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Technical Transfer: Cockpit Exposure Reconstruction via Physiologically-Based Pharmacokinetic Modeling for HPARS



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1.0 SUMMARY

Chemical irritants can pass through the on-board oxygen generation system in high-performance aircraft (HPA), but the level and further identification of irritants have not been thoroughly evaluated. The 711th Human Performance Wing (711 HPW) recently conducted a High-Performance Aircraft Respiratory Study (HPARS) to identify the etiology of reported respiratory pilot symptoms and mitigate a common health complaint in HPA. HPARS sampling included exhaled breath before and after hundreds of sorties to identify volatile organic compounds (VOCs). Typically, VOCs absorbed into the body via inhalation rapidly clear from the bloodstream after cessation of exposure. Thus, it is challenging to accurately reconstruct actual exposure concentrations and blood levels within a pilot's circulatory system and potential toxic chemical levels at the most responsive tissue sites. The current study seeks to overcome these issues by applying physiologically-based pharmacokinetic modeling to the HPARS exhaled breath samples to reconstruct pilot blood and tissue concentrations during each specific sortie. These reconstructions allow for the determination of possible exposure ranges experienced by pilots during flight (some modeled in-flight concentrations exceeded post-sortie breath samples by as much as 1000x), compare modeled exposure to permissible exposure limits and threshold limit values (TLVs) (some modeled in-flight concentrations exceeded TLVs), and compare modeled exposure to exposure levels and symptomology from the literature associated with various chemicals. This approach produced informed knowledge judgment as to the probability that any particular chemical could have both the potential to have achieved high enough in-flight exposure concentrations and have a known level of toxic potency to be of consequence.

2.0 INTRODUCTION

A significant incidence of F-22 pilots compared to F-16 pilots ($p < 0.0001$), who participated in a web-based questionnaire (on behalf of Colonel Kivi's SIB), reported experiencing coughing/respiratory symptoms of unknown etiology. The cough is dry and mild to moderate in severity, typically beginning within 30 minutes of sortie completion and extending out to four hours post-sortie. The current working hypothesis for cause was atelectasis induced by a combination of Gz and thoracic restriction, with high O₂ levels as a potential contributing factor. As a response, the 711th Human Performance Wing (711 HPW) F-22 Physiologic Analysis Team proposed, was funded, and has 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 significant unknown component of the proposed induction of coughing/respiratory symptoms is the identity and concentration of atmospheric contaminants in the cockpit air. USAFSAM/FHT Bioenvironmental Engineering performed two types of air sampling: diffusive monitoring of the cockpit air and pre- and post-sortie exhaled breath. Unfortunately, volatile organic chemicals which are absorbed into the body via inhalation often rapidly clear from the blood stream shortly after cessation of exposure. Thus it is challenging to accurately reconstruct the actual inhalation exposure concentration, blood levels within a pilot's circulatory system and potential toxic chemical levels at the most responsive tissue sites, like the lung respiratory tract or cognitive centers of the central nervous system. In order to best utilize these human bioassay samples, we applied a currently available analysis tool, physiologically-

based pharmacokinetic (PBPK) modeling, to “reconstruct” possible exposure profiles and blood chemical concentrations that could account for the post-sortie exposure samples.

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 or can be considered a contributing factor in reported symptomology.

The specific aims of this research were to:

- 1) Perform PBPK simulation reconstructions of pilot blood, tissue and exhaled breath concentrations during each specific sortie, based on each pilot’s physiology, and the pre- and post-sortie sampling contained within HPARS.
- 2) Produce informed knowledge judgment as to the probabilities that any particular chemical contaminant exposure scenario could have contributed to potential cases of coughing/respiratory symptoms. This approach is novel in that it further utilizes and expands on human exhaled breath exposure samples, via physiologically real simulation tools (PBPK modeling), to improve the decision process and potentially prevent the most significant reported health complaint for F-22 pilots.

3.0 MATERIALS AND METHODS

3.1 Selection of Chemicals

Chemicals chosen for analysis in this study were based on specific criteria as a first approach for submission to dose reconstruction analysis. Firstly, the chemical should be uniquely identified as having a definite chemical structure. Next, the chemical should be quantitated in both the pre- and post-flight exhaled breath samples at concentrations that indicated there was an actual increased presence of the chemical above the pre-flight “background” level, indicating a likely exposure during flight. This criteria was then aligned with chemicals measured in breath from a F-22 versus F-16 pilot web-based questionnaire reporting cough/respiratory symptoms of unknown etiology. From this culling process, four chemicals were self evident, those being isopropanol (IPA), acetone, toluene and cyclohexane. In addition, each of these chemicals is reported to cause toxicity to the respiratory tract and the central nervous system.

3.2 PBPK Model Structure

The PBPK model used for this work is a modification of a previously published PBPK model describing the pharmacokinetics from exposure to IPA and its metabolite, acetone [1]. 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 (Figure 1). 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. The model is executed using the Gear algorithm in acslX (Aegis Technologies Group, Inc., Huntsville, AL).

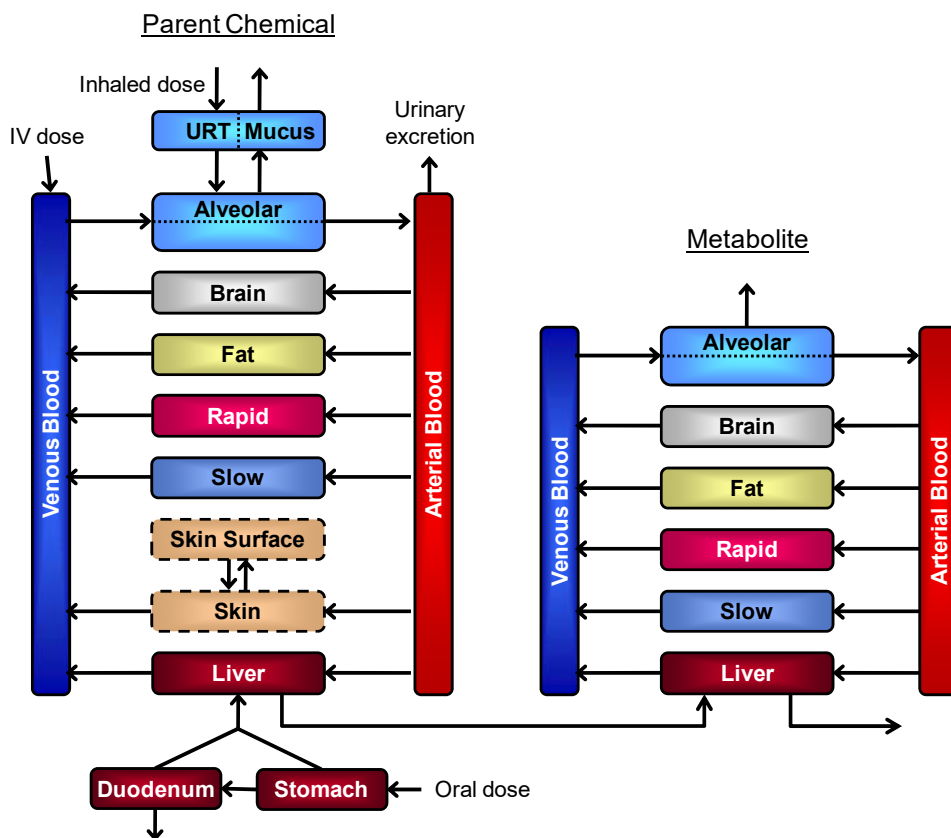


Figure 1. Schematic of PBPK Model for IPA and its Metabolite, Acetone [1]. Note that the compartments denoted by dashed boxes only exist when dosing via that route and are not used for the inhalation dose reconstructions presented here.

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 (Figure 2) was then used to simulate inhalation exposure to IPA, acetone, toluene and cyclohexane by changing the chemical-specific parameters of the model.

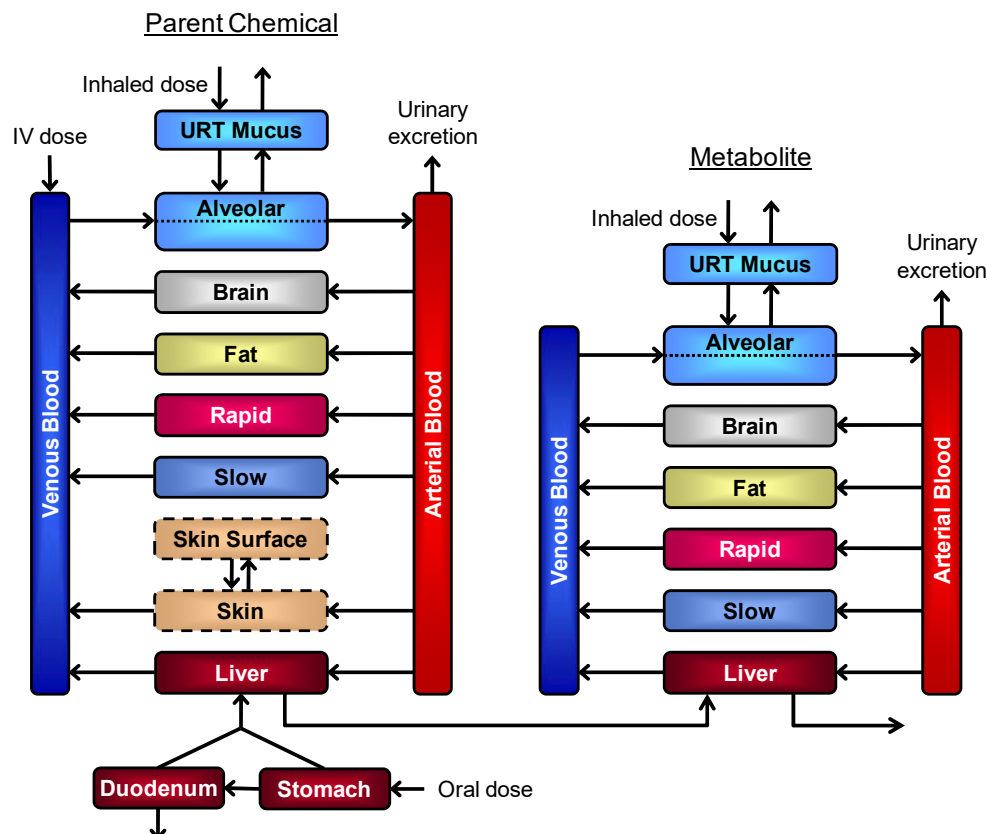


Figure 2. Schematic of Modified PBPK Model for IPA and its Metabolite, Acetone. This schematic shows modifications made to the Clewell *et al.* [1] model. Note that the compartments denoted by dashed boxes only exist when dosing via that route and are not used for the inhalation dose reconstructions presented here.

3.3 Model Parameters

Chemical-specific parameters were taken from papers describing the PBPK models for each of the chemicals to be simulated [1, 2, 3]. These parameters were used, along with physiological parameters from the papers, to validate endpoints predicted with the modified IPA model following exposure to IPA [1] (both IPA and acetone endpoints), acetone [1], toluene [3, 4] and cyclohexane [2]. The simulations for dose reconstructions used male or female body weights taken from an Air Force (AF) biometric database [5] (pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI), physiological parameters averaged across the studies, and chemical-specific parameters. These parameters are summarized in Tables 1 and 2. The ventilation rates for the toluene and cyclohexane models were alveolar and have been converted to total ventilation rates in Table 1 by dividing the alveolar rates by two-thirds [6]. The exponential power used for scaling was 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 Table 2 have 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. Parameters not used for the dose reconstruction simulations are not included in the tables (*i.e.*, parameters for dermal exposure); the values for these parameters were set to have no

effect on the model predictions and to not cause issues such as division by zero. Parameters included in the IPA model which are not included in the published models for toluene and cyclohexane [2, 3] were also 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.* [3] did not include a brain compartment but the modified IPA model used for the dose reconstructions does; therefore, parameter values for the brain compartment were taken from other sources. Toluene simulations for validation used the fractional tissue blood flow and volume from the IPA model [1]. The brain/blood partition used for the toluene simulations was calculated from a brain/gas partition from the literature [7] and the blood/air partition.

Table 1. Physiological Parameters

Parameter	Dose Reconstructions	IPA / Acetone	Toluene	Cyclohexane
Body weight (kg)	67.77 / 84.14 ^a	70 ^b	84.5	79.13
Cardiac output (L/min/kg ^{0.75})	0.2583	0.2148	0.24	0.3183
Pulmonary ventilation (L/min/kg ^{0.75})	0.4333	0.4625	0.36	0.4775
Fractional Tissue Blood Flows (fraction of cardiac output)				
Brain	0.123	0.114	0.114 ^c	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 ^c	0.0079 ^c
Brain	0.02	0.02	0.02 ^c	0.02
Fat	0.188	0.214	0.19	0.161
Liver	0.026	0.026	0.026	0.026
Rapidly perfused compartment	0.032	0.036	0.05	0.03
Slowly perfused compartment	0.602	0.536	0.62	0.649

^aAverage female and male body weights from an AF biometric database [5]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

^bUsed study specific when available

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

Table 2. 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/min/kg ^{0.75})	5.0	0.0583	0.08	0.0723
Michaelis-Menten affinity constant (mg/L)	10.0	10.0	0.55	0.13
First order rate constant (kg ^{0.75} /min)	0.0	0.0	0.0	0.0
Uptake and Clearance Parameters (L/min/kg^{0.75})				
Urinary clearance	6.67×10 ⁻⁵	6.67×10 ⁻⁵	-- ^a	-- ^a
Upper respiratory tract uptake	0.183 ^d	0.183 ^d	-- ^a	-- ^a

^aParameter not used for this chemical

^bCalculated using brain/gas partition [7] and the blood/air partition [3].

^cTissue/blood partitions calculated from blood/air partition and tissue/air partition [2, 3]

^dThe value for upper respiratory tract uptake was adjusted for the dose reconstruction simulations to maintain the value as the same fraction of pulmonary ventilation as for the validation figures. The adjusted value is 0.172 L/min/kg^{0.75}.

3.4 Model Validation

Given that all of the dose reconstructions will be for inhalation exposure, the validation figures will focus on this exposure route. The exceptions are two data sets for which the delivery route for the IPA dose was oral. These are shown to demonstrate the model's ability to predict acetone endpoints as a result of IPA dosing and to demonstrate the effect of the modifications on the metabolite portion of the model upon predictions. The parent portion of the Clewell *et al.* [1] model was not changed; therefore, the purpose of the validation figures for IPA and acetone endpoints following exposure to either IPA or acetone is to demonstrate that the model predictions for the parent have not changed. Validation figures for acetone endpoints following IPA exposure demonstrate that the modifications made to the model have little effect on acetone predictions. The purpose of the validation figures for toluene and cyclohexane is to demonstrate that the modified model is capable of adequately predicting the data and compares well with the predictions of the published models for these two chemicals [2, 3]. To this end, the simulations presented for toluene [3, 4] and cyclohexane [2] using their respective published models were digitized and included in the validation figures for ease of comparison.

3.5 Dose Reconstructions

For each of four of the most prevalent chemicals associated with cough/respiratory symptoms (IPA, acetone, toluene and cyclohexane), a PBPK model was parameterized based on published chemical specific values and then exercised to “reconstruct” the potential exposures that could have occurred with these four chemicals. 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. Table 3 shows the combination of flight lengths and durations simulated. Simulations used chemical-specific parameters from Table 2 and the physiological-parameters from Table 1 designated as dose reconstructions parameters. These simulations were repeated for males and females. For each combination of length and start of exposure, the model was run and the predicted exhaled air concentration was compared to the average measured exhaled breath concentrations from actual 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. For acetone breath concentrations, simulations were run for acetone exposure only, IPA exposure only, and simultaneous IPA and acetone exposure.

Table 3. Exposure Scenarios

Length of Exposure	Start of Exposure (from start of flight)
30 seconds	One minute intervals from 0 to 59 minutes (0, 0.5, 1, 1.5, 2, 2.5, ... 58, 58.5, 59, 59.5)
1 minute	One minute intervals from 0 to 59 minutes (0, 1, 2, 3, ... 57, 58, 59)
2 minutes	Two minute intervals from 0 to 58 minutes (0, 2, 4, 6, ... 54, 56, 58)
5 minutes	Five 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

3.6 Monte Carlo Analyses

A Monte Carlo analysis was conducted to demonstrate the potential impact in dose estimations for IPA for males 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 1, 2 and 4). Standard deviations were calculated from the means and coefficients of variation (CVs). The CVs were based on

those used in published analyses [8, 9]. Parameters that were not included in the published analysis were given CVs consistent similar parameters; metabolic parameters were given CVs of 30% which is less than used by Covington *et al.* [8] but larger than in David *et al.* [9]. 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 [5] (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 from an AF biometric database [5] (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. Figures were created to show the results of this analysis.

Table 4. Monte Carlo Settings for Model Parameters
(means for distributions are presented in Tables 1 and 2)

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/min/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/min/kg ^{0.75})	30	Log-Normal		
Michaelis-Menten affinity constant (mg/L)	30	Log-Normal		
Uptake and Clearance Parameters (L/min/kg^{0.75})				
Urinary clearance	30	Log-Normal		
Upper respiratory tract uptake	30	Log-Normal		

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

^bCalculated from mean and standard deviation from AF biometric database [5]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

^cMaximum and minimum values from AF biometric database [5]; pilot specific data from personal communication with Jeffrey Hudson, 711 HPW/HPI

4.0 RESULTS

4.1 Validation of Modified Model

Model predictions for IPA (Figures 3, 4 and 5) and acetone (Figures 6 and 7) exposure matched the simulations for parent chemical in Clewell *et al.* [1]. Predictions for acetone following IPA exposure using the modified version of the published model were slightly higher than the predictions in Clewell *et al.* [1] but provided as good a fit to the data as the published model simulations.

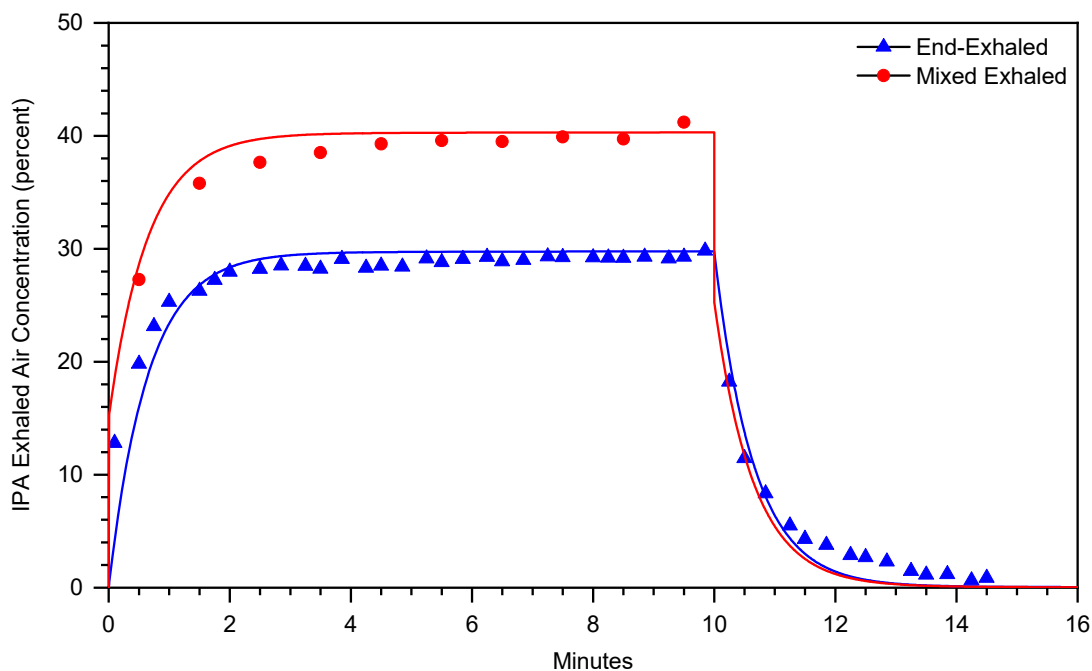


Figure 3. Kumagai *et al.* [10] Data for Human Inhalation Exposure to 100 ppm IPA for 10 Minutes. Lines represent simulations and symbols represent data for four volunteers from Kumagai *et al.* [10], as presented in Clewell *et al.* [1], for the concentration of IPA in exhaled air following inhalation exposure.

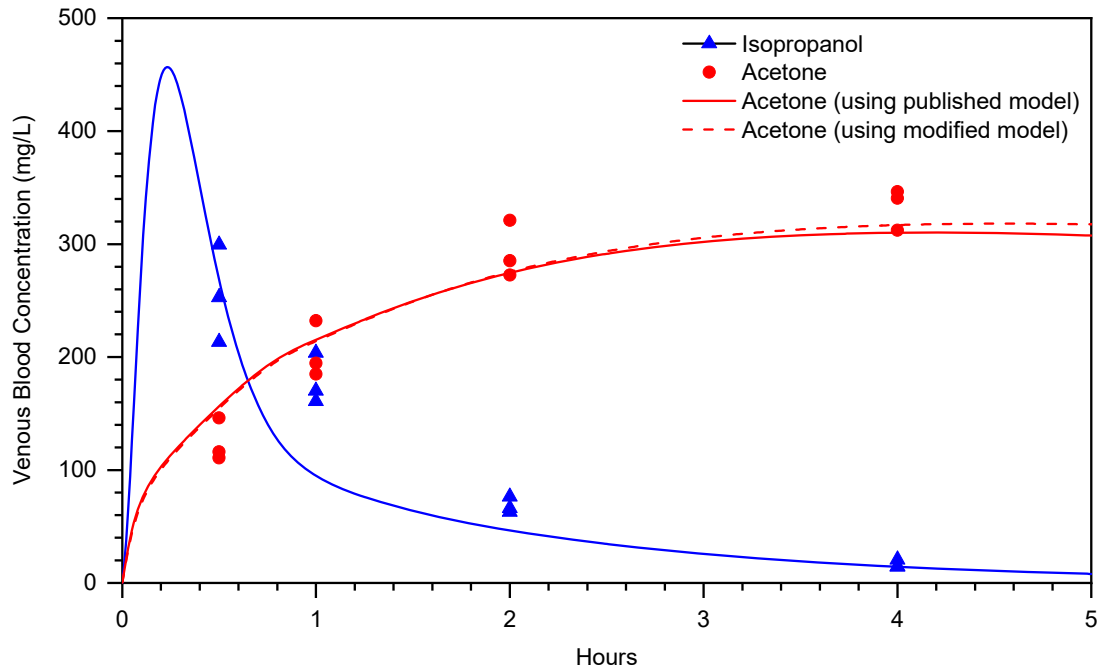


Figure 4. Lacouture *et al.* [11] Data for Human Oral Exposure to 218.5 mg/kg IPA. Lines represent simulations and symbols represent data for three subjects from Lacouture *et al.* [11], as presented in Clewell *et al.* [1], for the concentration of IPA and acetone in venous blood.

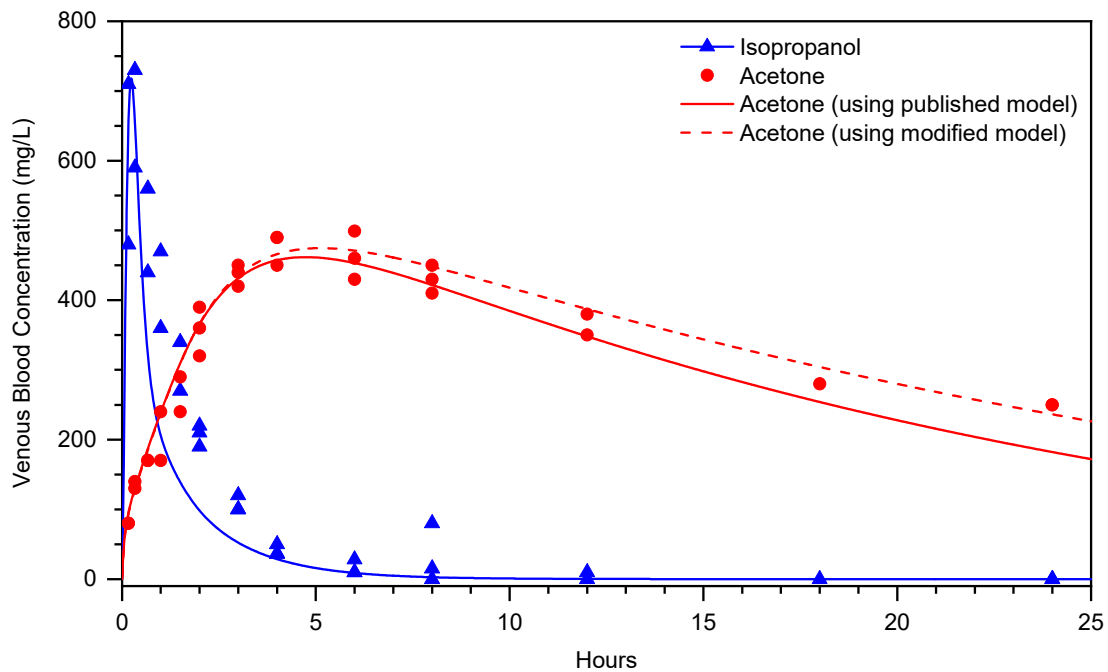


Figure 5. Monaghan *et al.* [12] Data for Human Oral Exposure to 325 mg/kg IPA. Lines represent simulations and symbols represent data for three subjects from Monaghan *et al.* [12], as presented in Clewell *et al.* [1], for the concentration of IPA and acetone in venous blood.

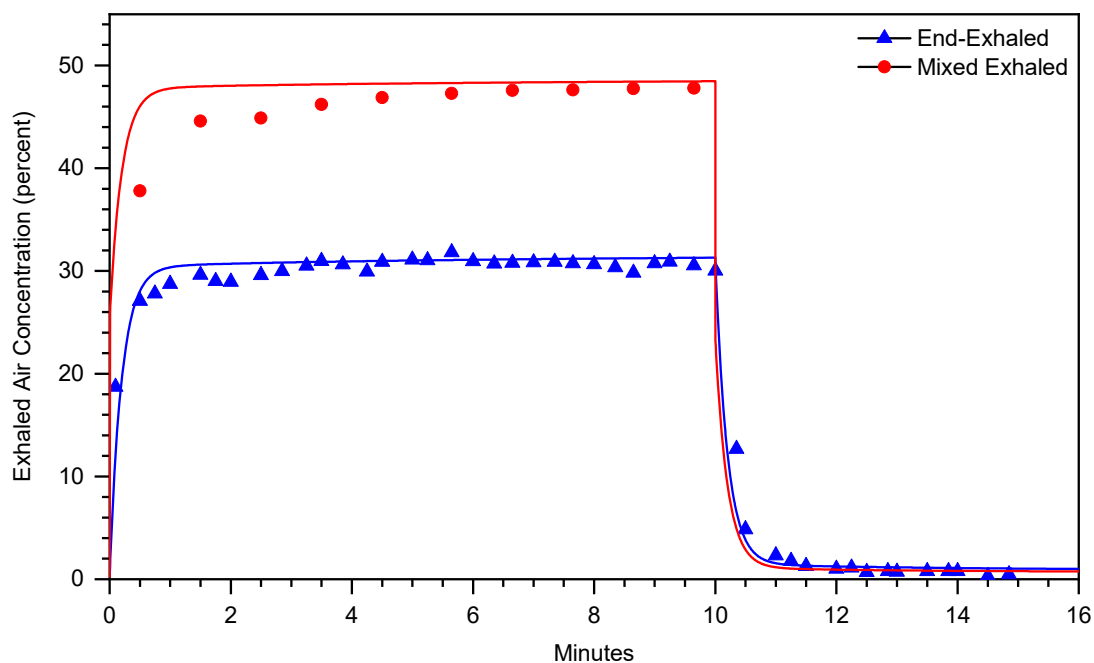


Figure 6. Kumagai *et al.* [10] Data for Human Inhalation Exposure to 100 ppm Acetone for 10 Minutes.
Lines represent simulations and symbols represent data for four volunteers from Kumagai *et al.* [10], as presented in Clewell *et al.* [1], for the concentration of acetone in end- and mixed-exhaled air.

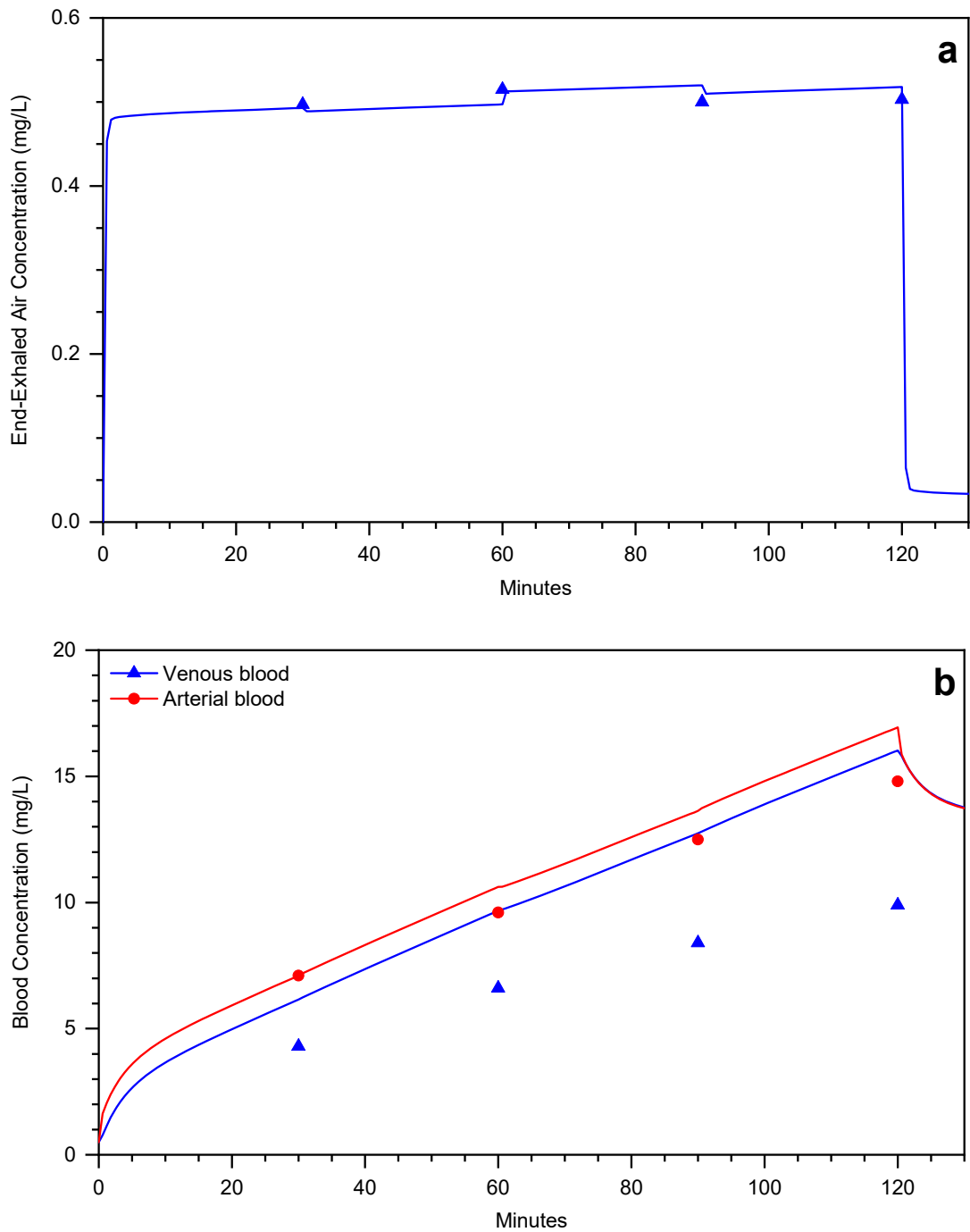


Figure 7. Wigaeus *et al.* [13] Data for Human Inhalation Exposure to 1.309 mg/L Acetone for Two Hours at Rest. Lines represent simulations and symbols represent data from Wigaeus *et al.* [13], as presented in Clewell *et al.* [1], for the concentration of acetone in (a) end-exhaled air, (b) arterial and venous blood and (c) the amount in urine.

