of the model, when the dilution of the alveolar breath by inhaled air was not considered. was statistically significant ($p<0.1$) in all four categories, especially during exposure.

3.4.1.2.4. Optimization of Model Parameters

Four of the selected model parameters, the blood/air, liver/blood, rapid/blood and slow/blood partition coefficients were statistically optimized for the subject using data collected on a single day. The purpose of this calibration was to examine whether improvements in the model prediction of biomonitoring data could be achieved by empirically optimizing the model parameters for the individual subject, compared to the values obtained with default parameters, without additional experimental determination of these parameters or a modification of the model's structure. The optimized values for these four parameters are listed in Appendix II. Two examples of postexposure breath concentrations and the model predictions are presented in Figure 3.14 and 3.15. The mean MAPE of the model predictions for the postexposure data, shown in Table 3.11 (upper section), improved from 2.53 to 2.06 for constant exposure and from 3.14 to 1.78 for variable exposure input when optimized parameter values were used in the simulation. The improvements for the variable exposure group were statistically significant ($p<0.1$). The largest overall error in predicting postexposure breath for any data set was ~25%. This was observed for data set p0310 (Table 3.11, Column 4), which has a MAPE value of 3.26, based on the logarithmic transformation. The 25% error corresponds to the uncertainty in the un-transformed data. Since postexposure breath data were collected more frequently at the beginning of the elimination phase, the breath concentrations collected right after exposure would have had a higher weight in

calculating the agreement of the model with postexposure breath measurements. Therefore, the goodness of fit of the model predictions was also determined separately for the first 20 minutes of the elimination phase. The mean MAPE of the model predictions for this portion of the elimination phase was also improved after using optimized parameters (Table 3.11, lower section). Again, the improvement was statistically significant ($p<0.1$) only for the variable exposure group.

3.4.2. Comparison of The Model Predictions Using CEF Data

3.4.2.1. Sensitivity Analysis

The sensitivity of the model outputs to individual model input parameter was assessed by comparing the fits of model after optimizing each of the parameters to that using the defaults, which are the geometric means of the available literature values. Seven major parameters, specifically blood/air, rapid/blood, liver/blood, slow/blood and fat/blood (PF) partition coefficients, Michaelis-Menten maximum metabolism rate and Michaelis constant, were analyzed. A representative result, from experiment p01106, for the four parameters is shown in Fig. 3.16 and 3.17.

3.4.2.2. Optimization of Parameters

The optimal values for the four parameters, which had a greater impact on the model output, were determined through the statistical optimization process using a pooled data, which includes all six experiments of constant exposures of the CEF study. Data collected within the first 10 minutes during exposure were not used for parameters optimization because the determination of parameter values through optimization,

especially for PB, would be greatly affected by the relatively large number (four data points) of data points in this region, since the increases in breath concentration at the beginning of exposure are much faster than the later period which can not be accounted for by the current PBPK models. Optimized values of 7.98, 2.35, 0.33 and 0.72 were obtained for PB, PS, Vmax and km, respectively.

3.4.2.3. The Model Predictions Using Constant and Variable Exposure Inputs

The fits of model prediction of exhaled breath to data were compared for the two different exposure inputs. All six experiments of the variable exposure settings (3 for each exposure duration) were used for the evaluation. The results are shown in Table 3.13. Two examples of the predictions during exposure are shown in Fig. 3.18 and 3.19, while two examples of the model predictions for the postexposure period are shown in Fig. 3.20 and 3.21.

3.4.2.4. The Prediction of Tissue Concentrations for The Different Exposures

The concentration-time profiles of Perc in the brain (Fig. 3.22, and 3.23) and the accumulative amounts metabolized in the liver (Fig. 3.25) were predicted for the four different exposure scenarios, which have the same total exposures, using the optimized model. The targeted exposure profiles/concentrations (Section 2.2.10.2.) were used as the exposure inputs for each exposure scenario.

Table 3.1 - The breathing-zone Perc air concentrations near the washer/dryer of three laundromats that also contain dry-cleaning operation.

Store	Sequence	Time of Measurement[a]	Air Conc. (mg/m^3)
SN	1[a]	10:15 AM	1.70
	2	10:15 AM	1.60
	3	10:25 AM	1.62
	4	10:32 AM	0.92
HP	1	11:08 AM	0.49
	2	11:08 AM	0.50
	3	11:18 AM	0.18
	4	11:28 AM	0.11
SP	1	11:57 AM	7.65
	2	11:57 AM	7.84
	3	12:06 PM	4.65
	4	12:11 PM	2.88

a measured in a single day
b the first and the second sample for each store are duplicates

Table 3.2 - The experimental data of Perc air and breath concentrations, air/breath ratios and percent absorption during exposure for three field exposure experiments with different exposure durations.

Experiment (exposure duration)	i th[a] data point										
	1	2	3	4	5	6	7	8	9	10	11
p1020 (60 minutes)											
Air conc[b]	0.74	0.68	0.78	1.24	1.34	0.12	0.16	0.16	0.49	0.22	0.14
Breath conc[c]	0.25	0.25	0.34	0.52	0.57	0.24	0.21	0.18	0.23	0.19	0.15
A/B	3.0	2.8	2.3	2.4	2.4	0.5	0.8	0.9	2.1	1.2	1.0
% Absorption[d]	66	60	58	58	45	-62[e]	-22	38	41	7	-
p1208 (45 minutes)											
Air conc	11.4	11.5	10.1	8.18	8.02	12.1	11.8	8.18	26.5		
Breath conc	3.24	2.85	3.07	2.56	2.64	3.26	4.36	2.95	8.18		
A/B	3.5	4.0	3.3	3.2	3.0	3.7	2.7	2.7	3.2		
% Absorption	73	73	69	68	70	68	63	68	-		
p1220 (30 minutes)											
Air conc	15.9	15.8	13.7	6.86	9.25	11.4	11.3	7.77			
Breath conc	3.63	3.82	3.68	2.98	3.15	3.90	4.67	3.05			
A/B	4.4	4.1	3.7	2.3	2.9	2.9	2.4	2.5			
% Absorption	77	75	68	62	66	62	59	-			

a from the beginning of the experiment
b concentration in mg/m^3
c concentration in mg/m^3
d between the current and next measurement
e negative value implies Perc is released through the lungs, not absorbed.

Table 3.3 - The exposure durations, average exposure concentrations and percent absorption of Perc during exposure for the field exposure experiments.

Experiment	Average Exposed Air Conc. ($\mu g/m^3$)	Exposure Duration (minutes)	Mean Percent Absorption (%)[a]	Average Mean Percent Absorption[b]
p1229	10710	30	69	
p0118	9168	30	69	
p0208	42050	30	70	
p0301	32890	30	70	
p0310	5679	30	69	
p0830	1709	30	67	
p1202	4277	30	67	
p1220	9860	30	67	**69±1.3[c] (69±1.3)[d]**
p0124	3036	45	70	
p1103	2644	45	64	
p1110	359.0	45	60	
p1122	2268	45	56	
p1129	673.0	45	37	
p1208	10730	45	69	
p1214	4725	45	69	**61±12 (65±5.7)**
p0106	1813	60	65	
p0131	2127	60	60	
p0216	6860	60	64	
p0322	4411	60	66	
p1020	429.0	60	29	
p1117	3637	60	65	
p0329	2600	60	68	**60±12 (65±2.7)**
			Grand Average[e]	**63±11 (67±4.0)**

a mean percent absorption for an experiment. percent absorption is calculated from [(AUC_A - AUC_B)/AUC_A] × 100

b the average of mean percent absorption for each exposure duration

c mean ± standard deviation

d excluding experiments with sharp decline in air concentration

e the average of mean percent absorption for all experiments

Table 3.4 - The exposure, calculated internal dose, postexposure breath concentrations, and amount and percent Perc expired for the experiments of the field exposure study

Data	Exposure[a] [($\mu g/m^3$) × minutes]	Calculated Internal Dose[b] (μg)	Postexposure Breath Conc. ($\mu g/m^3$)		Amount (μg) and Percent Expired (%)	
			6-minute	90-minute	0-6 minutes	0-400 minutes
p1229	321300	1940	1791	522	186 (6.4)	1407 (48.7)
p0118	275030	1580	1435	416	121 (5.2)	1170 (49.8)
p0208	1261410	6880	5995	1339	690 (6.7)	4857 (47.3)
p0301	986730	4180	3716	1004	260 (4.2)	2816 (45.2)
p0310	170370	722	682	188	69.9 (6.5)	600 (55.7)
p0830	51258	182	216	30.2	19.0 (7.0)	99.8 (36.7)
p1202	128300	-[c]	580	142	-	-
p1220	295800	1190	1135	354	84.6 (4.7)	945 (53.0)
p0124	136620	668	357	135	35.1 (3.5)	283 (28.3)
p1103	118990	480	337	117	31.9 (4.5)	-
p1110	16146	77.8	65.6	-[d]	7.2 (6.2)	-
p1122	102050	547	254	106	18.3 (2.2)	194 (23.7)
p1129	30272	45.4	52.5	-	-	-
p1208	482720	1960	1614	479	142 (4.8)	-
p1214	212630	1080	766	213	52.0 (3.2)	535 (33.3)
p0106	108780	482	228	89.3	9.7 (1.3)	222 (30.8)
p0131	127600	529	353	49.0	28.1 (3.6)	-
p0216	411600	1830	1007	350	70.3 (2.6)	922 (33.9)
p0322	264640	1320	620	147	54.8 (2.8)	417 (21.2)
p1020	25734	79.5	118	66.0	-	-
p1117	218210	1020	628	-	41.4 (2.7)	-
p0329	156000	937	334	123	-	-

a calculated from the average exposure concentration times exposure duration
b calculated from [(AUC_A - AUC_B) × mean alveolar ventilation rate]
c not determined due to missing data or data are too scattered
d not used in the analysis

Table 3.5 - The percent absorption, calculated internal dose and dose index[a] for the two constant exposures with different exposure durations of the CEF study.

Experiment	Percent Absorption (%)	Internal Dose (μg)		Dose Index (m^3/min)
		Calculated[b]	Predicted[c]	
30-minute Constant				
p12195	74.8	1454	1296	.0042
p01046	76.6	1374	1179	.0044
p02146	79.4	1266	1085	.0044
	76.9 ± 2.32[d]	-[e]	-	**.0043 ± .0001**
90-minute Constant				
p01166	65.9	1400	1456	.0036
p02276	69.5	1514	1494	.0038
p01106	67.6	1179	1189	.0037
	67.7 ± 1.80	-	-	**.0037 ± .0001**

a define as calculated internal dose/exposure
b calculated from [(AUC_A - AUC_B) × alveolar ventilation rate]
c predicted using the regression equation shown in Fig. 3.4.a
d mean ± standard deviation
e not determined

Table 3.6 - Values of the coefficients and their standard deviation of the estimate for the tri-exponential decay of postexposure Perc breath concentrations from the experiments of the CEF study.

Experiment[a]	Coefficient Values					
	A	B	C	D	E	F
p12195	0.00240 ± 0.00027	0.122 ± 0.03	0.00165 ± 0.00021	0.0185 ± 0.0035	0.00087 ± 0.00010	0.00362 ± 0.00026
p01046	0.00325 ± 0.00073	0.156 ± 0.06	0.00088 ± 0.00083	0.0385 ± 0.0263	0.00080 ± 0.00006	0.00356 ± 0.00019
p02146	0.00240 ± 0.00031	0.118 ± 0.03	0.00091 ± 0.00037	0.0250 ± 0.0098	0.00065 ± 0.00007	0.00347 ± 0.00024
p01166	0.00128 ± 0.00121	0.630 ± 0.460	0.00090 ± 0.00008	0.0288 ± 0.0055	0.00059 ± 0.00006	0.00306 ± 0.00024
p02276	0.00129 ± 0.00196	0.630 ± 0.720	0.00121 ± 0.00012	0.0287 ± 0.0051	0.00065 ± 0.00006	0.00328 ± 0.00020
p01106	0.00085 ± 0.00112	0.860 ± 0.660	0.00072 ± 0.00005	0.0247 ± 0.0039	0.00055 ± 0.00006	0.00306 ± 0.00031
p03276	0.00450 ± 0.00093	0.390 ± 0.093	0.00192 ± 0.00017	0.0303 ± 0.0046	0.00070 ± 0.00009	0.00361 ± 0.00032
p03196	0.00197 ± 0.00026	0.130 ± 0.034	0.00125 ± 0.00014	0.0139 ± 0.0027	0.00039 ± 0.00008	0.00184 ± 0.00039
p04186	0.00182 ± 0.00026	0.069 ± 0.015	0.00102 ± 0.00021	0.0112 ± 0.0056	0.00068 ± 0.00030	0.00272 ± 0.00076
p05296	0.00038 ± 0.00013	0.280 ± 0.180	0.00093 ± 0.00010	0.0260 ± 0.0054	0.00048 ± 0.00006	0.00226 ± 0.00027
p07036	0.00048 ± 0.00689	0.360 ± 3.930	0.00031 ± 0.00027	0.0295 ± 0.0470	0.00054 ± 0.00019	0.00519 ± 0.00112

a one experiment, p0620, did not converge

b coefficient value ± standard deviation of the estimate

Table 3.7 - The average exposure concentrations and the three elimination half-lives of the tri-phasic exponential decay for the experiments of the CEF study.

Experiment	Average Exposure Conc. (mg/m^3)	Elimination Half-lives (minutes)		
		First	Second	Third
30-minute Constant				
p12195	11.5	5.68	37.5	191
p01046	10.5	4.44	18.0	195
p02146	9.70	5.87	27.7	200
		5.33±0.78[a]	**27.7±9.75**	**195±4.50**
90-minute Constant				
p01166	4.29	1.10	24.1	226
p02276	4.40	1.10	24.1	211
p01106	3.53	0.81	28.1	226
		1.00±0.17	**25.4±2.31**	**221±8.66**
30-minute Variable				
p03196	11.4	5.33	49.9	377
p03276	5.52	1.78	22.9	192
p04186	15.6	10.0	61.3	255
		5.70±4.12	**44.7±19.7**	**275±94.1**
90-minute Variable				
p05296	7.62	2.48	26.7	307
p06206	2.29	-[b]	-	-
p07036	4.72	1.93	23.5	134
		2.21±0.39	**25.1±2.26**	**221±122**

a mean ± standard deviation
b did not converge

Table 3.8 - The area under the postexposure breath Perc concentration curve for the experiments of the CEF study with different exposure scenarios.

Experiment	AUC_B[a]		
	0-12 minutes	0-73 minutes	0-373 minutes
30-minute Constant			
p12195	0.023	0.084	0.200
p01046	0.022	0.064	0.138
p02146	0.021	0.063	0.135
	0.022 ± .001[b]	**0.070 ± .012**	**0.158 ± .037**
90-minute Constant			
p01166	0.011	0.039	0.102
p02276	0.012	0.046	0.117
p01106	0.008	0.032	0.091
	0.010 ± .002	**0.039 ± .007**	**0.103 ± .013**
30-minute Variable			
p03196	0.020	0.062	0.145
p03276	0.024	0.076	0.185
p04186	0.022	0.070	0.153
	0.022 ± .002	**0.069 ± .007**	**0.161 ± .021**
90-minute Variable			
p05296	0.011	0.037	0.097
p06206	0.008	0.022	0.065
p07036	-	0.011	0.053
	0.010 ± .002	**0.023 ± .013**	**0.072 ± .023**

a the area under the postexposure breath curve. Note that all of the breath levels are normalized to the total exposure

b mean ± standard deviation

Table 3.9 - The PBPK model simulation results of the fit of the model to the experimental data of the field Perc exposure study for two different types of exposure input, using the original model parameters, and corrected for method-specific inhaled air contribution.

