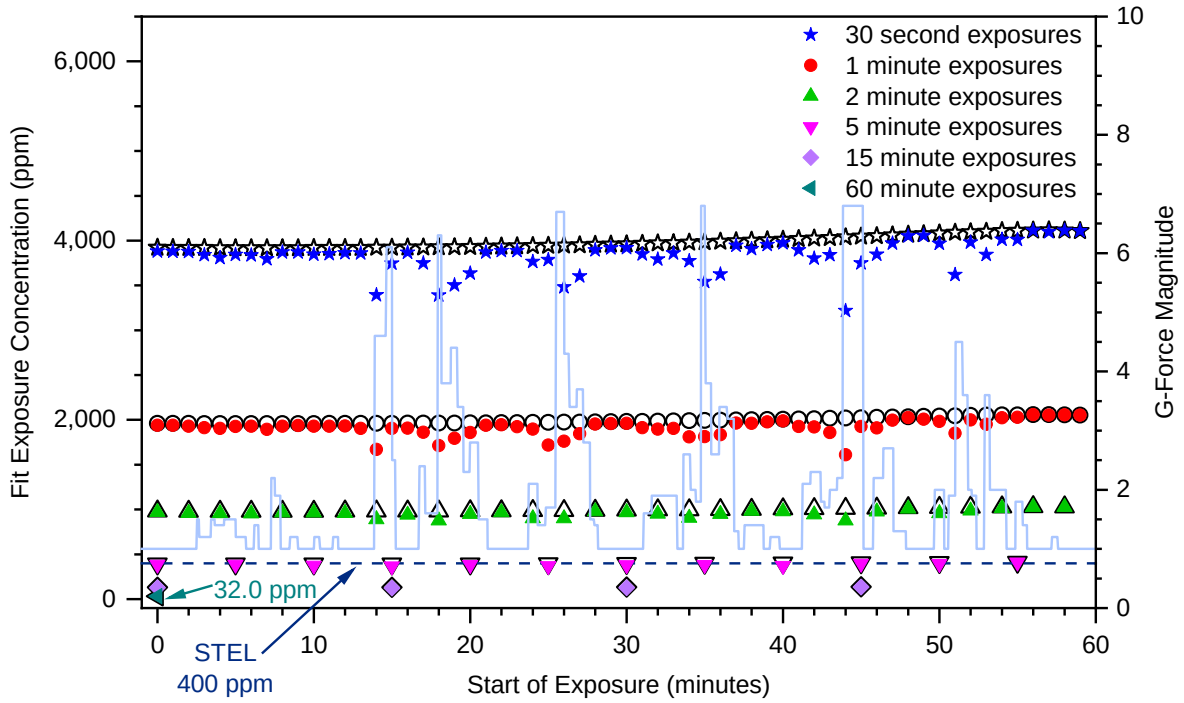

Figure 11. Estimated IPA Exposure Concentrations to Predict Acetone Target. Estimated IPA exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios. Dark blue dashed line represents the STEL.

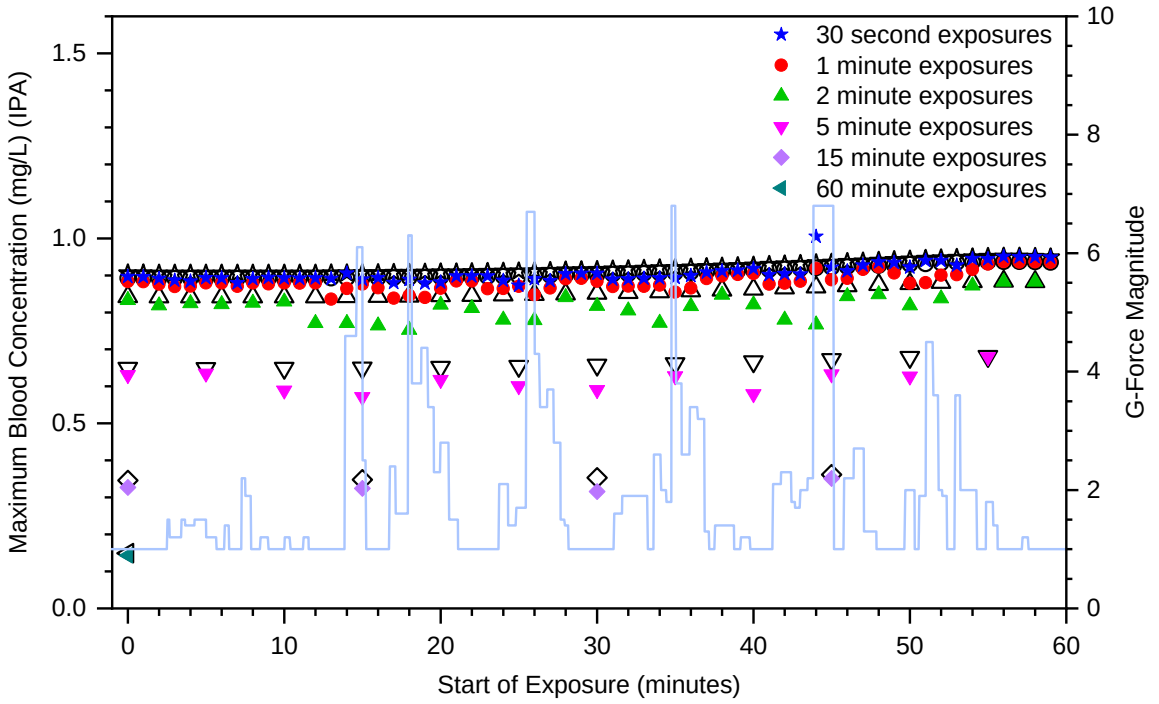

Figure 12. Predicted Maximum IPA Blood Concentrations for Acetone Target. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

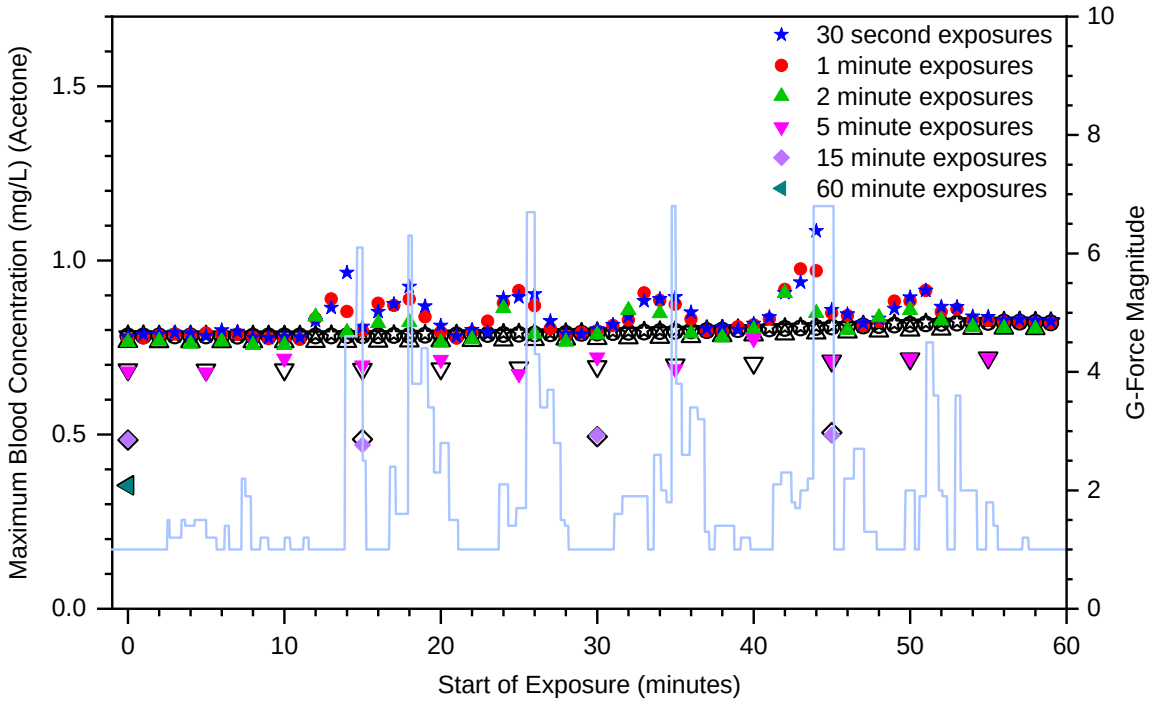

Figure 13. Predicted Maximum Acetone Blood Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