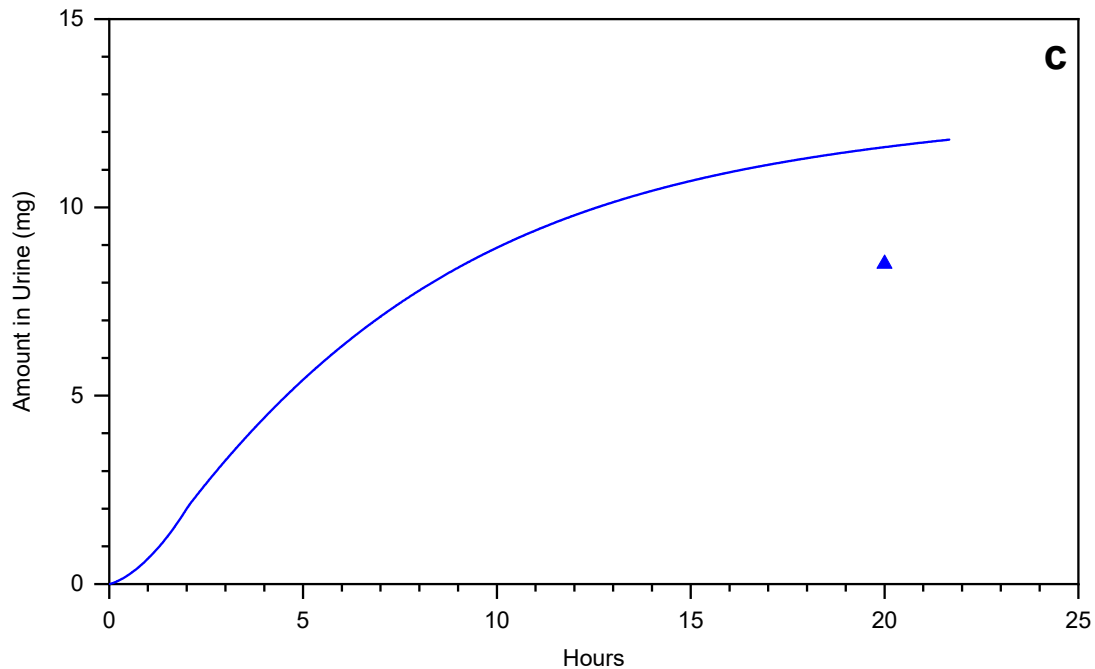


Figure 7. (continued)

Exhaled air and venous blood concentrations predicted by the modified IPA model using the parameters in Tardif *et al.* [3] and Tardif *et al.* [4] are shown in Figures 8 and 9; the digitized simulations from these papers are plotted as dotted lines for comparison with predictions from the modified IPA model (solid lines). Exhaled air predictions are very close to those in the published papers; however, venous blood concentrations are under-predicted in comparison to the predictions shown in the papers. Including and excluding the brain compartment in the modified IPA model for the toluene simulations made very little difference in predictions for exhaled breath and venous blood concentrations. As doses were fit based upon predicted exhaled air concentrations, the under-prediction of venous blood concentrations is less problematic than it would be for exhaled air concentration.

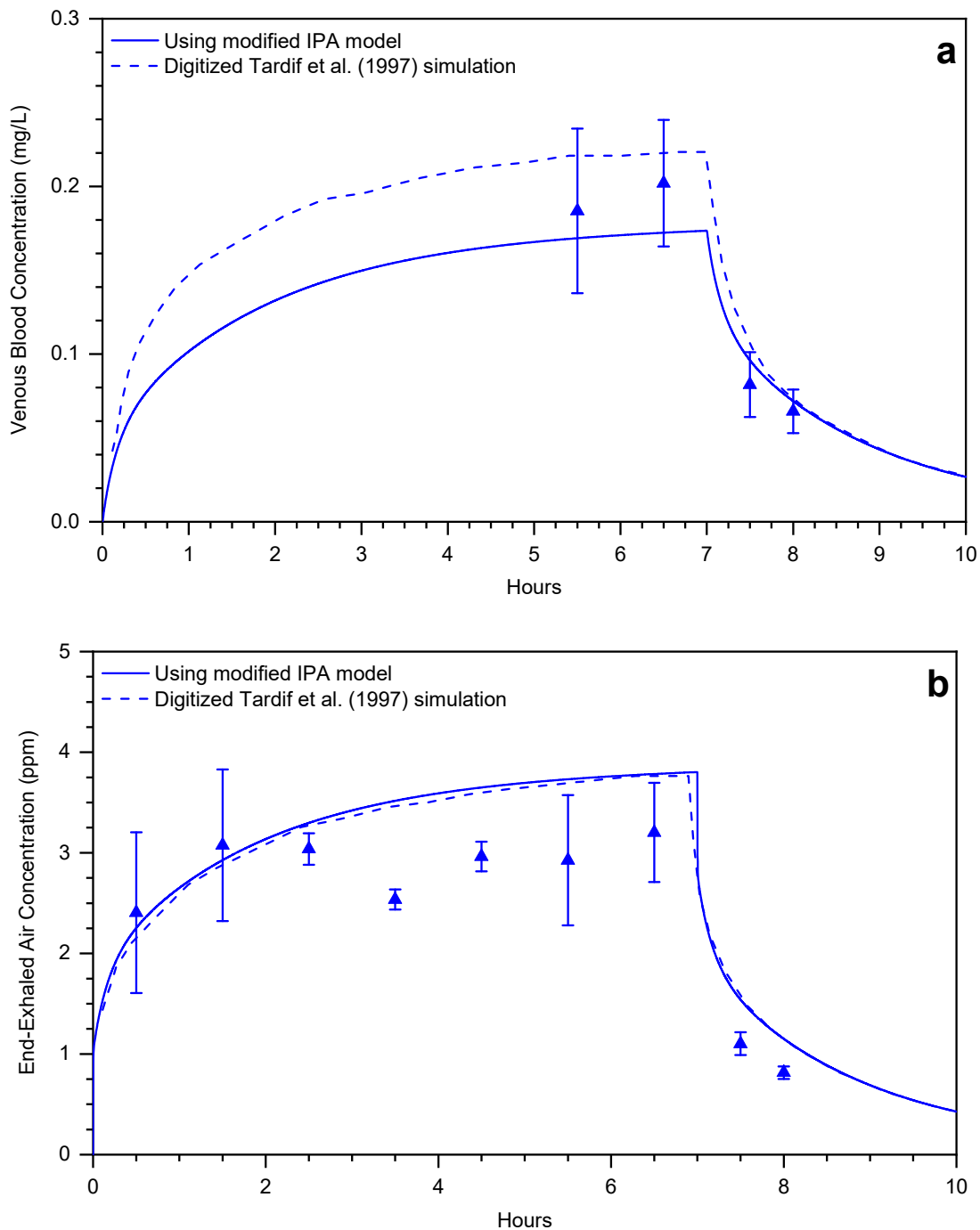


Figure 8. Tardif *et al.* [3] Data for Human Inhalation Exposure to 17 ppm Toluene for Seven Hours. Lines represent simulations and symbols represent data (mean $\pm$ one standard deviation, N=4) from Tardif *et al.* [3] for the concentration of toluene in (a) venous blood and (b) exhaled air. Solid lines are the simulations from the modified IPA model using toluene parameters from Tardif *et al.* [3]; dashed lines are the digitized model simulations from Tardif *et al.* [3].

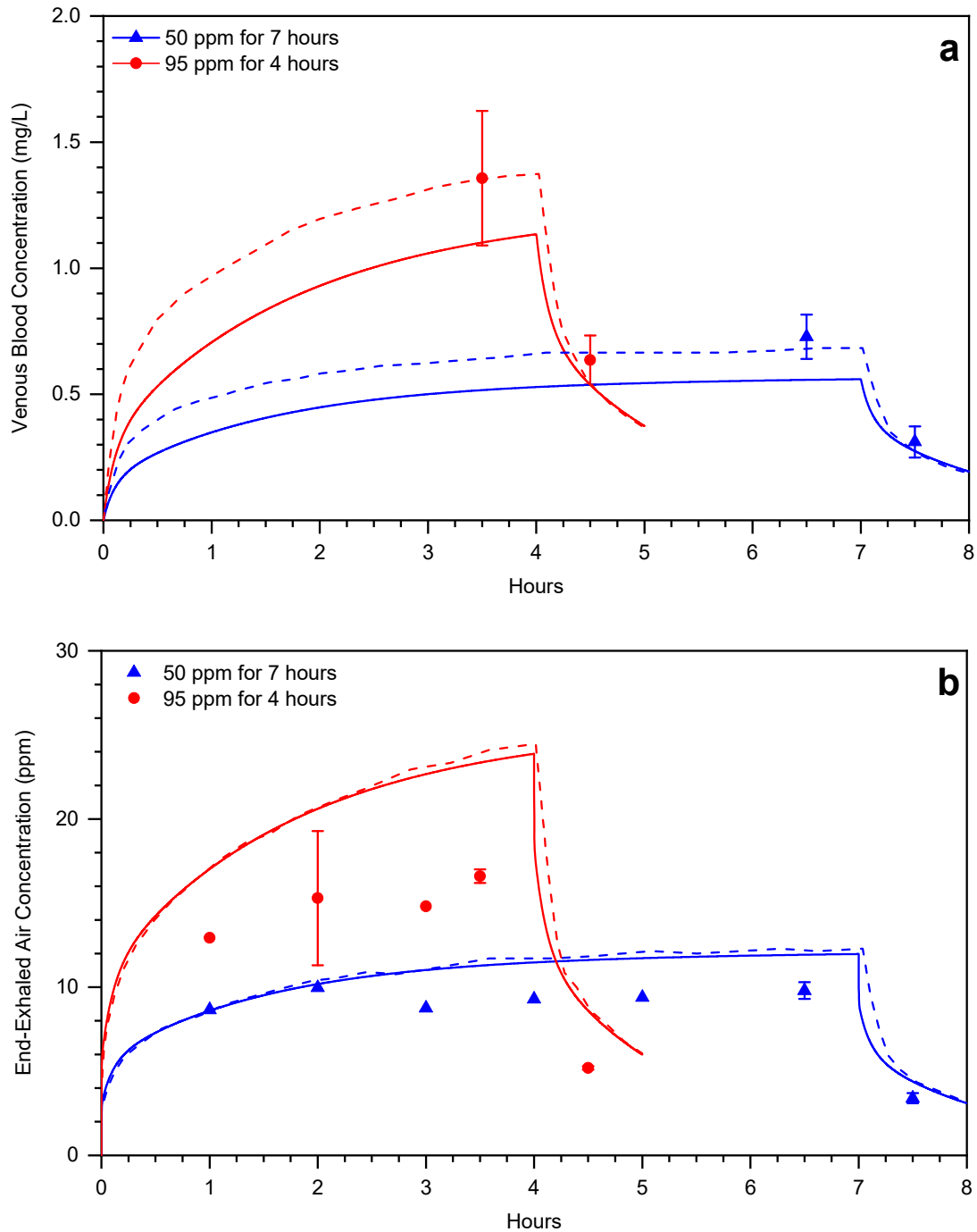


Figure 9. Tardif *et al.* [4] Data for Human Inhalation Exposure to 50 or 95 ppm Toluene for Seven or Four Hours. Lines represent simulations and symbols represent data (mean $\pm$ one standard deviation, N=5) from Tardif *et al.* [4] for the concentration of toluene in (a) venous blood and (b) exhaled air. Solid lines are the simulations from the modified IPA model using toluene parameters from Tardif *et al.* [4]; dashed lines are the digitized model simulations from Tardif *et al.* [4].

As with toluene, the simulations from the published paper were digitized and plotted as dotted lines for comparison with predictions (solid lines) from the modified IPA model (Figure 10). In contrast to the toluene predictions, cyclohexane predictions for venous blood concentration were very similar to the simulations in Hissink *et al.* [2]. Exhaled air concentration predictions, however, did not agree. The modified IPA model over-predicts the simulation of Hissink *et al.* [2] during exposure; however, there are no data presented for this time period to compare with either simulation. The modified IPA model appears to fit the data for the early clearance phase better than the Hissink *et al.* [2] simulation, but it does consistently under-predict the Hissink *et al.* [2] simulation following the end of the exposure period.

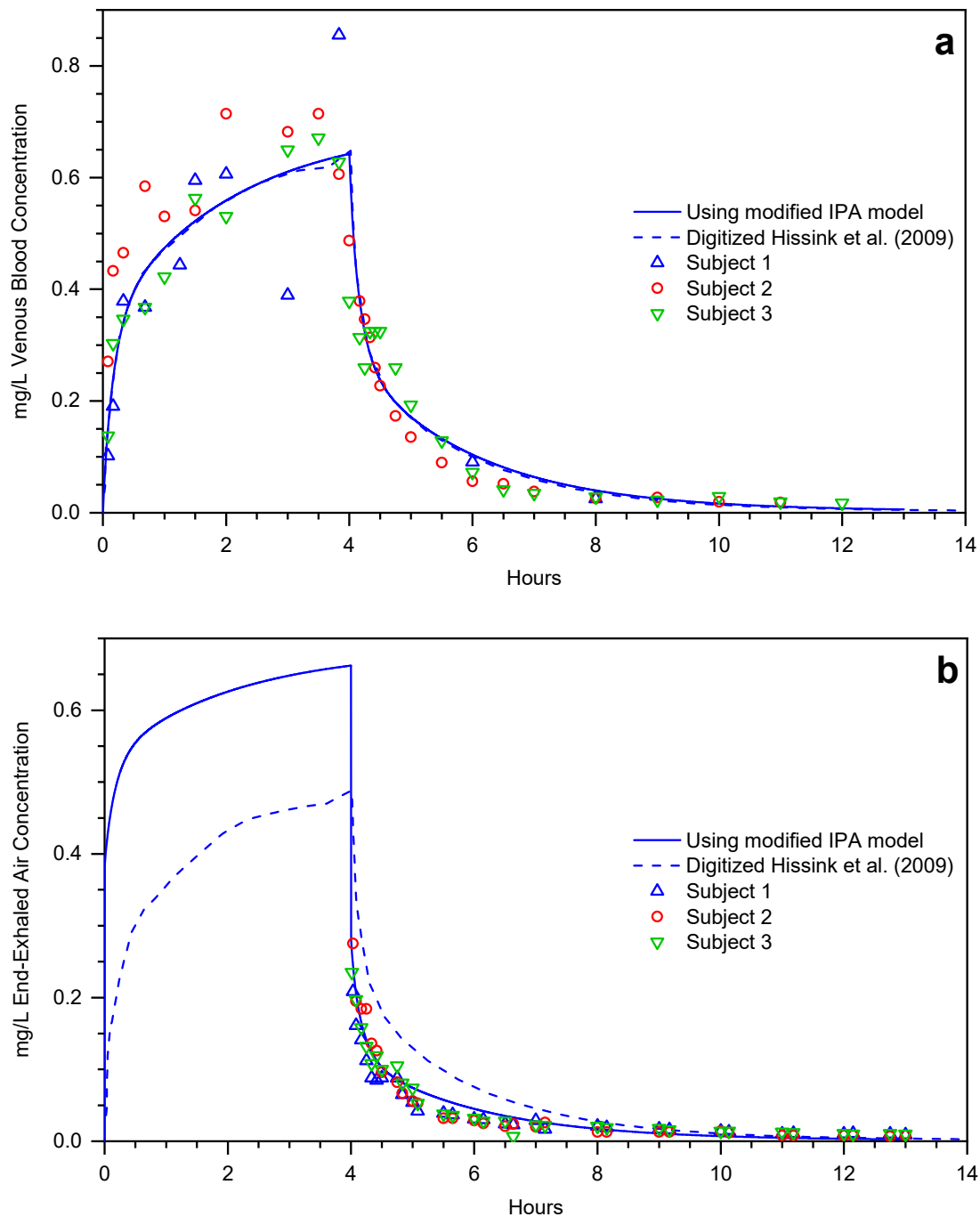


Figure 10. Hissink *et al.* [2] Data for Human Inhalation Exposure to 875 mg/m³ Cyclohexane for Four Hours. Lines represent simulations and symbols represent data for three subjects from Hissink *et al.* [2] for the concentration of cyclohexane in (a) venous blood and (b) exhaled air. Solid lines are the simulations from the modified IPA model using cyclohexane parameters from Hissink *et al.* [2]; dashed lines are the digitized model simulations from Hissink *et al.* [2].

4.2 Dose Reconstructions

Figure 11 shows a representation of the concept and results for two particular exposure scenarios – a five 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 for males. 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 lines are the predicted end-exhaled air concentrations for the given exposure concentrations for the two scenarios.

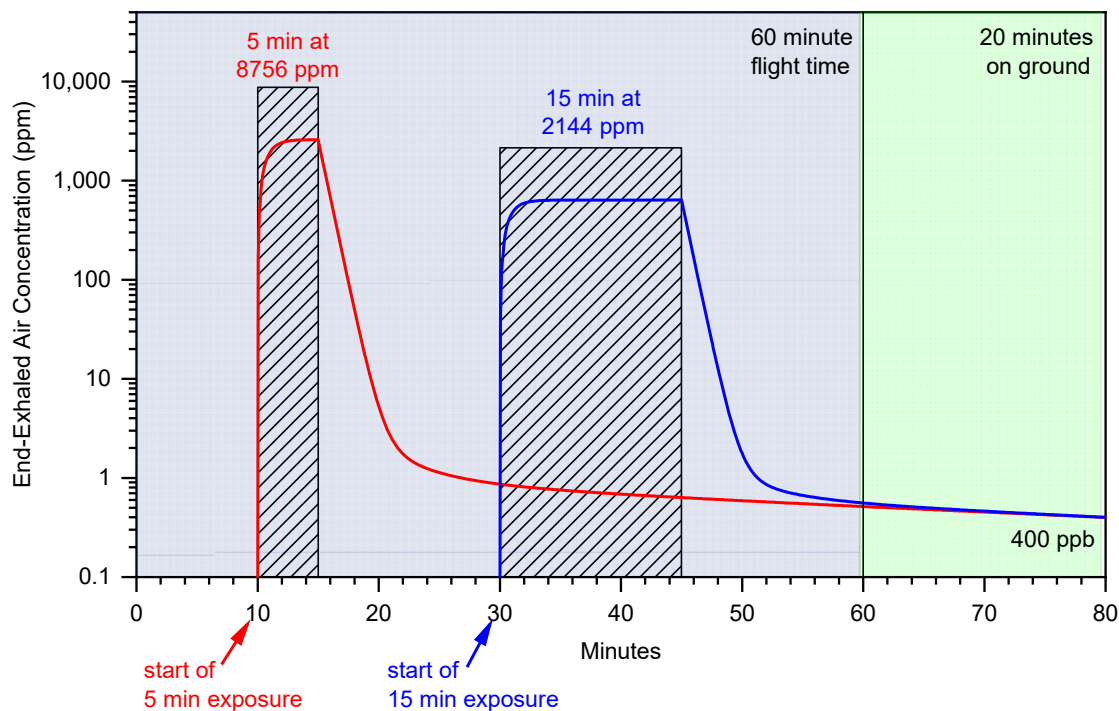


Figure 11. Scenario Used for Dose Reconstructions. This figure represents the scenarios for two of the exposures used for dose reconstruction (a five minute exposure occurring 10 minutes into the flight and a 15 minute exposure occurring 30 minutes into the flight) for males. The shaded blue area represents 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 for males and females along with the corresponding maximum predicted blood and brain concentrations are shown in Figures 12 through 31. There is little difference between males and females for the estimated doses and the predicted maximum blood and brain concentrations at these estimated doses for all of the chemicals. Not surprisingly, the highest doses were estimated for the chemical with the highest target exhaled breath concentration – 400 ppb for IPA. Estimated doses for IPA (Figure 12) are all above the short term exposure limit (STEL) for IPA of 400 ppm and range from a little less than 600 ppm to just under 100,000 ppm for males and females. Predicted maximum blood concentrations range from approximately 2.5 mg/L to just under 30 mg/L (Figure 13); predicted

maximum brain concentrations are about twice as high and range from just under 5 mg/L to about 45 mg/L (Figure 14).

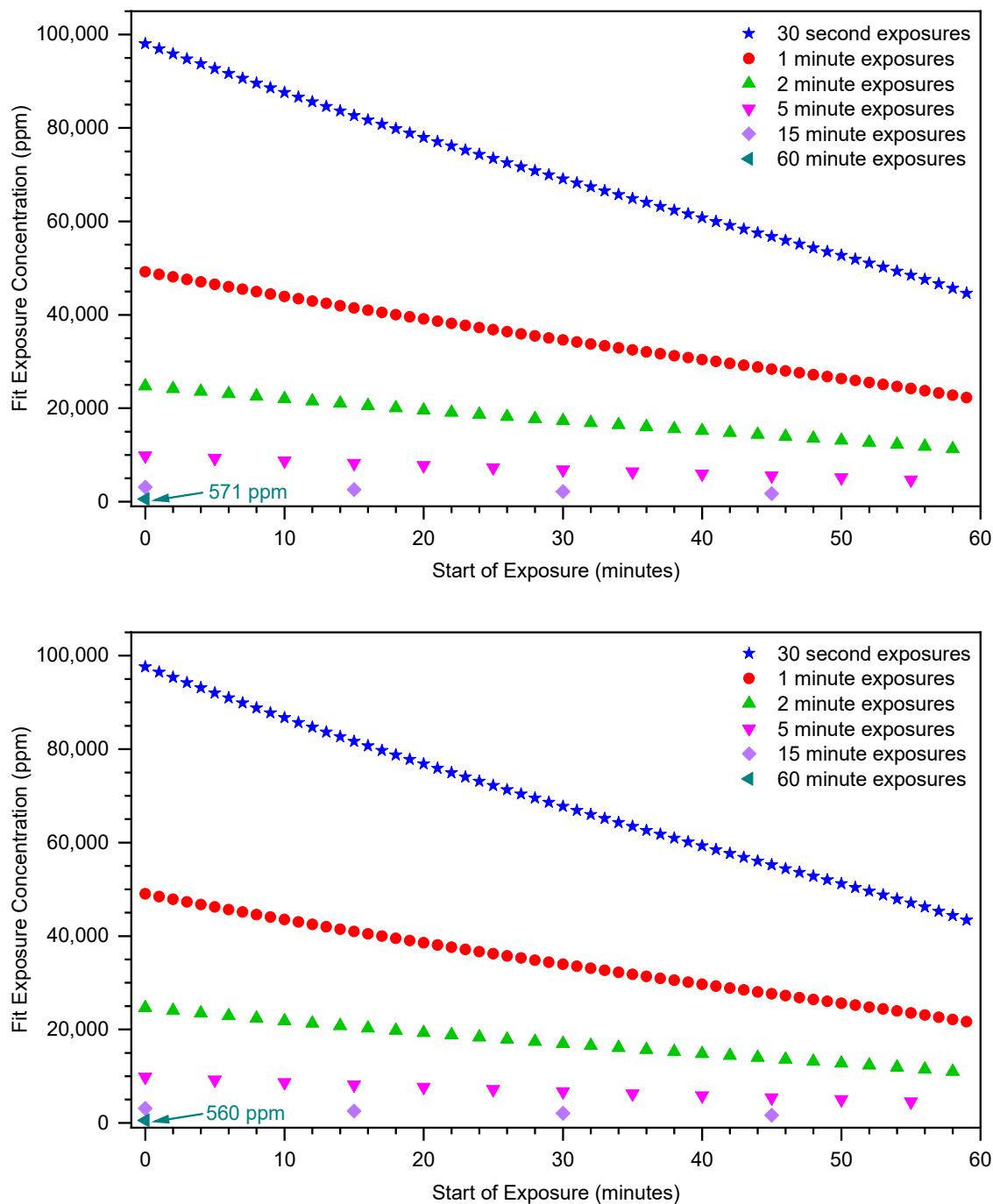


Figure 12. Estimated IPA Exposure Concentrations. Estimated exposure concentrations to predict an IPA exhaled breath target of 400 ppb for different exposure scenarios for males (upper) and females (lower). Dark blue dashed line represents the STEL.

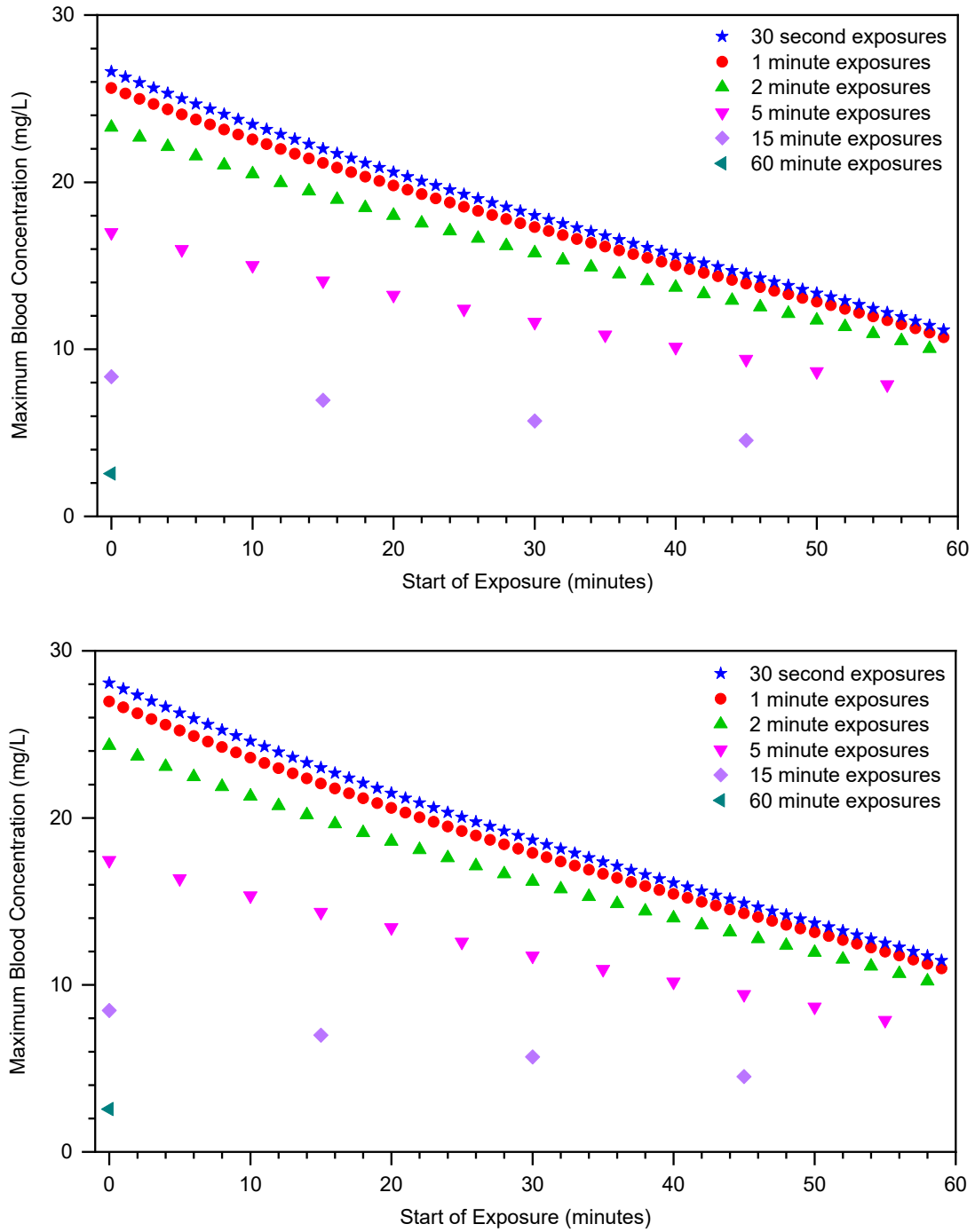


Figure 13. Predicted Maximum IPA Blood Concentrations. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 12 for males (upper) and females (lower).