Data	V/A Ratio[a]	Exposure Input	Mean Absolute Percent Error				
			During Exposure	First 20 min. Postexposure	Post Exposure	Total[b]	
p0301	1.10	Constant	7.91	2.97	2.75	4.65	
		Variable	4.52	3.30	2.70		3.37
p0310	1.12	Constant	6.24	1.20	2.91	4.14	
		Variable	5.04	3.66	3.38		3.99
p1220	1.09	Constant	7.89	2.14	1.94	4.58	
		Variable	4.66	2.95	1.87		3.11
p1208	1.07	Constant	5.81	1.61	2.45	3.96	
		Variable	4.33	4.61	3.56		3.91
p0216	1.23	Constant	5.72	2.25	2.45	3.85	
		Variable	2.79	5.11	4.00		3.48
p1214	1.35	Constant	8.02	3.78	2.69	5.24	
		Variable	2.31	4.56	3.33		2.84
				Column	Average	**4.40**	**3.45**

a Refers to the ratio of total exposures calculated from two different methods. Note that the total analytical uncertainty associated with these ratio is estimated to be ±20%, thus a number do not differ from unity

b The mean absolute percent error for the entire experiment

Table 3.10 - The PBPK model simulation results of the fit of the model to experimental data of the field Perc exposure study for two different types of exposure input, using the original model parameters, but not corrected for method-specific inhaled air contribution.

Data	Exposure Input	Mean Absolute Percent Error				
		During Exposure	First 20 min. Postexposure	Post-Exposure	Total	
p0301	Constant	11.44	3.86	2.88	6.03	
	Variable	8.07	4.19	3.07		4.91
p0310	Constant	9.49	1.90	2.87	5.31	
	Variable	8.43	4.36	3.53		5.33
p1220	Constant	11.24	2.89	2.00	6.11	
	Variable	8.04	3.69	2.02		4.69
p1208	Constant	8.26	2.39	2.70	5.20	
	Variable	6.11	5.39	3.81		4.85
p0216	Constant	8.12	2.60	2.58	4.95	
	Variable	5.55	5.81	4.44		4.92
p1214	Constant	10.65	4.51	2.99	6.65	
	Variable	4.84	5.29	3.78		4.29
			Column	Average	**5.71**	**4.83**

Table 3.11 - Summary of the PBPK model simulation results of the fit of the model to the postexposure data of the field Perc exposure study before and after parameter optimization forconstant and variable exposure inputs.

Data[a]	V/A Ratio	Mean Absolute Percent Error			
		Constant Exposure		Variable Exposure	
		default Parameters[b]	optimized Parameters[c]	default Parameters	optimized Parameters
I. Entire Postexposure					
p0301	1.10	2.75	1.82	2.70	1.24
p0310	1.12	2.91	3.26	3.38	2.40
p1220	1.09	1.94	2.05	1.87	1.29
p1208	1.07	2.45	2.22	3.56	1.90
p0216	1.23	2.45	1.95	4.00	2.24
p1214	1.35	2.69	1.08	3.33	1.61
		2.53 ± 0.14[d]	**2.06 ± 0.29**	**3.14 ± 0.31**	**1.78 ± 0.20**
II. First 20-minute Postexposure					
p0301	1.10	2.97	1.10	3.30	0.79
p0310	1.12	1.20	1.42	3.66	1.62
p1220	1.09	2.14	1.19	2.95	0.86
p1208	1.07	1.61	1.76	4.61	2.21
p0216	1.23	2.25	1.40	5.11	2.19
p1214	1.35	3.78	0.81	4.56	1.09
		2.33 ± 0.38	**1.28 ± 0.13**	**4.03 ± 0.35**	**1.46 ± 0.26**

a experiment p0301, p0310 and p1220 were 30-minute exposures; experiment p1208 and p0216 were 45-minute exposures; experiment p1214 was 60-minute exposure in a dry-cleaning store

b refers to the use of the same values as in Rao & Brown's work

c refers to the use of the optimized values

d mean ± standard deviation

Table 3.12 - The percent prediction errors between the model prediction and postexposure data using variable exposure input and default model parameters for two field Perc exposure experiments.

Time after exposure (min.)	Percent Error[a]	
	Experiment p0301[b]	Experiment p0310
3	-2.94	-3.81
6	-2.86	-3.71
11	-2.97	-3.98
16	-4.41	-3.15
31	-2.58	-1.99
61	-2.65	-0.86
90	-1.56	-0.91
150	-0.91	2.01
240	-0.33	3.08
360	4.53	4.78
480	3.97	5.63
600	2.77	6.59

a calculated from [100 × (Predicted-Observed)/Observed]. Note that all data and model prediction are in logarithmic unit, therefore a negative value indicates that the breath concentration is over-predicted by the model

b experiment p0301 and p0310 were 30-minute exposures in a dry-cleaning store

Table 3.13 - The PBPK model simulation results of the fit of the model to experimental data of the controlled Perc exposure study between two different types of exposure input using the optimized model.

Experiment	Exposure Input	Mean Absolute Percent Error				
		During Exposure	First 20 min. Postexposure	Post Exposure	Total[a]	
I. 30-minute Constant						
p12195	Constant[b]	4.16	1.80	2.66	3.23	
p01046	Constant	4.47	3.44	1.87	2.91	
p02146	Constant	3.96	3.88	2.11	2.81	
II. 90-minute Constant						
p01106	Constant	2.18	1.80	1.27	1.73	
p01166	Constant	2.32	2.02	1.26	1.79	
p02276	Constant	2.04	2.25	1.25	1.59	
III. 30-minute Variable						
p03196	Constant	13.4	4.50	2.57	7.00	
	Variable[c]	5.36	3.31	2.38		3.60
p03276	Constant	12.2	1.85	1.62	5.94	
	Variable	3.48	1.42	1.55		2.34
p04186	Constant	14.0	2.78	4.23	8.23	
	Variable	5.42	2.76	4.35		4.79
IV. 90-minute Variable						
p05296	Constant	8.03	3.06	2.18	4.57	
	Variable	3.52	3.36	2.23		2.76
p06206	Constant	5.42	6.30	5.49	5.46	
	Variable	2.55	6.57	5.58		4.07
p07036	Constant	4.24	10.0	10.1	7.76	
	Variable	2.49	10.1	10.0		7.00

a the mean absolute percent error for the entire experiment
b time-weighted average air concentration
c actual profiles of exposure air concentration

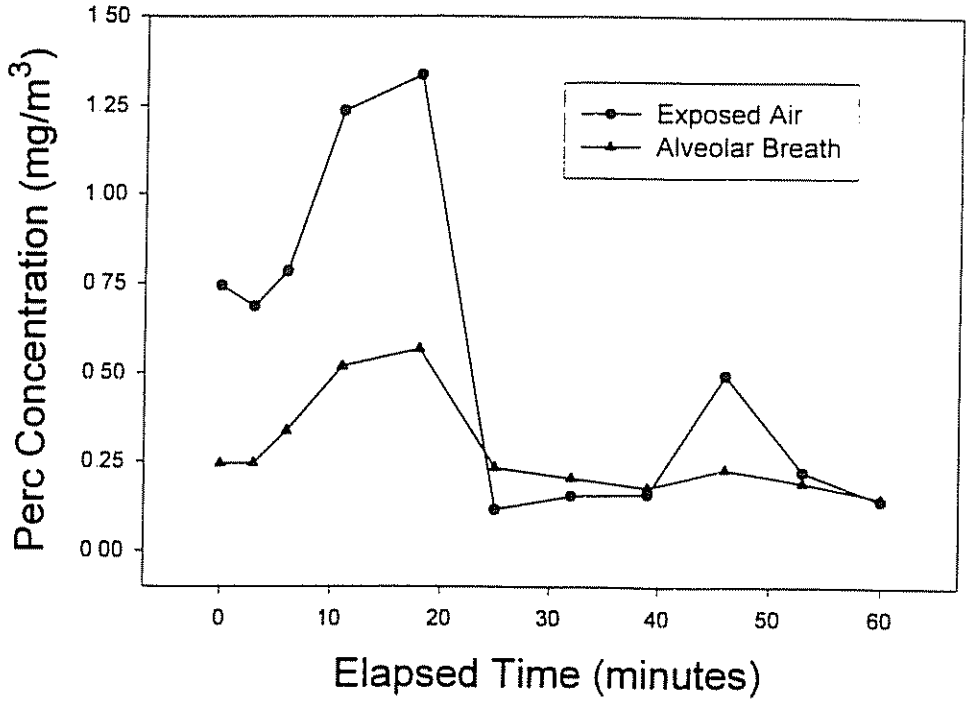

Figure 3.1 - The exposure air and exhaled breath concentration during a 60-minute field exposure (experiment p1020) at the front counter of a dry-cleaning store. Linear concentration change between two adjacent data points was assumed.

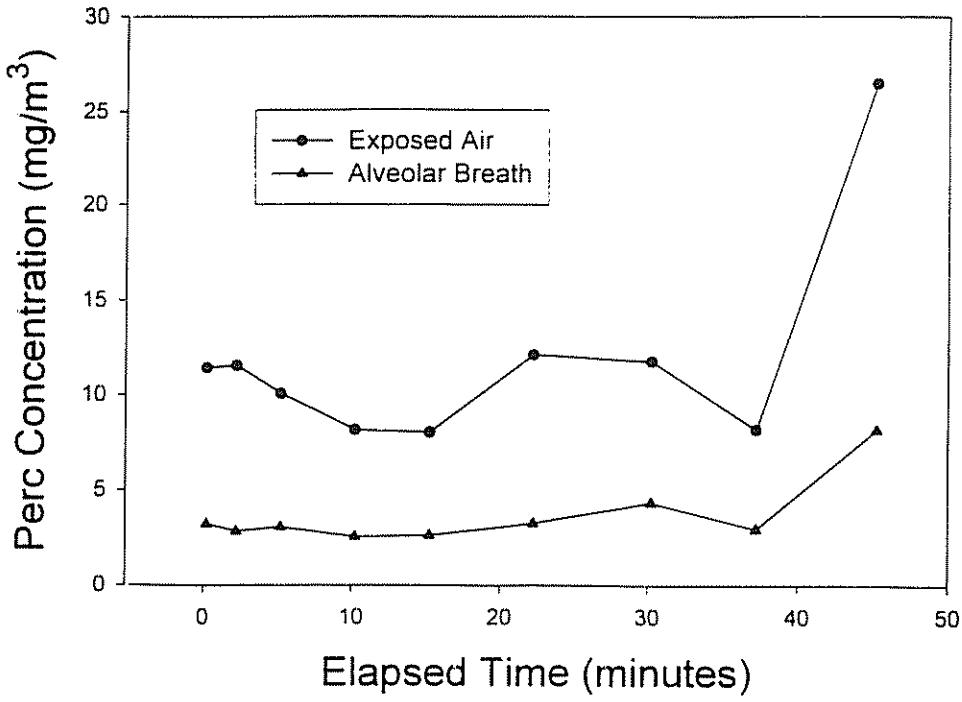

Figure 3.2 - The exposure air and exhaled breath concentration during a 45-minute field exposure (experiment p1208) at the front counter of a dry-cleaning store. Linear concentration change between two adjacent data points was assumed.

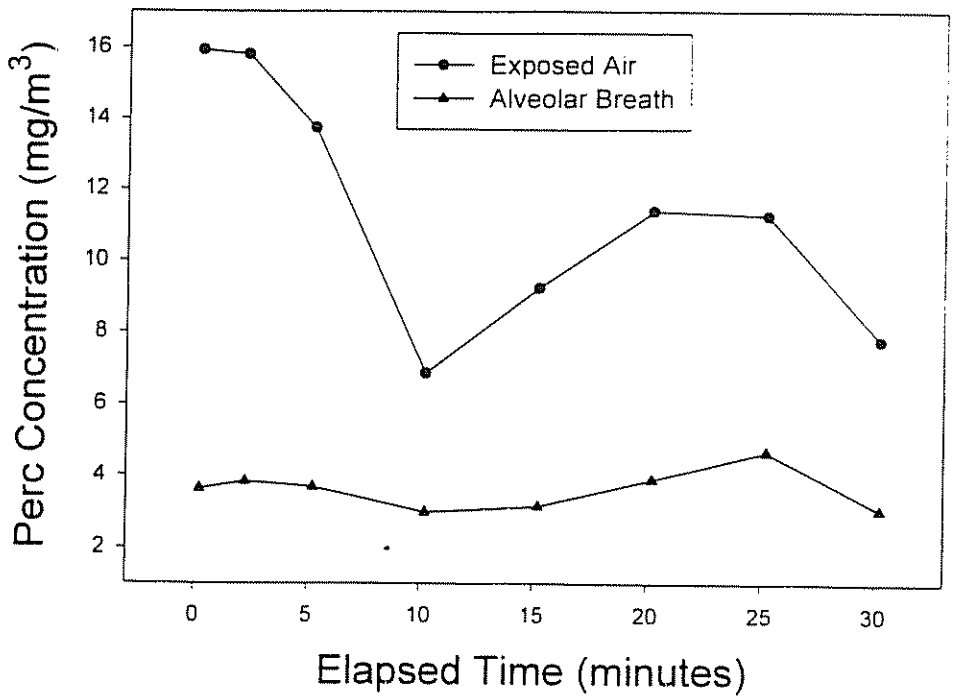

Figure 3.3 - The exposure air and exhaled breath concentration during a 30-minute field exposure (experiment p1220) at the front counter of a dry-cleaning store. Linear concentration change between two adjacent data points was assumed.