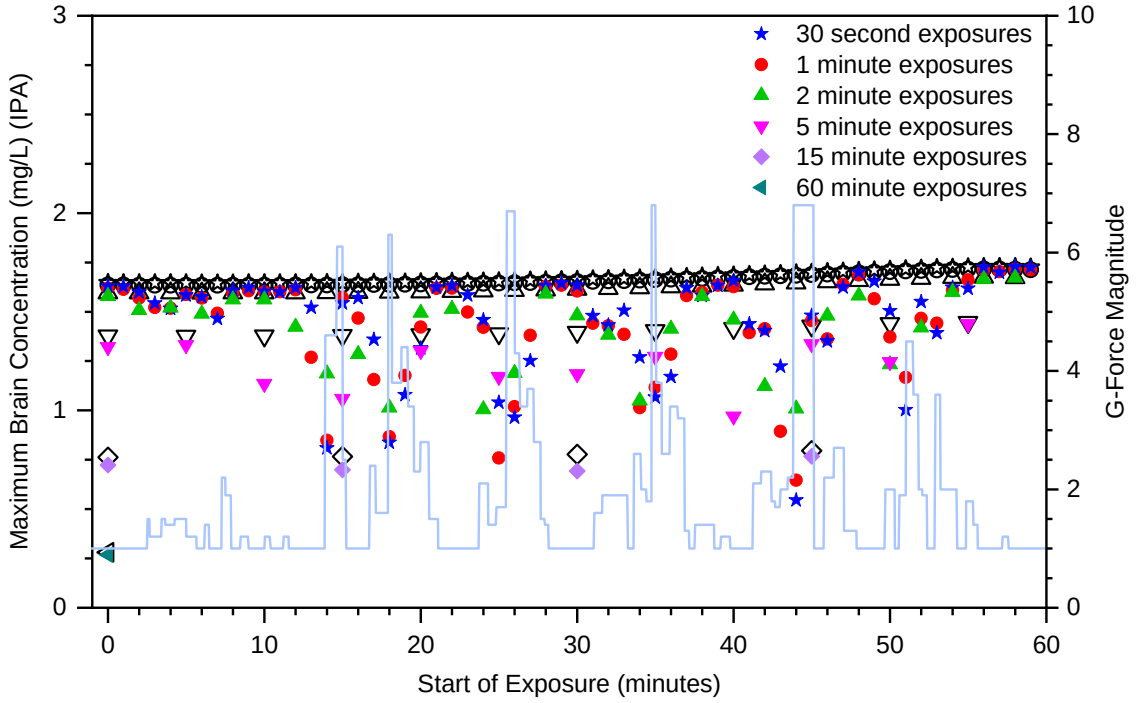

Figure 14. Predicted Maximum IPA Brain Concentrations for Acetone Target. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

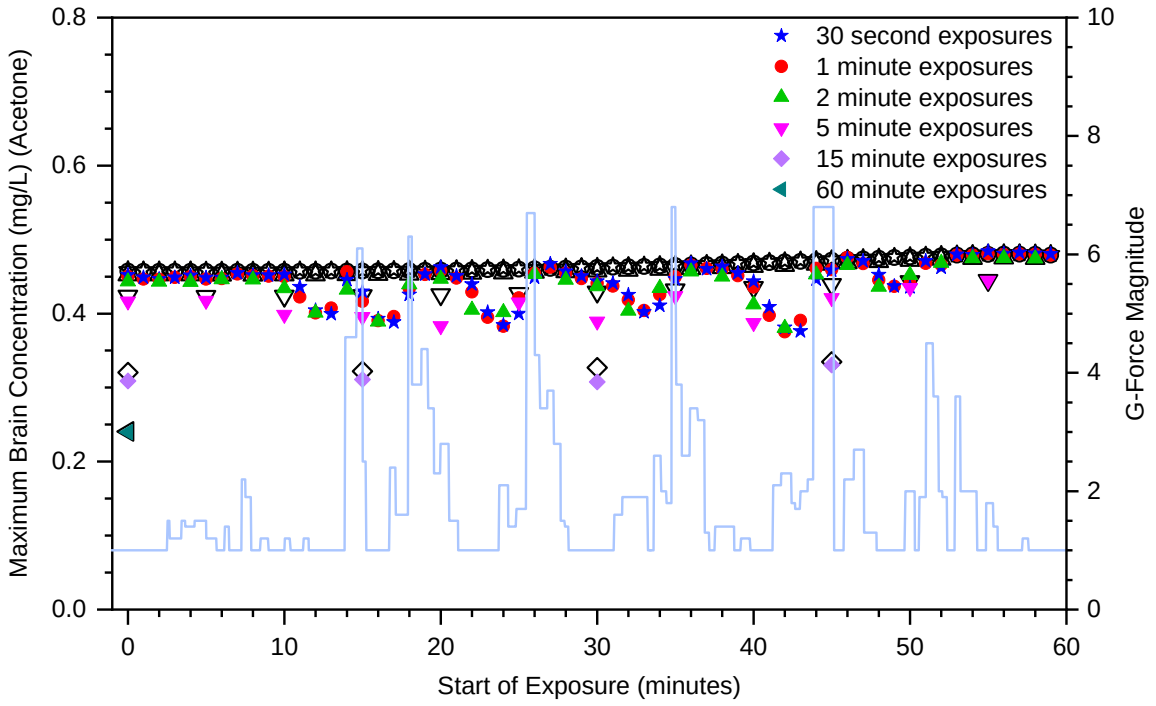

Figure 15. Predicted Maximum Acetone Blood Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 11.

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).

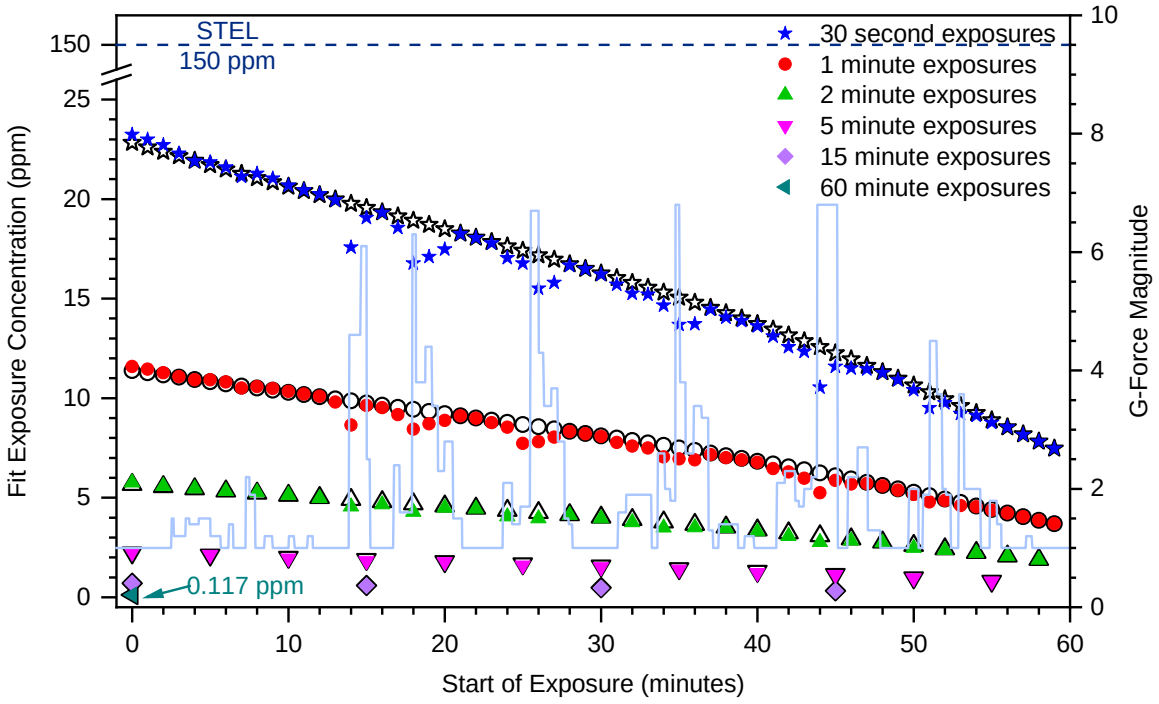

Figure 16. Estimated Toluene Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 6.3 ppb for different exposure scenarios.

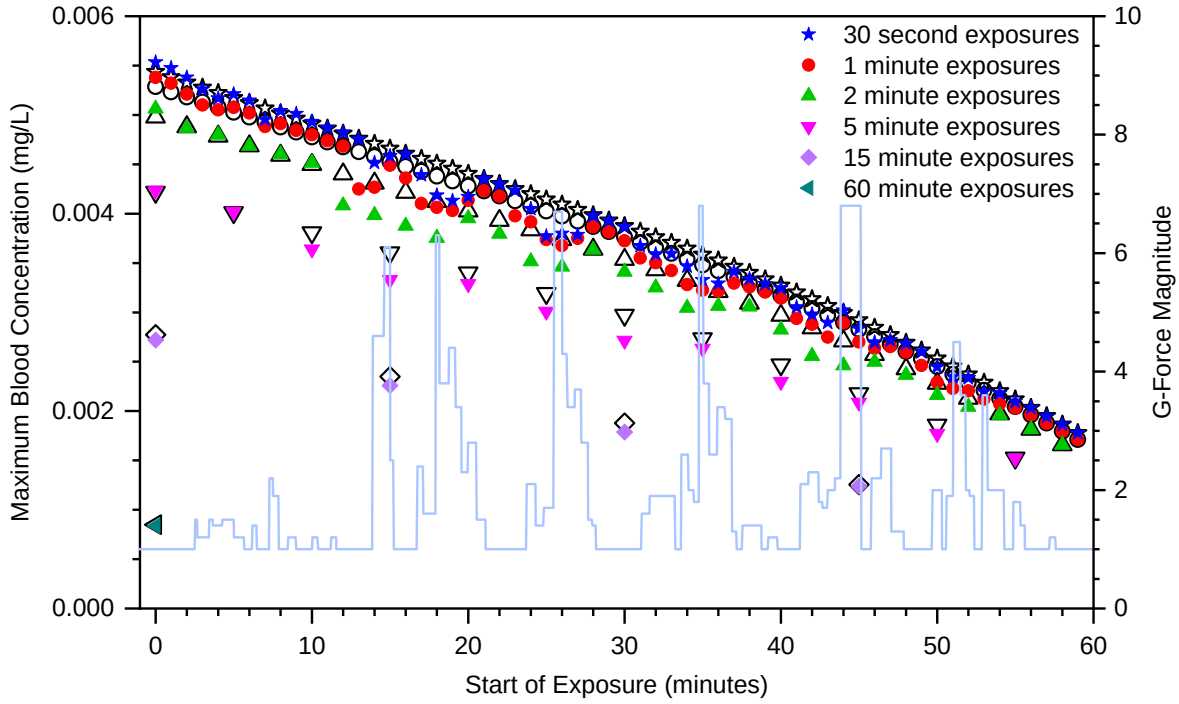

Figure 17. Predicted Maximum Toluene Blood Concentrations. Blood concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 16.