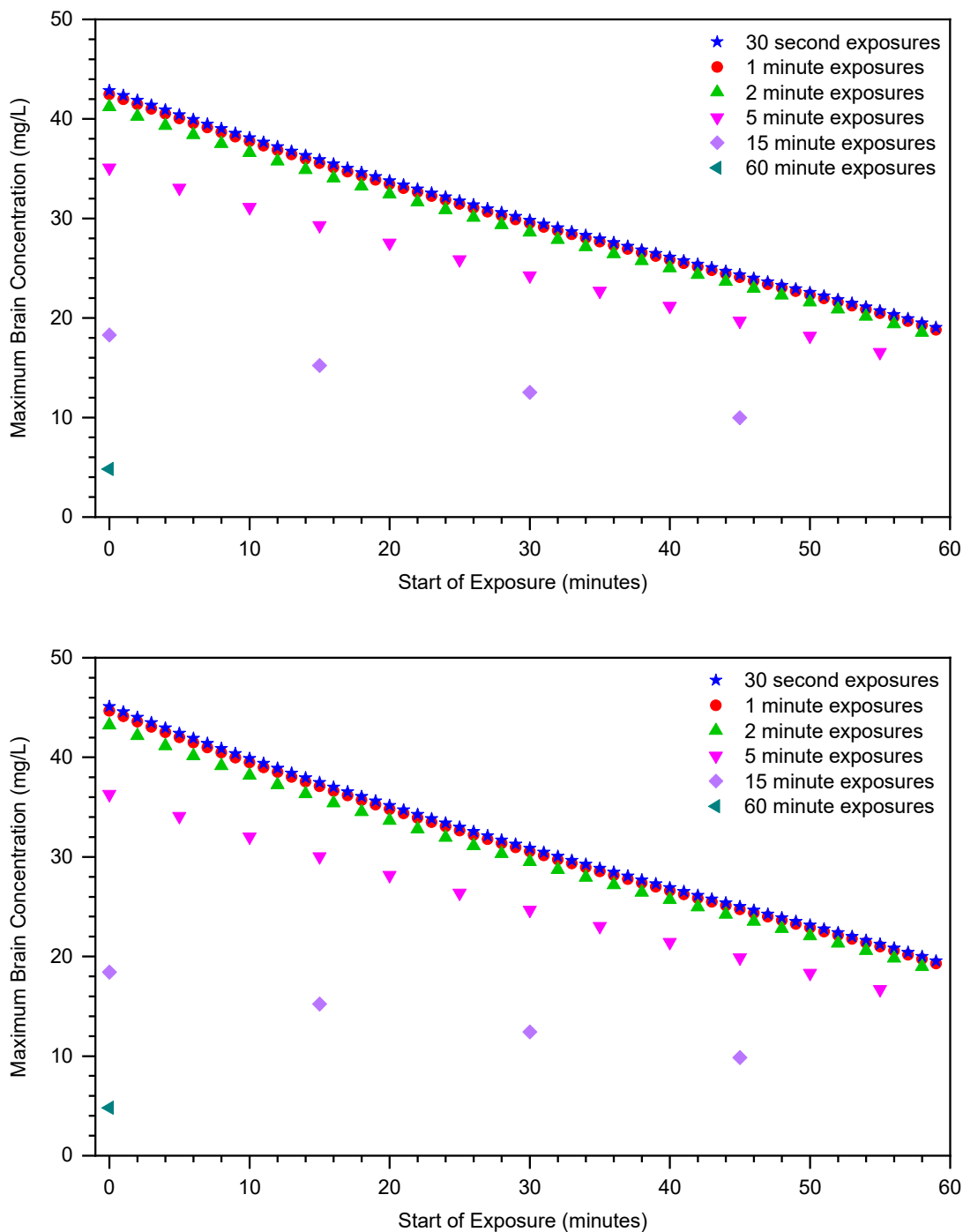


Figure 14. Predicted Maximum IPA Brain Concentrations. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 12 for males (upper) and females (lower).

While the target exhaled breath concentration for acetone (354 ppb) is only slightly lower than the target for IPA, the estimated doses (Figure 15) are a factor of 25 to 30 lower and range from approximately 25 ppm to 3200 ppm (slightly less for females). 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 concentrations for acetone (Figures 16 and 17) are between approximately 0.4 mg/L and 2 mg/L for blood and approximately 0.3 mg/L and 1.5 mg/L for brain.

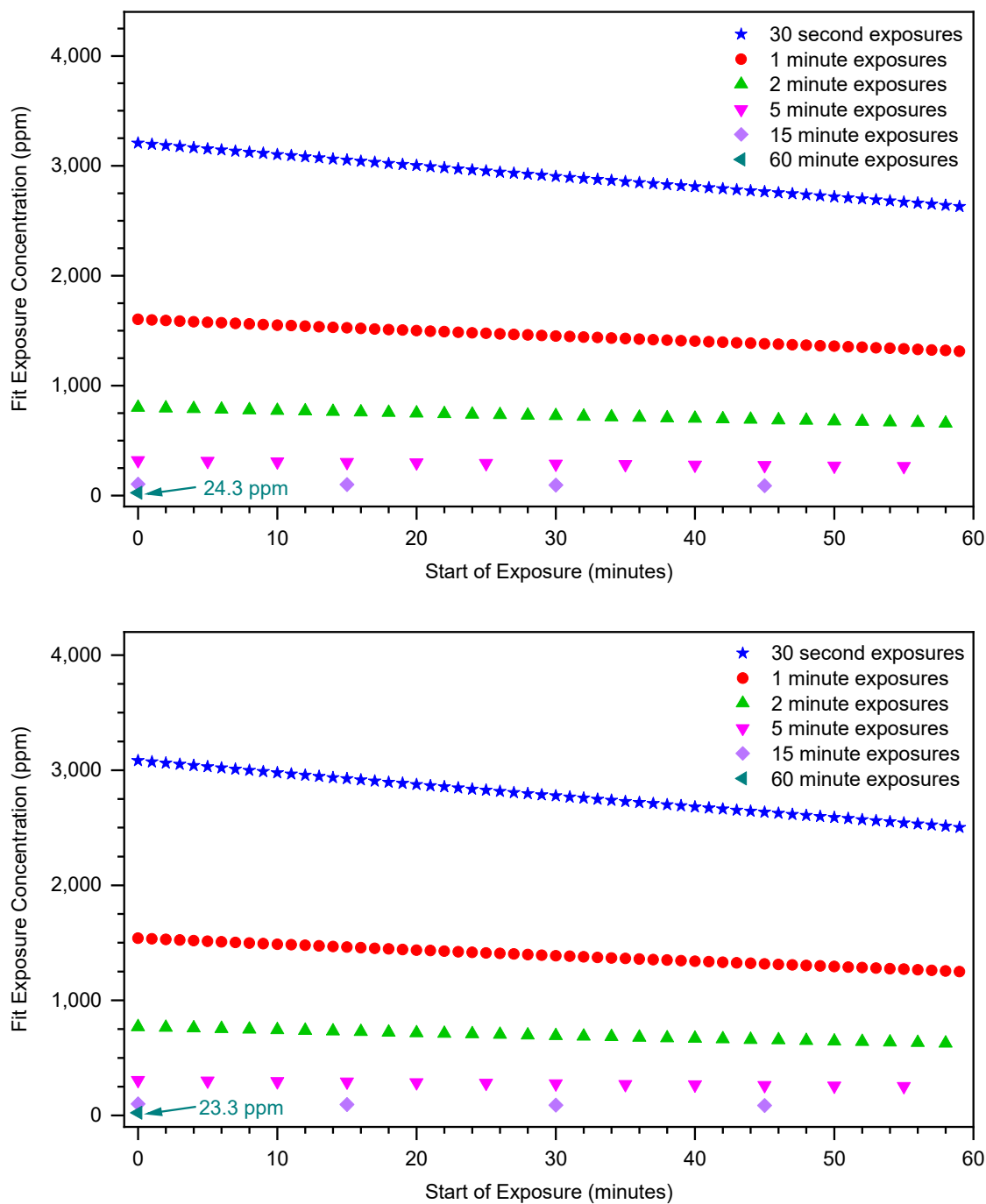


Figure 15. Estimated Acetone Exposure Concentrations. Estimated exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios for males (upper) and females (lower). Dark blue dashed line represents the STEL.

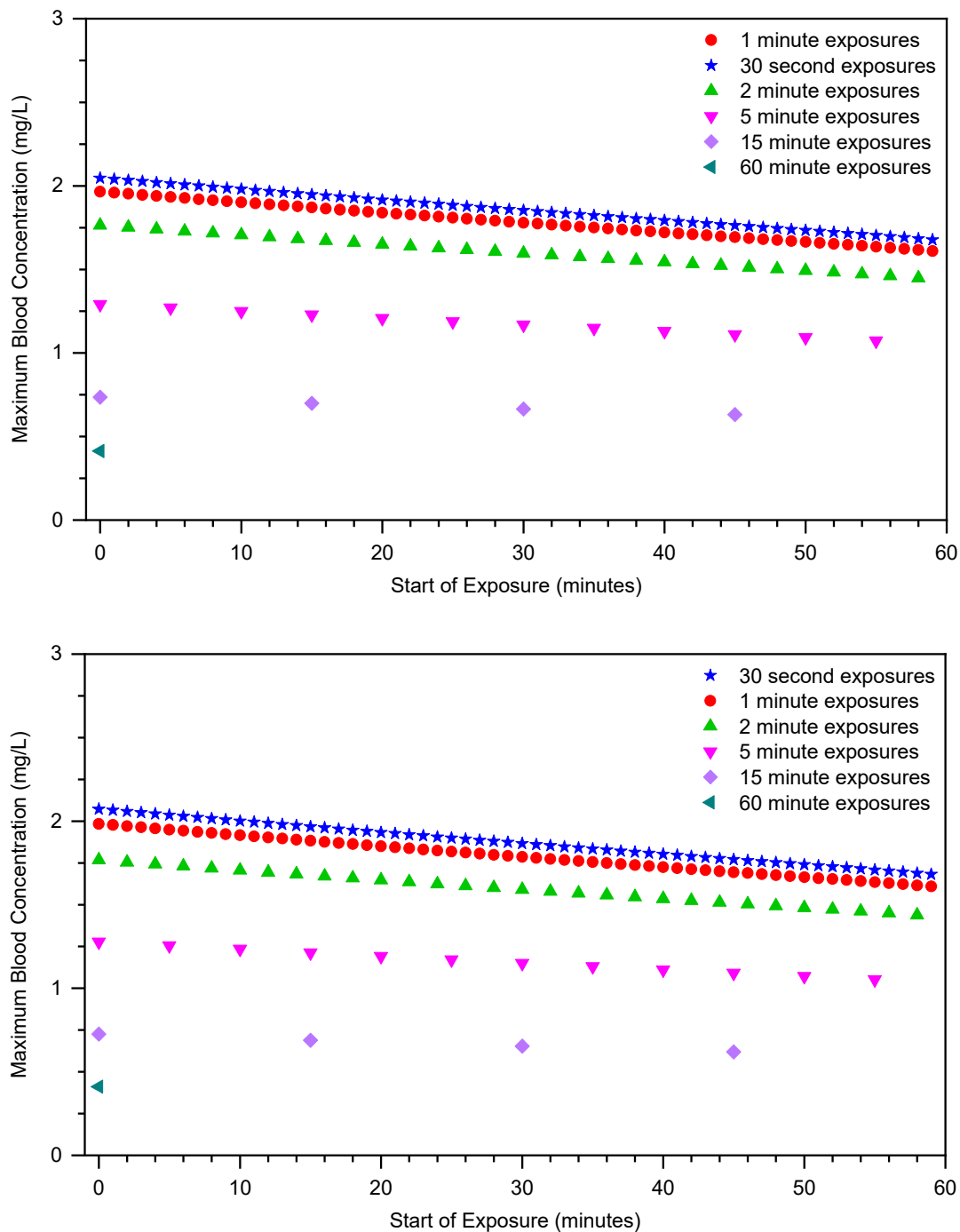


Figure 16. Predicted Maximum Acetone Blood Concentrations. Blood concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 15 for males (upper) and females (lower).

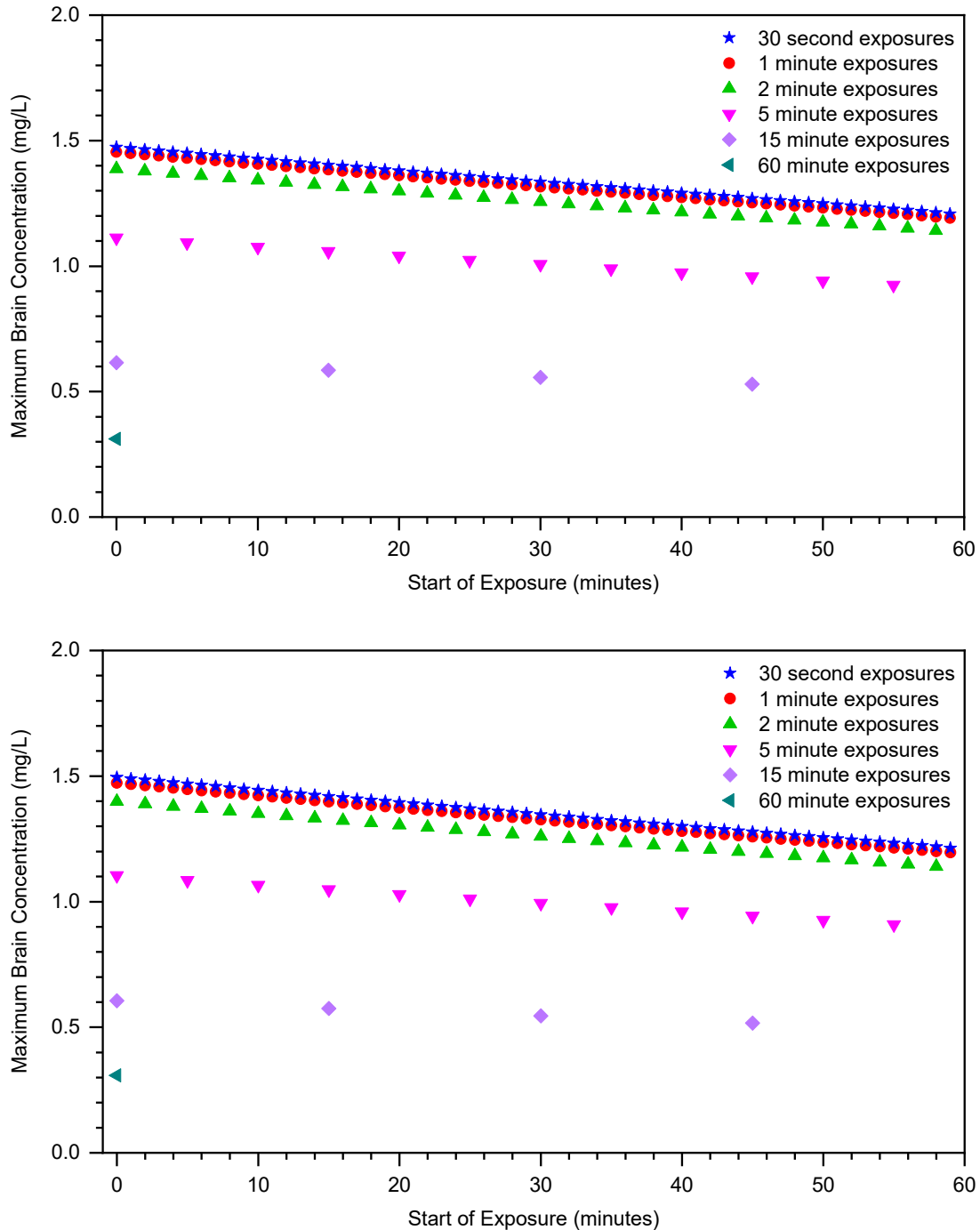


Figure 17. Predicted Maximum Acetone Brain Concentrations. Brain concentrations are those predicted for the acetone exposure concentrations and exposure scenarios in Figure 15 for males (upper) and females (lower).

Given that the presence of acetone in exhaled breath could be due from exposure to either acetone or IPA or both, doses were also estimated for IPA exposure resulting in the acetone target exhaled breath concentration of 354 ppb. Like for acetone exposure, the range of estimated IPA doses to match the acetone target (Figure 18) are considerably lower

(about 30 ppm to 4000 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 19 and 21) and acetone (Figures 20 and 22), that also display little variation for a given exposure length.

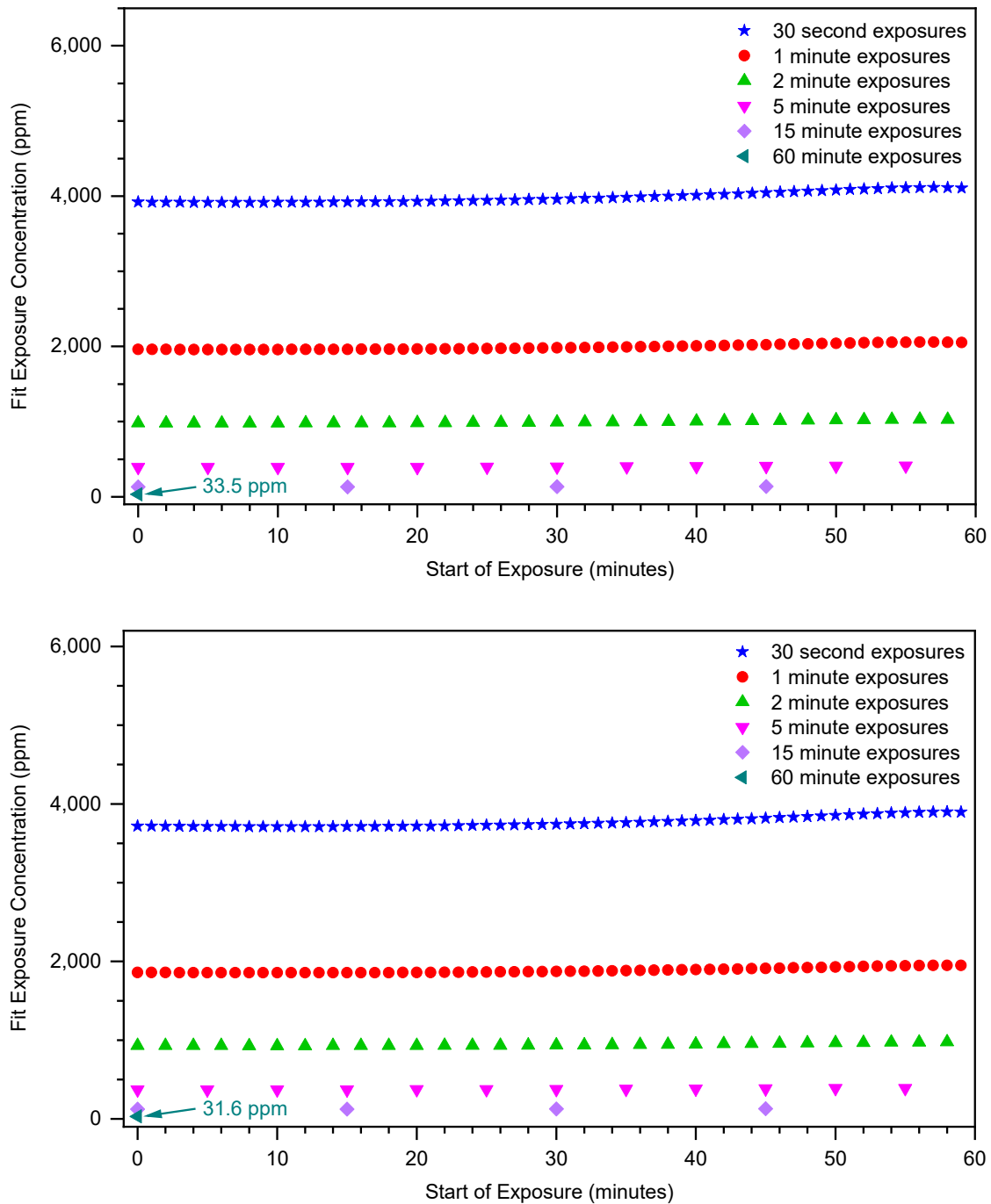


Figure 18. Estimated IPA Exposure Concentrations to Predict Acetone Target. Estimated IPA exposure concentrations to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios for males (upper) and females (lower). Dark blue dashed line represents the STEL.

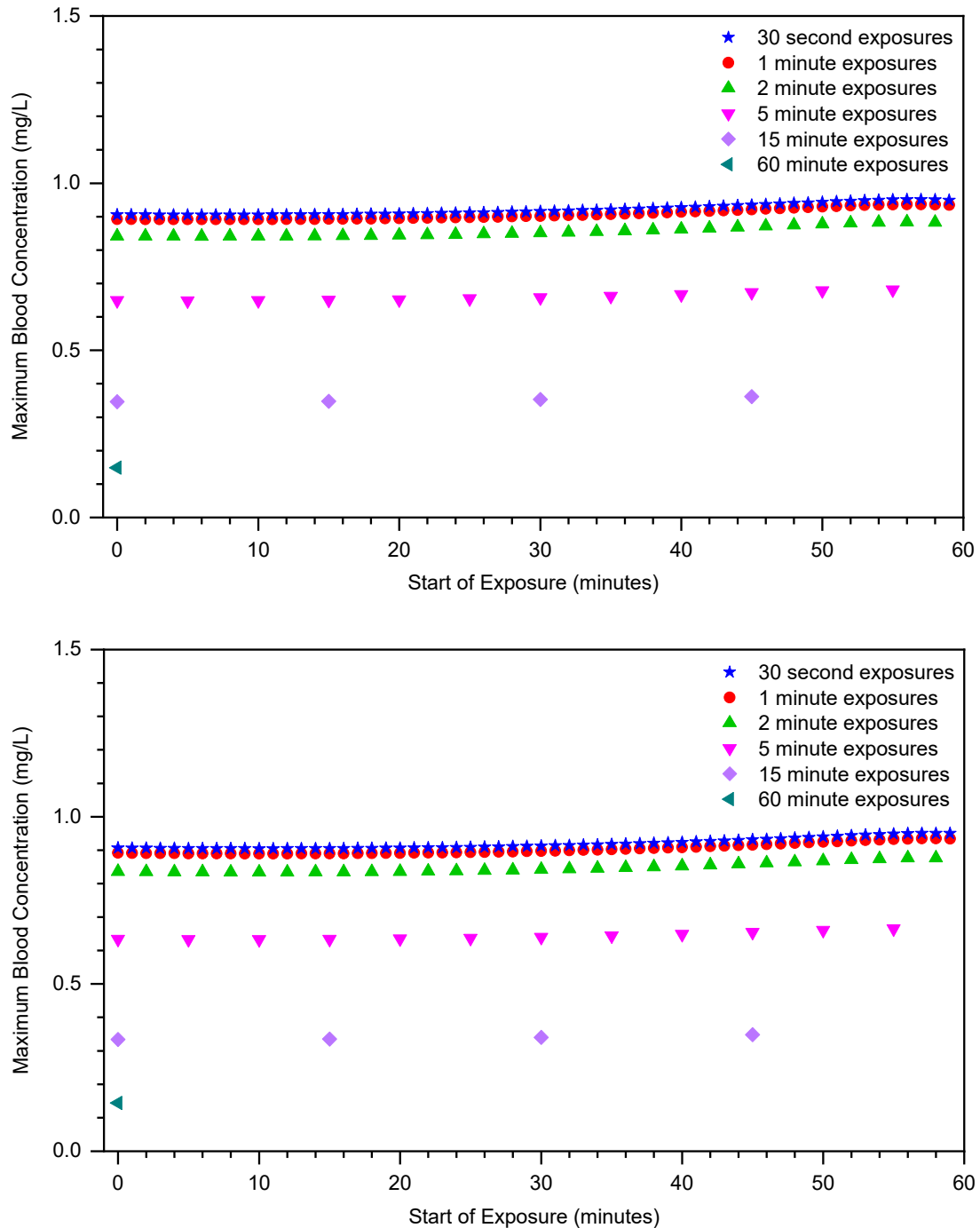


Figure 19. Predicted Maximum IPA Blood Concentrations for Acetone Target. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 18 for males (upper) and females (lower). Note that symbols for 30 second exposures and one minute exposures overlap.

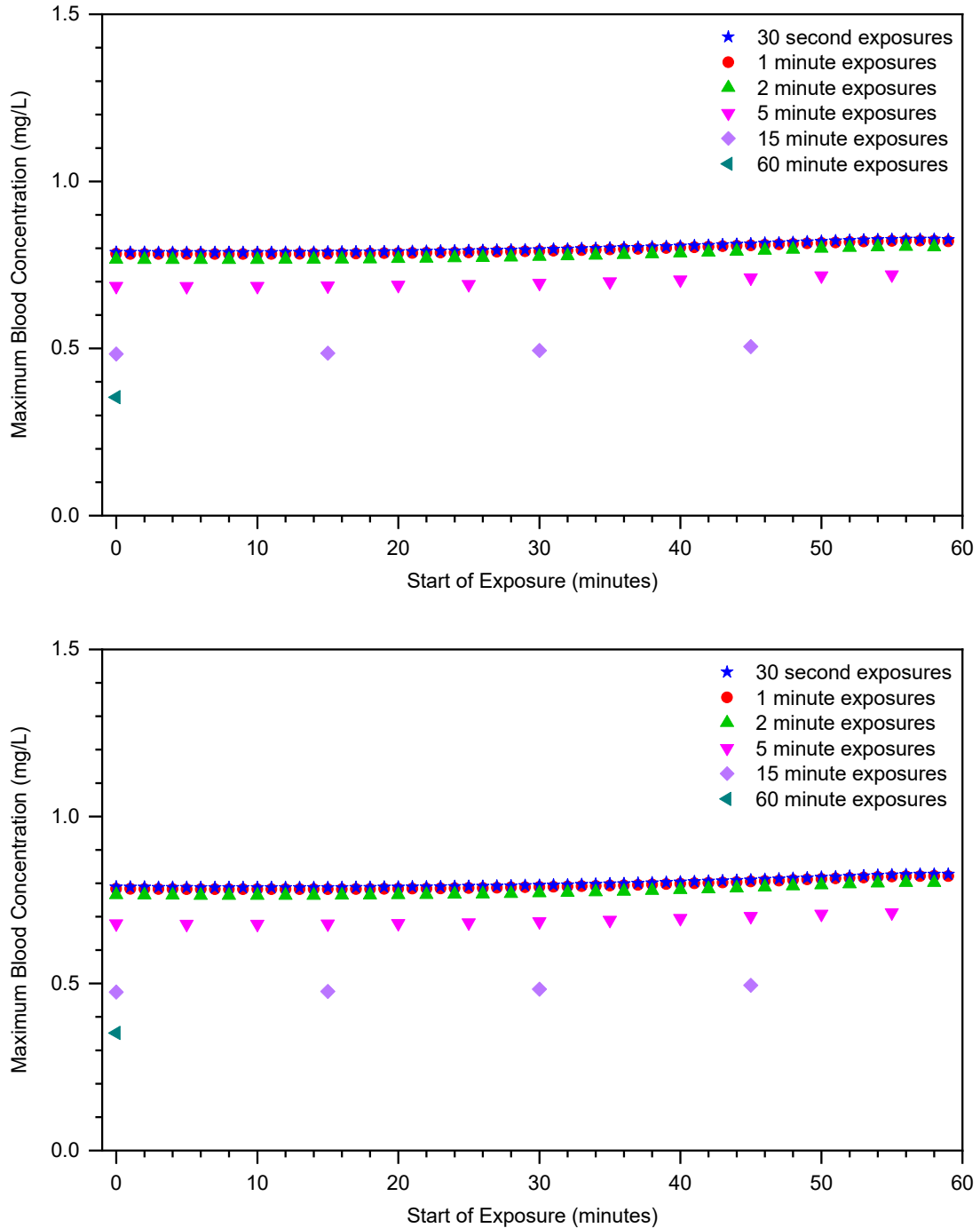


Figure 20. Predicted Maximum Acetone Blood Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 18 for males (upper) and females (lower). Note that symbols for 30 second exposures and one minute exposures overlap.

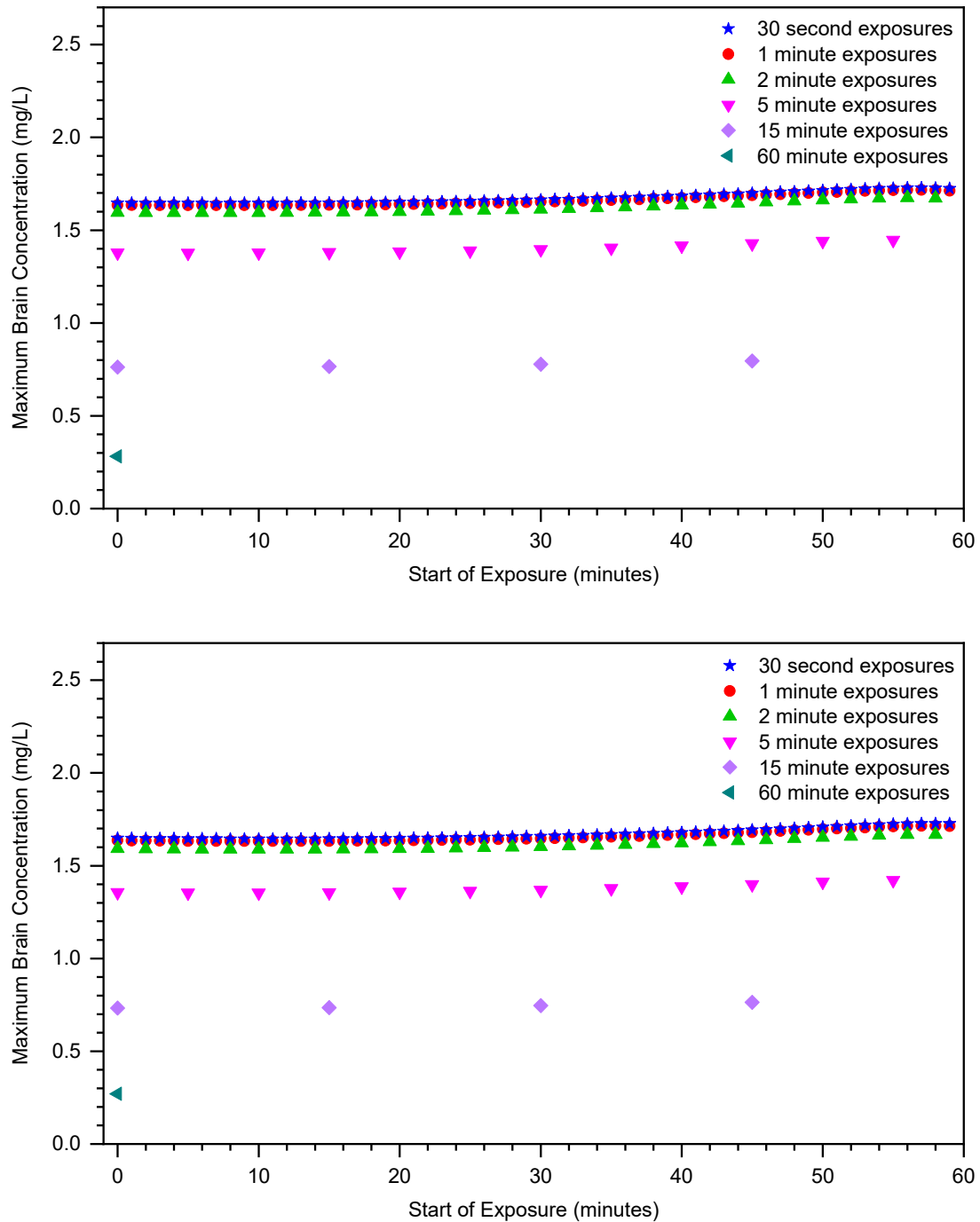


Figure 21. Predicted Maximum IPA Brain Concentrations for Acetone Target. Brain concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 18 for males (upper) and females (lower). Note that symbols for 30 second exposures and one minute exposures overlap.