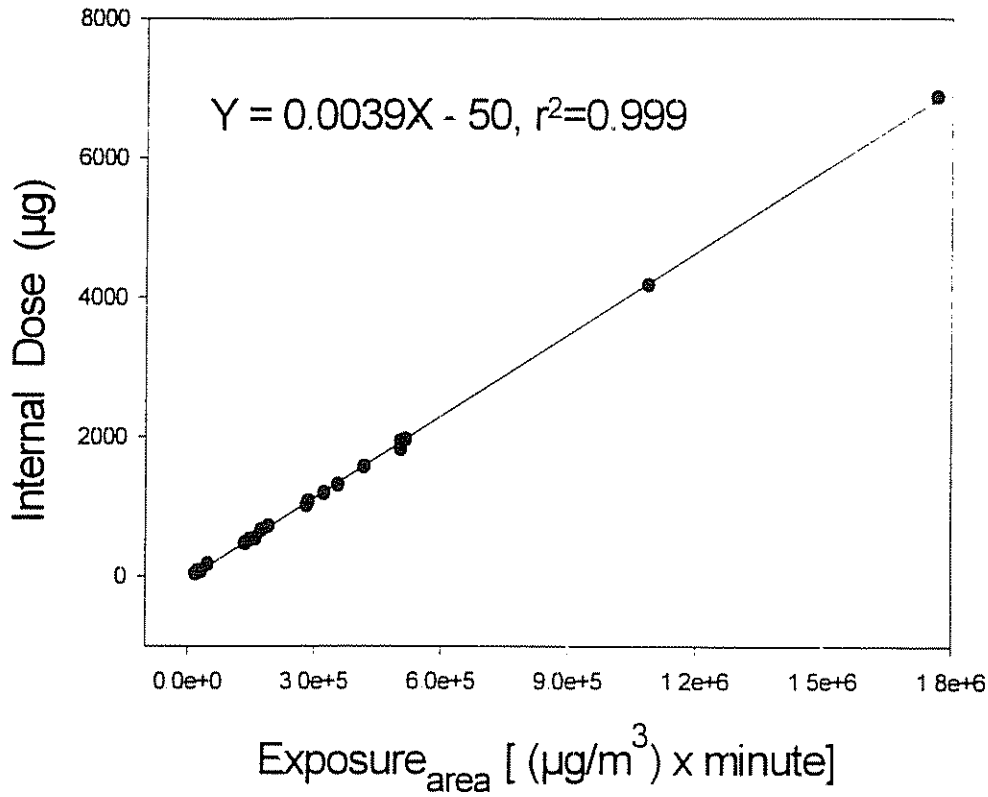

Figure 3.4.a - The correlation and regression plot between the internal doses calculated from the field Perc exposure study and the total exposures estimated from the area under the temporal short-term air measurements.

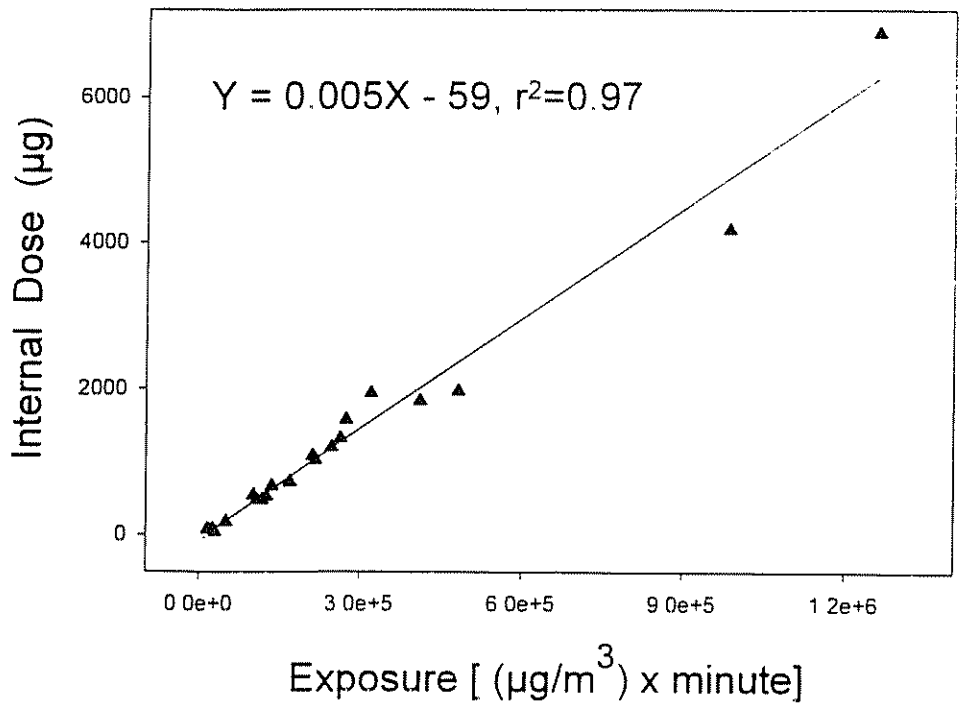

Figure 3.4.b - The correlation and regression plot between the internal doses calculated from the field Perc exposure study and the total exposures calculated from the product of average exposure air concentration and exposure duration.

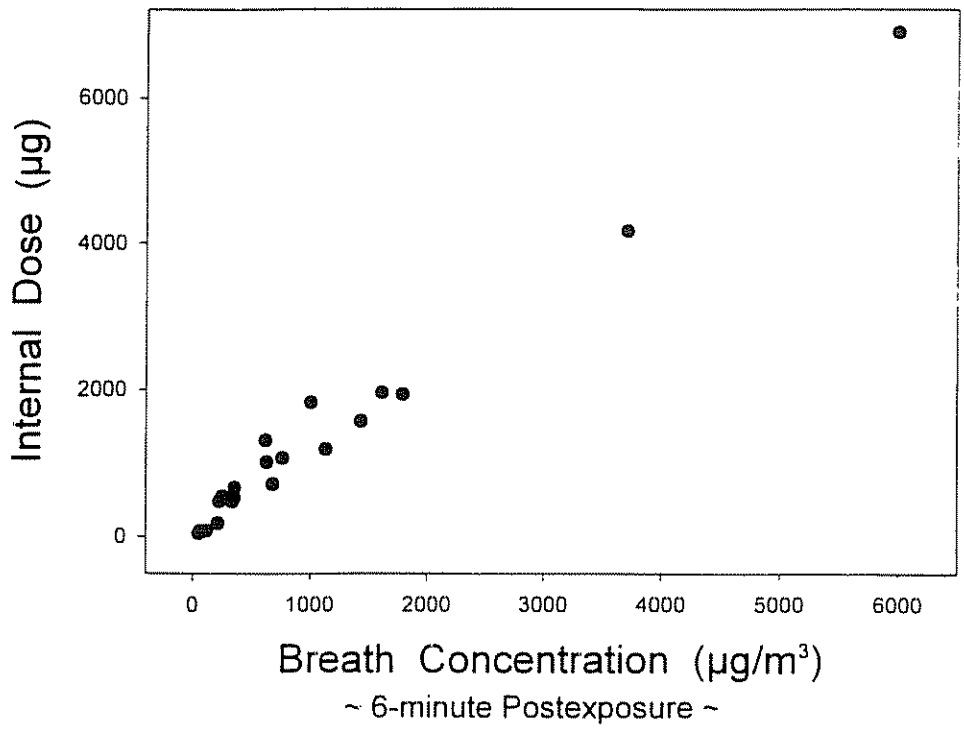

Figure 3.5 - The scatter plot between the internal dose and breath concentration measured at 6-minute postexposure for the field Perc exposure study

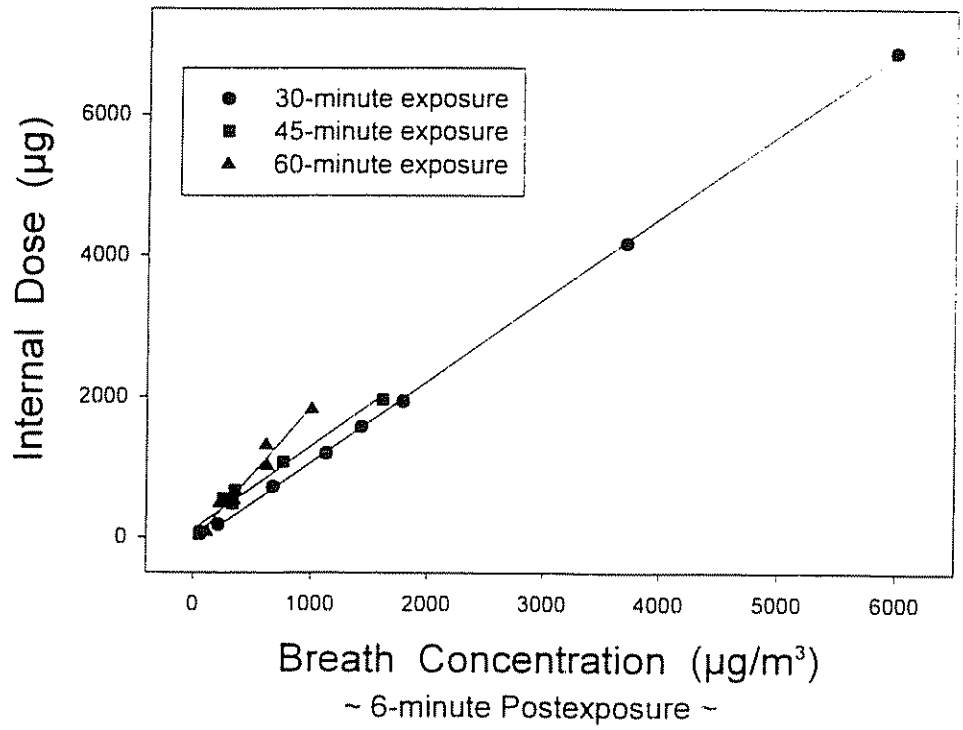

Figure 3.6 - The correlation and regression plot between the internal doses and breath concentrations measured at 6-minute postexposure for the field Perc exposure study, with the three different exposure durations indicated.

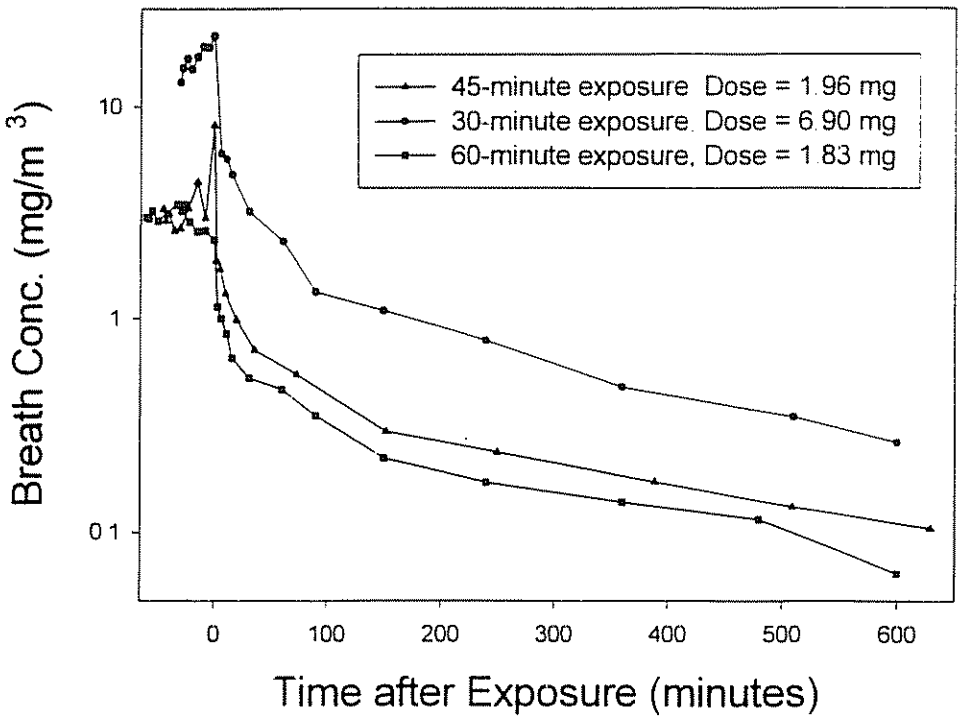

Figure 3.7 - The Breath Perc concentrations during and after exposure for three field exposure experiments with different exposure duration and resulting internal dose. Experiment p0208 (●), p1208 (▲) and p0216 (■). Time zero is the end of the exposure.

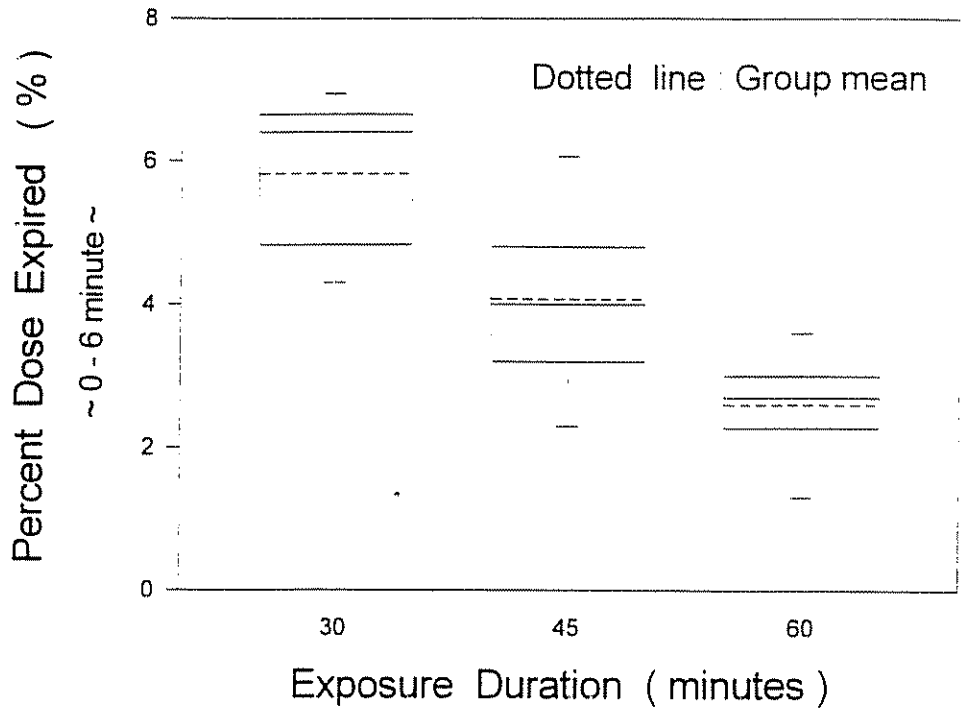

Figure 3.8 - The box plot of the percent dose expired for up to 6 minutes post exposure for the Perc field exposure experiments for three exposure durations. The dotted lines inside the boxes represent the group means.

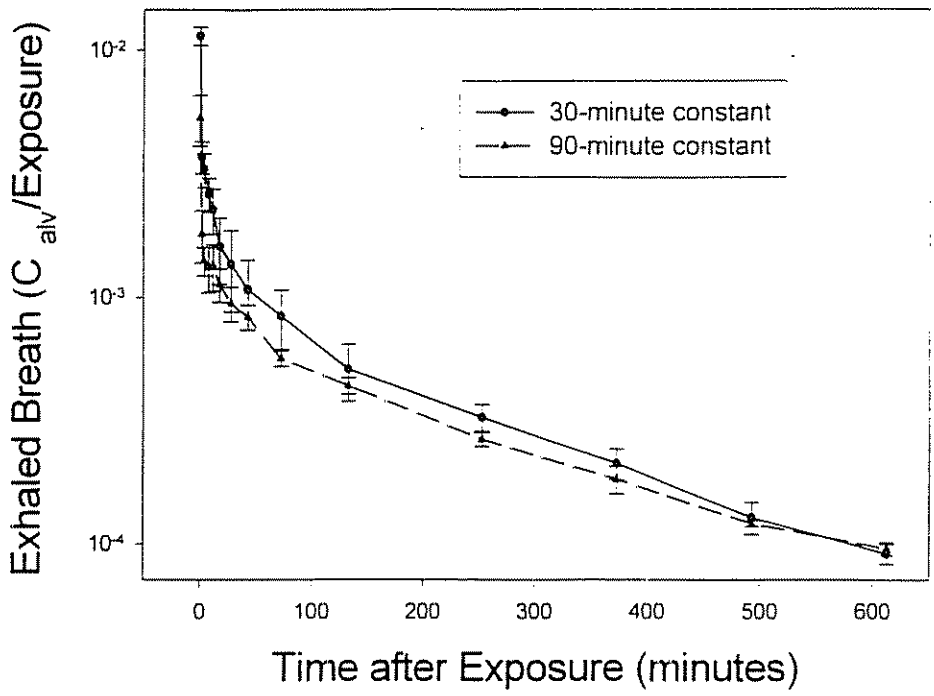

Figure 3.9 - The postexposure breath Perc levels for the 30- and 90-minute constant exposures of the controlled exposure study. Alveolar breath concentrations (C_{alv}) were normalized to the exposure by dividing it by the product of average exposure air concentration and exposure duration. Vertical bars indicate standard deviations of the means of triplicate experiments.