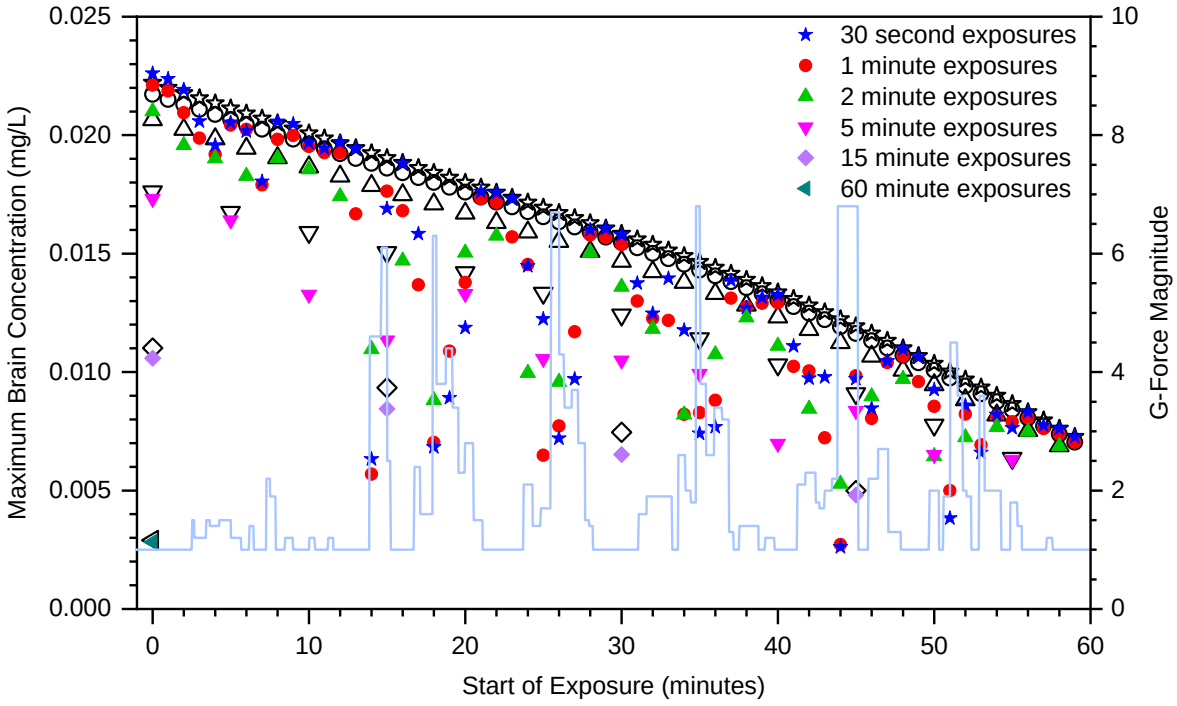

Figure 18. Predicted Maximum Toluene Brain Concentrations. Brain concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 16.

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.

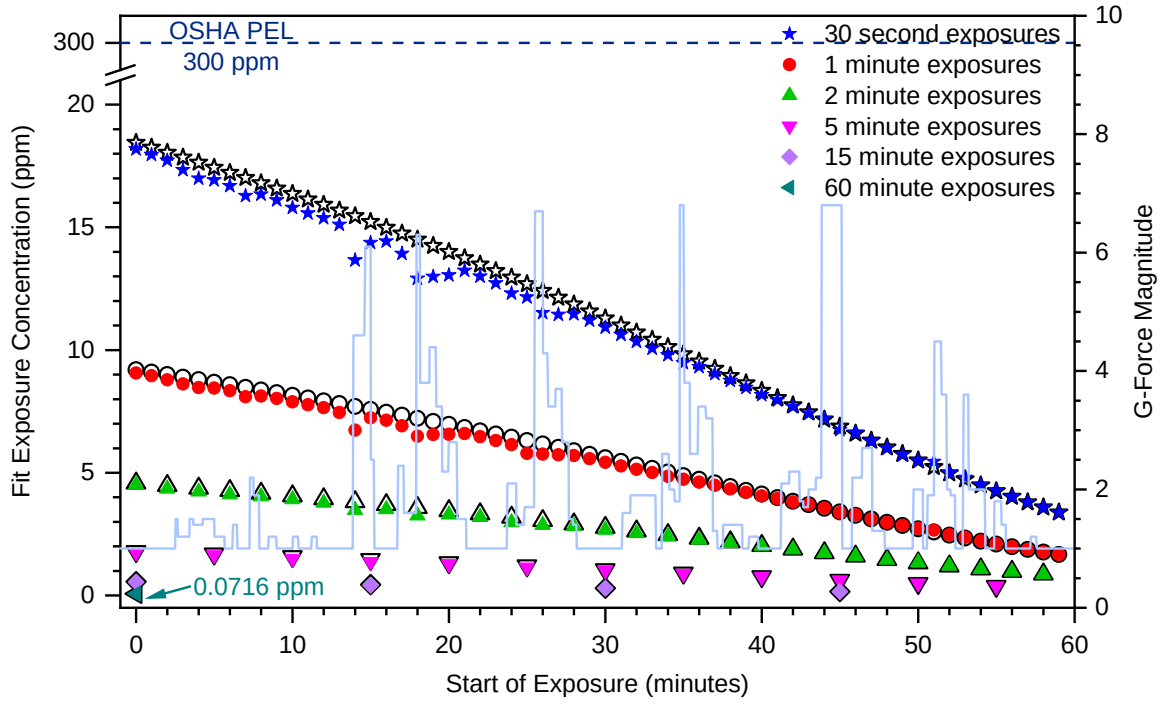

Figure 19. Estimated Cyclohexane Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 5.3 ppb for different exposure scenarios. Dark blue dashed line represents the OSHA PEL.

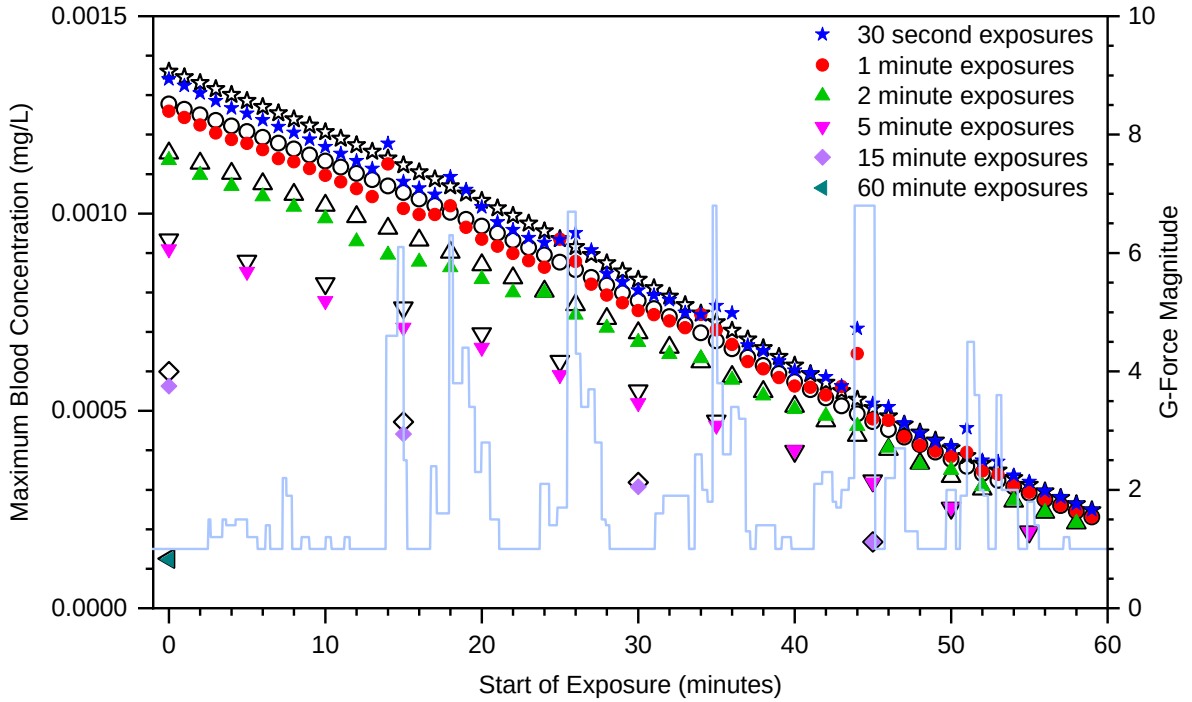

Figure 20. Predicted Maximum Cyclohexane Blood Concentrations. Blood concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 19.