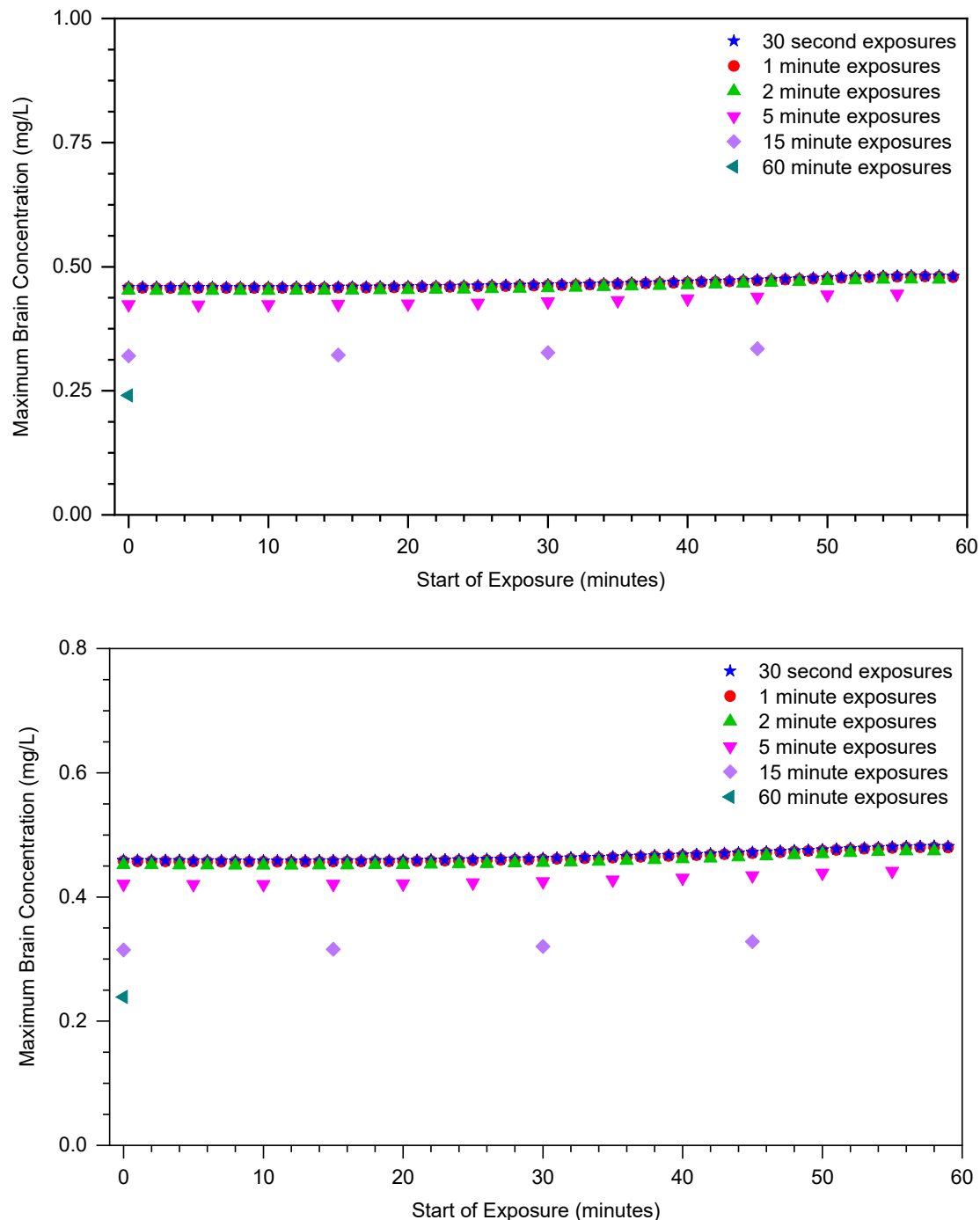


Figure 22. Predicted Maximum Acetone Brain Concentrations for IPA Exposure. Blood concentrations are those predicted for the IPA exposure concentrations and exposure scenarios in Figure 18 for males (upper) and females (lower). Note that symbols for 30 second exposures and one and two minute exposures overlap.

Acetone in measured exhaled breath samples could also be a result of concurrent IPA and acetone exposure. Ideally, in order to estimate IPA and acetone doses that would result in the acetone target exhaled breath concentration of 354 ppm, the IPA doses would be estimated to fit

the IPA target and then acetone doses would be estimated to fit the acetone in exhaled breath that was above the amount of acetone resulting from the IPA exposure. However, the predicted exhaled breath concentrations for acetone following simulated exposure to the estimated IPA doses to match the IPA target are all above the acetone target exhaled breath concentration. Therefore, a range of various IPA doses was used to simulate concurrent IPA and acetone, and acetone doses were estimated to predict the acetone target given the selected concurrent IPA doses. All of the IPA doses used are low enough to require an additional acetone dose in order to predict the acetone target. Figures 23 through 25 show the results for estimated acetone doses given a concurrent IPA dose of 30 ppm.

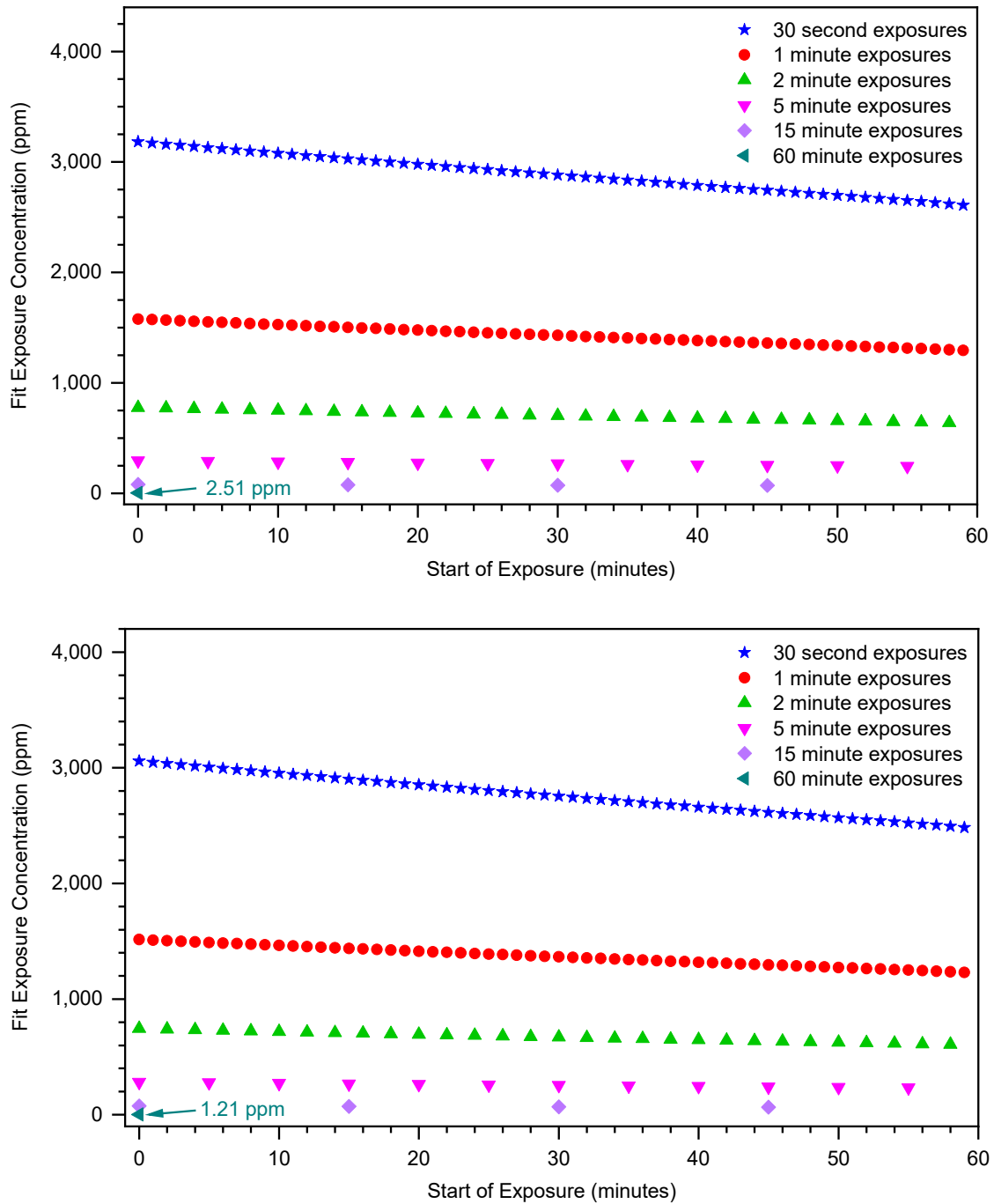


Figure 23. Estimated Acetone Exposure Concentrations with Co-Exposure to 30 ppm IPA. Estimated exposure concentrations, with co-exposure to 30 ppm IPA, to predict an acetone exhaled breath target of 354 ppb for different exposure scenarios for males (upper) and females (lower). Dark blue dashed line represents the acetone STEL.

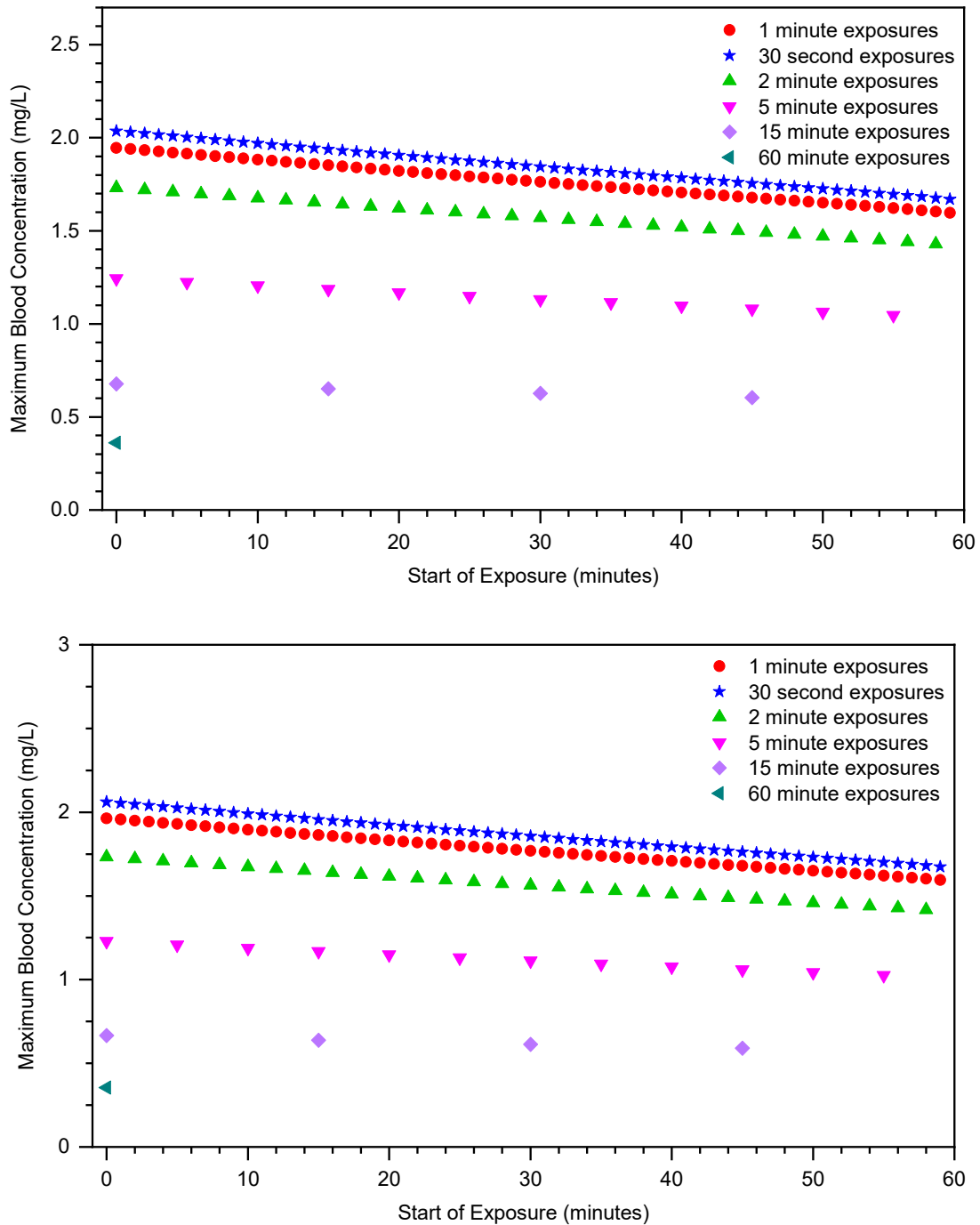


Figure 24. Predicted Maximum Acetone Blood Concentrations for Co-Exposure to 30 ppm IPA. Blood concentrations are those predicted for the acetone exposure concentrations, with co-exposure to 30 ppm IPA, and exposure scenarios in Figure 23 for males (upper) and females (lower).

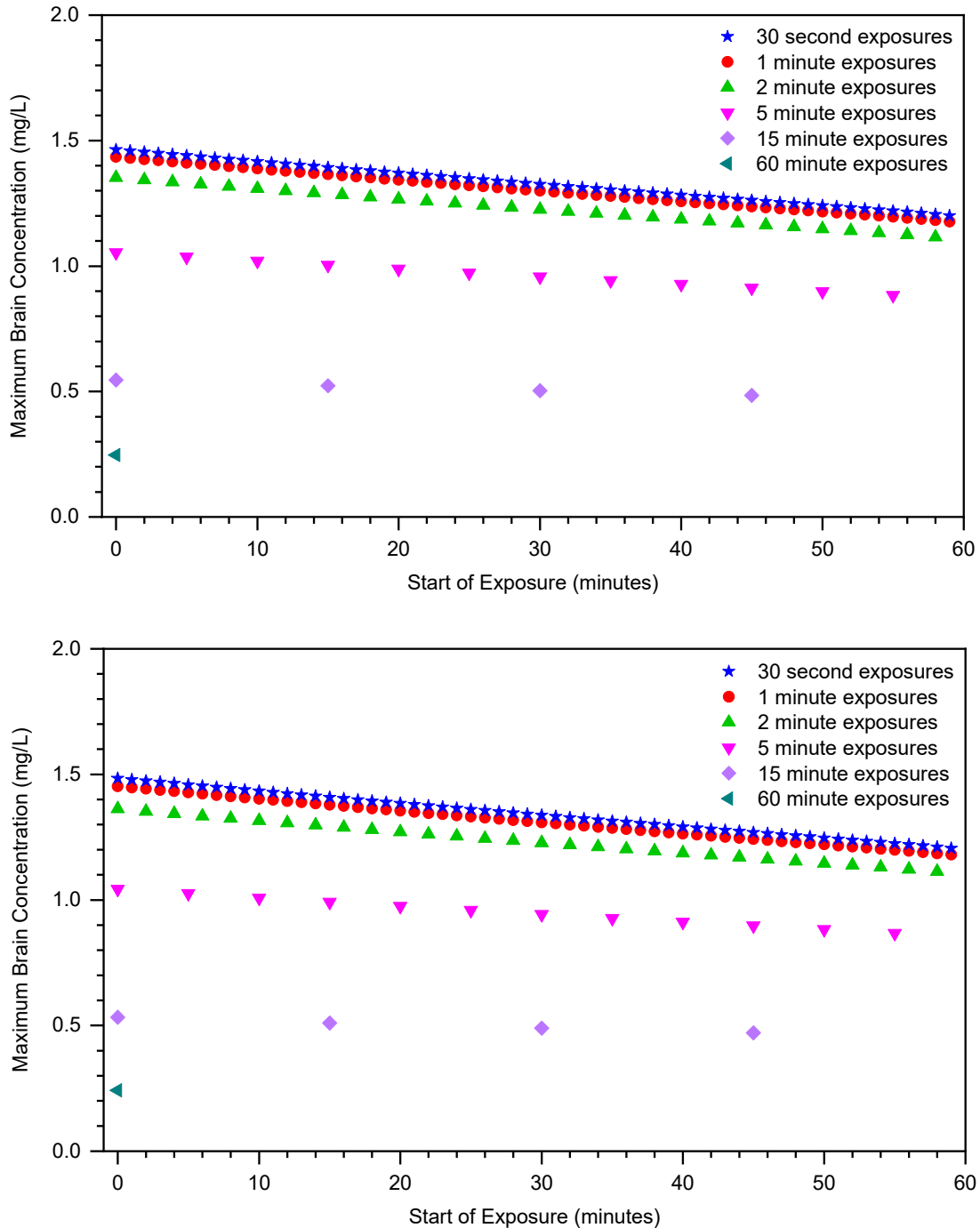


Figure 25. Predicted Maximum Acetone Brain Concentrations for Co-Exposure to 30 ppm IPA. Blood concentrations are those predicted for the acetone exposure concentrations, with co-exposure to 30 ppm IPA, and exposure scenarios in Figure 23 for males (upper) and females (lower).

The target exhaled breath concentration for toluene of 6.3 ppb is considerably lower than for IPA and acetone. Toluene estimated doses (Figure 26) are all well below the STEL for toluene of 150 ppm and range from approximately 0.12 ppm to 23 ppm. Predicted maximum

blood concentrations range from approximately 0.0009 mg/L to about 0.006 mg/L (Figure 27); predicted maximum brain concentrations are about four times higher and range from to about 0.003 mg/L to 0.02 mg/L (Figure 28).

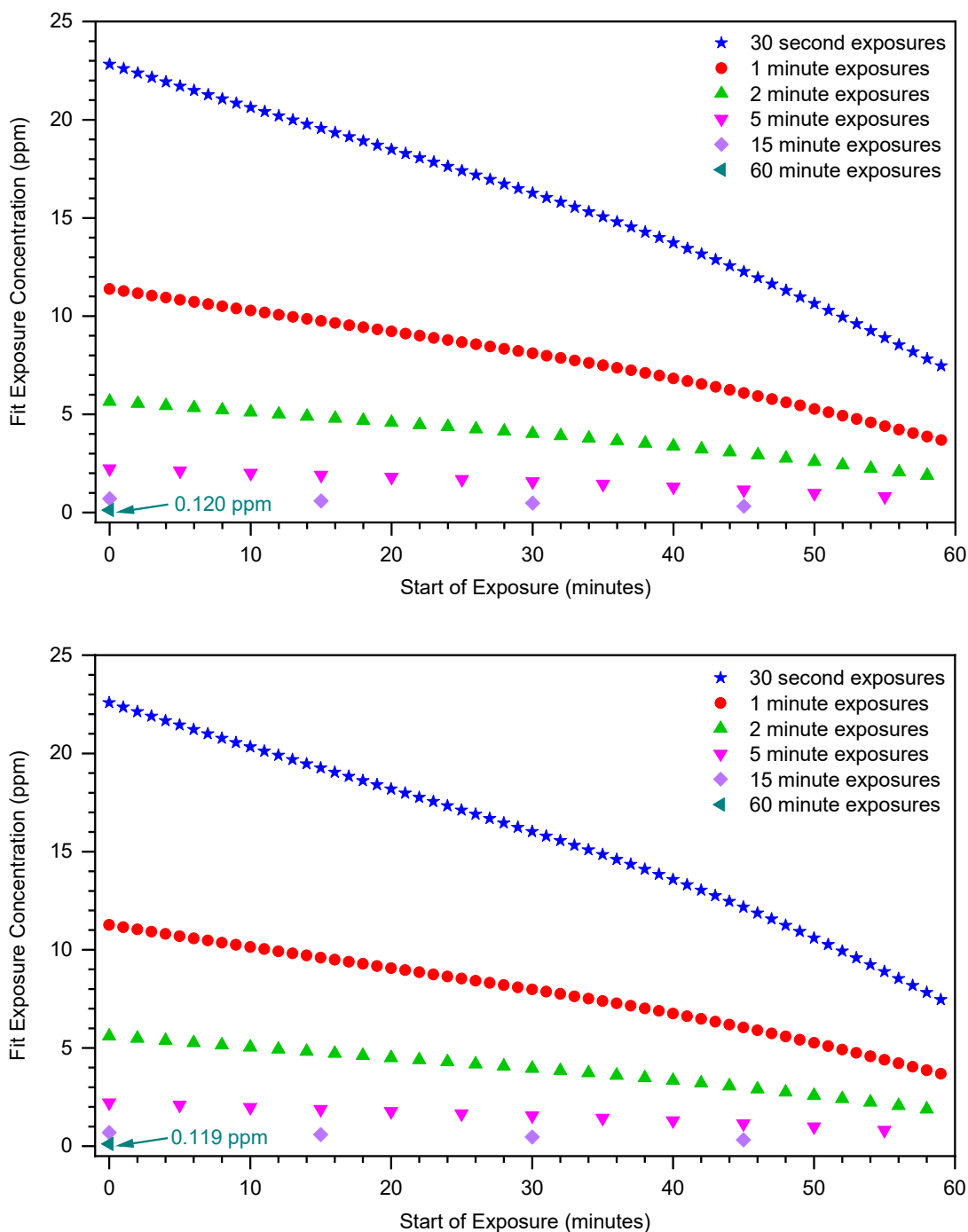


Figure 26. Estimated Toluene Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 6.3 ppb for different exposure scenarios for males (upper) and females (lower).

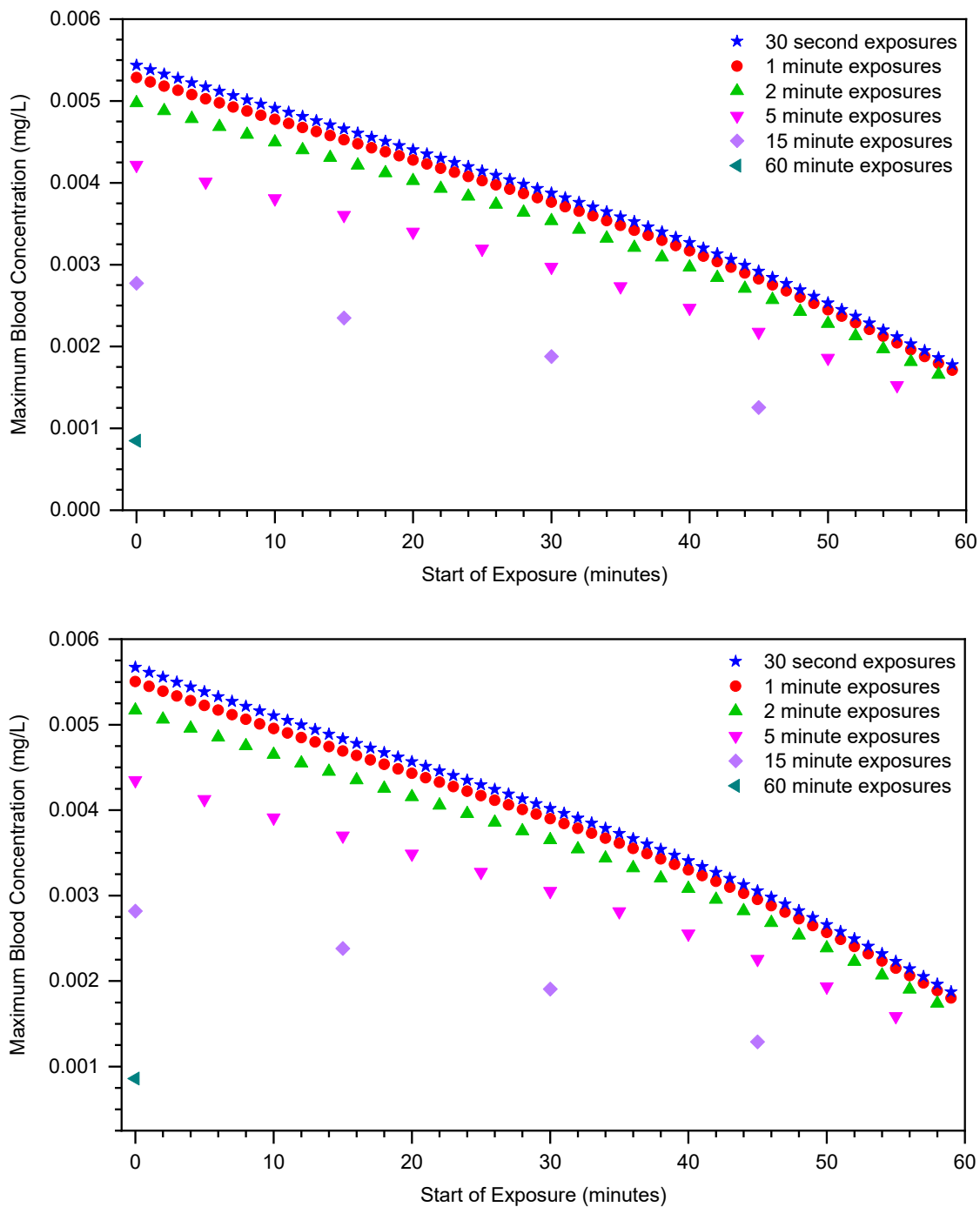


Figure 27. Predicted Maximum Toluene Blood Concentrations. Blood concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 26 for males (upper) and females (lower).

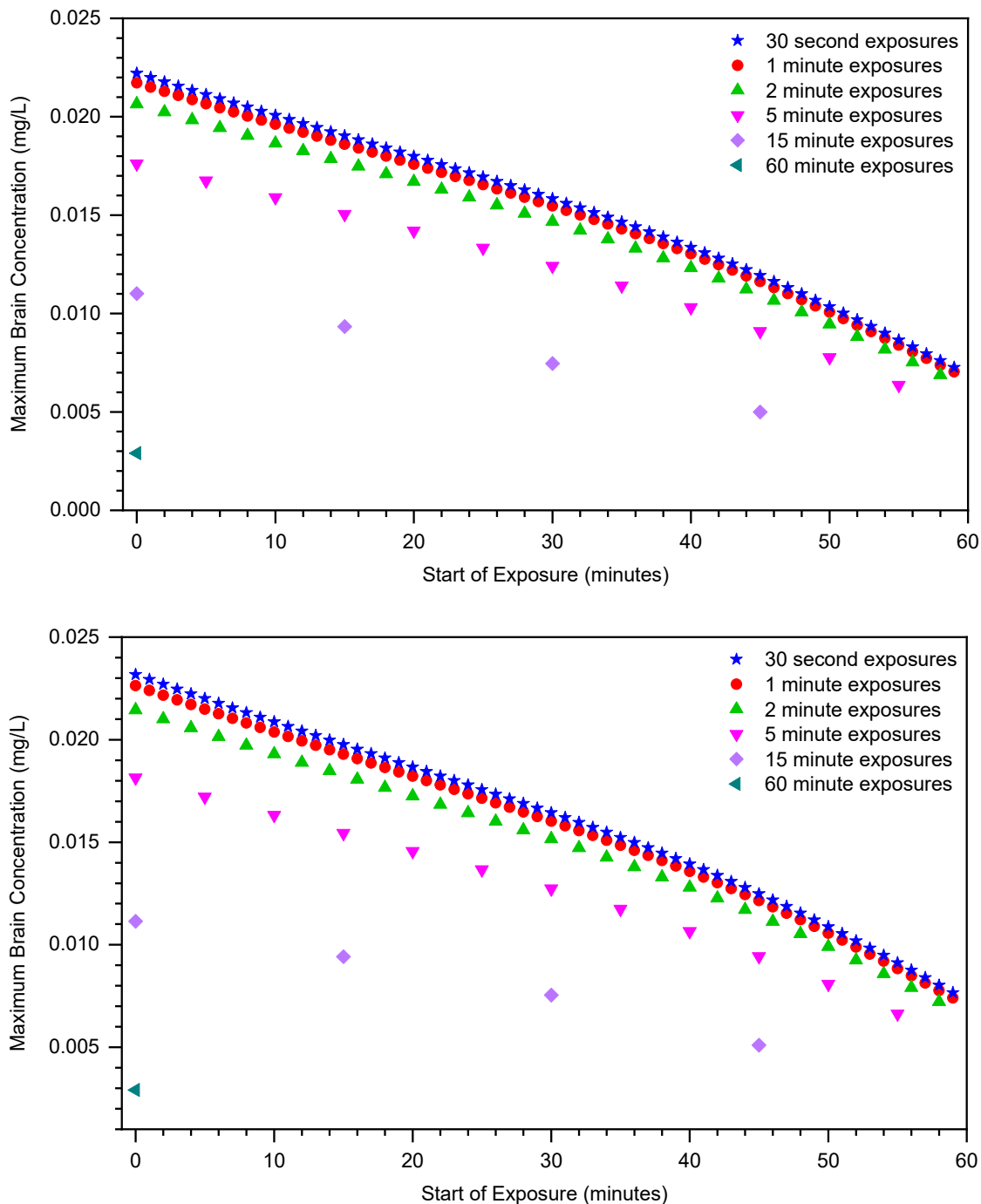


Figure 28. Predicted Maximum Toluene Brain Concentrations. Brain concentrations are those predicted for the toluene exposure concentrations and exposure scenarios in Figure 26 for males (upper) and females (lower).

Cyclohexane has the lowest target exhaled breath concentration of 5.3 ppb. 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 29) are well below this OSHA PEL and range from approximately 0.07 ppm to 18 ppm. The lowest

values for predicted maximum blood and brain concentrations (Figures 29 and 30) range are approximately a factor of 10 lower than the highest values and range from approximately 0.0001 mg/L to 0.0015 mg/L for blood and approximately 0.0016 mg/L to 0.01 mg/L for brain.

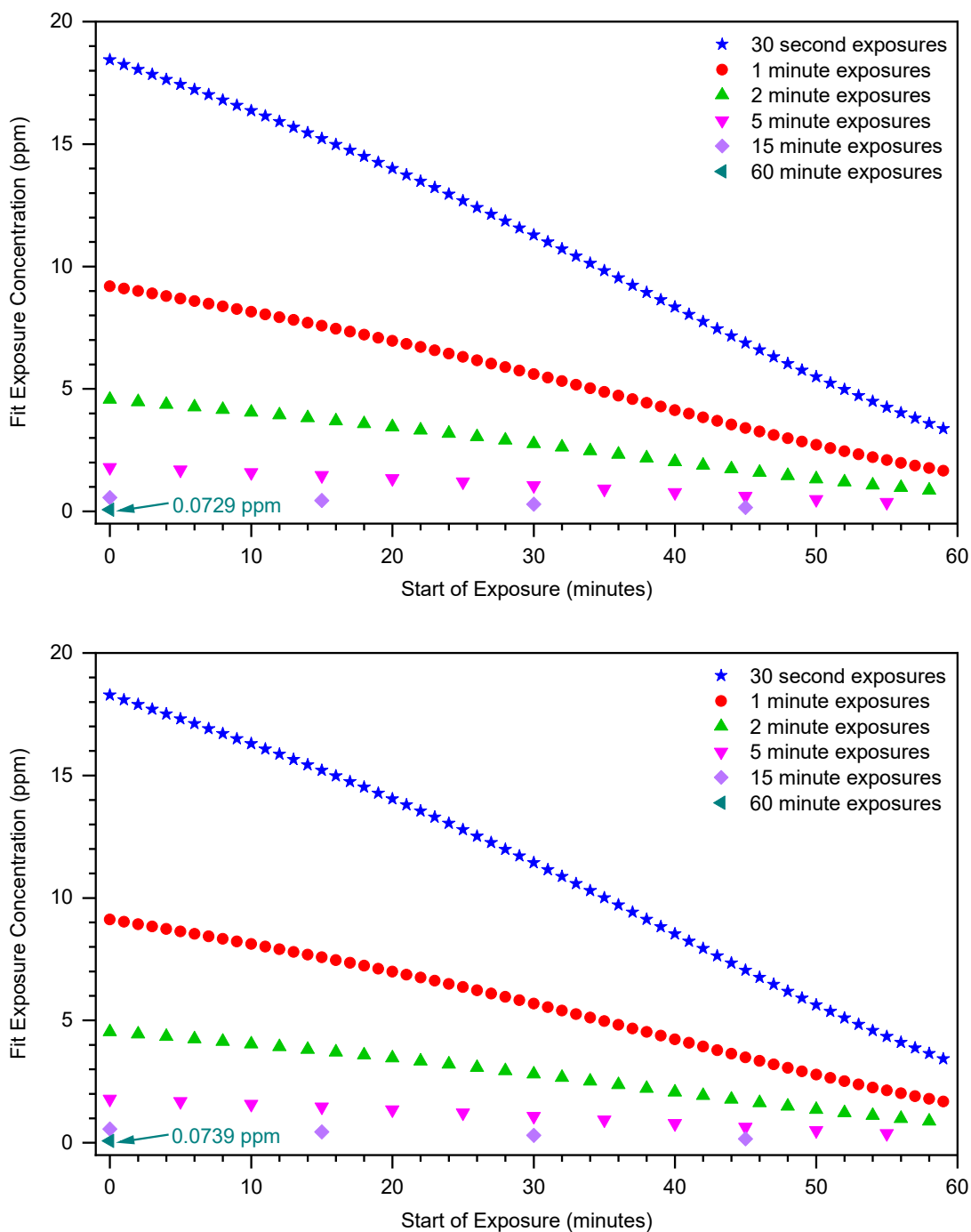


Figure 29. Estimated Cyclohexane Exposure Concentrations. Estimated exposure concentrations to predict an exhaled breath target of 5.3 ppb for different exposure scenarios for males (upper) and females (lower). Dark blue dashed line represents the OSHA PEL.