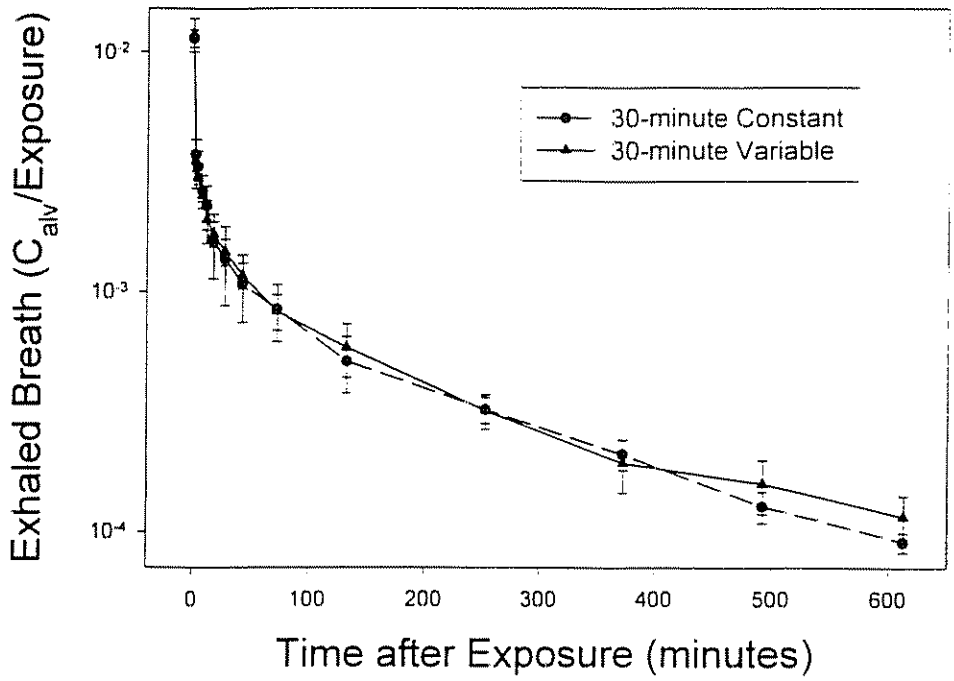

Figure 3.10 - The postexposure breath Perc levels for the two different exposure patterns of the 30 minutes exposure of the controlled exposure study. Alveolar breath concentrations (C_{alv}) were normalized to the exposure by dividing it by the product of average exposure air concentration and exposure duration. Vertical bars indicate standard deviations of the means of triplicate experiments.

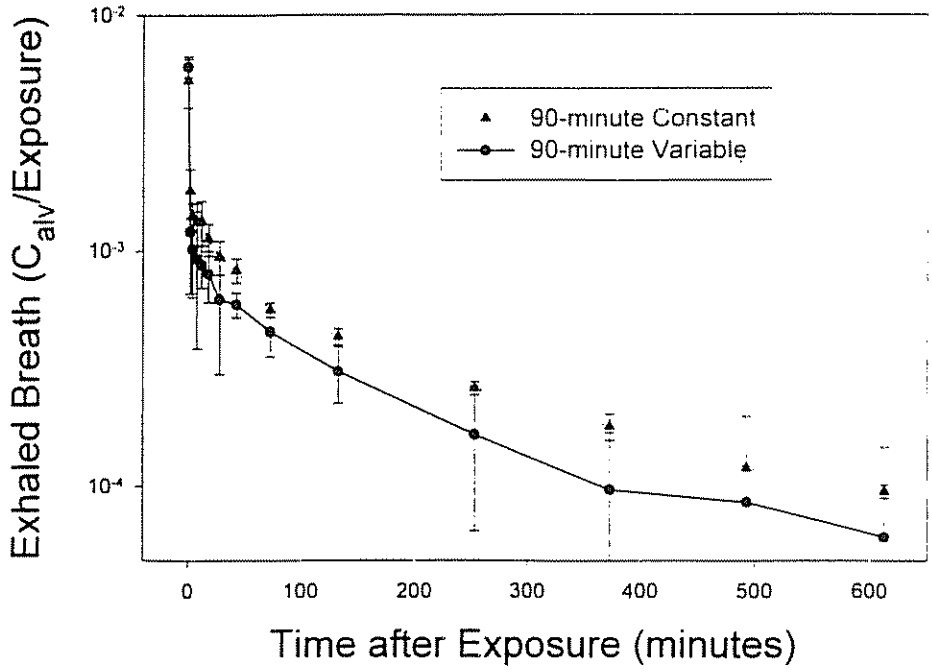

Figure 3.11 - The postexposure breath Perc levels for the two different exposure patterns of the 90 minutes exposure of the controlled exposure study. Alveolar breath concentrations (C_{alv}) were normalized to the exposure by dividing it by the product of average exposure air concentration and exposure duration. Vertical bars indicate standard deviations of the means of triplicate experiments.

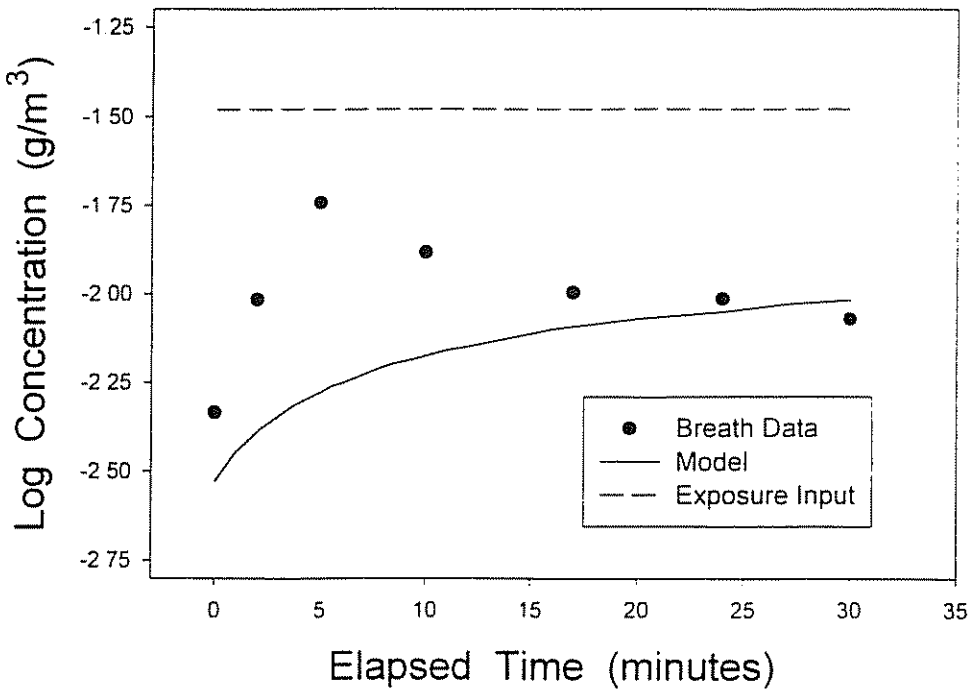

Figure 3.12 - The experiment data and PBPK model prediction of breath concentrations during exposure for a 30-minute Perc field exposure experiment (p0301) using the default PBPK model and an integrated exposure air concentration as the model exposure input (constant)

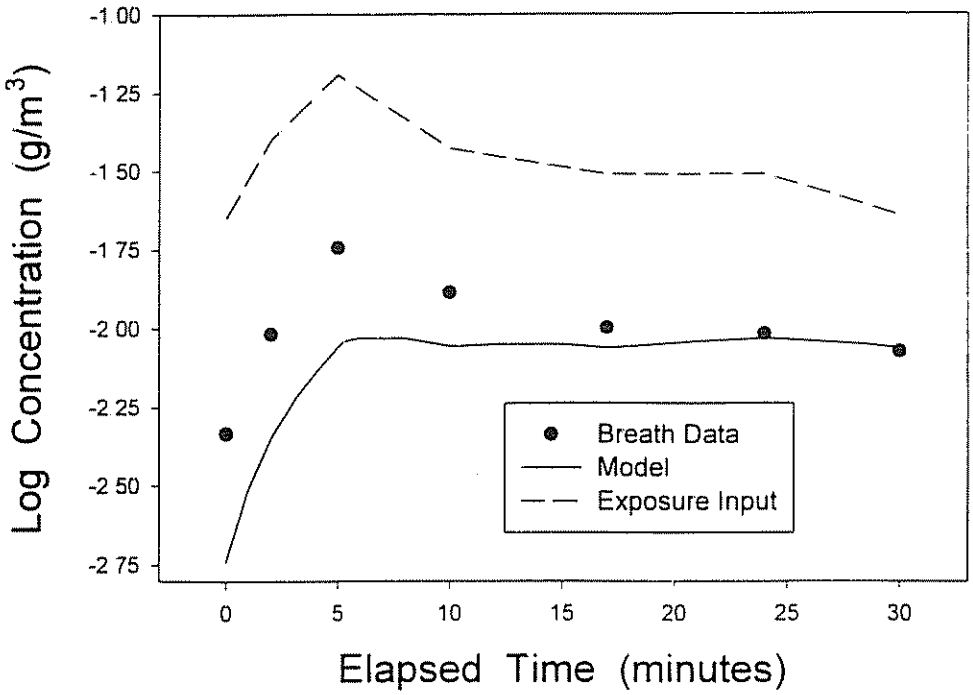

Figure 3.13 - The experiment data and PBPK model prediction of breath concentrations during exposure for a 30-minute Perc field exposure experiment (p0301) using the default PBPK model and temporal short-term air measurements as the model exposure input (variable).

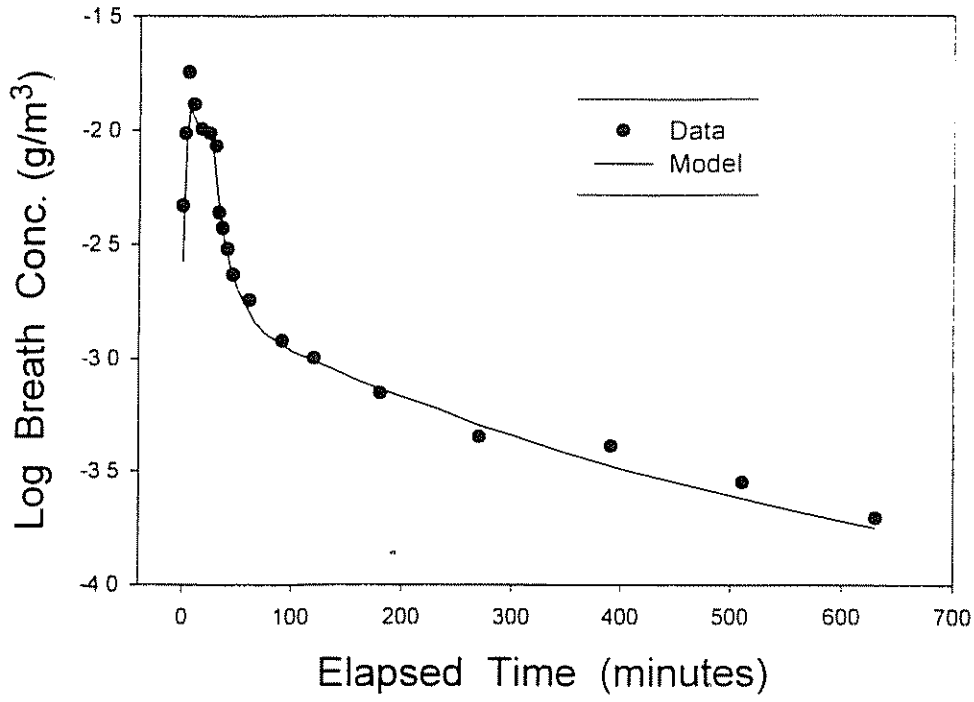

Figure 3.14 - The experiment data and PBPK model prediction during and after exposure for a 30-minute field exposure experiment (p0301) with a small V/A ratio (1.10) using variable exposure input and optimized parameters.

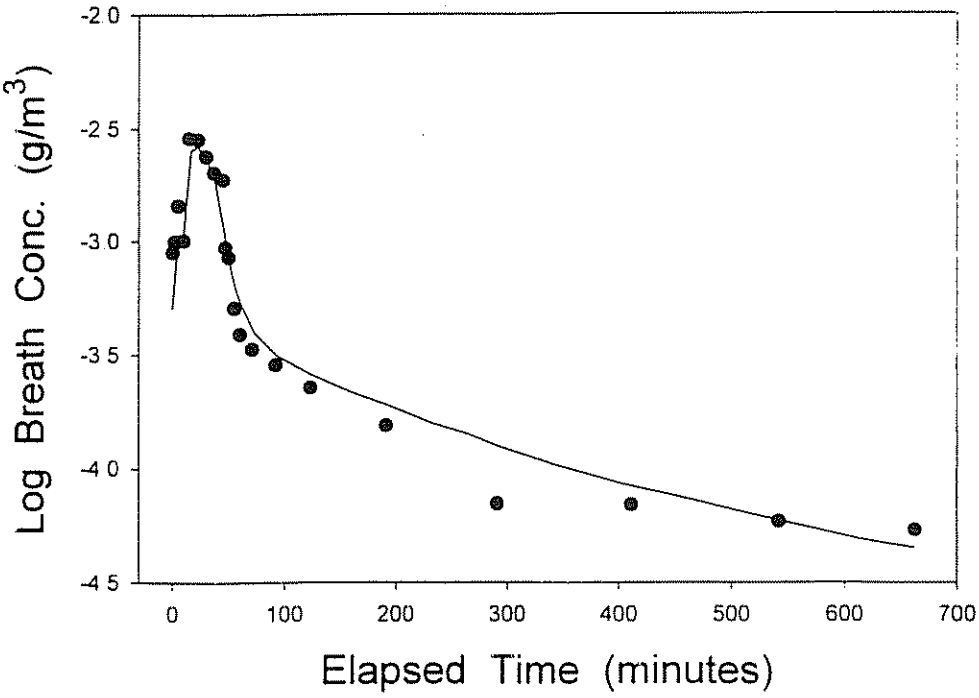

Figure 3.15 - The experiment data and PBPK model prediction during and after exposure for a 45-minute field exposure experiment (p1214) with a large V/A ratio (1.35) using variable exposure input and optimized parameters