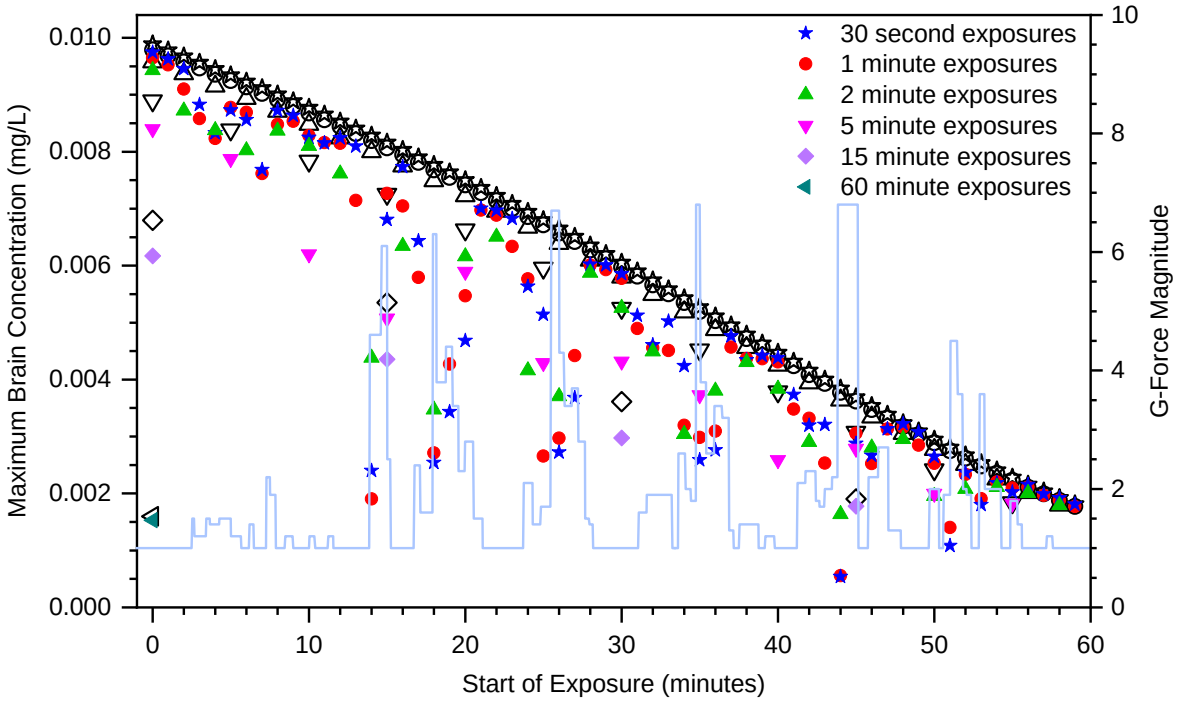

Figure 21. Predicted Maximum Cyclohexane Brain Concentrations. Brain concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 19.

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.

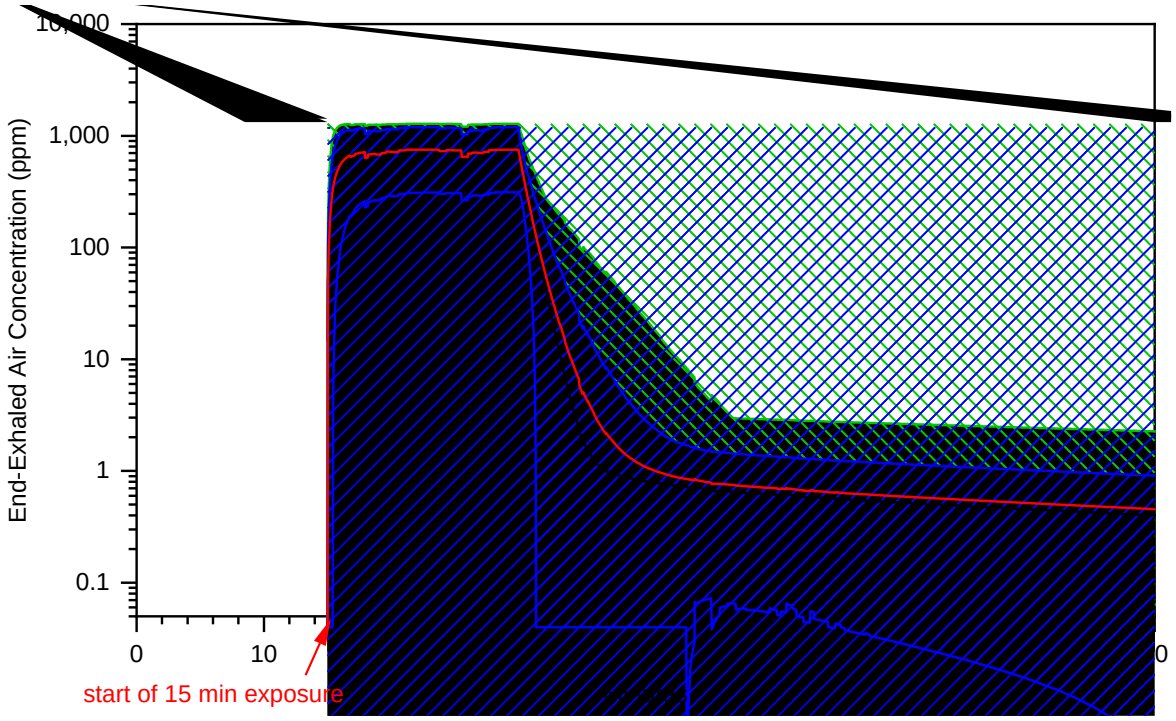

Figure 22. Monte Carlo Results for Exhaled IPA Concentrations for Fixed Exposure. Results are a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

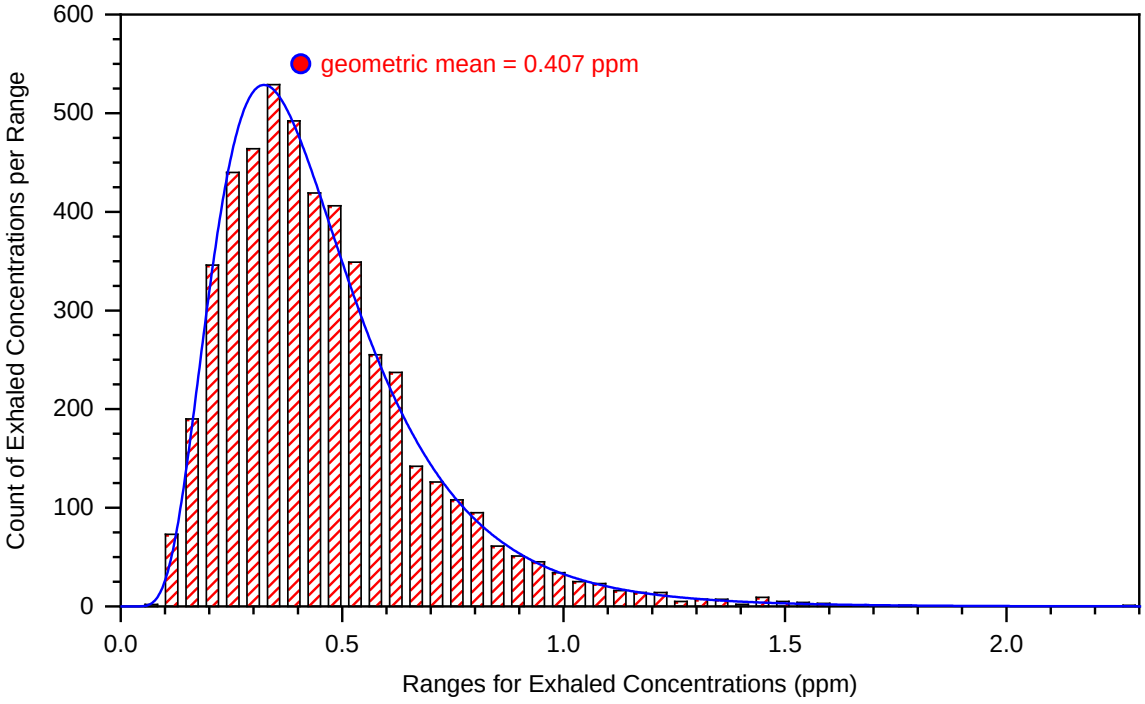

Figure 23. Histogram of Exhaled IPA Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

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 geometic 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).

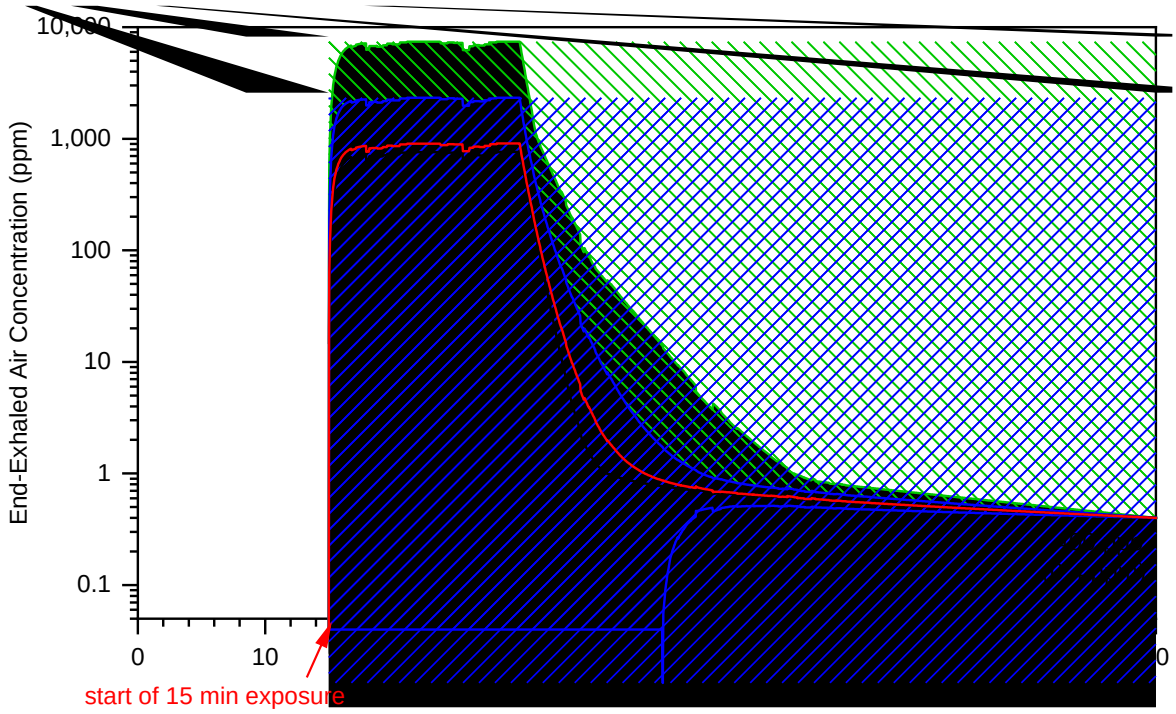

Figure 24. Monte Carlo Results for Exhaled IPA Concentrations from Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