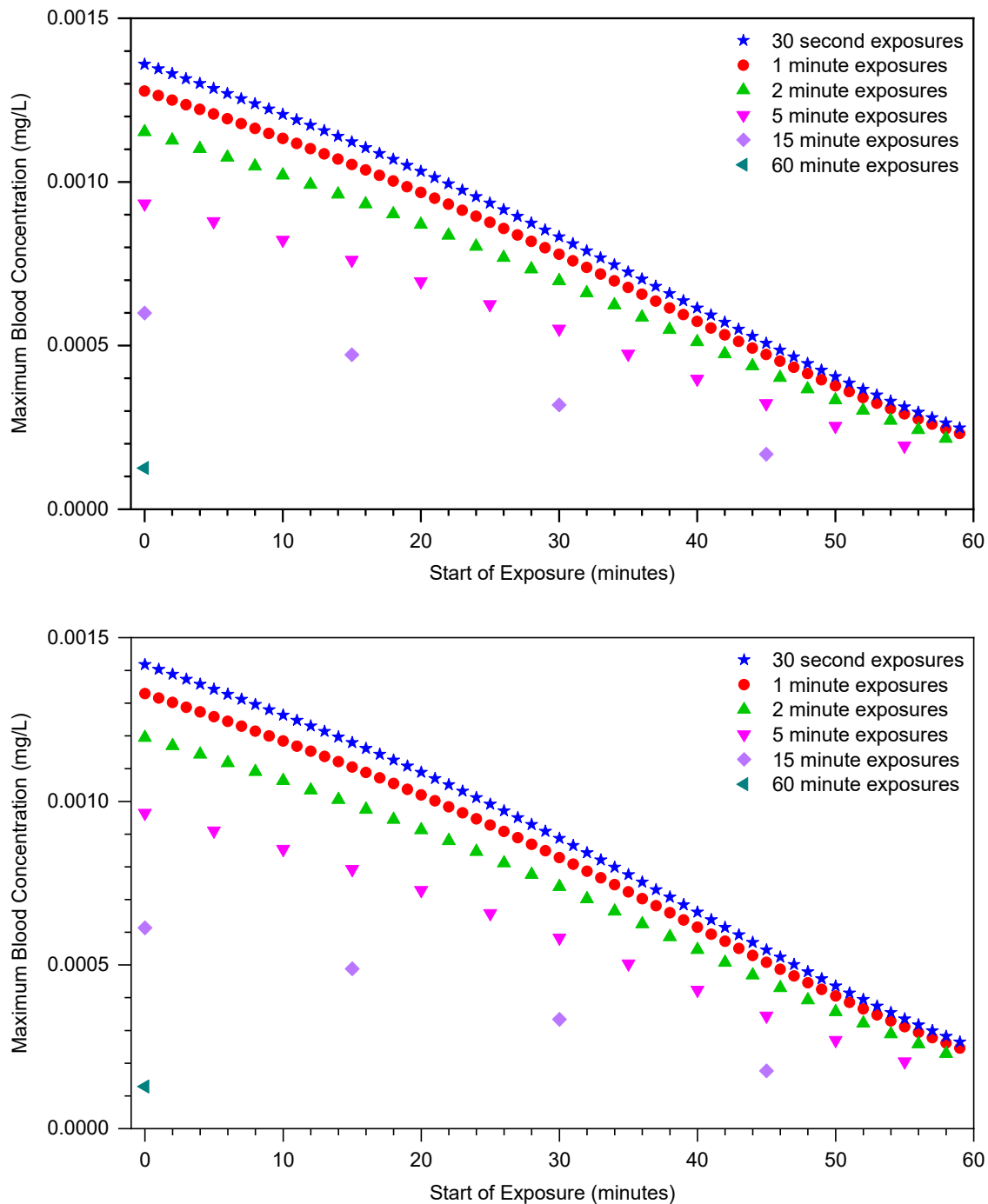


Figure 30. Predicted Maximum Cyclohexane Blood Concentrations. Blood concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 29 for males (upper) and females (lower).

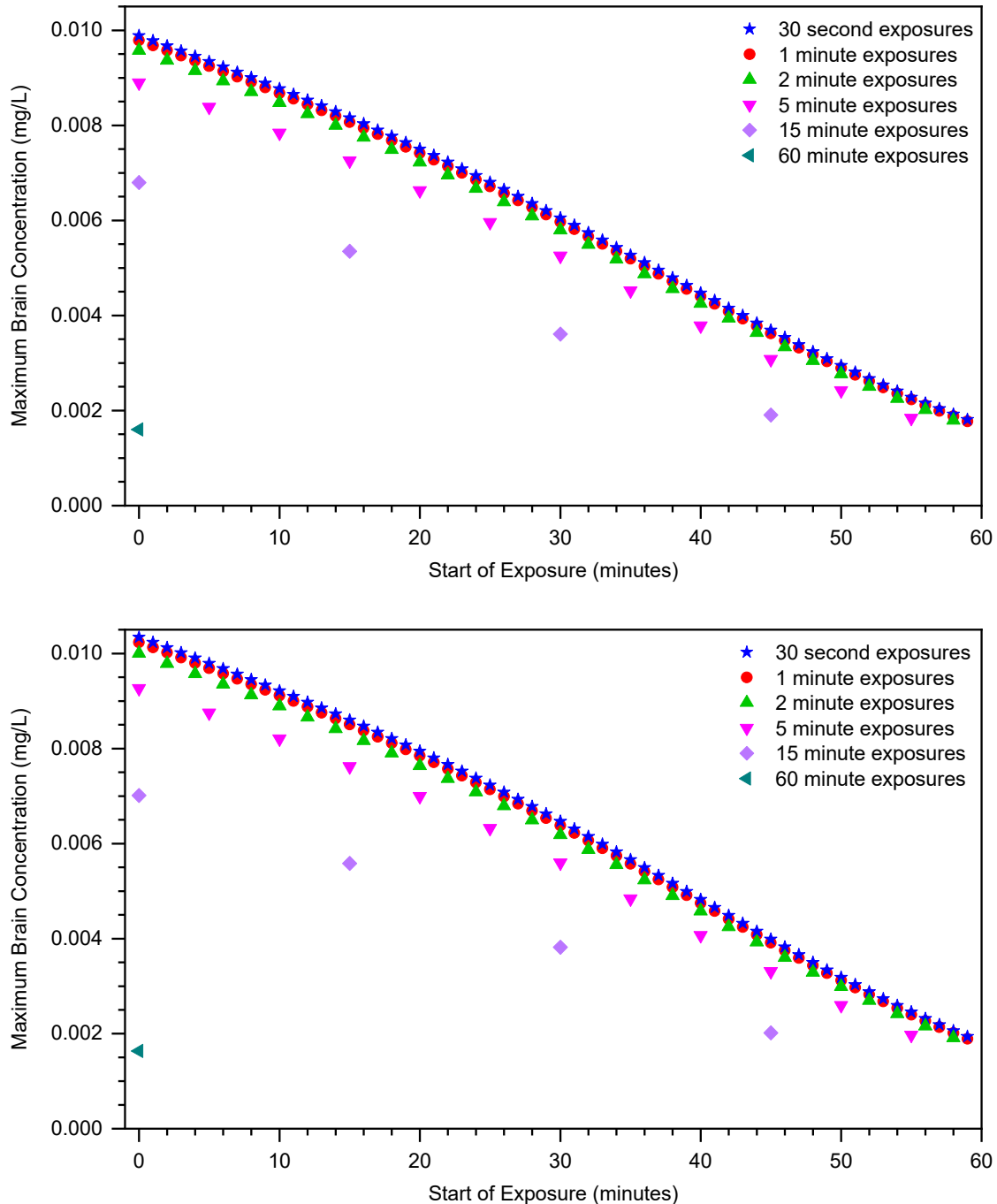


Figure 31. Predicted Maximum Cyclohexane Brain Concentrations. Brain concentrations are those predicted for the cyclohexane exposure concentrations and exposure scenarios in Figure 29 for males (upper) and females (lower). Note that symbols for 30 second exposures and one and two minute exposures overlap.

4.3 Monte Carlo Analyses

Figure 32 demonstrates the potential variability in predictions for IPA exhaled air concentration due to inter-individual variation. The black line represents the model prediction

using the same parameter values as the dose reconstruction simulations for IPA; these parameters are also used as the means to define the distributions for the Monte Carlo analysis. The red line represents the average, for each time point, of the 5000 simulations and is slightly higher during the clearance phase following exposure than the simulation using the mean parameters. The blue area represents two standard deviations, for each time point, of the Monte Carlo simulations, and the green area represents the maximum and minimum prediction at each time point for all of the simulations. The distribution of predicted exhaled breath concentrations from these simulations is shown in Figure 33. The log-normal curve fit to this distribution and the geometric mean of the predicted exhaled breath concentrations are also presented in Figure 33.

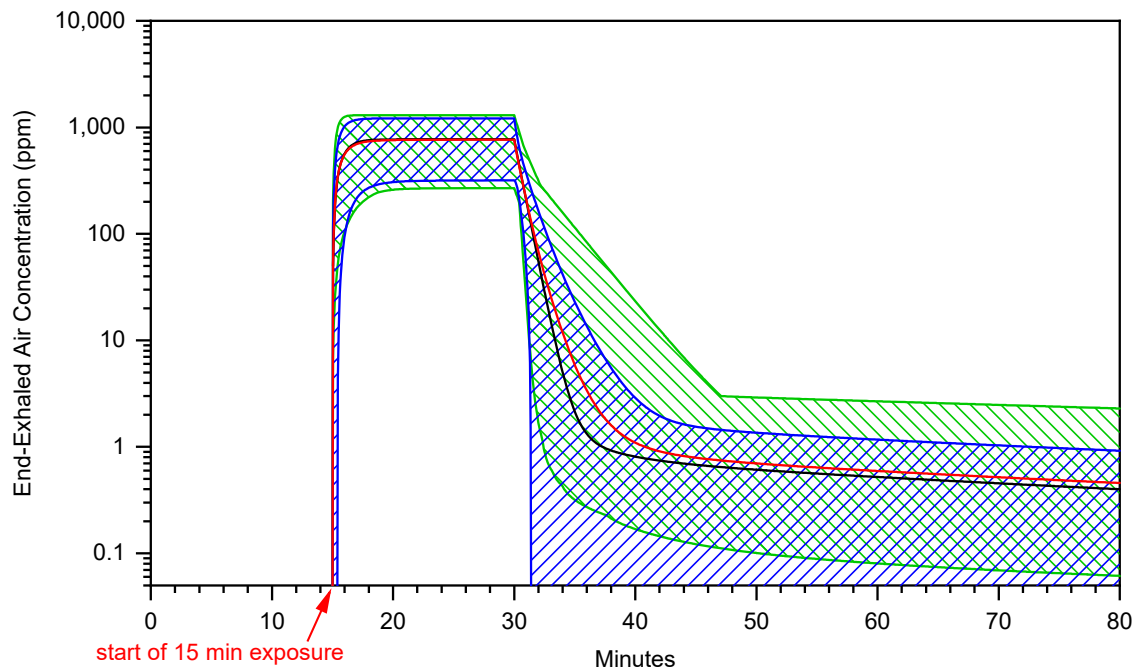


Figure 32. Monte Carlo Results for Exhaled IPA Concentrations for Fixed Exposure. Results are a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight for males.

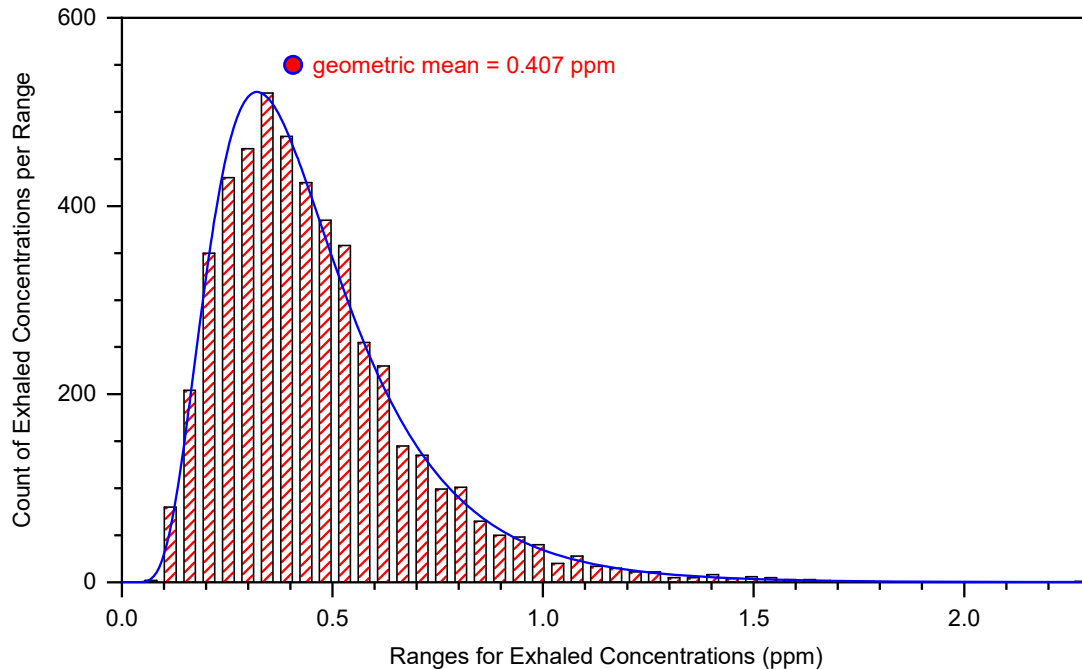


Figure 33. Histogram of Predicted Exhaled Breath Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

The 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 32, Figure 34 shows predicted IPA exhaled air concentrations; the difference is that for Figure 34 the dose for each parameter set has been estimated rather than all sets using the same dose. The black line represents the model prediction using the mean parameter values, and the red line represents the average of the Monte Carlo simulations. Again, the red line is slightly higher than the simulation using the mean parameters. The blue area represents two standard deviations, for each time point, of the Monte Carlo simulations, and the green area represents the maximum and minimum prediction at each time point for all of the simulations. 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 35. The log-normal curve fit to this distribution and the geometric mean of the estimated doses are also presented in Figure 35.

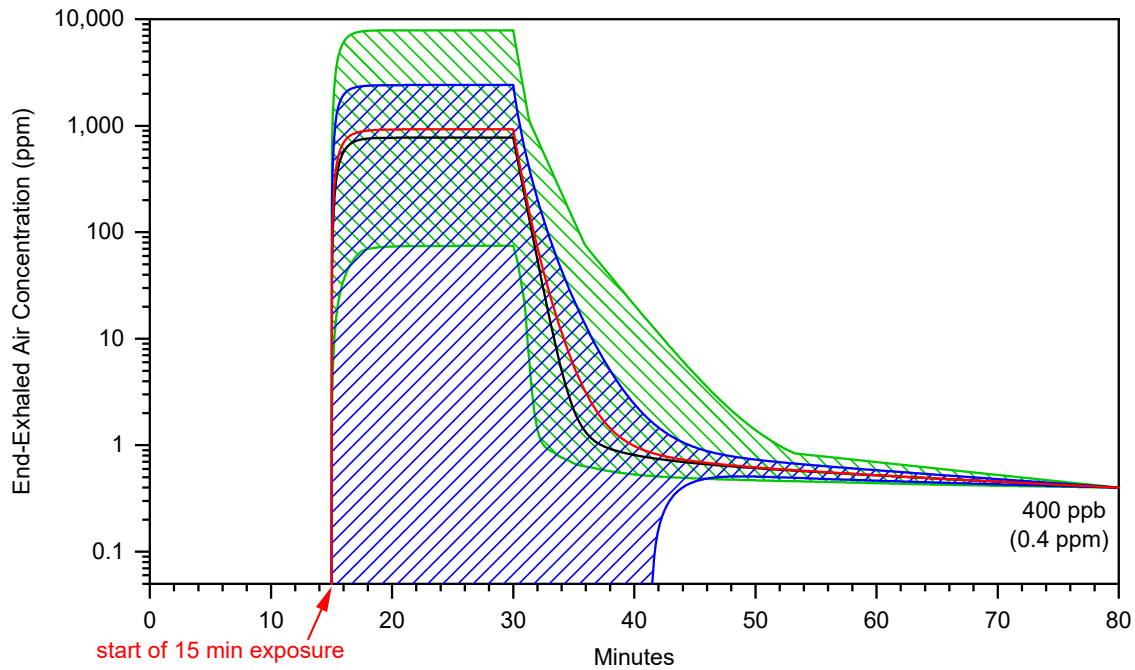


Figure 34. Monte Carlo Results for Exhaled IPA Concentrations from Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

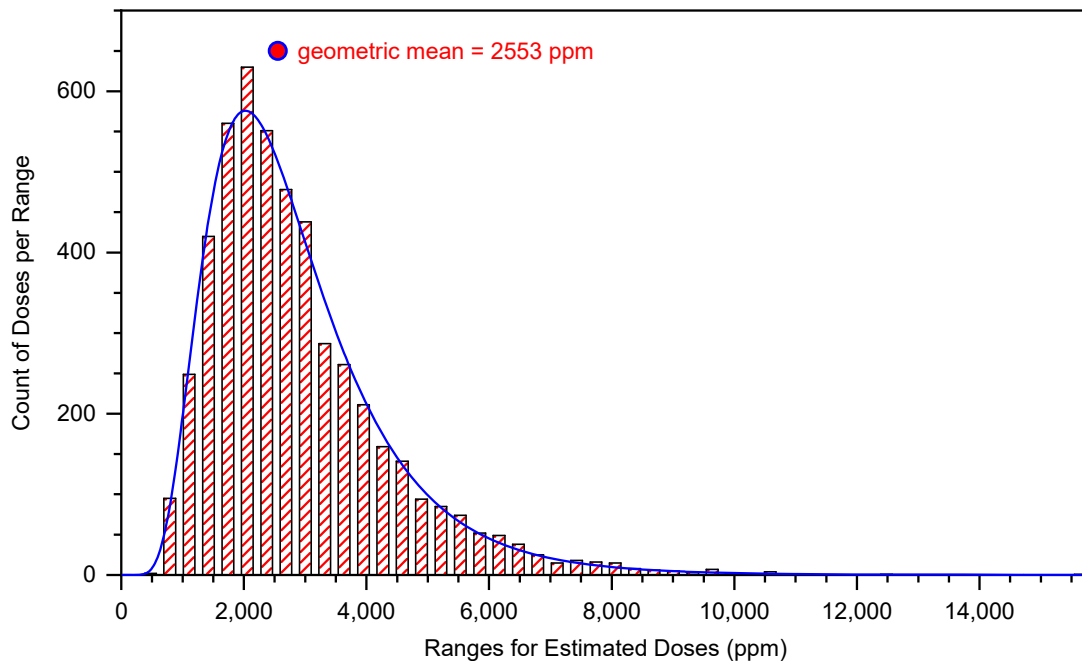


Figure 35. Histogram of Estimated IPA Exposure Concentrations for Fixed Exposure Scenario. Results are for a Monte Carlo analysis simulating IPA exposure of 15 minutes starting 15 minutes into the flight.

5.0 DISCUSSION

PBPK modeling and pilot exhaled breath exposures from HPARS were used to reconstruct potential cockpit exposures. Estimated potential exposures ranged from approximately 600 ppm to just under 100,000 ppm for IPA and from approximately 25 ppm to more than 300 ppm for acetone. These IPA estimates are all well above the STEL of 400 ppm with some estimates as almost 250 times the STEL. While some acetone estimates are a little more than 3 times the STEL of 1000 ppm, all estimates for exposures lasting two minutes or more are below the STEL regardless of the time for start of exposure. Toluene estimates, ranging from approximately 0.12 ppm to 23 ppm, were all well below the STEL of 150 ppm. Since a STEL for cyclohexane could not be located, the OSHA PEL of 300 ppm is used for comparison, but all estimated cyclohexane exposures, 0.07 ppm to 18 ppm, are well below this limit. The estimated IPA and acetone concentrations confirm the potential for exceptionally high concentrations during high performance aircraft flights. The limited Monte Carlo results demonstrate how these exposure estimates could vary even more due to inter-individual differences in pharmacokinetics. 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 the estimated doses may be used to better correlate the exposures to the reported respiratory pilot symptoms and prioritize which chemicals should be examined further. These results will hopefully help to develop better in-flight testing, air quality standards, and autonomous control systems to identify and react to system diversions.

6.0 REFERENCES

1. Clewell HJ, Gentry PR, Gearhart JM, Covington TR, Banton MI, Andersen ME. Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone. *Toxicol Sci.* 2001, 63:160-172.
2. Hissink AM, Kulig BM, Kruse J, Freidig AP, Verwei M, Muijsers H, Lammers JH, McKee RH, Owen DE, Sweeney LM, Salmon F. Physiologically based pharmacokinetic modeling of cyclohexane as a tool for integrating animal and human test data. *Int J Toxicol.* 2009, 28:498-509.
3. Tardif R, Charest-Tardif G, Brodeur J, Krishnan K. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. *Toxicol Appl Pharmacol.* 1997, 144:120-134.
4. Tardif R, Lapare S, Charest-Tardif G, Brodeur J, Krishnan K. Physiologically-based pharmacokinetic modeling of a mixture of toluene and xylene in humans. *Risk Anal.* 1995, 15:335-342.
5. Choi H, Coate A, Selby M, Hudson J, Whitehead C, Zehner G, Fleming S. Aircrew sizing survey 2011. 2014. Air Force Research Laboratory, 711th Human Performance Wing, Human Systems Integration Directorate, Wright-Patterson AFB, OH. AFRL-RH-WP-TR-2014-0113.
6. Guyton AC. *Textbook of Medical Physiology* (8th ed.), ed. W.B. Saunders. 1991. Philadelphia.
7. Fiserova-Bergerova V, Tichy M, Di Carlo FJ. Effects of biosolubility on pulmonary uptake and disposition of gases and vapors of lipophilic chemicals. 1984. *Drug Metab Rev.* 1984, 15:1033-1070.
8. Covington TR, Gentry PR, Van Landingham CB, Andersen ME, Kester JE, Clewell HJ. The use of Markov chain Monte Carlo uncertainty analysis to support a Public Health Goal for perchloroethylene. *Regul Toxicol Pharmacol.* 2007, 47:1-18.
9. David RM, Clewell HJ, Gentry PR, Covington TR, Morgott DA, Marino DJ. Revised assessment of cancer risk to dichloromethane II. Application of probabilistic methods to cancer risk determinations. *Regul Toxicol Pharmacol.* 2006, 45:55-65.
10. Kumagai S, Oda H, Matsunaga I, Kosaka H, Akasaka S. Uptake of 10 polar organic solvents during short-term respiration. *Toxicol Sci.* 1999, 48:255-263.
11. Lacouture PG, Heldreth DD, Shannon M, Lovejoy FH. The generation of acetonemia/acetonuria following ingestion of a subtoxic dose of isopropyl alcohol. *Am J Emerg Med.* 1989, 7:38-40.
12. Monaghan MS, Olsen KM, Ackerman BH, Fuller GL, Porter WH, Pappas AA. Measurement of serum isopropanol and the acetone metabolite by proton nuclear magnetic resonance: Application to pharmacokinetic evaluation in a simulated overdose model. *Clin Toxicol.* 1995, 33:141-149.
13. Wigaeus E, Holm S, Astrand I. Exposure to acetone: Uptake and elimination in man. *Scand J Work Environ Health.* 1981, 7:84-94.

APPENDIX A

acslX Model Code

```

PROGRAM: BrExp.CSL
! IPAPub.csl with the discrete block for half-life removed
! Added code to shift start of exposure and changed code for determining dosing interval
!   (added StrtExp and DoseInt parameters)
! Removed code for doing repeated exposures so may days per week (i.e., removed TMax and DaysWk)
! Removed dose routes not needed (IV, drinking water, dermal)
! Removed Calc discrete block
! Moved subtraction of urinary excretion from venous blood to arterial blood (made no difference
!   to predictions)
! Combined saturable and 1st order metabolism equations into a single rate equation (made no
!   difference to predictions)
! Changed steady state equation for arterial blood for metabolite to a rate equation (predictions
!   for CVen_Met are a little lower)
! Added urinary excretion of metabolite to metabolite sub-model -- did this because simulations
!   with just acetone exposure from publication were including urinary excretion but simulations
!   with isopropanol exposure were not including urinary excretion of acetone
! Added code to do simultaneous inhalation exposure of parent and metabolite -- if you turn off
!   scrubbing (i.e., kUrt_MetC equal to zero) there is no difference in predictions -- if you
!   have scrubbing turned on, the simulations for CVen_Met are higher. Since simulations for
!   acetone exposure use scrubbing, seems like simulations for isopropanol dosing should have
!   scrubbing of acetone
! Renamed parameters with "Bld" to "Art"

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

INITIAL

LOGICAL AdjQCQP ! Adjust QC and QP (QAlv) with exercise
LOGICAL AdjConc ! Ramp up exposure concentration from zero at start of exposure

! Physiological Parameters
CONSTANT BW = 70.0 ! Body weight (kg)
CONSTANT QCC = 0.2148 ! Cardiac output (L/min/kg^0.75)
CONSTANT VPR = 1.6774 ! Alveolar ventilation-perfusion ratio
! CONSTANT QPC = 0.4625 ! Total pulmonary ventilation (L/min/kg^0.75)

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

! Fractional Tissue Volumes (fraction of body weight)
CONSTANT 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
CONSTANT VBodyC = 0.84 ! Sum of mean fractional volumes

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

! Dose Timing Parameters
CONSTANT StrtExp = 0.0 ! Time to start exposure (min)
CONSTANT ExpEnd = 1.0 ! Time to stop all exposures (min)
CONSTANT DoseInt = 1000.0 ! Interval to repeat dosing (min)

! Simulation Control Parameters
CONSTANT TStop = 1440.0
CINTERVAL CINT = 0.6
CONSTANT AdjQCQP = .FALSE. ! Switch to adjust QC and QP for exercise
CONSTANT TExer = 30.0 ! Time to start exercise (min)

```

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CONSTANT      LExer = 15.0      ! Length of exercise period (min)
CONSTANT      ExerInc = 4.0      ! Factor increase in QC and QP for exercise
CONSTANT      RampUp = 3.0      ! Time frame to ramp up QC and QP (min)
CONSTANT      RampDn = 6.0      ! Time frame to ramp down QC and QP (min)

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

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

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

! Inhalation Exposure Parameters
CONSTANT      AdjConc = .FALSE.      ! Ramp up exposure concentration from zero
CONSTANT      ConcUp = 0.0      ! Time frame to ramp up exposure concentration (min)
CONSTANT      Conc = 0.0      ! Inhaled concentration (ppm) of parent

! Oral Exposure Parameters
CONSTANT      PDose = 0.0      ! Oral dose (mg/kg)
CONSTANT      kAD = 0.1333      ! Absorption from duodenum (/min)
CONSTANT      kAS = 0.01667      ! Absorption from stomach (/min)
CONSTANT      kTD = 0.0      ! Excretion (/min)
CONSTANT      kTSD = 0.1667      ! Transfer - stomach to duodenum (/min)

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

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

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```

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

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

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

! Scaled Blood Flows (L/min)
QCN = QCC * (BW**0.75)
QAdjus = QBrnC + QFatC + QLivC + QRapC + QSlwC
QBrnC = (QBrnC / QAdjus) * QCN      ! Brain
QFatC = (QFatC / QAdjus) * QCN      ! Fat
QLivC = (QLivC / QAdjus) * QCN      ! Liver
QRapC = (QRapC / QAdjus) * QCN      ! Rapidly perfused tissues
QSlwC = (QSlwC / QAdjus) * QCN      ! Slowly perfused tissues
QCInit = QBrnC + QFatC + QLivC + QRapC + QSlwC

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

! Calculate Parameters for Changing QC and QP with Exercise
FracInc = (ExerInc - 1.0) / RampUp
FracDec = (ExerInc - 1.0) / RampDn

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

! Initial Amounts of Endogenous Parent (mg) when Dosed with Parent
IAArt = CEndo * VAlv
IABrnC = CEndo * VBrnC * PBrnC
IAFatC = CEndo * VFatC * PFatC
IALivC = CEndo * VLivC * PLivC
IARapC = CEndo * VRapC * PRapC
IASlwC = CEndo * VSlwC * PSlwC
InitTot = IAArt + IABrnC + IAFatC + IALivC + IARapC + IASlwC

! Initial Amounts of Endogenous Metabolite (mg) when Dosed with Parent
IAArt_Met = CEndo_Met * VAlv
IABrnC_Met = CEndo_Met * VBrnC * PBrnC_Met
IAFat_Met = CEndo_Met * VFatC * PFat_Met
IALiv_Met = CEndo_Met * VLivC * PLiv_Met
IARap_Met = CEndo_Met * VRapC * PRap_Met
IASlw_Met = CEndo_Met * VSlwC * PSlw_Met
InitTot_Met = IAArt_Met + IABrnC_Met + IAFat_Met + IALiv_Met + IARap_Met + IASlw_Met

```

```

! Scaled Oral Doses
      Dose = PDose * BW                      ! Oral dose (mg)

! Ramp Up Exposure Concentration from Zero
      IF (AdjConc) THEN
        IncConc = 0.0
      ELSE
        IncConc = 1.0
      ENDIF