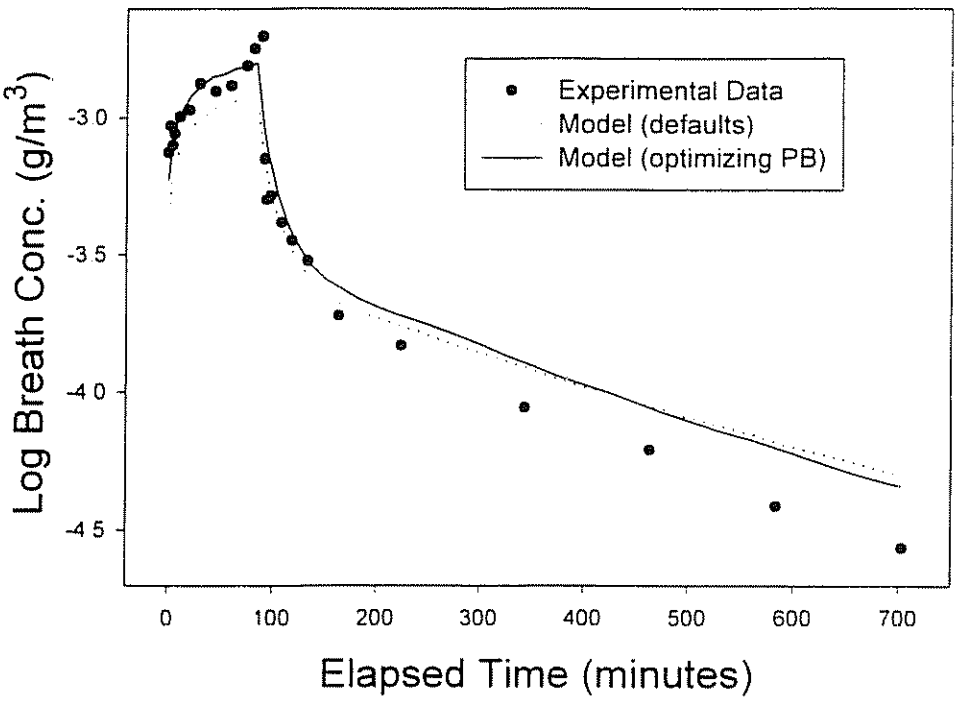

Figure 3.16 - Sensitivity analysis - the experimental data and PBPK model predictions using default parameters and optimized blood/air partition coefficient (PB) during and after exposure for a 90-minute constant exposure experiment (p01106) of the controlled exposure study.

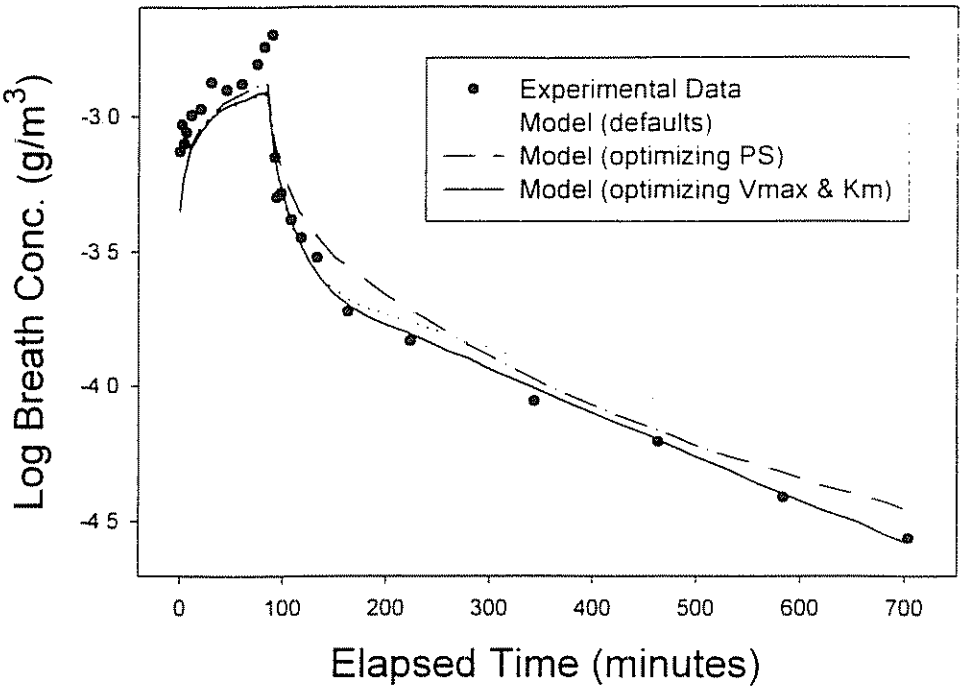

Figure 3.17 - Sensitivity analysis - the experimental data and PBPK model predictions using default parameters, and optimized slow perfused tissue-to-blood partition coefficient (PS) and metabolic constants (Vmax and Km) during and after exposure for a 90-minute constant exposure experiment (p01106) of the controlled exposure study.

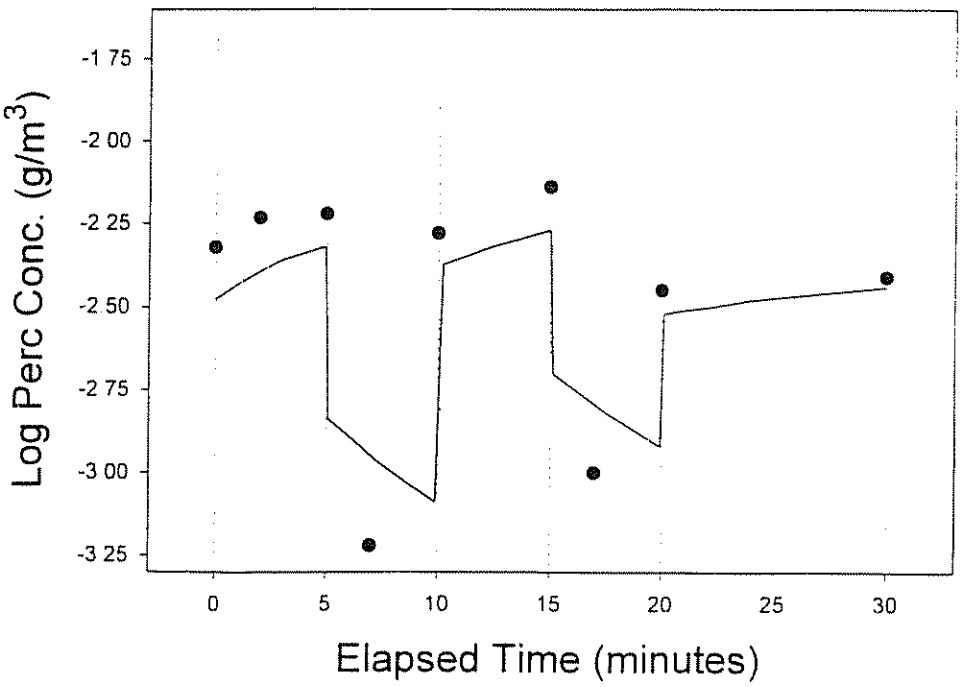

Figure 3.18 - The experimental data and PBPK model predictions of during-exposure breath concentration using variable exposure input and the optimized PBPK model for a 30-minute variable exposure experiment (p0319) of the controlled Perc exposure study. Breath data (•); Exposure (---); Model prediction (—).

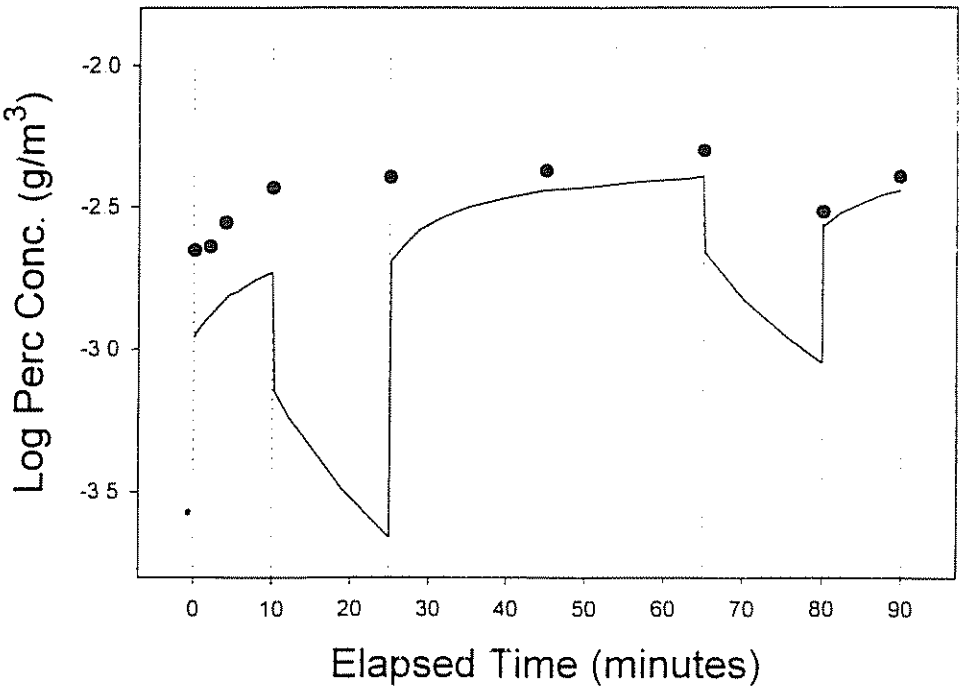

Figure 3.19 - The experimental data and PBPK model predictions of during-exposure breath concentration using variable exposure input and the optimized PBPK model for a 90-minute variable exposure experiment (p0529) of the controlled Perc exposure study. Breath data (•); Exposure (---): Model prediction (—).

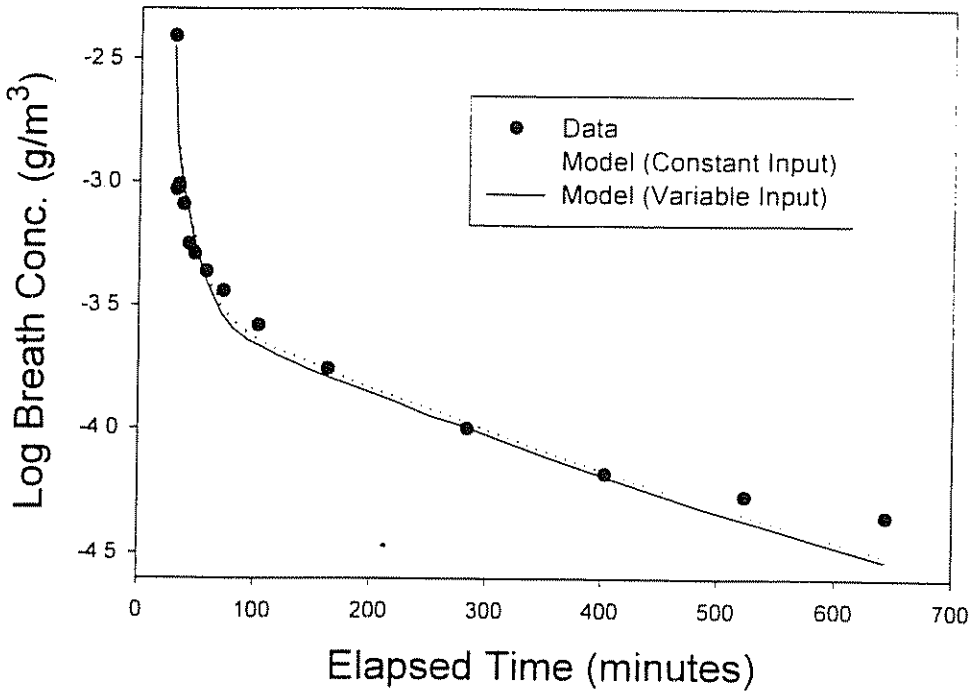

Figure 3.20 - The experimental data and PBPK model predictions of postexposure breath concentration for the two exposure inputs using the optimized PBPK model for a 30-minute variable exposure experiment (p03196) of the controlled Perc exposure study.

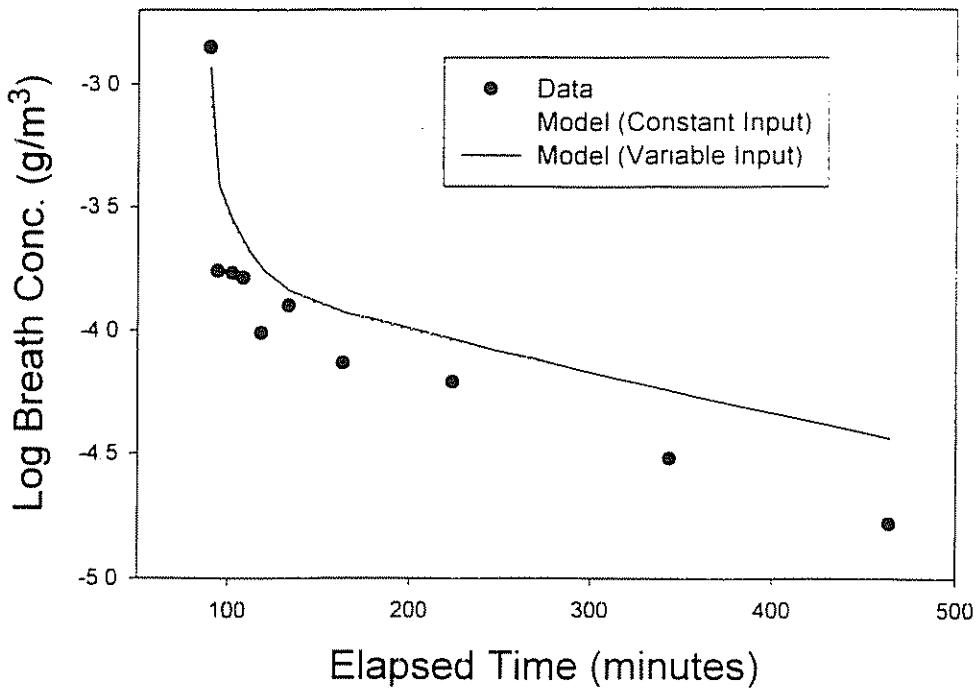

Figure 3.21 - The experimental data and PBPK model predictions of postexposure breath concentration for the two exposure inputs using the optimized PBPK model for a 90-minute variable exposure experiment (p06206) of the controlled Perc exposure study.