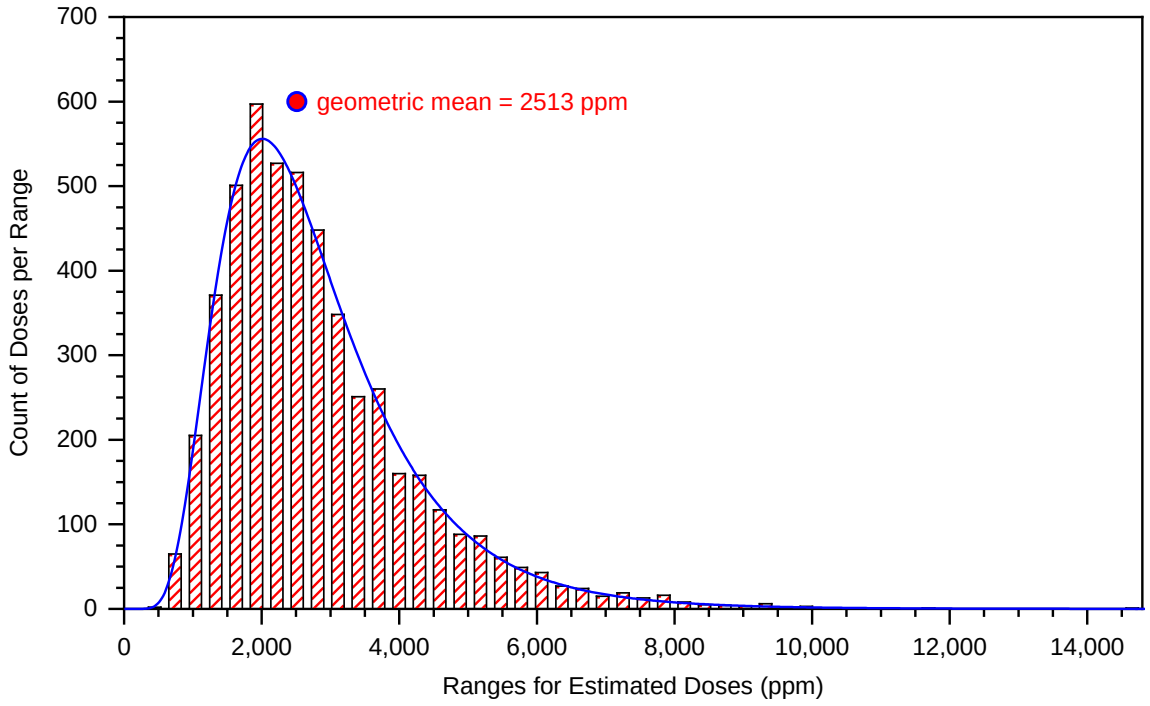

Figure 25. Histogram of Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

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).

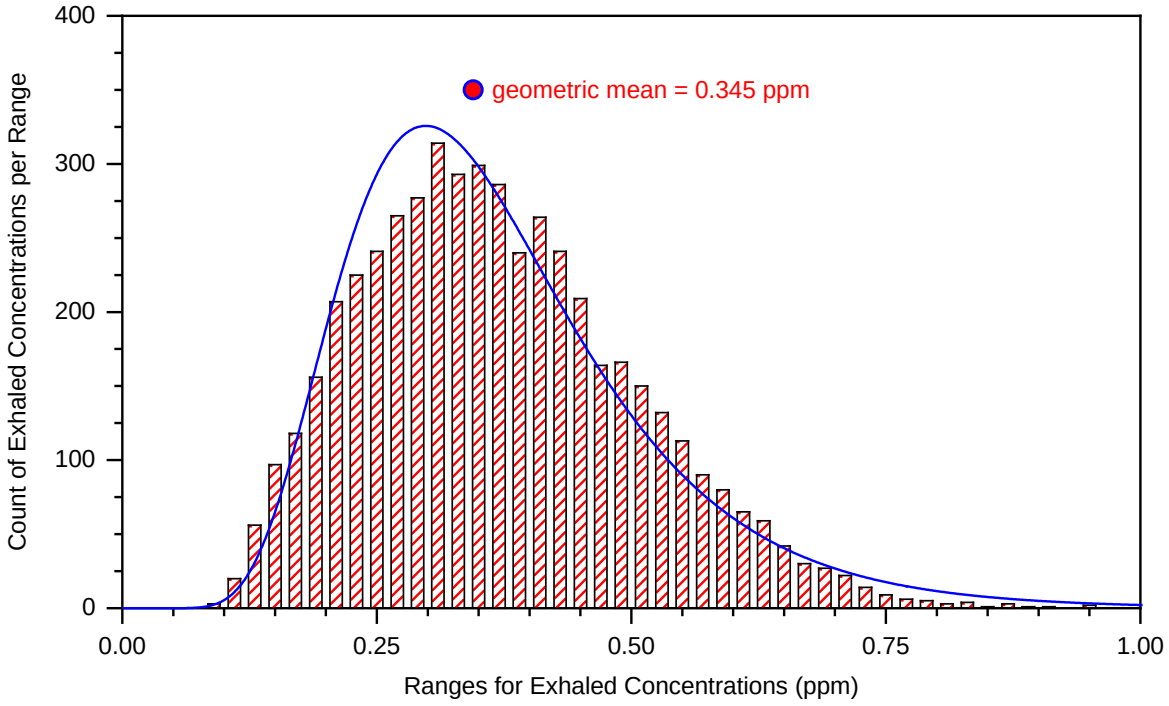

Figure 26. Histogram of Exhaled Acetone Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

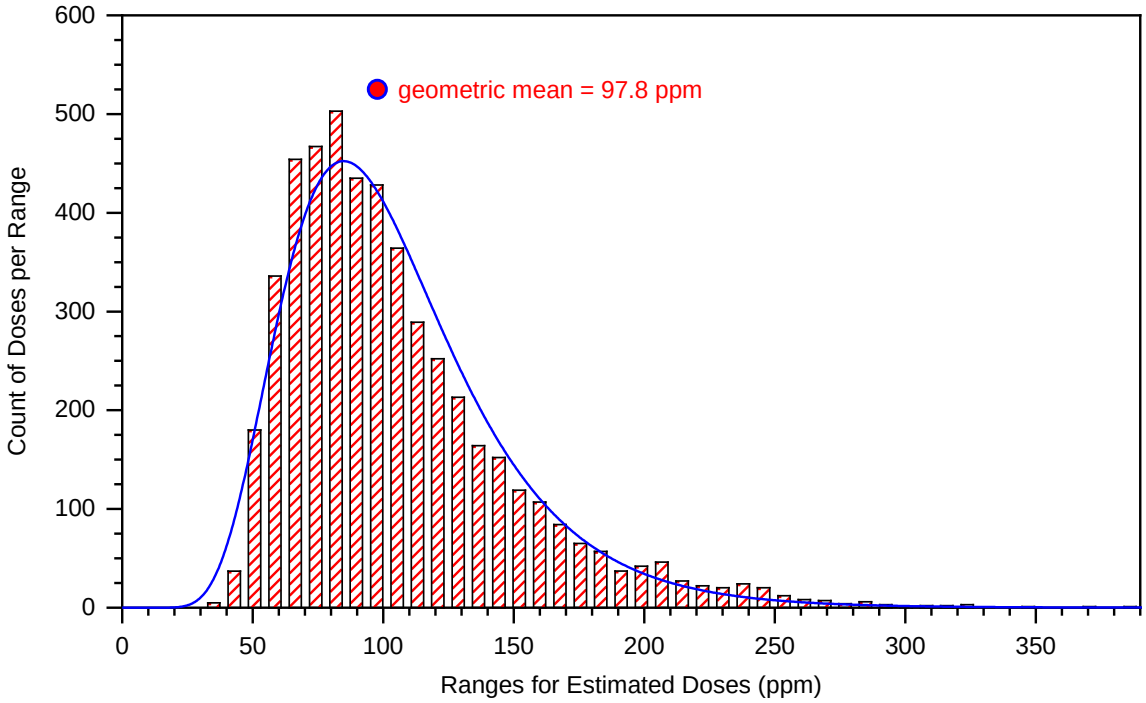

Figure 27. Histogram of Estimated Acetone Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

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).