! Initialize Starting Values
      CIZone = 0.0
      CIZone_Met = 0.0
      TotDose = 0.0
      PerEnd = 0.0
      PerEnd_Met = 0.0
      PerMix = 0.0
      PerMix_Met = 0.0

      SCHEDULE DoseOn .AT. StrtExp

END                                ! End of Initial

DYNAMIC
      ALGORITHM IALG = 2              ! Gear stiff method

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

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

DISCRETE DoseOff
      CIZone = 0.0
      CIZone_Met = 0.0
END

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

PROCEDURAL (QAlv, QBrn, QFat, QLiv, QRap, QSlw = QP, QCInit, QSlwC, FracInc, FracDec)
! Increase QC and QP (QAlv) with exercise
      IF (AdjQCQP .AND. (T. GE. TExer)) THEN
        IF (T. LE. (TExer+RampUp)) THEN
          IF (RampUp .GT. 0.0) THEN
            QAlv = 0.67 * QP * (1.0 + (FracInc * RAMP(TExer)))
            QBrn = ((QBrnC / QAdjus) * QCInit) * (1.0 + (FracInc * RAMP(TExer)))
            QFat = ((QFatC / QAdjus) * QCInit) * (1.0 + (FracInc * RAMP(TExer)))
            QLiv = ((QLivC / QAdjus) * QCInit) * (1.0 + (FracInc * RAMP(TExer)))
            QRap = ((QRapC / QAdjus) * QCInit) * (1.0 + (FracInc * RAMP(TExer)))
            QSlw = ((QSlwC / QAdjus) * QCInit) * (1.0 + (FracInc * RAMP(TExer)))
          ELSE
            QAlv = 0.67 * QP * ExerInc
            QBrn = (QBrnC / QAdjus) * QCInit * ExerInc
            QFat = (QFatC / QAdjus) * QCInit * ExerInc
            QLiv = (QLivC / QAdjus) * QCInit * ExerInc
            QRap = (QRapC / QAdjus) * QCInit * ExerInc
            QSlw = (QSlwC / QAdjus) * QCInit * ExerInc
          ENDIF
        ENDIF
      ENDIF
      IF ((T .GT. (TExer+RampUp+LExer)) .AND. (T .LE. (TExer+RampUp+LExer+RampDn))) THEN
        QAlv = 0.67 * QP * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
        QBrn = (QBrnC / QAdjus) * QCInit * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
        QFat = (QFatC / QAdjus) * QCInit * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
        QLiv = (QLivC / QAdjus) * QCInit * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
      ENDIF

```

```

        QRap = (QRapC / QAdjus) * QCInit * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
        QSlw = (QSlwC / QAdjus) * QCInit * (ExerInc - (FracDec * RAMP(TExer+RampUp+LExer)))
    ENDIF
ENDIF
END

! Cardiac Output (L/min)
    QC = QBrn + QFat + QLiv + QRap + QSlw

! ----- PARENT PBPK MODEL -----
! Ramp Up Exposure Concentration from Zero
    IF (AdjConc.AND.(T.GE.StrtExp).AND.(T.LE.(StrtExp+ConcUp))) IncConc = RAMP(StrtExp) / ConcUp

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

! Amount in Mucous (mg)
    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)

! Digestive Tract
! Amount Absorbed (mg)
    RAO = (kAS * ASst) + (kAD * ADu)
    AO = INTEG(RAO, 0.0)

! Amount Excreted (mg)
    RAExc = kTD * ADu
    AExc = INTEG(RAExc, 0.0)

! Amount in Duodenum (mg)
    RADu = (kTSD * ASst) - (kAD * ADu) - (kTD * ADu)
    ADu = INTEG(RADu, 0.0)

```

```

! Amount in Stomach (mg)
  RASt = (kAS * ASt) + (kTSD * ASt)
  ASt = TotDose - INTEG(RASt, 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)) + RAO + Rendo - RAMet
  ALiv = INTEG(RALiv, IALiv)
  CLiv = ALiv / VLiv
  CVLiv = CLiv / PLiv

! Amount of Endogenous Metabolite Produced when Dosing with Metabolite (mg)
  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 (mg)
  RARap = QRap * (CArt - CVRap)
  ARap = INTEG(RARap, IARap)
  CRap = ARap / VRap
  CVRap = CRap / PRap

! Amount in Slowly Perfused Tissue (mg)
  RASlw = QSlw * (CArt - CVSlw)
  ASlw = INTEG(RASlw, IASlw)
  CSlw = ASlw / VSlw
  CVSlw = CSlw / PSlw

! Concentration in Mixed Venous Blood (mg/L)
  CVen = (QBrn*CVBrn + QFat*CVFat + QLiv*CVLiv + QRap*CVRap + QSlw*CVSlw) / QC

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

! Amount in Mucous (mg)
  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 (mg)
AEndo_Met = INTEG(REndo_Met, 0.0)

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

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

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

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

! ----- CHECK MASS BALANCE -----
TDose = INTEG((QAlv*CInh), 0.0) + TotDose
Parent = AMuc + AArt + ABrn + AFat + ALiv + ARap + ASlw + AExh + AUrn + AMet + AExc + ADu &
& + ASt - InitTot - AEndo
Metabolite = AMuc_Met + AArt_Met + ABrn_Met + AFat_Met + ALiv_Met + ARap_Met + ASlw_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 fit the page width and were thus reformatted to fit the page; however, these additional line breaks and space may need to be removed for the M file to run correctly.

Acetone.m

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

MW=58.08;
DS=0.25;
PB=260.0; PMUC=260.0; PBRN=0.69; PFAT=0.44; PLIV=0.58; PRAP=0.69; PSLW=0.7;
VMAXC=3.5/60.0; KM=10.0; KFC=0.0;
CLURC=0.004/60.0; KURTC=(11.0/27.75)*QPC;
CENDO=0.5; RENDOC=0.207/60.0;
KAD=8.0/60.0; KAS=1.0/60.0; KTD=0.0; KTS=10.0/60.0;

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; RENDOC_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; KM=0.13; KFC=0.0;
CLURC=0.0; KURTC=0.0;
CENDO=0.0; RENDOC=0.0;
KAD=0.0; KAS=0.0; KTD=0.0; KTS=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; RENDOC_METC=0.0;
```

```
%% Adjusted PFat and PSlw to get better fit
% PSLW=2.5; PFAT=80.0;
```

Distrib Acetone.m

```
% Called through MC_Anal.m in MC_Male_Acetone.m and MC_Female_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);
VMAXC = 0 + 1 * lognrnd(-2.8847, 0.29356, 0.023333, 0.093333);
KM = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLURC = 0 + 1 * lognrnd(-9.6589, 0.29356, 0.000026667, 0.00010667);
KURTC = 0 + 1 * lognrnd(-1.8047, 0.29356, 0.068708, 0.27483);
```

Distrib_Cyclohex.m

% Called through MC_Anal.m in MC_Male_Cyclohex.m and MC_Female_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(-2.6696, 0.29356, 0.028933, 0.11573);
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 and MC_Female_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(1.5663, 0.29356, 2, 8);
KM = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLURC = 0 + 1 * lognrnd(-9.6589, 0.29356, 0.000026667, 0.00010667);
KURTC = 0 + 1 * lognrnd(-1.8047, 0.29356, 0.068708, 0.27483);
```

Distrib_IPA.m

% Called through MC_Anal.m in MC_Male_Acetone_from_IPA_Only.m and
% MC_Female_Acetone_from_IPA_Only.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(1.5663, 0.29356, 2, 8);
KM = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLURC = 0 + 1 * lognrnd(-9.6589, 0.29356, 0.000026667, 0.00010667);
KURTC = 0 + 1 * lognrnd(-1.8047, 0.29356, 0.068708, 0.27483);
```

```
PB_MET = 0 + 1 * lognrnd(5.5557, 0.099751, 208, 312);
PMUC_MET = 0 + 1 * lognrnd(5.5411, 0.19804, 156, 364);
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(-2.8847, 0.29356, 0.023333, 0.093333);
KM_MET = 0 + 1 * lognrnd(2.2595, 0.29356, 4, 16);
CLUR_METC = 0 + 1 * lognrnd(-9.6589, 0.29356, 0.000026667, 0.00010667);
KURT_METC = 0 + 1 * lognrnd(-1.8047, 0.29356, 0.068708, 0.27483);
```

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(0.25833, 0.02325, 0.21183, 0.30483);
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 and MC_Female_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(-2.5688, 0.29356, 0.032, 0.128);
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
end

```

Fit_Dose_Alt_Alg.m

% Alternate dose fitting algorithm -- uses interval halving

% Find doses that bound the target endpoint value

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

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

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

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

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

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

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

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

start @NoCallback
TCHNG
STRTEXP
CONC
CONC_MET
```

```

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

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

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

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

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

    if NumAttempt > 50
        break;
    end
end
end

```

FitAllDoses.m

% Called in FitDoses_Acetone_Only.m, FitDoses_Acetone_from_IPA_Only.m, FitDoses_Cyclohexane.m,
 % FitDoses_IPA_400ppb.m and FitDoses_Toluene.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
    end
end

```

```

%      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(_arap) min(_aslw) min(_cven) min(_amuc_met)
               min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met)
               min(_afat_met) min(_aliv_met) min(_amet_met) min(_arap_met)
               min(_aslw_met) min(_cven_met)];
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;
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) == 0.5
%          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));

```

FitAllDoses_Met.m

```
% Called in FitDoses_Acetone_and_IPA.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(_arap) min(_aslw) min(_cven)
                min(_amuc_met) min(_aexh_met) min(_aart_met) min(_aurn_met)
                min(_abrn_met) min(_afat_met) min(_aliv_met) min(_amet_met)
                min(_arap_met) min(_aslw_met) min(_cven_met)];
            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;
            fitdoses(i,j+1) = CONC;
            fitdoses(i,j+2) = CONC_MET;
            fitdoses(i,j+3) = CENDPPM;
            fitdoses(i,j+4) = max(_cven);
            fitdoses(i,j+5) = max(_cbrn);
            fitdoses(i,j+6) = CENDPPM_MET;
            fitdoses(i,j+7) = max(_cven_met);
            fitdoses(i,j+8) = max(_cbrn_met);

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

```

%           Move to next start time of exposure for a given length of exposure
%           if TChngList(iter) == 0.5
%               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_and_IPA.m
% Breath exposure runs for Acetone

% Calls FitAllDoses_Met.m

% load @format=model @file=BrExp

% 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
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
CENDO_MET=0.0; RENDO_METC=0.0;

% 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_Met';

% Define list of exposure lengths to be simulated
TChngList = [0.5 1.0 2.0 5.0 15.0 60.0];

% Define list of concentrations for IPA
ConcList = [3400.0 3200.0 3000.0 2800.0 2600.0 2400.0 2200.0 2000.0 1700.0 1600.0 1500.0 1400.0
1300.0 1200.0 1100.0 1000.0 850.0 750.0 650.0 600.0 550.0 500.0 450.0 400.0 350.0
325.0 300.0 275.0 250.0 200.0 175.0 150.0 115.0 100.0 90.0 80.0 70.0 60.0 50.0 35.0
30.0 25.0 20.0 15.0 11.0 9.0 6.0 3.0];

% Initialize arrays and counter
min_tiss = [];

% -----
% MALES -- EXPOSURE TO IPA AND ACETONE -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=84.14; CONC_MET=100.0;

FitAllDoses_Met

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

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

```

```

PlotFitDoses_Met

% -----
% FEMALES -- EXPOSURE TO IPA AND ACETONE -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=67.77; CONC_MET=100.0;

FitAllDoses_Met

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

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

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

PlotFitDoses_Met

FitDoses_Acetone_from_IPA_Only.m
% Breath exposure runs for Acetone

% Calls FitAllDoses.m

% load @format=model @file=BrExp

% 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
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
CENDO_MET=0.0; RENDO_METC=0.0;

% 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 = [0.5 1.0 2.0 5.0 15.0 60.0];

% Initialize arrays and counter
min_tiss = [];

% -----
% MALES -- EXPOSURE TO IPA ONLY -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=84.14; CONC=100.0;

FitAllDoses

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

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_acetone_from_ipa_only_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_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_acetone_from_ipa_only_cendppm.txt' @format=ascii
save cendmet_output @file='fitdoses_male_acetone_from_ipa_only_cendppm_met.txt' @format=ascii

```

```

PlotFitDoses

% -----
% FEMALES -- EXPOSURE TO IPA ONLY -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=67.77; CONC=100.0;

FitAllDoses

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

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_female_acetone_from_ipa_only_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_female_acetone_from_ipa_only_times.txt' @format=ascii
save cendoutput @file='fitdoses_female_acetone_from_ipa_only_cendppm.txt' @format=ascii
save cendmet_output @file='fitdoses_female_acetone_from_ipa_only_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_min_tiss.txt' @format=ascii

PlotFitDoses

FitDoses_Acetone_Only.m
% Breath exposure runs for Acetone

% Calls FitAllDoses.m

% load @format=model @file=BrExp

% 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
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
CENDO=0.0; RENDOC=0.0;

% Define tolerance and target value for endpoint (target for end-exhaled air of 353.706 ppb
% (0.3537 ppm))
Tolerance = 0.000000001; TargetParam = 'CEndPPM'; Target = 0.3537; ConcFit = 'Conc';

% Define list of exposure lengths to be simulated
TChngList = [0.5 1.0 2.0 5.0 15.0 60.0];

% Initialize arrays and counter
min_tiss = [];

% -----
% MALES -- EXPOSURE TO ACETONE ONLY -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=84.14; CONC=100.0;

FitAllDoses

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

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_acetone_only_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_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_acetone_only_cendppm.txt' @format=ascii
```

PlotFitDoses

```
% -----
% FEMALES -- EXPOSURE TO ACETONE ONLY -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
% Set parameters for simulations -- WITHOUT endogenous acetone production
BW=67.77; CONC=100.0;
```

FitAllDoses

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

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_female_acetone_only_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_female_acetone_only_times.txt' @format=ascii
save cendoutput @file='fitdoses_female_acetone_only_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_min_tiss.txt' @format=ascii
```

PlotFitDoses

FitDoses_Cyclohexane.m

```
% Breath exposure simulations for Cyclohexane for males and females
```

```
% Calls FitAllDoses.m
```

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

```
% Set parameters for simulations
Init
ResetDoses
HumanPilot
Cyclohexane
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
```

```
% Define tolerance and target value for endpoint (target for end-exhaled air of 5.314 ppb
(0.005314 ppm))
Tolerance = 0.0000000001; TargetParam = 'CEndPPM'; Target = 0.005314;
ConcFit = 'Conc';
```

```
% Define list of exposure lengths to be simulated
TChngList = [0.5 1.0 2.0 5.0 15.0 60.0];
```

```
% Initialize arrays and counter
min_tiss = [];
```

```
% MALES -----
% Set parameters for simulations
BW=84.14; CONC=0.7;
```

FitAllDoses

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

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_cyclohex_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_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_cyclohex_cendppm.txt' @format=ascii
```

```
PlotFitDoses
```

```
% FEMALES -----
% Set parameters for simulations
BW=67.77; CONC=0.7;
```

```
FitAllDoses
```

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

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_female_cyclohex_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_female_cyclohex_times.txt' @format=ascii
save cendoutput @file='fitdoses_female_cyclohex_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_min_tiss.txt' @format=ascii
```

```
PlotFitDoses
```

FitDoses_IPA_400ppb.m

```
% Breath exposure simulations for IPA for males and females
```

```
% Calls FitAllDoses.m
```

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

```
% 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
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
CENDO_MET=0.0; RENDO_METC=0.0;
```

```
% 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 = [0.5 1.0 2.0 5.0 15.0 60.0];
```

```
% Initialize arrays and counter
min_tiss = [];
```

```
% MALES -----
% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
BW=84.14; CONC=100.0;
```

```
FitAllDoses
```

```
% Save the results of the dose fitting
save fitdoses @file='fitdoses_male_ipa_400ppb.txt' @format=ascii
```

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_ipa_mb_400ppb.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_times_400ppb.txt' @format=ascii
save cendoutput @file='fitdoses_male_ipa_cendppm_400ppb.txt' @format=ascii
save cendmet_output @file='fitdoses_male_ipa_cendppm_met_400ppb.txt' @format=ascii
```

PlotFitDoses

```
% FEMALES -----
% Set parameters for simulations -- WITHOUT endogenous acetone production
% (assume that subtracting pre-flight conc from post-flight accounts for endogenous acetone)
BW=67.77; CONC=100.0;
```

FitAllDoses

```
% Save the results of the dose fitting
save fitdoses @file='fitdoses_female_ipa_400ppb.txt' @format=ascii
```

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_female_ipa_mb_400ppb.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_female_ipa_times_400ppb.txt' @format=ascii
save cendoutput @file='fitdoses_female_ipa_cendppm_400ppb.txt' @format=ascii
save cendmet_output @file='fitdoses_female_ipa_cendppm_met_400ppb.txt' @format=ascii
```

```
% Save the minimum tissue values for males and females to check for validity of simulations
save min_tiss @file='fitdoses_ipa_min_tiss_400ppb.txt' @format=ascii
```

PlotFitDoses

FitDoses_Toluene.m

```
% Breath exposure simulations for Toluene for males and females
```

```
% Calls FitAllDoses.m
```

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

```
% Set parameters for simulations
Init
ResetDoses
HumanPilot
Toluene
TSTOP=80.0; STRTEXP=0.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;
```

```
% 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 = [0.5 1.0 2.0 5.0 15.0 60.0];
```

```
% Initialize arrays and counter
min_tiss = [];
```

```
% MALES -----
% Set parameters for simulations
BW=84.14; CONC=0.7;
```

FitAllDoses

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

```
% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_male_toluene_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_times.txt' @format=ascii
save cendoutput @file='fitdoses_male_toluene_cendppm.txt' @format=ascii
```

PlotFitDoses

```
% FEMALES -----
% Set parameters for simulations
BW=67.77; CONC=0.7;
```

FitAllDoses

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

% Save the minimum and maximum mass balance values
save mb_maxmin @file='fitdoses_female_toluene_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_female_toluene_times.txt' @format=ascii
save cendoutput @file='fitdoses_female_toluene_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_min_tiss.txt' @format=ascii
```

PlotFitDoses

Human.m

```
BW=70.0; QCC=12.89/60.0; QPC=27.75/60.0; 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;

%% Tardif et al. (1997, 1995) Parameters
%% Adjusted QCC value from (18.0/60.0) to (14.4/60.0) so that IPA model scaling by BW to the
%% 0.75 gets same value as Tardiff who uses 0.7
%% Adjusted QPC value from (18.0/60.0/(2/3)) to (14.4/60.0/(2/3)) so that IPA model scaling by BW
%% to the 0.75 gets same value as Tardiff who uses 0.7
% BW=84.5; QCC=14.4/60.0; QPC=14.4/60.0/(2/3); QFATC=0.05; QLIVC=0.26; QRAPC=0.44; QSLWC=0.25;
% VFATC=0.19; VLIVC=0.026; VRAPC=0.05-VBRNC; VSLWC=0.62; VBODYC=0.8940;

%% Settings from VCCEP toluene document
%% All but BW, QCC and QPC are same as for Tardif et al. (1997, 1995)
%% Adjusted QCC value from 417.60 to 337.7 so that IPA model scaling by BW to the 0.75 gets same
%% value as Tardiff who uses 0.7 but DON'T change value of 417.60 in calculations for
%% fractional blood flows
%% Adjusted QPC value from 417.60 to 337.7 so that IPA model scaling by BW to the 0.75 gets same
%% value as Tardiff who uses 0.7
% BW=70.0;
% QCC=337.7/60.0/(BW^0.75);
% QPC=(337.7/60.0/(BW^0.75))/(2/3);
% QFATC=20.88/417.60; QLIVC=108.58/417.60; QRAPC=183.74/417.60; QSLWC=104.40/417.60;
% VFATC=13.3/BW; VLIVC=1.82/BW; VRAPC=(3.5/BW)-VBRNC; VSLWC=43.4/BW; VBODYC=0.8940;
```

```

%% Settings from Table 1 in Hissink et al. (2009) Cyclohexane model
%% Adjusted QCC value from (20.0/60.0) to (19.1/60.0) so that IPA model scaling by BW to the
%% 0.75 gets same value as Hissink who uses 0.74
%% Value in Table 1 is labeled "alveolar", but simulation matches paper better if used as total
%% ventilation (QPC)
%% Adjusted QPC value from (20.0/60.0) to (19.1/60.0) so that IPA model scaling by BW to the
%% 0.75 gets same value as Hissink who uses 0.74
% BW=79.1; QCC=19.1/60.0; QPC=19.1/60.0/(2/3); QBRNC=0.14; QFATC=0.05; QLIVC=0.25; QRAPC=0.31;
% QSLWC=0.25;
% VALVC=0.0079; VBRNC=0.02; VFATC=0.19; VLIVC=0.026; VRAPC=0.03; VSLWC=0.62; VBODYC=0.8940;

%% Used average of BWs and VFatCs reported in text of paper -- adjusted Vslwc accordingly
%% Subject 1 -- 80.2 kg, 18% body fat
%% Subject 2 -- 64.0 kg, 12.1% body fat
%% Subject 3 -- 93.2 kg, 18.1% body fat
% BW=79.133; VFATC=0.160667; VSLWC=0.649333; VBODYC=0.8940;

```

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; QPC=26.0/60.0; 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=0.0320; VSLWC=0.602;
VBODYC=0.8760;

%% Female body weight
% BW=67.77;

```

Init.m

```

prepare T HOURS MINUTES DAYS CART CALV CALVPPM AEXH CEND CENDPPM PEREND CMIX CMIXPPM PERMIX AMET
prepare CVEN MASSBAL
prepare CART_MET CALVPPM_MET AEXH_MET CENDPPM_MET AMET_MET CVEN_MET METBAL
prepare AMUC AART AURN ABRN AFAT ALIV ARAP ASLW CBRN CFAT CLIV CMUC CRAP CSLW
prepare AMUC_MET AART_MET AURN_MET ABRN_MET AFAT_MET ALIV_MET ARAP_MET ASLW_MET CBRN_MET CFAT_MET
prepare CLIV_MET CMUC_MET CRAP_MET CSLW_MET
prepare A0 AEXC ADU AST

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; KM=10.0; KFC=0.0;
CLURC=0.004/60.0; KURTC=(11.0/27.75)*QPC;
CENDO=0.0; RENDOC=0.0;
KAD=8.0/60.0; KAS=1.0/60.0; KTD=0.0; KTS=10.0/60.0;

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_MET=3.5/60.0; KM_MET=10.0; KF_MET=0.0;
CLUR_MET=0.004/60.0; KURT_MET=(11.0/27.75)*QPC;
CENDO_MET=0.5; RENDOC_MET=0.207/60.0;

```

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
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=15.0; STRTEXP=15.0;
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(_arap) min(_aslw) min(_cven) min(_amuc_met)
                 min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met) min(_afat_met)
                 min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_met) min(_cven_met)];
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(_aurnd) min(_abrn)
    min(_afat) min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)
    min(_amuc_met) min(_aexh_met) min(_aart_met) min(_aurnd_met)
    min(_abrn_met) min(_afat_met) min(_aliv_met) min(_amet_met)
    min(_arap_met) min(_aslw_met) min(_cven_met)];
tot_massbal = _metbal;
if (ChemName == 'Both')
    tot_massbal = addcolsj(tot_massbal, _metbal, @Justification = 'begin');
end

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

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

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

% Check mass balances to make sure simulation is valid
% If simulation is valid, save parameter set, time course for endpoint values,
% minimum tissue values and mass balance values
mins_fd_all = [];
mins_fd_all(:, :) = [mins_fd_all min(_amuc) min(_aexh) min(_aart) min(_aurnd)
    min(_abrn) min(_afat) min(_aliv) min(_amet) min(_arap)
    min(_aslw) min(_cven) min(_amuc_met) min(_aexh_met)
    min(_aart_met) min(_aurnd_met) min(_abrn_met) min(_afat_met)
    min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_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, minimum tissue values and
% mass balance values
else
    MC_BadParams
end

```

```

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

%      If simulation is NOT valid, save failed parameter set, minimum 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 minimum tissue values across all simulations
min_th = min(trans_min_tiss_th);
min_fd = min(trans_min_tiss_fd);
min_fd_all = min(trans_min_tiss_fd_all);

```

```

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

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

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

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

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

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

```

MC_BadParams.m

```

% 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(_arap) min(_aslw) min(_cven) min(_amuc_met)
    min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met) min(_afat_met)
    min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_met) min(_cven_met)];
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_Female_Acetone.m

```
% MC analysis for Acetone exposure -- females -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc = 95.53200316;

% Define gender and chemical being simulated
Gender = 'Female'; 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=67.77; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO=0.0; RENDOC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_female_acetone_baseline.txt' @format=ascii
save mb_maxmin @file='mc_female_acetone_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.000000001; TargetParam = 'CEndPPM'; Target = 0.3537; ConcFit = 'Conc';

% Initialize random seed
seedrnd(316133913, 718438246);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_female_acetone_good_params.txt' @format=ascii
save failed_params @file='mc_female_acetone_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_female_acetone_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_female_acetone_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Female_Acetone_from_IPA_Only.m

```
% MC analysis for Acetone exposure from IPA -- females -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc = 124.6616954;

% Define gender and chemical being simulated
Gender = 'Female'; ChemName = 'Both';

% 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=67.77; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO_MET=0.0; RENDO_METC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_female_acetone_from_ipa_only_baseline.txt' @format=ascii
save mb_maxmin @file='mc_female_acetone_from_ipa_only_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.000000000001; TargetParam = 'CEndPPM_Met'; 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_female_acetone_from_ipa_only_good_params.txt' @format=ascii
save failed_params @file='mc_female_acetone_from_ipa_only_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_female_acetone_from_ipa_only_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_female_acetone_from_ipa_only_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Female_Cyclohex.m

```
% MC analysis for Cyclohexane exposure -- females -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc=0.446181502;

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

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Cyclohexane
BW=67.77; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;

MC_Init

save baseline @file='mc_female_cyclohex_baseline.txt' @format=ascii
save mb_maxmin @file='mc_female_cyclohex_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000000001; TargetParam = 'CEndPPM '; Target = 0.005314;
ConcFit = 'Conc ';

% Initialize random seed
seedrnd(648698137, 504569316);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_female_cyclohex_good_params.txt' @format=ascii
save failed_params @file='mc_female_cyclohex_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_female_cyclohex_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_female_cyclohex_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Female_IPA.m

```
% MC analysis for IPA exposure -- females -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc = 2563.323985;

% Define gender and chemical being simulated
Gender = 'Female'; 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=67.77; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO_MET=0.0; RENDO_METC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_female_ipa_baseline.txt' @format=ascii
save mb_maxmin @file='mc_female_ipa_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(496334872, 3039479);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_female_ipa_good_params.txt' @format=ascii
save failed_params @file='mc_female_ipa_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_female_ipa_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_female_ipa_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Female_Toluene.m

```
% MC analysis for Toluene exposure -- females -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc=0.589506836;

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

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Toluene
BW=67.77; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;

MC_Init

save baseline @file='mc_female_toluene_baseline.txt' @format=ascii
save mb_maxmin @file='mc_female_toluene_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(282341374, 765715922);

MC_Anal

% Save parameters sets generated from Monte Carlo
save good_params @file='mc_female_toluene_good_params.txt' @format=ascii
save failed_params @file='mc_female_toluene_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_toluene_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_toluene_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

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.m

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

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc = 99.76856532;

% 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=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO=0.0; RENDOC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_male_acetone_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_acetone_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.000000001; 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_good_params.txt' @format=ascii
save failed_params @file='mc_male_acetone_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_acetone_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_acetone_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Male_Acetone_from_IPA_Only.m

```
% MC analysis for Acetone exposure from IPA -- males -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc = 131.8143062;

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

% 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=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO_MET=0.0; RENDO_METC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_male_acetone_from_ipa_only_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_acetone_from_ipa_only_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.000000000001; TargetParam = 'CEndPPM_Met'; 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_from_ipa_only_good_params.txt' @format=ascii
save failed_params @file='mc_male_acetone_from_ipa_only_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_acetone_from_ipa_only_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_acetone_from_ipa_only_mb_fail.txt' @format=ascii

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

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

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

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

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

zznubins = sqrt(250);
```

MC_Male_Cyclohex.m

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

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc=0.443672184;

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

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Cyclohexane
BW=84.14; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;

MC_Init

save baseline @file='mc_male_cyclohex_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_cyclohex_baseline_mb.txt' @format=ascii
mb_maxmin = [];

% Define tolerance, target parameter and target value for endpoint
Tolerance = 0.0000000001; 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_good_params.txt' @format=ascii
save failed_params @file='mc_male_cyclohex_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_cyclohex_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_cyclohex_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Male_IPA.m

```
% MC analysis for IPA exposure -- males -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% 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=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CENDO_MET=0.0; RENDO_METC=0.0;
CINT=0.05;

MC_Init

save baseline @file='mc_male_ipa_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_ipa_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_good_params.txt' @format=ascii
save failed_params @file='mc_male_ipa_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_ipa_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_ipa_mb_fail.txt' @format=ascii

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

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

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

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

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

zznumbins = sqrt(250);
```

MC_Male_Toluene.m

```
% MC analysis for Toluene exposure -- males -- fixed and varied exposure
% (fixed exposure is 15 minute exposure 15 minutes into flight)

% Calls MC_Init.m and MC_Anal.m

% load @format=model @file=BrExp

% Concentration for starting point with fitting
StartConc=0.599184545;

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

% Set parameters for simulations
Init
ResetDoses
HumanPilot
Toluene
BW=84.14; CONC=StartConc; TCHNG=15.0; TSTOP=80.0; STRTEXP=15.0; EXPEND=60.0; DOSEINT=90.0;
CINT=0.05;

MC_Init

save baseline @file='mc_male_toluene_baseline.txt' @format=ascii
save mb_maxmin @file='mc_male_toluene_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_good_params.txt' @format=ascii
save failed_params @file='mc_male_toluene_failed_params.txt' @format=ascii
save min_tiss_fail @file='mc_male_toluene_mintiss_fail.txt' @format=ascii
save mb_maxmin_fail @file='mc_male_toluene_mb_fail.txt' @format=ascii

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

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

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

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

% Save the minimum and maximum mass balance values
save mb_maxmin @file='mc_male_toluene_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("-----");
```

PlotFitDoses.m

```
% Called in FitDoses_Acetone_Only.m, FitDoses_Acetone_from_IPA_Only.m, FitDoses_Cyclohexane.m,
% FitDoses_IPA_400ppb.m and FitDoses_Toluene.m