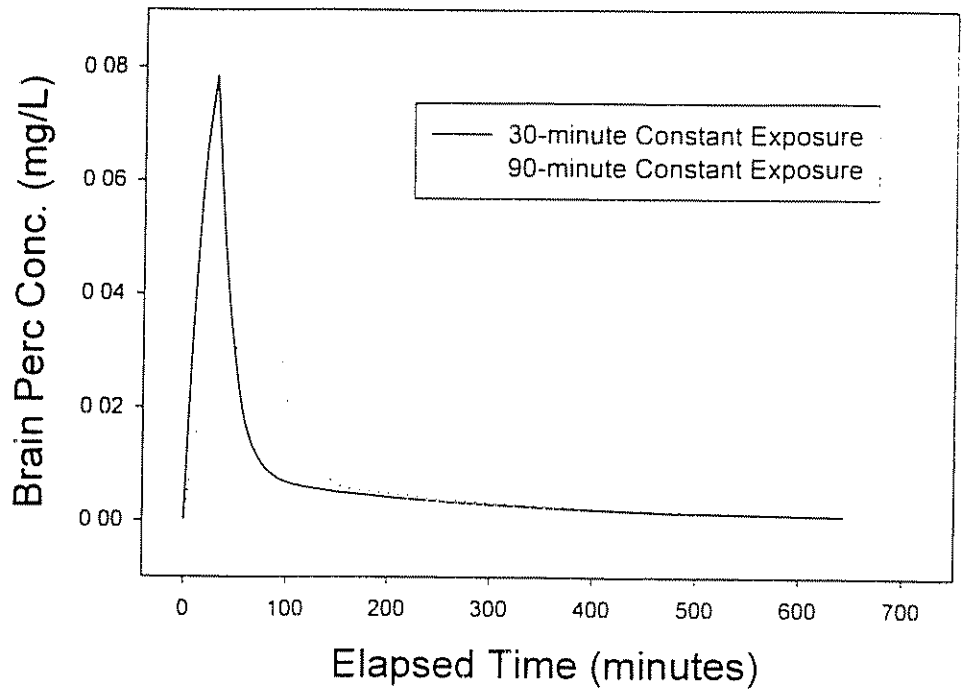

Figure 3.22 - The prediction of brain Perc concentration during and after exposure using the optimized PBPK model for the two constant exposures of the controlled Perc exposure study with the same total exposures [297 (mg/m^3) × minutes].

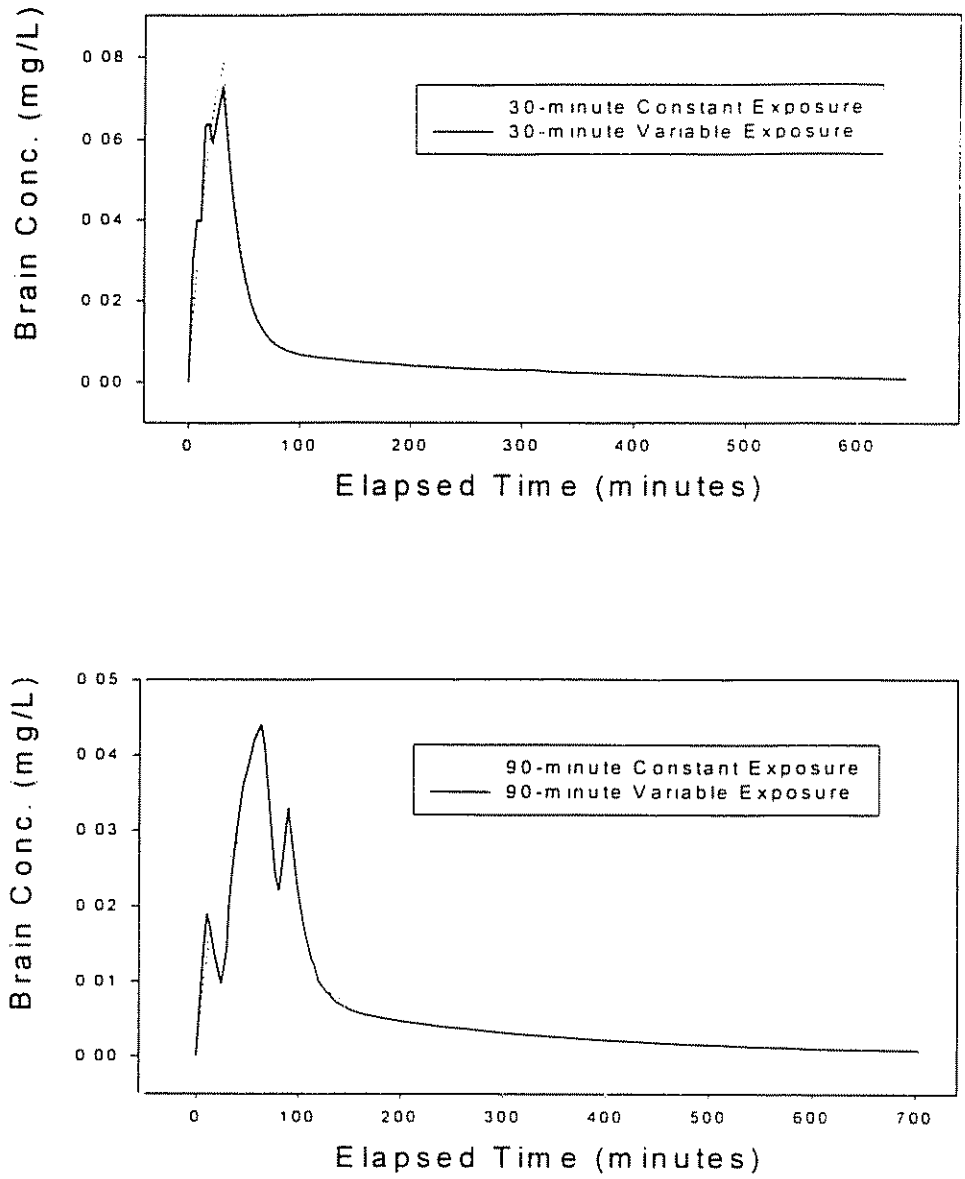

Figure 3.23 - The prediction of brain Perc concentration during and after exposure using the optimized PBPK model for the two different exposure patterns of 30-minute (upper) and 90-minute (lower) exposures of the controlled exposure study with the same total exposures [297 (mg/m^3) × minutes].

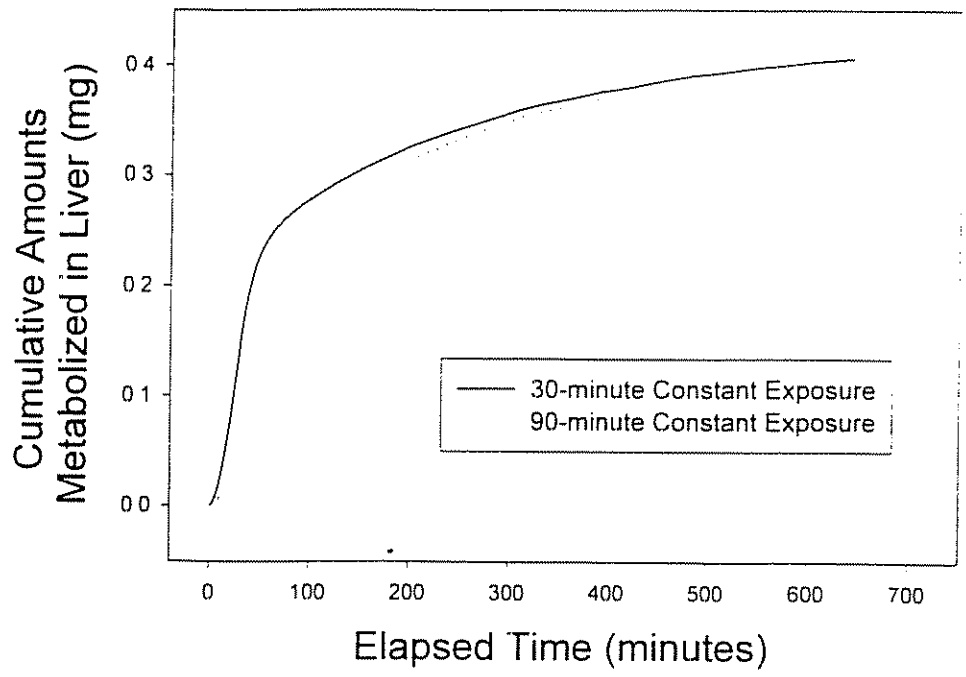

Figure 3.24 - The prediction of cumulative amounts of Perc metabolized in the liver using the optimized PBPK model for the two constant exposures of the controlled exposure study with the same total exposures [297 (mg/m^3) × minutes]

4. DISCUSSION

The current study was designed to investigate the potential influence of different exposure durations and patterns on the body kinetics using exhaled breath concentrations and PBPK modeling. These influences are important not only because their existence would diminish the accuracy of utilizing exhaled breath concentration as a biological marker of exposure and dose but also because the body's pharmacokinetics/toxicokinetics and the associated health risks are altered if exposure duration and pattern affects body kinetics. The elimination of Perc after inhalation exposure depends on its body kinetics, which include the processes of pulmonary absorption, distribution within the body, differential absorption by various tissues, metabolism, and elimination. Any change in these dynamic processes may cause alternations in the overall elimination via exhalation.

The absorption kinetics was investigated by examining the relationships between exposure air and exhaled breath concentrations collected concurrently during the exposure. These relationships were also used to estimate absorbed (internal) dose attributable to the exposures for both constant and variable exposures. Measurements were made under field conditions, where only the exposure duration could be controlled, and in a controlled setting where exposure intensity, duration and pattern were controlled. The results of the body kinetics from both the field and the controlled exposure study were evaluated and compared to understand the influences from exposure duration and pattern. The distribution of Perc within the body was studied through the

use of compartment and PBPK modeling since the distribution within the body, *i.e.*, the Perc concentration profiles in each body organ/tissue, can not be determined experimentally. A compartment model assumes that the elimination of Perc can be represented by the sum of the elimination from different body compartments, such as arterial blood, rapidly-perfused tissues and slowly-perfused tissues, each of which follow exponential decay once an exposure ceases. The elimination half-lives, obtained from fitting the compartment model to experimental data, provided an estimate of the residence time and the concentration of Perc within each compartment. A PBPK model compartmentalizes the body tissues/organs and utilizes realistically physiological parameters to represent a biological system, thus it provides a more detailed method to investigate the distribution of Perc within the body. The differences in body's distribution, particularly the target tissue (brain) concentration and amount metabolized in the liver, among different exposure durations and patterns were obtained from the PBPK model simulation results, and used to examine the differences in the potential health risks, particularly acute neurological effects and carcinogenesis, associated with the changes in exposure conditions. The elimination kinetics among various exposure conditions were compared using percent dose expired, AUC_B, and elimination half-lives. These results were then used to test the current hypothesis that changes in exposure duration and pattern alter the body elimination kinetics, more than the variability that exist for a single person on different days.

The field exposure and breath concentration data were also used to examine whether a previously calibrated PBPK model can effectively predict exhaled breath concentrations

under non-constant exposure conditions, whether model parameters can be optimized for a single subject, and which parameters the model were most sensitive to.

The overall experimental data and modeling results were used to understand realistic exposure scenarios in laundromats containing dry-cleaning operation, and to evaluate the accuracy of using exhaled breath concentrations as a biomarker of exposure and internal dose after fluctuating environmental Perc exposures.

4.1. The Body Absorption Kinetics and Percent Absorption During Exposures

The body's absorption kinetics during exposures were examined to determine the amount entering the body. Differences in absorption due to the changes in exposure condition may change the total uptake of Perc and the subsequent distribution and elimination process. During exposure, the breath concentrations closely reflected the air concentrations measured simultaneously (Fig. 3.2 and 3.3). The air to breath concentration ratio (A/B) during exposure was higher for the initial approximately 10 minutes of the exposure, before remaining nearly constant at about 3.0. When the air levels were almost constant, as seen between 6th and 7th data points in both Fig. 3.2 and Fig. 3.3 (or Table 3.2), a continued increase in the breath levels were observed. This air to breath relationship has been found in controlled exposure studies using constant exposures prior to the uptake and release reaching a steady state (Opdam and Smolders, 1989; Fernandez *et al.*, 1976; our CEF data). The increase in breath concentrations in the controlled studies reported here indicates that an increase in body burden is occurring and that a steady-state between the environment and exposed subject was not reached.

When there was a sharp reduction in the air concentration, as found between the 5th and 6th data points in Fig. 3.1, the breath concentration also decreases, with the breath concentration exceeding the air concentration indicating a net elimination of Perc from the body via expiration.

The percent absorption during the first minutes of exposure was consistently higher, by approximately 10-15%, than the values calculated during the later exposure periods (Table 3.2). The greater proportion of the Perc exposure absorbed across the lung barrier at the beginning of exposure is probably due to a greater concentration difference between the air and blood when the exposure began. Previous studies have also observed that the retention of Perc during exposure decreases, first rapidly and then slowly (Fernandez *et al.* 1976). In one study the percent absorption during the first exposure hour of a 4-hour constant exposure experiment was 70%, which was about 25% higher than that during the last hours (Monster *et al.* 1979), and in a second study the relative uptake was 60% during the first 20-minute of exposure, decreasing to 55% at the end of 4-hour constant exposure (Imbriani *et al.* 1988). The percent absorption remained nearly constant in the field study as exposures proceeded, which is different from the results of constant exposures in which percent absorptions continue to decrease until the end of exposures (Fernandez *et al.* 1976; Monster *et al.* 1979; our CEF data). The near-constant percent absorption does not imply that steady-state was established between the air and blood but are presumed to result from constant fluctuations of the exposure air concentration.

The mean percent absorptions were 0.69±0.03 and 0.66±0.07 for experiments p1020 and p1220, respectively. The variations within each experiment were relatively small when the air concentration changes was small, and thus the mean percent absorption could be used to approximate the total amount absorbed during fluctuating exposure situations. However, when a sharp decline in air concentration occurred, as seen in experiment p1020, a mean value of 0.29±0.42, was obtained which was smaller than the average values by a factor of two. The overall mean absorption coefficients for 30, 45 and 60 minute exposures were 0.69, 0.61 and 0.60, respectively (Table 3.2). The mean for the 30-minute exposures was statistically higher ($p<0.05$) than that for the 60-minute exposures. The percent absorption increases with decreasing exposure duration since the higher percent absorption during the initial minutes of exposures contributes more to the mean absorption value for shorter exposures. The grand average of mean percent absorption for all field experiments was 0.63, with a value of 0.67 when the results from the two experiments (p1020 and p1129) with sharp decreases in the air concentration were excluded from the analysis. The mean percent absorption for each field experiment was not a function of the average exposure air concentration.

The mean percent absorptions for the 30- and 90-minute constant exposures of the controlled study are 76.9% and 67.7%, respectively, which are statistically significantly different ($p<.05$) (Table 3.5). These results support the findings from the field experiments that the percent absorption increases as the exposure duration decreased. The actual values were somewhat higher during the controlled experiments than from the field data. A slight increase in ventilation rate due to a small increase in subject's body

weight may have contributed towards this discrepancy. Therefore for the same total exposure, shorter exposure duration will result in higher percent absorption and larger resulting internal dose, as indicated in Table 3.5 by higher ($p< 05$) dose index, and higher body burden (Fig. 3.9). Thus changes in the exposure duration will affect the amount actually absorbed into the body.