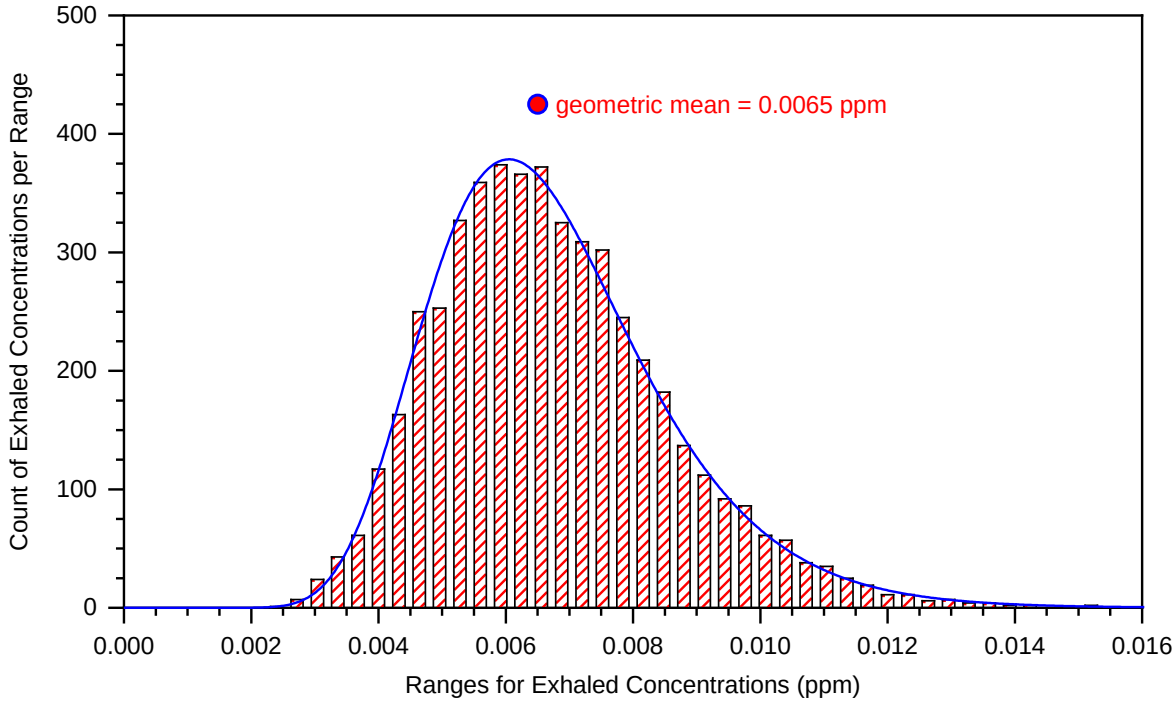

Figure 28. Histogram of Exhaled Toluene Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating toluene exposure of 15 minutes starting 15 minutes into the flight.

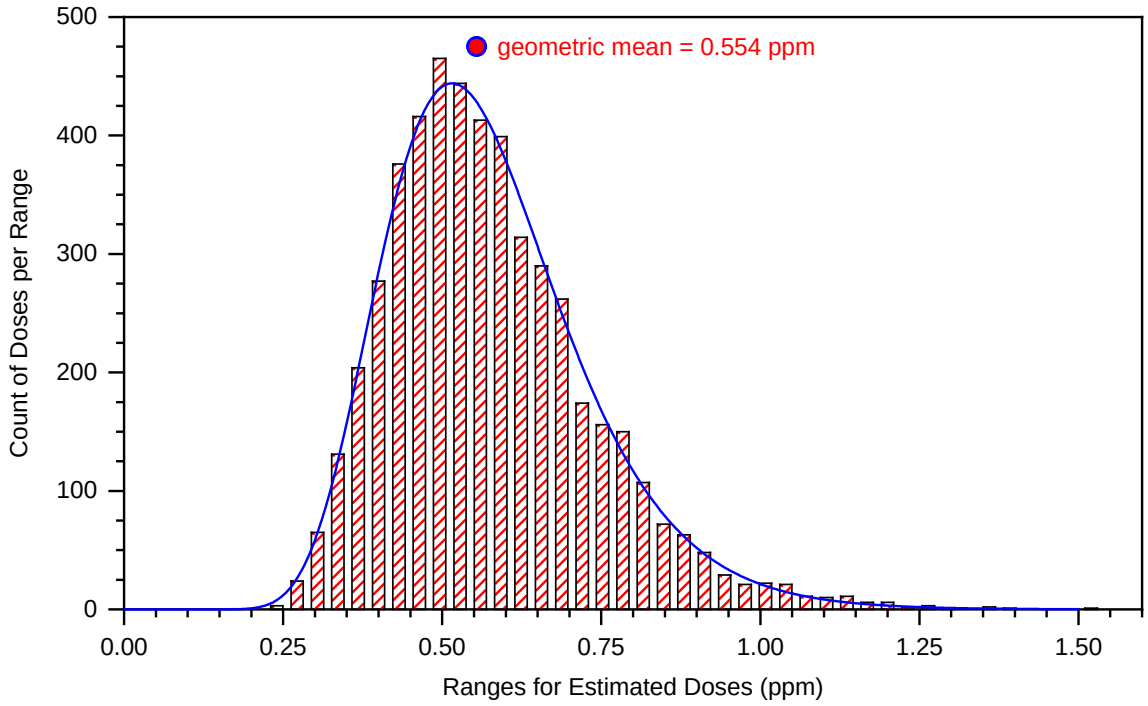

Figure 29. Histogram of Estimated Toluene Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating toluene exposure of 15 minutes starting 15 minutes into the flight.

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).

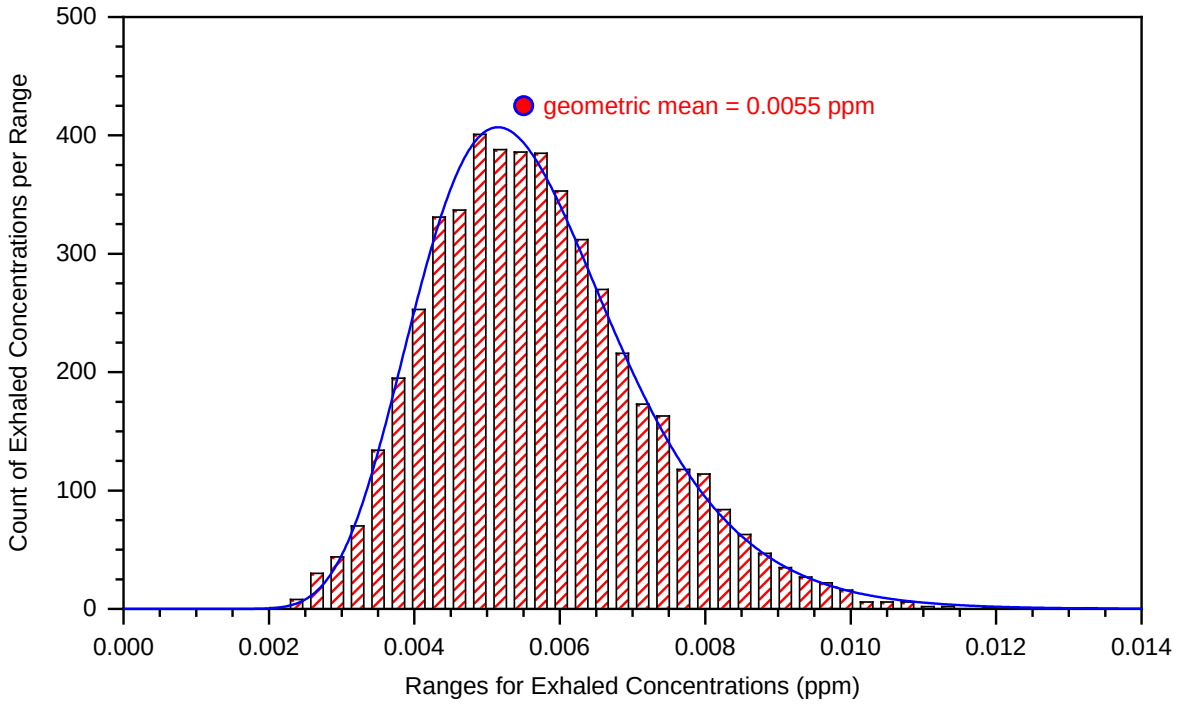

Figure 30. Histogram of Exhaled Cyclohexane Concentrations for Fixed Exposure. Results are for a Monte Carlo analysis simulating cyclohexane exposure of 15 minutes starting 15 minutes into the flight.