% Shift values in arrays for plotting so there aren't zero values filling in at the top of the
% array columns
for iter = [1 : 6]
    i = 2;
    j = 1 + ((iter-1) * 9);
    while i <= MaxI
        if (fitdoses(i,j) == 0.0)
            fitdoses(i,j) = fitdoses(i-1,j);
            fitdoses(i,j+1) = fitdoses(i-1,j+1);
            fitdoses(i,j+2) = fitdoses(i-1,j+2);
            fitdoses(i,j+3) = fitdoses(i-1,j+3);
            fitdoses(i,j+4) = fitdoses(i-1,j+4);
            fitdoses(i,j+5) = fitdoses(i-1,j+5);
            fitdoses(i,j+6) = fitdoses(i-1,j+6);
            fitdoses(i,j+7) = fitdoses(i-1,j+7);
            fitdoses(i,j+8) = fitdoses(i-1,j+8);
        end
        i = i + 1;
    end
end

set @preference=BackslashEscapes

% Plot results of fit doses versus exposure time
plot1=plot(0, fitdoses(:,1), fitdoses(:,2))
plot(plot1, 1, fitdoses(:,10), fitdoses(:,11))
plot(plot1, 1, fitdoses(:,19), fitdoses(:,20))
plot(plot1, 1, fitdoses(:,28), fitdoses(:,39))
plot(plot1, 1, fitdoses(:,37), fitdoses(:,38))
plot(plot1, 1, fitdoses(:,46), fitdoses(:,47))

pltscript(plot1, "Chart.Header.Text=\\"Fit Dose versus Start of Exposure for Target End-Exhaled
    Air Concentration\\";")
pltscript(plot1, "Chart.SubHeader.Visible=true;")
pltscript(plot1, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
    minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\\"Exposure Concentration (ppm)\\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\";")
pltscript(plot1, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot1, "Chart.Series[1].Title=\\"1 minute exposures\\";")
pltscript(plot1, "Chart.Series[2].Title=\\"2 minute exposures\\";")
pltscript(plot1, "Chart.Series[3].Title=\\"5 minute exposures\\";")
pltscript(plot1, "Chart.Series[4].Title=\\"15 minute exposures\\";")
pltscript(plot1, "Chart.Series[5].Title=\\"60 minute exposures\\";")

% Plot maximum venous blood concentration versus exposure time
plot2=plot(0, fitdoses(:,1), fitdoses(:,4))
plot(plot2, 1, fitdoses(:,10), fitdoses(:,13))
plot(plot2, 1, fitdoses(:,19), fitdoses(:,22))
plot(plot2, 1, fitdoses(:,28), fitdoses(:,31))
plot(plot2, 1, fitdoses(:,37), fitdoses(:,40))
plot(plot2, 1, fitdoses(:,46), fitdoses(:,49))

pltscript(plot2, "Chart.Header.Text=\\"Maximum Venous Blood Concentration versus Start of
    Exposure for Target End-Exhaled Air Concentration at 80
    minutes\\";")
pltscript(plot2, "Chart.SubHeader.Visible=true;")
pltscript(plot2, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
    minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
```

```

pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Maximum Venous Blood Concentration (mg/L)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Start of Exposure (minutes)\";")
pltscript(plot2, "Chart.Series[0].Title=\"30 second exposures\";")
pltscript(plot2, "Chart.Series[1].Title=\"1 minute exposures\";")
pltscript(plot2, "Chart.Series[2].Title=\"2 minute exposures\";")
pltscript(plot2, "Chart.Series[3].Title=\"5 minute exposures\";")
pltscript(plot2, "Chart.Series[4].Title=\"15 minute exposures\";")
pltscript(plot2, "Chart.Series[5].Title=\"60 minute exposures\";")

% Plot maximum brain concentration versus exposure time
plot3=plot(0, fitdoses(:,1), fitdoses(:,5))
plot(plot3, 1, fitdoses(:,10), fitdoses(:,14))
plot(plot3, 1, fitdoses(:,19), fitdoses(:,23))
plot(plot3, 1, fitdoses(:,28), fitdoses(:,32))
plot(plot3, 1, fitdoses(:,37), fitdoses(:,41))
plot(plot3, 1, fitdoses(:,46), fitdoses(:,50))

pltscript(plot3, "Chart.Header.Text=\"Maximum Brain Concentration versus Start of Exposure for  
Target End-Exhaled Air Concentration at 80 minutes\";")
pltscript(plot3, "Chart.SubHeader.Visible=true;")
pltscript(plot3, "Chart.SubHeader.Text=\"Exposure starting at various times between 0 and 60  
minutes -- Last exposure ends at about 60 minutes\";")

pltscript(plot3, "Chart.Axes.Left.Automatic=false;")
pltscript(plot3, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Left.Title.Text=\"Maximum Brain Concentration (mg/L)\";")
pltscript(plot3, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot3, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot3, "Chart.Axes.Bottom.Title.Text=\"Start of Exposure (minutes)\";")
pltscript(plot3, "Chart.Series[0].Title=\"30 second exposures\";")
pltscript(plot3, "Chart.Series[1].Title=\"1 minute exposures\";")
pltscript(plot3, "Chart.Series[2].Title=\"2 minute exposures\";")
pltscript(plot3, "Chart.Series[3].Title=\"5 minute exposures\";")
pltscript(plot3, "Chart.Series[4].Title=\"15 minute exposures\";")
pltscript(plot3, "Chart.Series[5].Title=\"60 minute exposures\";")

set @preference=NoBackslashEscapes

```

PlotFitDoses_Met.m

```

% Called in FitDoses_Acetone_and_IPA.m

% Shift values in arrays for plotting so there aren't zero values filling in at the top of the
% array columns
for iter = [1 : 6]
    i = 2;
    j = 1 + ((iter-1) * 10);
    while i <= MaxI
        if (fitdoses(i,j) == 0.0)
            fitdoses(i,j) = fitdoses(i-1,j);
            fitdoses(i,j+1) = fitdoses(i-1,j+1);
            fitdoses(i,j+2) = fitdoses(i-1,j+2);
            fitdoses(i,j+3) = fitdoses(i-1,j+3);
            fitdoses(i,j+4) = fitdoses(i-1,j+4);
            fitdoses(i,j+5) = fitdoses(i-1,j+5);
            fitdoses(i,j+6) = fitdoses(i-1,j+6);
            fitdoses(i,j+7) = fitdoses(i-1,j+7);
            fitdoses(i,j+8) = fitdoses(i-1,j+8);
            fitdoses(i,j+9) = fitdoses(i-1,j+9);
        end
        i = i + 1;
    end
end
end

```

```
set @preference=BackslashEscapes
```

```
% Plot results of fit doses versus exposure time
plot1=plot(0, fitdoses(:,1), fitdoses(:,3))
plot(plot1, 1, fitdoses(:,11), fitdoses(:,13))
plot(plot1, 1, fitdoses(:,21), fitdoses(:,23))
plot(plot1, 1, fitdoses(:,31), fitdoses(:,33))
plot(plot1, 1, fitdoses(:,41), fitdoses(:,43))
plot(plot1, 1, fitdoses(:,51), fitdoses(:,53))

pltscript(plot1, "Chart.Header.Text=\\"Fit Acetone Dose versus Start of Exposure for Target
End-Exhaled Air Concentration\\";")
pltscript(plot1, "Chart.SubHeader.Visible=true;")
pltscript(plot1, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\\"Exposure Concentration (ppm)\\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\";")
pltscript(plot1, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot1, "Chart.Series[1].Title=\\"1 minute exposures\\";")
pltscript(plot1, "Chart.Series[2].Title=\\"2 minute exposures\\";")
pltscript(plot1, "Chart.Series[3].Title=\\"5 minute exposures\\";")
pltscript(plot1, "Chart.Series[4].Title=\\"15 minute exposures\\";")
pltscript(plot1, "Chart.Series[5].Title=\\"60 minute exposures\\";")

% Plot maximum venous blood concentration versus exposure time
plot2=plot(0, fitdoses(:,1), fitdoses(:,5))
plot(plot2, 1, fitdoses(:,11), fitdoses(:,15))
plot(plot2, 1, fitdoses(:,21), fitdoses(:,25))
plot(plot2, 1, fitdoses(:,31), fitdoses(:,35))
plot(plot2, 1, fitdoses(:,41), fitdoses(:,45))
plot(plot2, 1, fitdoses(:,51), fitdoses(:,55))

pltscript(plot2, "Chart.Header.Text=\\"Maximum IPA Venous Blood Concentration versus Start of
Exposure for Target End-Exhaled Air Concentration at 80
minutes\\";")
pltscript(plot2, "Chart.SubHeader.Visible=true;")
pltscript(plot2, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\\"Maximum Venous Blood Concentration (mg/L)\\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\";")
pltscript(plot2, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot2, "Chart.Series[1].Title=\\"1 minute exposures\\";")
pltscript(plot2, "Chart.Series[2].Title=\\"2 minute exposures\\";")
pltscript(plot2, "Chart.Series[3].Title=\\"5 minute exposures\\";")
pltscript(plot2, "Chart.Series[4].Title=\\"15 minute exposures\\";")
pltscript(plot2, "Chart.Series[5].Title=\\"60 minute exposures\\";")

% Plot maximum brain concentration versus exposure time
plot3=plot(0, fitdoses(:,1), fitdoses(:,6))
plot(plot3, 1, fitdoses(:,11), fitdoses(:,16))
plot(plot3, 1, fitdoses(:,21), fitdoses(:,26))
plot(plot3, 1, fitdoses(:,31), fitdoses(:,36))
plot(plot3, 1, fitdoses(:,41), fitdoses(:,46))
plot(plot3, 1, fitdoses(:,51), fitdoses(:,56))
```

```

pltscript(plot3, "Chart.Header.Text=\\"Maximum IPA Brain Concentration versus Start of Exposure
                                     for Target End-Exhaled Air Concentration at 80
                                     minutes\\";")
pltscript(plot3, "Chart.SubHeader.Visible=true;")
pltscript(plot3, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
                                     minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot3, "Chart.Axes.Left.Automatic=false;")
pltscript(plot3, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Left.Title.Text=\\"Maximum Brain Concentration (mg/L)\\\";")
pltscript(plot3, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot3, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot3, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\\";")
pltscript(plot3, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot3, "Chart.Series[1].Title=\\"1 minute exposures\\";")
pltscript(plot3, "Chart.Series[2].Title=\\"2 minute exposures\\";")
pltscript(plot3, "Chart.Series[3].Title=\\"5 minute exposures\\";")
pltscript(plot3, "Chart.Series[4].Title=\\"15 minute exposures\\";")
pltscript(plot3, "Chart.Series[5].Title=\\"60 minute exposures\\";")

% Plot maximum venous blood concentration versus exposure time
plot4=plot(0, fitdoses(:,1), fitdoses(:,8))
plot(plot4, 1, fitdoses(:,11), fitdoses(:,18))
plot(plot4, 1, fitdoses(:,21), fitdoses(:,28))
plot(plot4, 1, fitdoses(:,31), fitdoses(:,38))
plot(plot4, 1, fitdoses(:,41), fitdoses(:,48))
plot(plot4, 1, fitdoses(:,51), fitdoses(:,58))

pltscript(plot4, "Chart.Header.Text=\\"Maximum Acetone Venous Blood Concentration versus Start
                                     of Exposure for Target End-Exhaled Air Concentration at
                                     80 minutes\\";")
pltscript(plot4, "Chart.SubHeader.Visible=true;")
pltscript(plot4, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
                                     minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot4, "Chart.Axes.Left.Automatic=false;")
pltscript(plot4, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot4, "Chart.Axes.Left.Title.Text=\\"Maximum Venous Blood Concentration (mg/L)\\\";")
pltscript(plot4, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot4, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot4, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot4, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\\";")
pltscript(plot4, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot4, "Chart.Series[1].Title=\\"1 minute exposures\\";")
pltscript(plot4, "Chart.Series[2].Title=\\"2 minute exposures\\";")
pltscript(plot4, "Chart.Series[3].Title=\\"5 minute exposures\\";")
pltscript(plot4, "Chart.Series[4].Title=\\"15 minute exposures\\";")
pltscript(plot4, "Chart.Series[5].Title=\\"60 minute exposures\\";")

% Plot maximum brain concentration versus exposure time
plot5=plot(0, fitdoses(:,1), fitdoses(:,9))
plot(plot5, 1, fitdoses(:,11), fitdoses(:,19))
plot(plot5, 1, fitdoses(:,21), fitdoses(:,29))
plot(plot5, 1, fitdoses(:,31), fitdoses(:,39))
plot(plot5, 1, fitdoses(:,41), fitdoses(:,49))
plot(plot5, 1, fitdoses(:,51), fitdoses(:,59))

pltscript(plot5, "Chart.Header.Text=\\"Maximum Acetone Brain Concentration versus Start of
                                     Exposure for Target End-Exhaled Air Concentration at 80
                                     minutes\\";")
pltscript(plot5, "Chart.SubHeader.Visible=true;")
pltscript(plot5, "Chart.SubHeader.Text=\\"Exposure starting at various times between 0 and 60
                                     minutes -- Last exposure ends at about 60 minutes\\";")
pltscript(plot5, "Chart.Axes.Left.Automatic=false;")
pltscript(plot5, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot5, "Chart.Axes.Left.Title.Text=\\"Maximum Brain Concentration (mg/L)\\\";")
pltscript(plot5, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot5, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot5, "Chart.Axes.Bottom.Maximum=60.0;")
pltscript(plot5, "Chart.Axes.Bottom.Title.Text=\\"Start of Exposure (minutes)\\\";")
pltscript(plot5, "Chart.Series[0].Title=\\"30 second exposures\\";")
pltscript(plot5, "Chart.Series[1].Title=\\"1 minute exposures\\";")

```

```

pltscript(plot5, "Chart.Series[2].Title=\"2 minute exposures\";")
pltscript(plot5, "Chart.Series[3].Title=\"5 minute exposures\";")
pltscript(plot5, "Chart.Series[4].Title=\"15 minute exposures\";")
pltscript(plot5, "Chart.Series[5].Title=\"60 minute exposures\";")

```

```
set @preference=NoBackslashEscapes
```

ResetDoses.m

```

TCHNG=0.0;
STRTEXP=0.0; EXPEND=1.0; DOSEINT=10000.0;
CINT=0.5;
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;
PDOSE=0.0;
CONC_MET=0.0;

```

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; KM=0.55; KFC=0.0;
CLURC=0.0; KURTC=0.0;
CENDO=0.0; RENDOC=0.0;
KAD=0.0; KAS=0.0; KTD=0.0; KTS=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; KUR_METC=0.0;
CENDO_MET=0.0; RENDOC_MET=0.0;

```

```

%% To get better fit
% PB=20.0;

```

```

%% Tardif et al. (1997) Parameters
% PB=15.6; PFAT=1021.0/PB; PLIV=83.6/PB; PRAP=83.6/PB; PSLW=27.7/PB;
% VMAXC=4.8/60.0; KM=0.55;
% PFAT=65.4; PLIV=5.36; PRAP=5.36; PSLW=1.78;
% VMAXC=0.08;

```

```

%% VCCEP Parameters
%% Partitions are the same as for Tardif et al. (1997) except for those listed
%% VMaxC and KM are the same as for Tardif et al. (1997)
% PFAT=65.8; PLIV=2.98; PRAP=2.66; PSLW=1.37;
% VMAXC=116.2/60.0/(BW^0.75);

```

```

%% Tardif et al. (1995) Parameters
%% Tissue partitions are the same as for VCCEP and are different from Tardif et al. (1997)
%% VMaxC and KM are the same as for Tardif et al. (1997) and VCCEP

```

```

% From Eric's version
% PB from Pierce et al., 1996.
% PLu from Abraham, Ibrahim, and Acree (2008).
% PBrn, PFat, and PLiv from Fiserova-Bergerova and Diaz (1986)
% PBRN IS ACTUALLY FROM FISEROVA-BERGEROVA ET AL. (1984) AND IS SHOWN WITH A CALCULATED VALUE
% IN FISEROVA-BERGEROVA AND DIAZ BRAIN/AIR VALUE IN 1986 PAPER IS GIVEN AS 36 BUT IN 1984
% PAPER IS GIVEN AS 36.4 (resulting in PBrn of 2.33 instead of 2.31)
% PRap is the kidney value from Fiserova-Bergerova and Diaz (1986)
% PSlw is the muscle value from Fiserova-Bergerova and Diaz (1986)

```

```
%% Katrizky et al 2005 PCs for comparison
%% PB=15.8; PMUC=ndet; PBRN=2.31; PFAT=61.0; PLIV=3.06; PRAP=ndet; PSLW=ndet; Pmuscle=2.213,
%% Pkidney=1.127
% PB=21.2; PMUC=21.2; PLU=1.5; PBRN=3.6; PFAT=96.2; PLIV=4.8; PRAP=1.8; PSLW=3.5;
```

APPENDIX C

M Files for Validation Figures

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

Hissink.m

```
% Hissink AM et al. 2009. Physiologically based pharmacokinetic modeling of cyclohexane as a
% tool for integrating animal and human test data. International Journal of Toxicology
% 28(6):498-509.
% Data from Figure 6
% 3 male volunteers exposed by inhalation to 875 mg/m3 (~250 ppm) (1 mg/m3 = 0.29 ppm)
% Actual air concentration was 880.9 mg/m3 (~255.46 ppm)
% Plots concentration in blood and exhaled air
% Subject 1 -- 80.2 kg, 18% body fat
% Subject 2 -- 64.0 kg, 12.1% body fat
% Subject 3 -- 93.2 kg, 18.1% body fat

% DATA Hissink1 (Hours, CVen, CEnd)
Hissink1 = [ ...
0.0833 0.101731602 nan
0.1667 0.190476191 nan
0.3333 0.378787879 nan
0.6833 0.367965368 nan
1.25 0.443722944 nan
1.5 0.595238095 nan
2.0 0.606060606 nan
3.0 0.38961039 nan
3.8333 0.854978355 nan
4.0333 nan 0.208208208
4.0833 nan 0.161161161
4.1667 nan 0.141141141
4.25 nan 0.112112112
4.3333 nan 0.088088088
4.4167 nan 0.085085085
4.5 nan 0.088088088
4.75 nan 0.088088088
4.8333 nan 0.065065065
5.0 nan 0.054054054
5.0833 nan 0.042042042
5.5 nan 0.039039039
5.65 nan 0.037037037
6.0 0.090909091 0.031031031
6.15 nan 0.03003003
6.5 nan 0.024024024
6.6333 nan 0.023023023
7.0 nan 0.029029029
7.15 nan 0.017017017
8.0 0.024891775 0.021021021
8.15 nan 0.019019019
9.0 nan 0.017017017
9.1667 nan 0.016016016
10.0 nan 0.014014014
10.133 nan 0.013013013
11.0 nan 0.01001001
11.183 nan 0.011011011
12.0 nan 0.01001001
12.15 nan 0.011011011
12.75 nan 0.01001001
13.0 nan 0.009009009];
```

```
% DATA Hissink2 (Hours, CVen, CEnd)
Hissink2 = [ ...
0.0833 0.270562771 nan
0.1667 0.432900433 nan
0.3333 0.465367965 nan
0.6833 0.584415584 nan
1.0 0.53030303 nan
1.5 0.541125541 nan
2.0 0.714285714 nan
3.0 0.681818182 nan
3.5 0.714285714 nan
3.8333 0.606060606 nan
4.0 0.487012987 nan
4.0333 nan 0.275275275
4.0833 nan 0.195195195
4.1667 0.378787879 0.184184184
4.25 0.346320346 0.184184184
4.3333 0.313852814 0.136136136
4.4167 0.25974026 0.126126126
4.5 0.227272727 0.096096096
4.75 0.173160173 0.082082082
4.8333 nan 0.067067067
5.0 0.135281385 0.056056056
5.0833 nan 0.053053053
5.5 0.08982684 0.032032032
5.65 nan 0.032032032
6.0 0.056277056 0.029029029
6.15 nan 0.025025025
6.5 0.051948052 0.021021021
6.6333 nan 0.024024024
7.0 0.037878788 0.02002002
7.15 nan 0.026026026
8.0 0.025974026 0.013013013
8.15 nan 0.013013013
9.0 0.027056277 0.013013013
9.1667 nan 0.013013013
10.0 0.019480519 0.014014014
10.1333 nan 0.012012012
11.0 0.018398268 0.008008008
11.1833 nan 0.008008008
12.0 nan 0.008008008
12.15 nan 0.008008008
12.75 nan 0.007007007
13.0 nan 0.008008008];
```

```
% DATA Hissink3 (Hours, CVen, CEnd)
Hissink3 = [ ...
0.0833 0.137445887 nan
0.1667 0.303030303 nan
0.3333 0.346320346 nan
0.6833 0.367965368 nan
1.0 0.422077922 nan
1.5 0.562770563 nan
2.0 0.53030303 nan
3.0 0.649350649 nan
3.5 0.670995671 nan
3.8333 0.627705628 nan
4.0 0.378787879 nan
4.0167 nan 0.235235235
4.0833 nan 0.197197197
4.1667 0.313852814 0.158158158
4.25 0.25974026 0.132132132
4.3333 0.324675325 0.108108108
4.4167 0.324675325 0.119119119
4.5 0.324675325 0.1001001
4.75 0.25974026 0.105105105
4.8333 nan 0.081081081
5.0 0.192640693 0.074074074
5.0833 nan 0.053053053
5.5 0.128787879 0.038038038
5.65 nan 0.036036036
```

6.0	0.072510823	0.032032032
6.15	nan	0.028028028
6.5	0.041125541	0.028028028
6.6333	nan	0.007007007
7.0	0.034632035	0.023023023
7.15	nan	0.022022022
8.0	0.028138528	0.021021021
8.15	nan	0.019019019
9.0	0.022727273	0.018018018
9.1667	nan	0.016016016
10.0	0.029220779	0.014014014
10.1333	nan	0.014014014
11.0	0.019480519	0.013013013
11.1833	nan	0.012012012
12.0	0.017316017	0.011011011
12.15	nan	0.01001001
12.75	nan	0.011011011
13.0	nan	0.01001001];

ResetDoses
Human
Cyclohexane

```
% Adjusted QCC value from (20.0/60.0) to (19.1/60.0) so that IPA model scaling by BW to the
% 0.75 gets same value as Hissink who uses 0.74
% Adjusted QPC value from (20.0/60.0/(2/3)) to (19.1/60.0/(2/3)) so that IPA model scaling by BW
% to the 0.75 gets same value as Hissink who uses 0.74
% Adjusted Conc based on actual air concentration value given in text
```

```
BW=79.1;
QCC=19.1/60.0; QPC=19.1/60.0/(2/3); VPR=QPC/QCC; QBRNC=0.14; QFATC=0.05; QLIVC=0.25;
QRAPC=0.31; QSKNC=0.058; QSLWC=0.25;
VALVC=0.0079; VBRNC=0.02; VFATC=0.19; VLIVC=0.026; VMUCC=0.0001; VRAPC=0.03; VSLWC=0.62;
VBODYC=0.8940;
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;
CONC=255.46; TCHNG=240.0; TSTOP=780.0; STRTEXP=0.0; EXPEND=800.0; DOSEINT=800.0;
CINT=0.05;
```

```
% Average parameters for all 3 subjects
% VFatC adjusted to be average of 3 volunteers (adjusted VSLWC accordingly)
BW=79.133; VFATC=0.161; VSLWC=0.62+0.19-VFATC; VBODYC=0.8940;
```

```
%% Adjusted PFat and PSLw to get better fit
% PSLW=2.5; PFAT=80.0;
```

```
%% Subject 1 -- 80.2 kg, 18% body fat
% BW=80.2; VFATC=0.18; VSLWC=0.62+0.19-VFATC; VBODYC=0.8940;
```

```
start @NoCallback
min_tiss = [];
mins = [];
mins(:, :) = [mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
output = _hours;
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _cend, @Justification = 'begin');
```

```
set @preference=BackslashEscapes
plot1=plot(0, Hissink1(:,1), Hissink1(:,2), 'b+', _hours, _cven, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Hissink et al. (2009) Inhalation of ~250 ppm
Cyclohexane (3 volunteers)\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=0.9;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Cyclohexane Concentration in Venous Blood
(mg/L)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=13.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
plot(plot1, 1, Hissink2(:,1), Hissink2(:,2), 'r+')
```

```

plot(plot1, 1, Hissink3(:,1), Hissink3(:,2), 'g+')

plot2=plot(0, Hissink1(:,1), Hissink1(:,3), 'b+', _hours, _cend, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Hissink et al. (2009) Inhalation of ~250 ppm
                  Cyclohexane (3 volunteers)\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Left.Maximum=0.7;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Cyclohexane Concentration in End-Exhaled Air
                  (mg/L)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=13.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
plot(plot2, 1, Hissink2(:,1), Hissink2(:,3), 'r+')
plot(plot2, 1, Hissink3(:,1), Hissink3(:,3), 'g+')

% Simulation to plot black square to indicate end of exposure
TCHNG=240.0; TSTOP=240.5;
start @NoCallback
mins = [];
mins(:, :)=[mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrnr) min(_afat) min(_aliv)
            min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
save min_tiss @file='Hissink_min_tiss.txt' @format=ascii

output = addcolsj(output, _hours, @Justification = 'begin');
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _cend, @Justification = 'begin');
save output @file='Hissink_output.txt' @format=ascii

plot(plot2, 1, HOURS, CEND, 'k+')
set @preference=NoBackslashEscapes

```

Kum3Ace.m

```

% Kumagai S, Oda H, Matsumaga I, Kosaka H, and Akasaka S. 1999. Uptake of 10 polar organic
% solvents during short-term respiration. Toxicological Sciences 48:255-263.
% Data from Figure 3 - acetone
% 4 male volunteers with an average body weight of 60.5 kg were exposed by inhalation to 100 ppm
% acetone for 10 minutes
% Dead space was 0.3
% Plots concentration in end-exhaled air or mixed exhaled air as percent versus time in minutes

```

```

% DATA Kum3Ace (Minutes, PerEnd, PerMix)

```

```

Kum3AceDat = [ ...
0.1    18.728    nan
0.5    27.077    37.813
0.75   27.808    nan
1.0    28.751    nan
1.5    29.615    44.602
1.75   29.023    nan
2.0    28.955    nan
2.5    29.592    44.892
2.85   29.979    nan
3.25   30.516    nan
3.5    30.967    46.202
3.85   30.631    nan
4.25   29.931    nan
4.5    30.875    46.883
5.0    31.117    nan
5.25   31.033    nan
5.65   31.830    47.300
6.0    30.959    nan
6.35   30.727    nan
6.65   30.804    47.588
7.0    30.847    nan
7.35   30.892    nan
7.65   30.749    47.619
8.0    30.648    nan
8.35   30.355    nan

```

```

8.65    29.837    47.753
9.0     30.749    nan
9.25    30.899    nan
9.65    30.552    47.814
10.0    30.039    nan
10.35   12.680    nan
10.5    4.860     nan
11.0    2.312     nan
11.25   1.776     nan
11.5    1.278     nan
12.0    1.019     nan
12.25   1.120     nan
12.5    0.690     nan
12.85   0.782     nan
13.0    0.717     nan
13.5    0.796     nan
13.85   0.778     nan
14.0    0.780     nan
14.5    0.293     nan
14.85   0.473     nan];

ResetDoses
Human
Acetone
BW=60.5; CONC=100.0; TCHNG=10.0; TSTOP=18.0; STRTEXP=0.0; EXPEND=20.0; DOSEINT=20.0;
CINT=0.006;
start @NoCallback
min_tiss = [];
min_tiss(:)=[min_tiss min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
              min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)];
save min_tiss @file='Kum3Ace_min_tiss.txt' @format=ascii

output = _minutes;
output = addcolsj(output, _perend, @Justification = 'begin');
output = addcolsj(output, _permix, @Justification = 'begin');
save output @file='Kum3Ace_output.txt' @format=ascii

% SET TITLE='Kumagai et al., 1999. Inhalation Acetone'
% SET TITLE(41)='Four Male Volunteers - 100 ppm Acetone '
% SET TITLE(81)='

set @preference=BackslashEscapes
plot1=plot(0, Kum3AceDat(:,1), Kum3AceDat(:,2), 'b+', _minutes, _perend, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Kumagai et al. (1999) Inhalation of 100 ppm Acetone
                  (4 male volunteers)\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=55.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Acetone Concentration in End-Exhaled Air
                  (%)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=16.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Minutes\";")

plot2=plot(0, Kum3AceDat(:,1), Kum3AceDat(:,3), 'b+', _minutes, _permix, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Kumagai et al. (1999) Inhalation of 100 ppm Acetone
                  (4 male volunteers)\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Left.Maximum=55.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Acetone Concentration in Mixed Exhaled Air
                  (%)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=16.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Minutes\";")
set @preference=NoBackslashEscapes

```

Kum3Iso.m

% Kumagai S, Oda H, Matsumaga I, Kosaka H, and Akasaka S. 1999. Uptake of 10 polar organic
% solvents during short-term respiration. Toxicological Sciences 48:255-263.
% Data from Figure 3 - iso-propyl alcohol
% 4 male volunteers with an average body weight of 60.5 kg were exposed by inhalation to 100 ppm
% isopropyl alcohol for 10 minutes
% Dead space was 0.3
% Plots concentration in end-exhaled air or mixed exhaled air as percent versus time in minutes

% DATA Kum3Iso (Minutes, PerEnd, PerMix)

```
Kum3IsoDat = [ ...  
0.1    12.818    nan  
0.5    19.825    27.269  
0.75   23.158    nan  
1.0    25.291    nan  
1.5    26.286    35.794  
1.75   27.247    nan  
2.0    27.963    nan  
2.5    28.227    37.668  
2.85   28.525    nan  
3.25   28.483    nan  
3.5    28.239    38.510  
3.85   29.087    nan  
4.25   28.311    nan  
4.5    28.503    39.303  
4.85   28.413    nan  
5.25   29.132    nan  
5.5    28.808    39.588  
5.85   29.104    nan  
6.25   29.290    nan  
6.5    28.902    39.496  
6.85   29.019    nan  
7.25   29.315    nan  
7.5    29.270    39.916  
8.0    29.246    nan  
8.25   29.228    nan  
8.5    29.202    39.716  
8.85   29.296    nan  
9.25   29.140    nan  
9.5    29.300    41.219  
9.85   29.842    nan  
10.25  18.230    nan  
10.5   11.457    nan  
10.85  8.337     nan  
11.25  5.498     nan  
11.5   4.306     nan  
11.85  3.777     nan  
12.25  2.872     nan  
12.5   2.697     nan  
12.85  2.307     nan  
13.25  1.479     nan  
13.5   1.143     nan  
13.85  1.180     nan  
14.25  0.627     nan  
14.5   0.857     nan  
14.85  0.395     nan];
```

ResetDoses

Human

IPA

BW=60.5; CONC=100.0; TCHNG=10.0; TSTOP=18.0; STRTEXP=0.0; EXPEND=20.0; DOSEINT=20.0;