4.2. The Effects From Exposure Duration on Internal Dose Estimation

The total uptake (or internal dose) is the product of the percent absorption (or absorption efficiency), ventilation rate and exposure, which has been experimentally confirmed using breath analysis (Imbriani *et al* 1988; Weisel *et al*. 1992). This relationship allows for the prediction of the internal dose from the exposure with the slope of the regression line being the subject's ventilation rate (m^3/minute) times the percent absorption. In the field study, the average percent absorption and ventilation rate were stable across all experiments for the subject studied, therefore, internal doses are highly correlated with exposures, and the latter can be directly used to estimate internal dose (Fig. 3.4.a). Conversely, any fluctuations in the ventilation rate or percent absorption during exposure will alter the uptake and thus affect the prediction of internal dose. Previous studies of exercising individuals have demonstrated that increasing ventilation rate results in an increase in internal dose (Imbriani *et al* 1988). Total exposures can be calculated from either the AUC_A of short-term air measurements or directly from the product of average exposure concentration and exposure duration. Differences existed between these two estimates even though the

correlation between them was relatively high (r^2=0.97, $p < .05$). The ratios between this two exposure estimations (referred to as V/A ratios) ranged from 0.65 to 1.56, with a mean value of 1.25±0.23. The deviations from unity of these ratios suggests an under-/over-estimation of the total exposure occurred for some of the experiments when using the area under the short-term air measurements as a surrogate of total exposure because of large changes that occurred in the air concentration between the collection of two short-term measurements. The internal dose calculations in this study were based on the AUC_A of temporal air measurements, rather than average air concentration times duration, therefore, using the latter to estimate the exposure estimates resulted in a slight reduce in the correlation/regression coefficient with the internal dose. (Fig 3.4.b).

The accuracy of using postexposure breath concentration as a biomarker of exposure or internal dose were also examined. The breath level measured at 6-minute post exposure correlated well with calculated internal dose (Fig. 3.5). The scatter in this relationship is caused by variations in the exposure durations (Fig. 3.6), indicating that the predictions of internal dose from the early postexposure breath concentration are sensitive to exposure duration. When the prediction of internal dose was based on the postexposure breath level measured at a later postexposure period, such as 90-minute post exposure, the gradient differences in regression lines among the three durations diminished. These findings indicated that the postexposure breath concentrations are a function of internal dose and exposure duration, and suggest that

exposure duration should be determined if the early postexposure breath concentrations are used to estimate internal dose.

4.3. Elimination Half Lives of Perc in the Exhaled Breath

Numerous studies have attempted to use compartmental models and elimination half-lives to study the distribution of Perc within the body and to explain the body elimination kinetics (Monster and Houthooper, 1979; Gordon *et al.* 1988; Raymer *et al.* 1991; Pellizzari *et al.* 1992; Wallace *et al.* 1993). The exponential functions in the compartmental model are considered to correspond to the following body compartments: the initial rapid elimination is associated with the clearance from arterial blood, while the second with the slower elimination from the vessel-rich tissues and the third with even slower elimination from the vessel-poor tissues. The slowest elimination (fourth compartment) is from the adipose tissues but is rarely modeled mainly due to the lack of postexposure data within the corresponding time frame (usually >50 hours post exposure) for Perc. An empirical model can be used to predict the concentration profiles of Perc in these lumped compartments, and/or to estimate past exposures.

The exhaled breath concentrations after Perc exposures in the current study (Fig. 3.7, 3.9, 3.10, 3.11) followed an exponential decay as reported previously (Stewart *et al.* 1970; Fernandez *et al.* 1976; Monster *et al.* 1979; Wallace *et al.* 1993). The elimination half lives were calculated using the postexposure breath data from the CEF study based on a three-compartment model. Using the sum of three exponential expressions provided the best empirical fit of the data. The results (Table 3.7, upper sections) show that, for

the same total exposures, a shorter exposure duration leads to a longer ($P<.05$) first but shorter ($p<.05$) third elimination half-life. Larger variations in the half-life values were observed among the variable exposures (Table 3.7, lower section). But the first half-life values increased with increasing exposure concentration. This reveals that, in addition to between- and within-subject variations, the determination of elimination half lives also must consider the exposure duration. For the experiments performed, a difference of 60 minutes in exposure duration had a greater effect on the half-lives calculated than that from the intra-individual variation. Thus the empirical biological half lives of Perc should not be considered as constants, rather may be a function of exposure duration or the concentration/amount of Perc in each compartment since higher exposure concentrations resulted from shorter exposure durations for the same total exposure. One possible explanation for different exposure concentrations resulting in different half-lives is that, unlike the decay of radioactive materials which occur spontaneously, the elimination (clearance) of Perc from the blood after exposure depends upon the amounts either exchanging with other body tissues or being metabolized which may not simply follow a first-order kinetic and can vary with time as the amounts of active enzyme vary. Therefore, larger amounts of Perc in the body (resulting from an higher exposure concentration) would result in a longer elimination "half-life" than from smaller amounts being in the body. Conversely, the third half-lives for the 90-minute constant exposures were longer than that of 30-minute constant exposures. The overall means of half-lives for the first, second and third compartment of the current study are 3.68, 31.3 and 229 minutes, respectively.

The half-lives calculated in this study were compared to the other literature values, and are summarized in Table 4.1. The determination of half-lives depends upon the numbers of compartment used in the model (study # 2A and 2B). The values of the earlier half-lives seem to decrease as the number of compartments increased due to a smaller influences from the latter data points, which reflect the elimination from the deeper compartment. Studies #3 and #4 found a similar mean third half-life value since they shared the same exposure data and both used three-compartment models. Study #4 also found that an increase in exposure duration may increase the amounts being transferred into the fourth (fat) compartment and subsequently increased the third elimination half-life compared to shorter exposure durations due to the greater contribution from the 4th compartment to the breath data collected during the latter postexposure period which is weighted heavily in the calculation of the third half-life. It is universally observed that Perc concentrations in exhaled breath decline very rapidly during the initial decay. Therefore, data collected during the initial decay are most critical in characterizing the elimination kinetics and in determining the first (and second) half-lives. None of the aforementioned studies have collected breath samples at the beginning of the postexposure period, resulting in a lack of the "starting point" for the decay curve. This may cause an over-estimation of the first and second half-life. In a more extreme case (study # 1), the first postexposure breath sample was collected 2 hours after a 2-hour exposure which resulted in losing all information on the early elimination phase, as was observed by the researchers. The relatively long half-life obtained in that study (21 hours, fitting to a one compartment model) was caused by a small rate constant (slope)

estimate, resulting from the lack of breath data collected before the first data point (2 hours post exposure) that may contain higher Perc concentrations.

The current study was designed to closely examine the early elimination phase by collecting 5-6 samples during the first 30 minutes of the postexposure period, beginning from 2 minutes post exposure, with more frequent collection initially. This arrangement also allows a more precise estimation of the first one or two half-lives (study 5A). When the first two data points of this study were excluded from the half-life calculation (study # 5B), the values of first and second half-lives increased to the half-life values reported previously. Thomas and co-workers (1992) also found that the half-lives calculation are sensitive to the uncertainty of data. These findings suggest that the determination of empirical half-lives also depend upon the available data used in the calculation. The current study had sampling durations for the first few postexposure breath samples of 15 seconds, which were relatively long, compared to the calculated first half live of a few minutes. This also increases the uncertainty in calculating half life even though the sampling duration was incorporated (Section 2.2.14.2.) into the calculations of the half-lives.

In addition to the differences in exposure condition, inter-individual variability in half-life values were also observed in the multiple-subject studies (Raymer *et al.* 1991; Pellizzari *et al.* 1992) which confound the interpretation of results. The use of a single subject in this study eliminates the interference from the variation between subjects, which is believed to be much larger than the intra-individual variability, and thus facilitating the comparison of half lives (as well as other kinetic behaviors) between

different exposure scenarios. The coefficient of variance (CV) of half-lives among triplicate experiments of similar exposure levels for an individual calculated in the current study are in general no greater than 20%.

Compartmental models, which are calculated from an empirical fit of postexposure breath concentrations, provide a simple method to understand the concentration changes in certain body compartments. The biological elimination half-life values of Perc determined using the compartment model, were found to be a function of exposure duration/concentration and dependent upon the postexposure time that the breath samples were collected. These dependencies limit the usefulness of elimination half-lives in explaining the body elimination kinetics, and strengthen the importance of using an alternative mathematical tool that is robust to these dependencies for relating data, such as PBPK modeling.

4.4. The Elimination of Perc Via Exhalation After Exposure

The elimination of Perc has been found to be slow compared to other halogenated compounds, such as trichloroethylene, because of the solvent's affinity for fat tissue and its relatively inefficient metabolism in humans (Stewart *et al.* 1970; Monster *et al.* 1979). The concentration of Perc in alveolar air depends upon the total amount absorbed by the body and the time elapsed after the exposure (Fernandez *et al.* 1976). Consequently, lower postexposure breath concentrations can be expected in the experiments with lower estimated internal doses (Fig. 3.7). It was estimated that ~15% of the absorbed dose was excreted in breath within an hour after a single breath exposure to Cl^{38}-labelled Perc

(Morgan *et al.* 1970). In the current study, less than 7% of the absorbed dose was exhaled within the first 6 minutes, while a maximum of about 50% was expired by the end of 400 minutes postexposure (Table 3.3). These results suggest that, for a typical 7-8 hours occupational exposure at ppm levels, a long period of time is required to eliminate the majority of the un-metabolized Perc from the body, consisted with previous findings (Stewart *et al.* 1970; Fernandez *et al.* 1976; Monster *et al.* 1979).

In order to determine the differences in elimination kinetics among various controlled exposures, elimination half-lives and postexposure AUC_B, were used as the quantifiers for the differences in the elimination breath curve. AUC_B is a function of the amplitude while elimination half-lives reflect the slopes (shapes) of the postexposure breath curves. The CEF study was designed to test the effects from both factors (exposure duration and pattern), while the field study only examined the influence from one potential controlling factor, exposure duration. The postexposure breath concentrations from the CEF study were normalized to total exposure (the average exposure concentration times exposure duration) to compensate for the differences in exhaled breath among replicate experiments that could result from differences in average exposure concentration among experiments. The theoretical basis for the normalization is based on the previous findings that postexposure breath levels are proportional to the average exposure air concentration (Fernandez *et al.* 1976; Lapare *et al* 1993 & 1995).

The AUC_B is proportional to the amount of Perc expired for a constant ventilation rate. Therefore, the AUC_B of normalized breath among different exposures from the same subject, with constant ventilation, can be directly compared to examine the

differences in elimination curves resulting from different exposures. The AUC_B of normalized breath for the CEF study were calculated for the three time intervals, *i.e.*, 0-12, 0-73 and 0-373 minutes postexposure, which correspond to the time frames of 1st, 2nd and 3rd elimination half lives, respectively, for Perc (Pellizzari *et al.* 1992; Wallace *et al.* 1993).

4.5. The Influences from Exposure Duration and Pattern on Elimination Kinetics

Total exposure is the sum of the actual exposure duration times exposure concentration. An exposure with shorter duration but higher exposure concentration results in the same total exposure as the second exposure with longer duration and lower concentration. Similarly, a exposure with highly varying exposure concentrations may also result in the same total exposure as another exposure with nearly constant exposure concentration. However, differences in body kinetics, including elimination via exhalation, may exist among exposures with different exposure durations and patterns. Therefore the widely-accepted assumption that an average exposure, which is usually measured to estimate total exposure, is a good representation of real-world fluctuating exposures may not be valid.

4.5.1. The Effects from The Exposure Duration

Postexposure breath concentrations in general reflect the absorbed doses (Fig 3.7) indicating postexposure breath levels can be potentially used to approximate dose. However, the relationship between the internal dose and postexposure breath is

complicated by the exposure durations (section 4.2). The same postexposure breath concentrations predict different internal doses when the exposure durations are different.

The percentage of dose eliminated for up to 6-minute post exposure also varied with different exposure durations (Fig. 3.8). The variation of percent dose eliminated decreased as the postexposure period was increased to 0-400 minutes, though the percent analytical uncertainty also increased for these samples, which usually have lower concentrations. These findings indicate that the elimination kinetics after environmental exposures are a function of exposure duration, especially at the beginning of postexposure period. Results from the controlled study (Fig. 3.9) show that for the same total exposures, the body's elimination kinetics are affected by the exposure duration. The same exposures obtained over a shorter period of time (30 minutes) resulted in a higher body burden, evidenced by higher mean postexposure breath concentrations for the entire postexposure period studied than from a longer exposure time (90 minutes). The shorter exposures also resulted in statistically significantly longer ($p<.05$) first elimination half-lives and shorter ($p<.05$) third elimination half-lives, though the differences of the latter between the two durations was relatively smaller (Table 3.7). Differences in the amount eliminated with exposure durations were also found in the CEF study. The statistically significantly different means (Table 3.8) of AUC_B for the first two postexposure time frames (0-12 and 0-73 minutes) between the 30 and 90 minutes constant exposures indicated that the amounts of Perc eliminated, particularly during the early postexposure period, were different for the different exposure durations. The higher postexposure breath concentrations during the early elimination phase

following the 30-minute exposures are due to the higher air concentration used in the shorter study to obtain the same total exposure for both durations. The difference in the elimination curves of two exposures gradually diminishes, and the two curves merged at about 500-600 minutes post exposure. Two possible explanations for this are: 1) larger amounts of Perc were absorbed during the 30-minute exposure than the 90-minute exposure (section 4.1 and Table 3.5), thus resulting a higher body burden; and 2) when Perc is inhaled over a longer time period, a greater percentage is transferred into tissues, such as the adipose tissues, which exchange with the air in the lungs more slowly and thus Perc is accumulated deeper in the body and not release in the exhaled breath as quickly. These findings agree with previously reported results following high level occupational exposures (100-200 ppm), which are approximately two orders of magnitude higher than that of the current study (Fernandez *et al.* 1976).

These results support the hypothesis that elimination of Perc via exhalation after exposure is affected by exposure duration, and emphasize the need to determine the exposure duration accurately if exhaled breath levels are to be used to estimate past exposures. Alternatively, using breath samples collected hours following exposure may also provide relatively accurate exposure estimates since the differences in elimination curve between different exposure duration diminish with time.

4.5.2. The Effects from The Exposure Pattern

The second factor under consideration that affects the body kinetics is the exposure pattern. It was predicted, using a mathematical model, that the postexposure breath curve

would only be slightly influenced by the hourly fluctuations in exposure level when the total exposures and exposure durations were the same (Guberan and Fernandez, 1974). In this study, short-term fluctuating exposure scenarios (Section 2.2.10.2), which represent realistic situations, were used to simulate activity patterns that may be encountered in laundromats, and to examine the possible effects on elimination from different exposure patterns. The two quantifiers of the elimination curves, *i.e.*, the elimination half-lives and postexposure AUC_B, were not statistically significantly different ($p>.05$) between the constant and variable exposure settings for either exposure durations (Table 3.7 and 3.8). However, larger variations in the postexposure breath levels exist among replicated experiments of the 90-minute variable exposures due to larger variations in the exposure concentration. Experiment p05296, which had an exposure level of 7.62 mg/m^3 which was nearly twice the mean concentrations of 90-minute constant settings (4.07 mg/m^3), resulted in am elimination curve similar, in terms of AUC_B and half-lives, to the curves of the 90-minute constant exposure. Experiment p07036 had an exposure concentration of 4.72 mg/m^3, which was similar to that of 90-minute constant exposures. However, the elimination curve from p07036 had a lower amplitude than the curves from the 90-minute constant exposure. The third 90-minute variable exposure experiment, p06206, had an exposure concentration of 2.29 mg/m^3, which was less than the mean exposure of 90-minute constant exposure, and the AUC_B was smaller than the 90-minute constant exposure AUC_B values. The difference in the AUC_B for 0-73 and 0-373 minutes post exposure between the curves for p06206 and p07036 was approximately four standard deviation lower than the means of AUC_B of

the curves from the 90-minute constant exposure. These findings suggest that the influences from exposure pattern on body elimination kinetics may be a function of exposure level. An effect of pattern on elimination kinetic also supports the second explanation presented for the differences in elimination between 30-minute and 90-minute constant exposure (previous section), that the change in body's elimination kinetics between different exposure durations may be due to a difference in distribution in the body. The 90-minute variable exposure scenario contained an initial higher concentration and interruptions in the continuous exposure, which may have altered the distribution of Perc, causing more to enter deeper body tissues, accumulating Perc and slowing the subsequent elimination via exhalation.