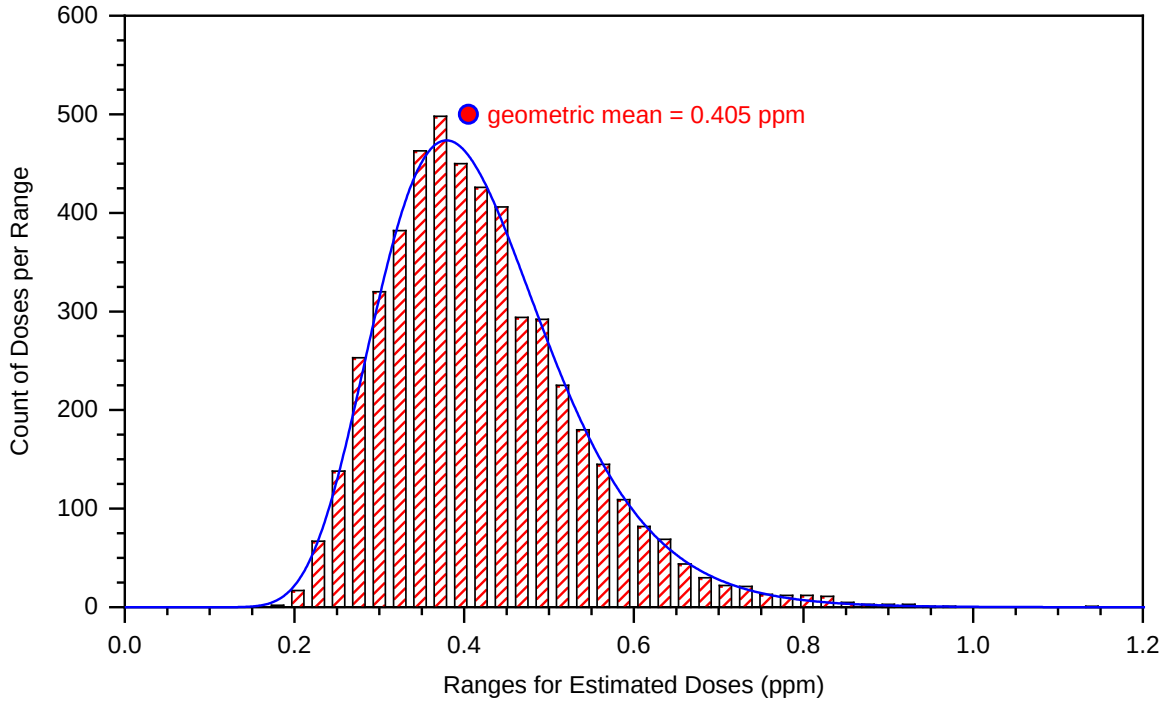

Figure 31. Histogram of Estimated Cyclohexane Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating cyclohexane exposure of 15 minutes starting 15 minutes into the flight.

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.

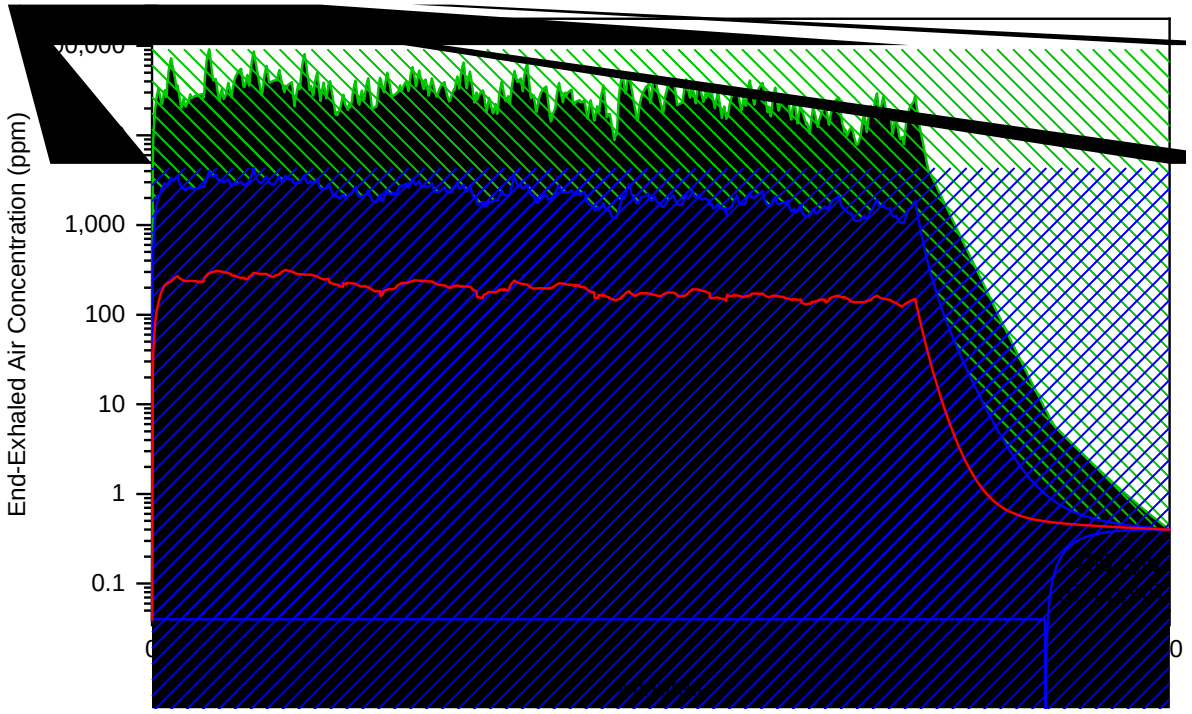

Figure 32. Monte Carlo Results for Exhaled IPA Concentrations from Estimated IPA Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating IPA exposure of random lengths and start times.

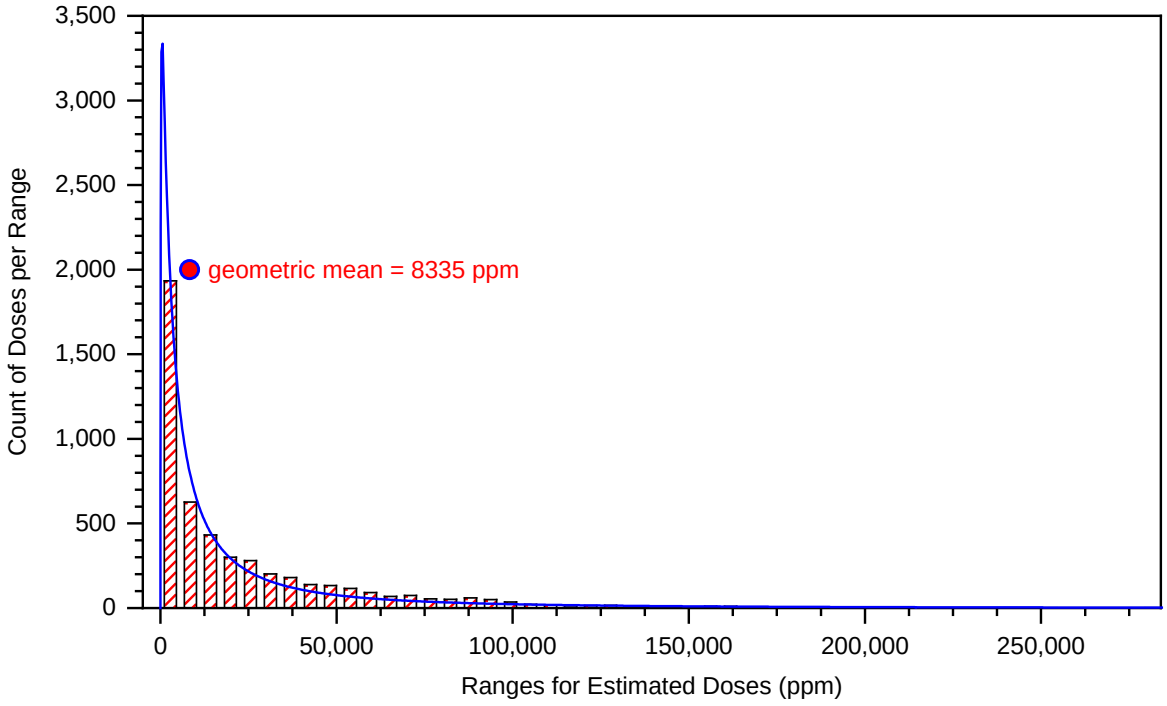

Figure 33. Histogram of Estimated IPA Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating IPA exposure of random lengths and start times.

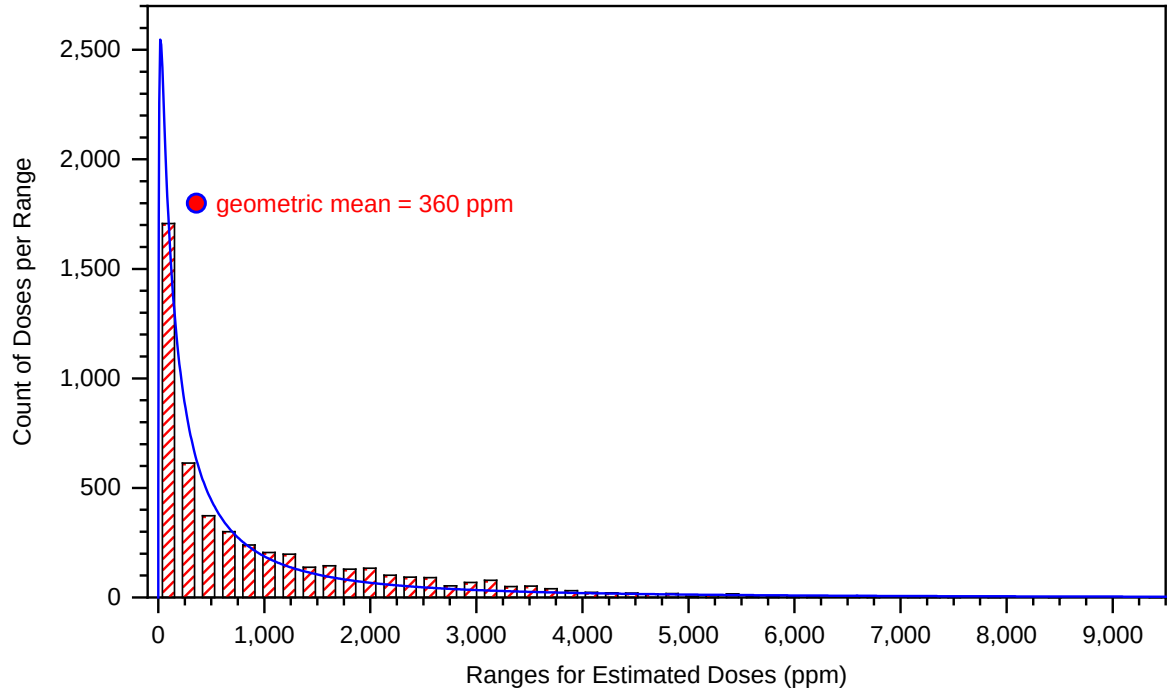

Figure 34. Histogram of Estimated Acetone Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating acetone exposure of random lengths and start times.