CINT=0.006;

start @NoCallback

min_tiss = [];

```
min_tiss(:,:)=[min_tiss min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)  
               min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven) min(_amuc_met)  
               min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met) min(_afat_met)  
               min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_met) min(_cven_met)];
```

save min_tiss @file='Kum3Iso_min_tiss.txt' @format=ascii

```

output = _minutes;
output = addcolsj(output, _perend, @Justification = 'begin');
output = addcolsj(output, _permix, @Justification = 'begin');
save output @file='Kum3Iso_output.txt' @format=ascii

% SET TITLE='Kumagai et al., 1999. Inhalation Isopro '
% SET TITLE(41)='Four Male Volunteers - 100 ppm Isopropyl'
% SET TITLE(81)='

set @preference=BackslashEscapes
plot1=plot(0, Kum3IsoDat(:,1), Kum3IsoDat(:,2), 'b+', _minutes, _perend, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Kumagai et al. (1999) Inhalation of 100 ppm Isopropyl
(4 male volunteers)\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=55.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Isopropanol Concentration in End-Exhaled Air
(%)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=16.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Minutes\";")

plot2=plot(0, Kum3IsoDat(:,1), Kum3IsoDat(:,3), 'b+', _minutes, _permix, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Kumagai et al. (1999) Inhalation of 100 ppm Isopropyl
(4 male volunteers)\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Left.Maximum=55.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Isopropanol Concentration in Mixed Exhaled Air
(%)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=16.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Minutes\";")
set @preference=NoBackslashEscapes

```

Lacout.m

```

% Figure 1 in Lacouture et al., 1989
% Human oral ingestion of isopropanol - measured SERUM IPA / ACTONE

```

```

% DATA Lacout (Minutes, Hours, Cven, Cven1)

```

```

LacoutDat1 = [ ...
    30.0    0.5    299.48    146.16
    60.0    1.0    170.12    232.14
    120.0   2.0     62.85    321.03
    240.0   4.0     14.49    346.31];

```

```

LacoutDat2 = [ ...
    30.0    0.5    213.38    116.02
    60.0    1.0    160.98    184.96
    120.0   2.0     66.26    272.59
    240.0   4.0     14.54    340.59];

```

```

LacoutDat3 = [ ...
    30.0    0.5    252.89    110.83
    60.0    1.0    203.81    194.48
    120.0   2.0     76.36    285.33
    240.0   4.0     20.68    312.26];

```

```

ResetDoses

```

```

Human

```

```

IPA

```

```

BW=78.0; PD0SE=218.5; TSTOP=300.0;

```

```

CINT=0.6;

```

```

start @NoCallback

```

```

min_tiss = [];

```

```

min_tiss(:,:)= [min_tiss min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
               min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven) min(_amuc_met)
               min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met) min(_afat_met)
               min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_met) min(_cven_met)
               min(_ao) min(_aexc) min(_adu) min(_ast)];
save min_tiss @file='Lacout_min_tiss.txt' @format=ascii

output = _hours;
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _cven_met, @Justification = 'begin');
save output @file='Lacout_output.txt' @format=ascii

% SET TITLE='Lacouture et al., 1989. Oral Isopropanol'
% SET TITLE(41)='Serum Concentration of Isopropanol and '
% SET TITLE(81)='Acetone for 3 Men (about 218.5 mg/kg) '

set @preference=BackslashEscapes
plot1=plot(0, LacoutDat1(:,2), LacoutDat1(:,3), 'b+', _hours, _cven, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Lacouture et al. (1989) Oral Isopropanol Exposure
               (about 218.5 mg/kg) (3 men) \";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=500.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L) (blue=IPA,
               red=acetone)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=5.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
plot(plot1, 1, LacoutDat1(:,2), LacoutDat1(:,4), 'r+', _hours, _cven_met, 'r-')

plot(plot1, 1, LacoutDat2(:,2), LacoutDat2(:,3), 'b+', LacoutDat3(:,1), LacoutDat3(:,3), 'b+')
plot(plot1, 1, LacoutDat2(:,2), LacoutDat2(:,4), 'r+', LacoutDat3(:,1), LacoutDat3(:,4), 'r+')
set @preference=NoBackslashEscapes

```

Monaghan.m

```

% Monaghan MS, Olsen KM, Ackerman BH, Fuller GL, Porter WH, and Pappas AA. 1995. Measurement of
% serum isopropanol and the acetone metabolite by proton nuclear magnetic resonance:
% application to pharmacokinetic evaluation in a simulated overdose model. Clinical
% Toxicology 33:141-149.
% Data from personal correspondance with Dr. Pappas
% Three non-smoking health males from 25 to 45 years of age and weighing between 65 and 85 kg
% were given oral doses of isopropanol (85 kg BW and 322 mg/kg -- 69 or 65 kg BW and
% 329 mg/kg)
% Plots serum concentration in mg/L versus time in minutes or hours

```

```

% DATA Monaghan (Minutes, Hours, CVen, CVen_Met)

```

```

Monaghan1 = [ ...
    120.0    2.0    190.0    390.0
    180.0    3.0    100.0    440.0
    240.0    4.0     37.0    490.0
    360.0    6.0     10.0    460.0
    480.0    8.0      0.0    430.0
    720.0   12.0      0.0    380.0
   1080.0   18.0      0.0    280.0];

```

```

Monaghan2 = [ ...
    10.0    0.1667    480.0     80.0
    20.0    0.3333    730.0    140.0
    40.0    0.6667    560.0    170.0
    60.0    1.0      470.0    240.0
    90.0    1.5      340.0    290.0
   120.0    2.0      220.0    360.0
   180.0    3.0      120.0    450.0
   240.0    4.0       50.0    490.0
   360.0    6.0       28.0    499.0
   480.0    8.0       80.0    450.0
  1440.0   24.0        0.0    250.0];

```

```

Monaghan3 = [ ...
    10.0  0.1667  710.0  80.0
    20.0  0.3333  590.0  130.0
    40.0  0.6667  440.0  170.0
    60.0  1.0     360.0  170.0
    90.0  1.5     270.0  240.0
    120.0 2.0     210.0  320.0
    180.0 3.0     100.0  420.0
    240.0 4.0     36.0   450.0
    360.0 6.0     10.0   430.0
    480.0 8.0     15.0   410.0
    720.0 12.0    10.0   350.0
    1440.0 24.0   0.0    250.0];

ResetDoses
Human
IPA
BW=73.0; PD0SE=326.667; TSTOP=1500.0;
CINT=0.6;
start @NoCallback
min_tiss = [];
min_tiss(:, :)=[min_tiss min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
    min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven) min(_amuc_met)
    min(_aexh_met) min(_aart_met) min(_aurn_met) min(_abrn_met) min(_afat_met)
    min(_aliv_met) min(_amet_met) min(_arap_met) min(_aslw_met) min(_cven_met)
    min(_ao) min(_aexc) min(_adu) min(_ast)];
save min_tiss @file='Monaghan_min_tiss.txt' @format=ascii

output = _hours;
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _cven_met, @Justification = 'begin');
save output @file='Monaghan_output.txt' @format=ascii

% SET TITLE='Monaghan et al., 1995. Oral Isopropanol'
% SET TITLE(41)='Serum Concentration of Isopropanol and '
% SET TITLE(81)='Acetone for 3 Men (about 325 mg/kg dose)'

set @preference=BackslashEscapes
plot1=plot(0, Monaghan1(:,2), Monaghan1(:,3), 'b+', _hours, _cven, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Monaghan et al. (1995) Oral Isopropanol Exposure
    (about 325 mg/kg) (3 men)\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=800.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Venous Concentration (mg/L) (blue=IPA,
    red=acetone)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=25.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
plot(plot1, 1, Monaghan1(:,2), Monaghan1(:,4), 'r+', _hours, _cven_met, 'r-')

plot(plot1, 1, Monaghan2(:,2), Monaghan2(:,3), 'b+', Monaghan3(:,1), Monaghan3(:,3), 'b+')
plot(plot1, 1, Monaghan2(:,2), Monaghan2(:,4), 'r+', Monaghan3(:,1), Monaghan3(:,4), 'r+')
set @preference=NoBackslashEscapes

```

Tardif_1997.m

```
% Simulate human data of Tardif et al. 1997
% 4 adult males, ages 22-47, weight 79-90 kg, non-smokers and no recent occupational exposure
% 7 hour exposure to 17 ppm toluene in a 18.1 m**3 chamber
% Urine collected and analyzed for hippuric acid, the major metabolite of toluene

% Figure 7 and 8 data (minutes, hours, cven, cendppm or calvppm)
Fig7and8_Data = [...
    30.0    0.5    nan        2.40543
    90.0    1.5    nan        3.07582
   150.0    2.5    nan        3.03777
   210.0    3.5    nan        2.53611
   270.0    4.5    nan        2.96308
   330.0    5.5    0.18543    2.92642
   390.0    6.5    0.20194    3.20280
   450.0    7.5    0.08175    1.10146
   480.0    8.0    0.06587    0.81447];

% One standard deviation (N = 4)
Fig7and8_Data_Upper = [...
    30.0    0.5    nan        3.20429
    90.0    1.5    nan        3.82951
   150.0    2.5    nan        3.19430
   210.0    3.5    nan        2.63666
   270.0    4.5    nan        3.10949
   330.0    5.5    0.23459    3.57381
   390.0    6.5    0.23967    3.69697
   450.0    7.5    0.10111    1.21490
   480.0    8.0    0.07888    0.87712];

Fig7and8_Data_Lower = [...
    30.0    0.5    nan        1.60658
    90.0    1.5    nan        2.32213
   150.0    2.5    nan        2.88124
   210.0    3.5    nan        2.43556
   270.0    4.5    nan        2.81668
   330.0    5.5    0.13627    2.27903
   390.0    6.5    0.16421    2.70864
   450.0    7.5    0.06239    0.98803
   480.0    8.0    0.05287    0.75183];

ResetDoses
Human
Toluene

% Adjusted QCC value from (18.0/60.0) to (14.4/60.0) so that IPA model scaling by BW to the
% 0.75 gets same value as Tardiff who uses 0.7
% Adjusted QPC value from (18.0/60.0/(2/3)) to (14.4/60.0/(2/3)) so that IPA model scaling by BW
% to the 0.75 gets same value as Tardiff who uses 0.7
BW=84.5; QCC=14.4/60.0; QPC=14.4/60.0/(2/3); VPR=QPC/QCC;
QFATC=0.05; QLIVC=0.26; QRAPC=0.44-QBRNC; QSLWC=0.25;
VFATC=0.19; VLIVC=0.026; VRAPC=0.05-VBRNC; VSLWC=0.62; VBODYC=0.8940;

CONC=17.0; TCHNG=420.0; TSTOP=720.0; STRTEXP=0.0; EXPEND=800.0; DOSEINT=800.0;
CINT=0.05;
start @NoCallback
min_tiss = [];
min_tiss(:,:)= [min_tiss min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat)
                min(_aliv) min(_amet) min(_arap) min(_aslw) min(_cven)];
save min_tiss @file='Tardif_1997_min_tiss.txt' @format=ascii

output = _hours;
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _cendppm, @Justification = 'begin');
output = addcolsj(output, _calvppm, @Justification = 'begin');
output = addcolsj(output, _cmixppm, @Justification = 'begin');
save output @file='Tardif_1997_output.txt' @format=ascii
```

```

set @preference=BackslashEscapes
% Concentration in Venous Blood (mg/L or ppb*10^3)
plot1=plot(0, Fig7and8_Data(:,2), Fig7and8_Data(:,3), 'b+', _hours, _cven, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Human Exposure to Toluene for 7 Hours\";")
pltscript(plot1, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot1, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.01;")
pltscript(plot1, "Chart.Axes.Left.Maximum=1.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood (mg/L)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=12.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Hours\";")

% Concentration in Exhaled Air (ppm or ppb*10^3)
plot2=plot(0, Fig7and8_Data(:,2), Fig7and8_Data(:,4), 'b+', _hours, _cendppm, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Human Exposure to Toluene for 7 Hours\";")
pltscript(plot2, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot2, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.1;")
pltscript(plot2, "Chart.Axes.Left.Maximum=50.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Toluene in Alveolar Air (ppm)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=12.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
plot(plot2, 1, _hours, _calvppm, 'r-')
% plot(plot2, 1, _hours, _cmixppm, 'g-')
set @preference=NoBackslashEscapes

```

Tardif 1995.m

```

% Simulate human data of Tardif et al. 1995
% 5 volunteers exposed for 7 hours to 50 ppm toluene OR
% for 4 hours to 95 ppm toluene in a 18.1 m**3 chamber

% Figure 2 data (minutes, hours, blood concentration in mg/L, alveolar air concentration in ppm)
Fig2Data = [...
    60.0    1.0    nan    8.65568
    120.0   2.0    nan    9.96902
    180.0   3.0    nan    8.75406
    240.0   4.0    nan    9.28917
    300.0   5.0    nan    9.39474
    390.0   6.5    0.728    9.8
    450.0   7.5    0.311    3.4];

% One standard deviation (N = 5)
Fig2Data_Upper = [...
    390.0   6.5    0.816    10.3
    450.0   7.5    0.373    3.7];

Fig2Data_Lower = [...
    390.0   6.5    0.640    9.3
    450.0   7.5    0.249    3.1];

% Figure 3 data (minutes, hours, blood concentration in mg/L, alveolar air concentration in ppm)
Fig3Data = [...
    60.0    1.0    nan    12.93997
    120.0   2.0    nan    15.29684
    180.0   3.0    nan    14.81029
    210.0   3.5    1.357    16.6
    270.0   4.5    0.636    5.2];

% One standard deviation (N = 5)
Fig3Data_Upper = [...
    120.0   2.0    nan    19.28783
    210.0   3.5    1.624    17.0
    270.0   4.5    0.733    5.3];

```

```

Fig3Data_Lower = [...
120.0 2.0 nan 11.30585
210.0 3.5 1.09 16.2
270.0 4.5 0.539 5.1];

ResetDoses
Human
Toluene

% Adjusted QCC value from (18.0/60.0) to (14.4/60.0) so that IPA model scaling by BW to the
% 0.75 gets same value as Tardiff who uses 0.7
% Adjusted QPC value from (18.0/60.0/(2/3)) to (14.4/60.0/(2/3)) so that IPA model scaling by BW
% to the 0.75 gets same value as Tardiff who uses 0.7
BW=84.5; QCC=14.4/60.0; QPC=14.4/60.0/(2/3); VPR=QPC/QCC; QFATC=0.05; QLIVC=0.26;
QRAPC=0.44-QBRNC; QSLWC=0.25;
VFATC=0.19; VLIVC=0.026; VRAPC=0.05-VBRNC; VSLWC=0.62; VBODYC=0.8940;
PFAT=65.8; PLIV=2.98; PRAP=2.66; PSLW=1.37;

CONC=50.0; TCHNG=420.0; TSTOP=480.0; STRTEXP=0.0; EXPEND=500.0; DOSEINT=500.0;
CINT=0.05;
start @NoCallback
min_tiss = [];
mins = [];
mins(:)=[mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');

output = _hours;
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _calvppm, @Justification = 'begin');

set @preference=BackslashEscapes
% Concentration in Venous Blood (mg/L)
plot1=plot(0, Fig2Data(:,2), Fig2Data(:,3), 'b+', _hours, _cven, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Human Exposure to Toluene for 7 Hours\";")
pltscript(plot1, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot1, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.01;")
pltscript(plot1, "Chart.Axes.Left.Maximum=2.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood (mg/L)\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=8.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Hours\";")

% Concentration in Alveolar Air (ppm)
plot2=plot(0, Fig2Data(:,2), Fig2Data(:,4), 'b+', _hours, _calvppm, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Human Exposure to Toluene for 7 Hours\";")
pltscript(plot2, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot2, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.1;")
pltscript(plot2, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Toluene in Alveolar Air (ppm)\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=8.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Hours\";")

CONC=95.0; TCHNG=240.0; TSTOP=300.0;
start @NoCallback
mins = [];
mins(:)=[mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
save min_tiss @file='Tardif_1995_min_tiss.txt' @format=ascii

output = addcolsj(output, _hours, @Justification = 'begin');
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _calvppm, @Justification = 'begin');

```

```

save output @file='Tardif_1995_output.txt' @format=ascii

% Concentration in Venous Blood (mg/L)
plot3=plot(0, Fig3Data(:,2), Fig3Data(:,3), 'b+', _hours, _cven, 'b-')
pltscript(plot3, "Chart.Header.Text = \"Human Exposure to Toluene for 4 Hours\";")
pltscript(plot3, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot3, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot3, "Chart.Axes.Left.Automatic=false;")
pltscript(plot3, "Chart.Axes.Left.Minimum=0.1;")
pltscript(plot3, "Chart.Axes.Left.Maximum=5.0;")
pltscript(plot3, "Chart.Axes.Left.Title.Text=\"Toluene in Venous Blood (mg/L)\";")
pltscript(plot3, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot3, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Bottom.Maximum=8.0;")
pltscript(plot3, "Chart.Axes.Bottom.Title.Text=\"Hours\";")

% Concentration in Alveolar Air (ppm)
plot4=plot(0, Fig3Data(:,2), Fig3Data(:,4), 'b+', _hours, _calvppm, 'b-')
pltscript(plot4, "Chart.Header.Text = \"Human Exposure to Toluene for 4 Hours\";")
pltscript(plot4, "Chart.Axes.Left.LogarithmicBase=10;")
pltscript(plot4, "Chart.Axes.Left.Logarithmic=true;")
pltscript(plot4, "Chart.Axes.Left.Automatic=false;")
pltscript(plot4, "Chart.Axes.Left.Minimum=1.0;")
pltscript(plot4, "Chart.Axes.Left.Maximum=100.0;")
pltscript(plot4, "Chart.Axes.Left.Title.Text=\"Toluene in Alveolar Air (ppm)\";")
pltscript(plot4, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot4, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot4, "Chart.Axes.Bottom.Maximum=8.0;")
pltscript(plot4, "Chart.Axes.Bottom.Title.Text=\"Hours\";")
set @preference=NoBackslashEscapes

```

Wigauss.m

```

% Wigauss E, Holm S, and Astrand I. 1981. Exposure to acetone - uptake and elimination in man.
% Scand J Work Environ Health 7:84-94.
% QCC vs. QPC values for work loads are from
% Astrand, I. 1983. Effect of physical exercise on uptake, distribution, and elimination of
% vapors in man (Chapter 5). in Modeling of Inhalation Exposure to Vapors: Uptake,
% Distribution, and Elimination. Volume 2. Edited by V. Fiserova-Bergerova, Boca Raton, FL:
% CRC Press, Inc., pp. 107-130.
% Actual inhaled concentrations taken from Table 2

```

```

% Data from Table 3 and Table 5
% Eight healthy men from 22 to 28 years of age were exposed to acetone for 2 hours at
% concentrations of approximately 1309, 712 or 737 mg/m3 (1.309, 0.712 or 0.737 mg/L = 551.1,
% 299.7 or 310.3 ppm)
% Plots concentration in mg/L versus time in minutes

```

```

% DATA Wig3a (Minutes, Hours, CEnd, CArt, CVen, AURN)

```

```

Wig3Dat_1 = [ ...
    30.0    0.5    0.497    7.1    4.3    nan
    60.0    1.0    0.515    9.6    6.6    nan
    90.0    1.5    0.500   12.5    8.4    nan
   120.0    2.0    0.503   14.8    9.9    nan
   1200.0   20.0    nan      nan    nan    8.5];

```

```

% One standard deviation (N=8)

```

```

Wig3Dat_1_Upper = [ ...
    30.0    0.5    0.632764502    8.23137085    5.71421356    nan
    60.0    1.0    0.591367532   10.44852814    8.01421356    nan
    90.0    1.5    0.570710678   13.63137085    9.53137085    nan
   120.0    2.0    0.568053824   15.93137085   11.59705627    nan
   1200.0   20.0    nan          nan          nan      12.74264069];

```

```

Wig3Dat_1_Lower = [ ...
    30.0    0.5    0.361235498    5.96862915    2.885786438    nan
    60.0    1.0    0.438632468    8.75147186    5.185786438    nan
    90.0    1.5    0.429289322   11.36862915    7.268629150    nan
   120.0    2.0    0.437946176   13.66862915    8.202943725    nan
   1200.0   20.0    nan          nan          nan      4.257359313];

```

```

% DATA Wig3b (Minutes, Hours, CEnd, CArt, CVen, AUrn)
Wig3Dat_2a = [ ...
    30.0    0.5    0.258    4.4    3.6    nan
    60.0    1.0    0.244    8.8    7.5    nan
    90.0    1.5    0.231   12.7   11.8    nan
    120.0   2.0    0.256   16.9   15.3    nan
    1200.0  20.0    nan      nan    nan    8.5];

% One standard deviation (N=4)
Wig3Dat_2a_Upper = [ ...
    30.0    0.5    0.314    5.2    4.2    nan
    60.0    1.0    0.282    9.6    8.9    nan
    90.0    1.5    0.271   14.9   15.0    nan
    120.0   2.0    0.288   20.5   18.5    nan
    1200.0  20.0    nan      nan    nan   11.5];

Wig3Dat_2a_Lower = [ ...
    30.0    0.5    0.202    3.6    3.0    nan
    60.0    1.0    0.206    8.0    6.1    nan
    90.0    1.5    0.191   10.5    8.6    nan
    120.0   2.0    0.224   13.3   12.1    nan
    1200.0  20.0    nan      nan    nan    5.5];

% DATA Wig3c (Minutes, Hours, CEnd, CArt, CVen, AUrn)
Wig3Dat_2b = [ ...
    30.0    0.5    0.325    4.8    3.2    nan
    60.0    1.0    0.249    9.0    6.2    nan
    90.0    1.5    0.234   15.9   12.2    nan
    120.0   2.0    0.262   25.4   21.9    nan
    1200.0  20.0    nan      nan    nan   13.4];

% One standard deviation (N=4)
Wig3Dat_2b_Upper = [ ...
    30.0    0.5    0.391    5.4    3.8    nan
    60.0    1.0    0.277    9.6    7.2    nan
    90.0    1.5    0.262   17.9   13.6    nan
    120.0   2.0    0.306   27.8   22.7    nan
    1200.0  20.0    nan      nan    nan   15.0];

Wig3Dat_2b_Lower = [ ...
    30.0    0.5    0.259    4.2    2.6    nan
    60.0    1.0    0.221    8.4    5.2    nan
    90.0    1.5    0.206   13.9   10.8    nan
    120.0   2.0    0.218   23.0   21.1    nan
    1200.0  20.0    nan      nan    nan   11.8];

ResetDoses
Human
Acetone
BW=70.0; QPC=0.37667; VPR=QPC/QCC;
CONC=551.1; TCHNG=120.0; TSTOP=30.0; STRTEXP=0.0; EXPEND=1400.0; DOSEINT=1400.0;
CINT=0.6;
start @NoCallback

QP=9.2; QALV=0.67*QP; VPR=QP/QC; TSTOP=60.0;
continue @NoCallback

QP=8.9; QALV=0.67*QP; VPR=QP/QC; TSTOP=90.0;
continue @NoCallback

QP=9.1; QALV=0.67*QP; VPR=QP/QC; TSTOP=1300.0;
continue @NoCallback
min_tiss = [];
mins = [];
mins(:, :) = [mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
    min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');

output = _minutes;
output = addcolsj(output, _hours, @Justification = 'begin');
output = addcolsj(output, _cend, @Justification = 'begin');

```

```

output = addcolsj(output, _cart, @Justification = 'begin');
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _aurn, @Justification = 'begin');

% SET TITLE='Wigaeus et al., 1981 1.309 mg/L Acetone'
% SET TITLE(41)='2 hour exposure, no work load '
% SET TITLE(81)='uses average QP for each time period '

% SET TITLE='Wigaeus et al., 1981 0.712 mg/L Acetone'
% SET TITLE(41)='2 hour exposure, 0 to 50 W work load '
% SET TITLE(81)='uses average QP for each time period '

% SET TITLE='Wigaeus et al., 1981 0.737 mg/L Acetone'
% SET TITLE(41)='2 hour exposure, 0 to 150 W work load '
% SET TITLE(81)='uses average QP for each time period '

set @preference=BackslashEscapes
plot1=plot(0, Wig3Dat_1(:,1), Wig3Dat_1(:,3), 'b+', _minutes, _cend, 'b-')
pltscript(plot1, "Chart.Header.Text = \"Wigaeus et al. (1981) 2 hour Inhalation Exposure to
1.309 mg/L Acetone with Changing Work Load\\\";")
pltscript(plot1, "Chart.Axes.Left.Automatic=false;")
pltscript(plot1, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Left.Maximum=1.0;")
pltscript(plot1, "Chart.Axes.Left.Title.Text=\"Acetone Alveolar Air Concentration (mg/L)\\\";")
pltscript(plot1, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot1, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot1, "Chart.Axes.Bottom.Maximum=125.0;")
pltscript(plot1, "Chart.Axes.Bottom.Title.Text=\"Minutes\\\";")

plot2=plot(0, Wig3Dat_1(:,1), Wig3Dat_1(:,4), 'b+', _minutes, _cart, 'b-')
pltscript(plot2, "Chart.Header.Text = \"Wigaeus et al. (1981) 2 hour Inhalation Exposure to
1.309 mg/L Acetone with Changing Work Load\\\";")
pltscript(plot2, "Chart.Axes.Left.Automatic=false;")
pltscript(plot2, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Left.Maximum=50.0;")
pltscript(plot2, "Chart.Axes.Left.Title.Text=\"Acetone Arterial Blood Concentration (mg/L)\\\";")
pltscript(plot2, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot2, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot2, "Chart.Axes.Bottom.Maximum=125.0;")
pltscript(plot2, "Chart.Axes.Bottom.Title.Text=\"Minutes\\\";")

plot3=plot(0, Wig3Dat_1(:,1), Wig3Dat_1(:,5), 'b+', _minutes, _cven, 'b-')
pltscript(plot3, "Chart.Header.Text = \"Wigaeus et al. (1981) 2 hour Inhalation Exposure to
1.309 mg/L Acetone with Changing Work Load\\\";")
pltscript(plot3, "Chart.Axes.Left.Automatic=false;")
pltscript(plot3, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Left.Maximum=50.0;")
pltscript(plot3, "Chart.Axes.Left.Title.Text=\"Acetone Venous Blood Concentration (mg/L)\\\";")
pltscript(plot3, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot3, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot3, "Chart.Axes.Bottom.Maximum=125.0;")
pltscript(plot3, "Chart.Axes.Bottom.Title.Text=\"Minutes\\\";")

plot4=plot(0, Wig3Dat_1(:,2), Wig3Dat_1(:,6), 'b+', _hours, _aurn, 'b-')
pltscript(plot4, "Chart.Header.Text = \"Wigaeus et al. (1981) 2 hour Inhalation Exposure to
1.309 mg/L Acetone with Changing Work Load\\\";")
pltscript(plot4, "Chart.Axes.Left.Automatic=false;")
pltscript(plot4, "Chart.Axes.Left.Minimum=0.0;")
pltscript(plot4, "Chart.Axes.Left.Maximum=40.0;")
pltscript(plot4, "Chart.Axes.Left.Title.Text=\"Amount of Acetone in Urine (mg)\\\";")
pltscript(plot4, "Chart.Axes.Bottom.Automatic=false;")
pltscript(plot4, "Chart.Axes.Bottom.Minimum=0.0;")
pltscript(plot4, "Chart.Axes.Bottom.Maximum=21.0;")
pltscript(plot4, "Chart.Axes.Bottom.Title.Text=\"Hours\\\";")

CONC=299.7; QPC=0.425; VPR=QPC/QCC; TSTOP=30.0;
start @NoCallback

QP=22.5; QALV=0.67*QP; VPR=QP/QC; TSTOP=60.0;
continue @NoCallback

```

```

QP=24.5; QALV=0.67*QP; VPR=QP/QC; TSTOP=90.0;
continue @NoCallback

QP=24.4; QALV=0.67*QP; VPR=QP/QC; TSTOP=120.0;
continue @NoCallback

QP=10.3; QALV=0.67*QP; VPR=QP/QC; TSTOP=1300.0;
continue @NoCallback
mins = [];
mins(:, :)=[mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
             min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');

output = addcolsj(output, _minutes, @Justification = 'begin');
output = addcolsj(output, _hours, @Justification = 'begin');
output = addcolsj(output, _cend, @Justification = 'begin');
output = addcolsj(output, _cart, @Justification = 'begin');
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _aurn, @Justification = 'begin');

plot(plot1, 1, Wig3Dat_2a(:,1), Wig3Dat_2a(:,3), 'r+', _minutes, _cend, 'r-')
plot(plot2, 1, Wig3Dat_2a(:,1), Wig3Dat_2a(:,4), 'r+', _minutes, _cart, 'r-')
plot(plot3, 1, Wig3Dat_2a(:,1), Wig3Dat_2a(:,5), 'r+', _minutes, _cven, 'r-')
plot(plot4, 1, Wig3Dat_2a(:,2), Wig3Dat_2a(:,6), 'r+', _hours, _aurn, 'r-')

CONC=310.3; QPC=0.50333; VPR=QPC/QCC; TSTOP=30.0;
start @NoCallback

QP=23.7; QALV=0.67*QP; VPR=QP/QC; TSTOP=60.0;
continue @NoCallback

QP=35.3; QALV=0.67*QP; VPR=QP/QC; TSTOP=90.0;
continue @NoCallback

QP=50.1; QALV=0.67*QP; VPR=QP/QC; TSTOP=120.0;
continue @NoCallback

QP=12.2; QALV=0.67*QP; VPR=QP/QC; TSTOP=1300.0;
continue @NoCallback
mins = [];
mins(:, :)=[mins min(_amuc) min(_aexh) min(_aart) min(_aurn) min(_abrn) min(_afat) min(_aliv)
             min(_amet) min(_arap) min(_aslw) min(_cven)];
min_tiss = addcolsj(min_tiss, mins, @Justification = 'begin');
save min_tiss @file='Wigaeus_min_tiss.txt' @format=ascii

output = addcolsj(output, _minutes, @Justification = 'begin');
output = addcolsj(output, _hours, @Justification = 'begin');
output = addcolsj(output, _cend, @Justification = 'begin');
output = addcolsj(output, _cart, @Justification = 'begin');
output = addcolsj(output, _cven, @Justification = 'begin');
output = addcolsj(output, _aurn, @Justification = 'begin');
save output @file='Wigaeus_output.txt' @format=ascii

plot(plot1, 1, Wig3Dat_2b(:,1), Wig3Dat_2b(:,3), 'g+', _minutes, _cend, 'g-')
plot(plot2, 1, Wig3Dat_2b(:,1), Wig3Dat_2b(:,4), 'g+', _minutes, _cart, 'g-')
plot(plot3, 1, Wig3Dat_2b(:,1), Wig3Dat_2b(:,5), 'g+', _minutes, _cven, 'g-')
plot(plot4, 1, Wig3Dat_2b(:,2), Wig3Dat_2b(:,6), 'g+', _hours, _aurn, 'g-')
set @preference=NoBackslashEscapes

```

LIST OF ABBREVIATIONS AND ACRONYMS

711 HPW	711 th Human Performance Wing
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
TLV	threshold limit value
TWA	time-weighted average
VOC	volatile organic compound