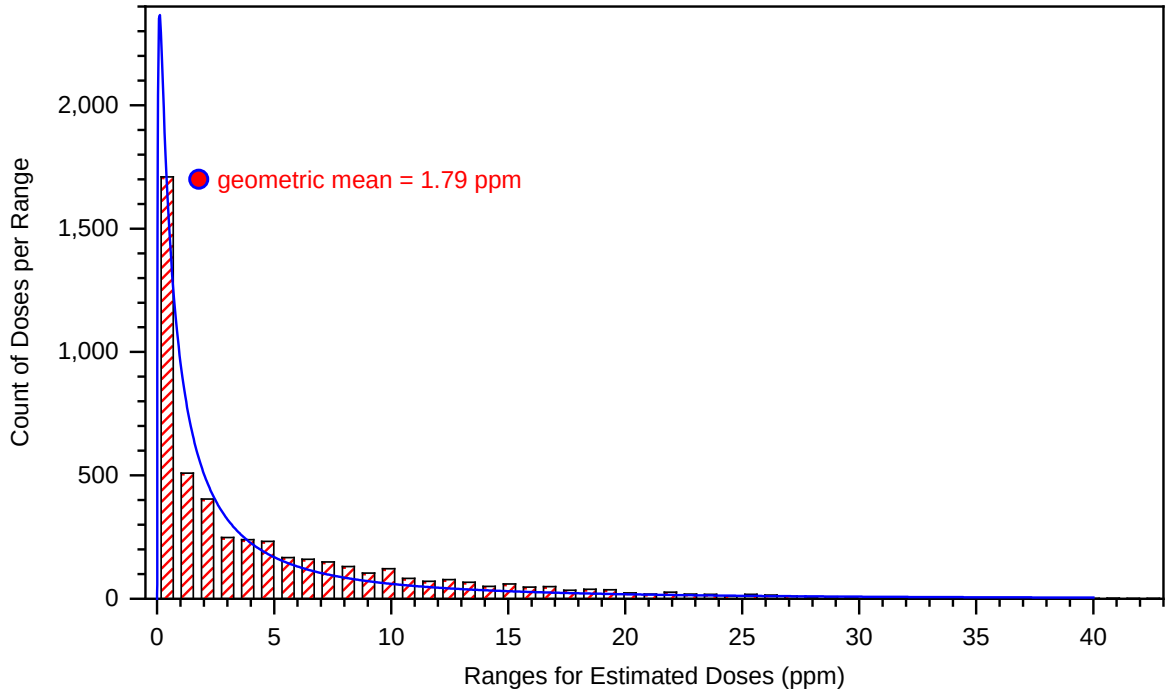

Figure 35. Histogram of Estimated Toluene Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating toluene exposure of random lengths and start times.

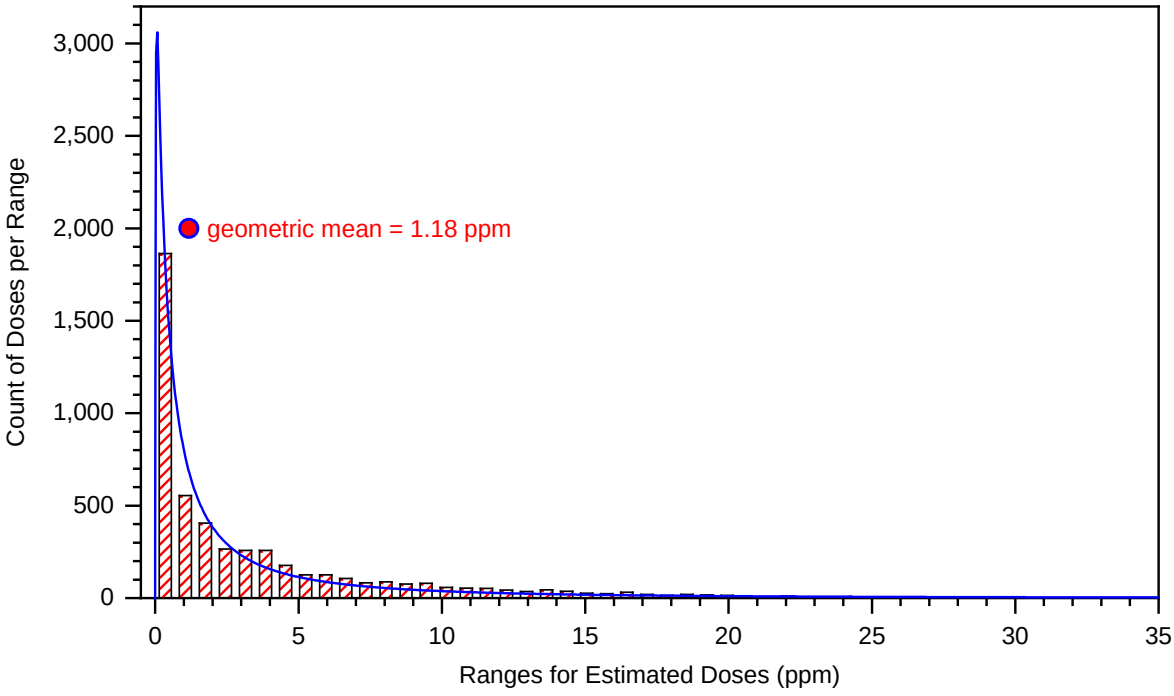

Figure 36. Histogram of Estimated Cyclohexane Exposure Concentrations for Random Exposures. Results are for a Monte Carlo analysis simulating cyclohexane exposure of random lengths and start times.

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

```
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 manuevers (sec)
  CONSTANT     TGForce = 5000.0        ! Time G-force manuevers 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
```

```
  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 manuever
  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*CInh), 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*CInh_Met), 0.0) + (AMet * Stoch) - Metabolite

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

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

APPENDIX B
Utility M Files for Simulations

The following M files are called within various M files utilized for this work. Some lines were too long to for the page width and were thus reformatted to fit the page; however, these additional line breaks and space may need to be removed for the M file to run correctly.

Acetone.m

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

  MW=58.08;
  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
```

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
```

```
%           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 exposue 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
```

```
%               Move to next start time of exposue 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; RENDO_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 = 0.000000000001;  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, _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_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
```

```
%             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);
```

```
            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 minimm 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;
  CENDO=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;
  ADJQCQP=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

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1800	1560	1560	1680	1620	2400	1800	480
1440	0	2760	2400	3060	480	0	0
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1800	1920	1800	0	2760	2130	900	3300
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3240	2100	0	0	1200	810	1470	0
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1980	0	2520	3360	1980	2520	900	900
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0	1500	0	2760	240	900	0	2700
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0 900 0 0 2100 0 1500 900
2250 900 0 1200 1080 0 0 0
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1710 2850 0 2700 900 2400 3300 0
480 900 2400 2820 1800 1920 510 3360
0 3540 2760 1500 900 2700 0 2400
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0 300 720 1200 930 900 1560 450
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2220 2340 0 2700 3300 0 0 600
2160 600 2880 3480 1350 0 840 900
0 0 1740 0 3420 2100 1920 2220
180 0 0 2760 1920 3300 0 1200
1920 1320 900 1800 3240 240 2700 240
0 0 630 0 1320 0 600 1200
2880 330 1260 3300 960 0 3000 2700
1800 1800 2100 3240 0 720 660 0
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3480 2880 480 1800 2400 1800 600 1860
900 2670 30 2640 0 0 0 0
1440 1800 0 0 1920 0 2700 420
780 1800 3000 0 3480 1500 0 2700
630 3000 1050 900 3390 0 600 1680
0 2700 420 0 3300 2910 900 3480
3480 1440 2700 870 0 3300 1800 2880
1560 1890 0 900 300 3240 0 3300
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1200 3000 2400 2700 360 1800 0 2160
750 1560 1500 2400 60 1260 1560 780
3000 1500 1800 360 1080 3300 1080 1560
1800 660 2940 3390 0 2700 0 2280
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
0 2400 1320 3120 2700 900 0 2400
900 600 0 720 0 1080 1020 3300
900 2730 840 2400 1200 2580 2400 960
1800 360 600 660 2100 2700 3300 2700
0 300 2010 840 750 3390 3480 870
1800 2880 2700 1680 2580 540 1500 900
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780	1050	1500	0	1560	1800	0	0
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1980	1440	1200	1680	0	2700	1800	2520
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2100	1800	3390	480	2100	1080	0	720
1800	1680	2400	2700	0	0	1800	450
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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
120	3000	1800	1740	2700	420	2970	720
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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
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1800	0	2700	1800	3000	960	2040	900
0	0	0	2700	360	1500	1920	720
3360	2700	3120	0	2880	1680	900	2640
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3480	0	1380	0	900	2100	2880	2760
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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
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0	900	1920	0	2280	2040	0	3150
480	2700	1500	1170	900	0	240	1920
2400	960	480	2880	900	540	540	1200
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1800	2160	2700	2760	600	1320	660	2700
2100	0	900	0	1500	1200	0	2340
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1680	2910	2820	780	900	3420	0	2520
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VarExp_TChngLst.dat

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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	900	

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