The exposures modeled here, individuals walking into and out of a room where an exposure occurs, represents an extreme in fluctuations of exposure concentration. Other environmental exposures have less extreme fluctuations than modeled here since they may not have complete discontinuation in exposure. Smaller variations in exposure are expected to have smaller differences in elimination kinetics, which may not be readily distinguished from the analytical uncertainties and intra- and inter-individual variability. Therefore, a time-weighted exposure measurement can be considered as a simple and useful practice to estimate non-constant environmental exposures.

4.6. The Exposures from Visiting a Perc-Contaminated Facility

This study examined the changes in body kinetics after environmental Perc exposures, specifically for individuals who utilize laundromats that also contain dry-cleaning

operations. Air concentrations inside this type of laundromat as well as at the front counter of the dry-cleaning stores were measured to estimate the exposures and to serve as reference exposure level for the CEF study. The highest Perc air concentration measured near the conventional washing/drying machines of the laundromat was 7.8 mg/m^3 (~1.2 ppm v/v) while the highest air concentration at the front counter of a dry cleaning store was 65.3 mg/m^3 (~9.6 ppm v/v). These values depend upon not only the store's ventilation condition (Materna, 1985) but also the activities that were occurring when the measurements were made. For example, the Perc air concentrations inside laundromats measured within a day decreased with time (Table 2.1), coinciding with the fact that the dry-cleaning processes in these stores were completed before 10 AM of the sampling day. The exposures from a 5-minute visit of dry cleaning store and a 90-minute stay in a laundromat can be as high as 327 and 702 [$(mg/m^3) \times$ minutes], respectively, assuming that the maximum measured air concentration in this study existed for the entire exposure period. These exposure levels are orders of magnitude higher than that from the background ambient air, which are usually in the low-ppb ranges (Ligocki *et al.* 1985; Wallace, 1986; Hartwell *et al.* 1987). The internal dose attributed from these exposures will be 1.23 mg and 2.63 mg, respectively, assuming an absorption coefficient of 0.67 and an alveolar ventilation rate of 5.6 l/min. Estimations of the health risks associated with these exposures should not rely solely on the OSHA's standard of 100 ppm TLV but need to consider the facts that Perc is not only a possible carcinogen and affects the CNS, but differences in susceptibility between healthy workers and the wide ranges of population who utilize laundromats exist. The results indicated that Perc air

concentrations inside the laundromats were higher after Perc had recently been used. The exposures in the laundromats can therefore be minimized by using it several hours after the dry-cleaning processes, which usually occur in the morning, are finished. A further reduction could be accomplished by not staying in the facility but rather walking out of the store when possible. This would not only minimize the exposure but may also reduce the Perc body burden for the same total exposures, as were discussed in section 4.5.2.

4.7. Pharmacokinetic Model Evaluation

The body kinetics were also predicted and studied using PBPK modeling. PBPK mathematical models are based on the compartmentalization of body tissue/organ and incorporate biological phenomena, therefore allow for detailed examinination of the body kinetics. Unfortunately, most of the PBPK models have been evaluated using the literature data of controlled human exposure studies with constant exposure concentrations (Ward *et al.* 1988; Andersen *et al* 1991; Rao & Brown, 1993). Therefore, the abilities of these evaluated models to predict the biological data from non-constant exposures are unknown. Secondly, the effectiveness of using an integrated air concentration (a constant value) to represent real-world fluctuating exposure concentrations, as the exposure input, is critical in utilizing PBPK models but is rarely studied. Therefore, these areas of concern were evaluated using the data from the field study, which had varying exposure concentrations, and from the controlled study, which controlled the actual exposure profiles. The differences in the distribution of

Perc within the body among different exposure durations and patterns were examined using the optimized model calibrated against the controlled exposure data.

4.7.1. Field Exposure Data with Temporal Variability

Personal exposure (breathing-zone air) monitoring is a direct and useful method to assess the exposure that occurs in the environment and work place. Typically, only an average (integrated) exposure concentration for the entire exposure period is measured because of the limitations in resources. Real world exposure concentrations vary over time, as shown earlier and documented in the literature, and body pharmacokinetics may be influenced by different exposure durations and patterns (Imbriani *et al.* 1988; Smith, 1992; Lapare *et al.* 1993 & 1995). Such influences may have profound impacts on the exposure/dose estimation and affect the associated health risks. The field exposure concentration, which was stochastic in nature, was used to evaluate the model's performance under fluctuating exposure conditions, and whether an integrated air concentration is an adequate exposure input for a PBPK model to predict the exhaled breath concentrations for the real-world exposures. These simulation results were further examined during the later discussion using the controlled exposure data with well-controlled exposure conditions.

4.7.1.1. The Model Predictions During and After Exposure

One goal of biological monitoring is to be able to characterize the previous exposure/dose with the minimum number of measurements. However, a valid

relationship between bio-monitoring data and actual exposure must be established before any inference can be drawn. PBPK models predict a smooth increase in breath concentrations during the exposure when an average (constant) exposure concentration is used as the input, thus did not predict the true variability in the breath concentrations (Fig. 3.12). The use of variable exposure concentrations as the input provided more realistic model predictions for the same data set (Fig. 3.13), indicating that this model does have the potential to accurately predict breath levels during exposure for non-constant exposure conditions when variations in the exposure concentrations are known. Separate evaluations of the fit during and after exposure were performed since the overall fit of the model predictions to the entire data of an experiment did not differentiate the "weight" of the fit between data collected during, which was known to have variable air concentrations, and after the exposure. Recent studies have demonstrated the success of a PBPK model in predicting breath concentrations under various exposure scenarios for some VOCs (Lapare *et al* 1993 & 1995), but the agreement of the model predictions with the measured postexposure breath levels was not thoroughly studied due to the limited number of data points in the postexposure region. Therefore, a major focus of this sub-study was to determine the degree of agreement between the model and the postexposure breath data in order to evaluate the ability of a previously validated PBPK model to predict tissue concentrations from known exposures. The magnitude of deviations between model and data as well as the direction, *i.e.*, either under- or over-prediction, of these deviations is an important indicator of the potential of the model to reconstruct past exposures.

4.7.1.2. The Nature of The Data

PBPK models are typically evaluated/validated with selected data sets obtained from various controlled studies. One biomarker used for evaluation of PBPK models is exhaled breath concentration, which can be collected by a variety of methods (Stewart *et al.* 1970; Fernandez *et al.* 1976; Monster *et al.* 1979). The contribution from dead-space (or inhaled) air to alveolar breath sample varies across different methods but is often not specified in human exposure studies. Dead-space air contributed approximately 5% to the sample for the current sampling method. PBPK models would underestimate measured breath concentrations during exposure and overestimate them following exposure if the dead-space air contributions are not considered. Improvements in the agreement between the model predictions and the experimental data (Table 3.9 vs. Table 3.10) were observed after considering this relationship. This finding reveals the importance of understanding the nature of the data before using it in PBPK model calibration and validation.

4.7.1.3. The Uncertainty in Model Parameters

The accuracy of model parameters is one of the key factors determining the performance of the model (Koizumi, 1989). The accuracy of the predictions from a generalized PBPK model for any single individual strongly depends on the uncertainty in available estimates of the model parameters, which is influenced by various factors including the variability of parameters within the general population (Bois *et al.* 1994). Often critical parameters are either adapted from the literature values, obtained from

in vitro studies, or extrapolated/scaled from animal studies. The uncertainties in these parameters may result in large or even cumulative effects on the model output. Exhaled breath concentrations are mainly governed by the blood/air partition coefficient, the pulmonary ventilation rate and the metabolic rate (Gearhart *et al.* 1993; Wallace *et al.* 1993). The latter is expressed as Vmax and Km in the Perc PBPK model, in which only a saturable pathway (Michaelis-Menten kinetics) is assumed. The uncertainties in the above factors are expected to have an effect on the model performance (prediction). A study considering the variability of the model parameters found significant inter-species differences (Gearhart et al. 1993). Differences in gender, race and health status may also contribute to the total variations of the model parameters. Moreover, the use of different data sets in model calibration has resulted in different parameter values and predicted risks (Hattis *et al.* 1990 & 1993). Consequently, a set of parameters that is validated in animals or in one group of individuals may not be optimal for the entire population.

4.7.1.4. Optimization of Model Parameters

The consistent over-prediction of postexposure breath concentrations for all data sets (two examples shown in Table 3.12) during the early elimination phase, after correction for sampling duration and dead-space air contribution, suggests that the rate of elimination during this period may have been underestimated for the subject. The elimination rate during this time period is controlled by exchanges between the blood and the rapid- and slow-perfused tissues, thus the accuracy of the liver/blood (PL),

rapidly-perfused tissues/blood (PR) and slowly-perfused tissues/blood (PS) partition coefficient for the subject were examined using an empirical optimization routine. The blood/air partition coefficient (PB) was also optimized because it is the major factor controlling the model predictions for during exposure and the early elimination phase. The pulmonary ventilation rate, which has a large effect on the estimates of breath concentration, was estimated from the measured total ventilation rate to be 330 l/hour (alveolar ventilation rate) for the subject and that value was used in the simulation. Therefore the above four partition coefficients (PB, PL, PR, PS) were selected for statistical optimization/calibration.

4.7.1.5. Comparison of the Fit with Different Exposure Inputs

All data were collected from a single subject to control for inter-individual variability, which is present in the multiple-subject studies and can confound the interpretation of the results. The variability of each parameter is expected to be relatively small within the same subject across the different sampling days. Therefore, any discrepancies between the model output and data should not be associated with the errors in parameters used in the model after the parameters are optimized. The four selected parameters were first optimized using the variable exposure input for data set p0301. The variable exposure input for experiment p0301 was considered to be a good estimate of the total exposure since it had a variable exposure to integrated exposure measurement (V/A ratio) of 1.10, which is not different from unity considering the total uncertainty associated with the V/A ratio estimate. These optimized values were

then applied to the other five data sets to test the consistency of the model predictions The mean of the mean absolute percent error (MAPE) of the predictions for the complete postexposure data (Table 3.11, upper section) for variable exposures (1.78) was better, though not statistically significant, than that of constant exposures (2.06), but the MAPEs for experiments with V/A exposure ratio similar to that of experiment p0301 (*i.e.* experiments p1208, p1220, p0301 and p0310) were consistently better than that of constant exposures. This reveals that variable exposure concentration is a more reliable exposure input if the temporal fluctuations of air concentrations accurately reflect the true weighted average air concentration. Conversely, the model predictions with constant exposure inputs were superior for the data sets when the V/A ratios deviated from 1.00±0.20, such as experiments p0216 (V/A=1.23) and p1214 (V/A=1.35). The cause for this discrepancy was that postexposure breath levels would be over-predicted when exposure was overestimated. It should be noted that, even though the fit of model to the measurement (2.24 and 1.61 for experiments p0216 and p1214, respectively) did not differ from that of the other four experiments, most of the postexposure breath levels for these two experiments were overestimated, indicating a bias in the prediction existed (Fig. 3.15), whereas, systematic overestimation of postexposure levels was not found for the other four experiments, but rather random error associated with analytical uncertainties were evident (an example shown in Fig. 3.14). These four experiments had V/A ratios close to 1.0, which reflect that the exposure estimation based on the short-term air measurements were accurate.

4.7.2 Controlled Exposure Data of Constant and Variable Exposures

PBPK model simulation results using the field data showed that using the temporal air measurements in an optimized PBPK model resulted in better model predictions of exhaled breath concentration than the use of integrated air concentrations. The significance of this finding was further examined using the data from the controlled study since the differences in the prediction errors between these two exposure estimates/inputs found earlier were small and within the analytical uncertainty. A second cause of the difference between the two inputs could be from the uncertainty in exposure input estimate since the model parameters were optimized from a single experiment with varying exposure concentrations.

4.7.2.1. Sensitivity of The Model Predictions to Selected Parameters

In order to closely examine the body kinetics utilizing the controlled exposure data, sensitivity analysis was performed to identify which parameters have the largest impacts on the model prediction and need to be optimized. The default parameter values, determined from the geometric means of available literature values, were not found to be optimal for the subject studied. The PBPK model under-predicted the breath concentrations during exposure but mostly over-predicted the postexposure breath levels using the default parameters (Fig. 3.16). The fit of the model to the experimental data during exposure was improved by varying the blood/air partition coefficient (PB), with the optimized values (ranged from 5.9 to 9.3) being physiologically realistic. However, using these lower values for PB resulted in the

postexposure breath levels being over-predicted even more. The sensitivity analysis of the slow/blood partition coefficient showed that the model predictions improved only during the first 100 minutes post exposure (Fig. 3.17). Changes in the liver/blood, rapid perfused tissue/blood and fat/blood had very limited impact on the model prediction. Changing Vmax and Km improves the model prediction for the entire postexposure region, including the last few data points (Fig. 3.17). The improvement during the latter part of the post-exposure exhalation curve could not be achieved by varying any other single parameter considered. The model prediction of postexposure Perc breath concentrations were found to be sensitive to the changes in the metabolic parameters, and the default values seem to under-estimate the overall metabolism. The findings from sensitivity analysis suggested the selection of four parameters, PB, PS, Vmax and Km, for simultaneous statistical optimization.

4.7.2.2. Comparison of the Model Fit for The Two Exposure Inputs

One of the major focuses of the model evaluation was to examine differences in the fit of the model to data for two exposure inputs: time-weighted average (constant) and the exposure profiles (variable), to examine the validity of the assumption that an average exposure is a good representation of non-constant exposures when calculating dose and subsequent health risk. A time-weighted average air concentration is not a valid exposure input for predicting the breath concentrations during exposure due to a large MAPE of the model prediction (Table 3.13, column 3) but could adequately define the exposure to understand the distribution within the body and the subsequent elimination. The use of

variable exposure input, which accounted for the fluctuations of exposure concentration, resulted in smaller prediction errors than constant input. One consistent error in the model's prediction was an under-prediction of the breath concentrations (or over-predicted the absorption) at the beginning of 30-minute variable exposure, followed by over-predicting the breath concentration during the short non-exposure time periods (fig. 3.18). The differences between model prediction and data were smaller as the exposure proceeded. One explanation for these discrepancies in the model prediction is that a PBPK model assumes instantaneous equilibrium between alveolar air and alveolar blood while barrier/resistance may exist. A partial kinetic limitation on the transfer across the lung barrier could result in an equilibrium-based model predicting a greater absorption during exposure (manifested by lower breath concentrations) and larger amounts eliminated after exposure than actually occurs. As exposure proceeds, the difference between the contribution from an instantaneous equilibrium and a partial equilibrium to exhaled breath concentrations became smaller as the Perc body burden increases. Therefore, the differences between a model prediction that assumes instantaneous equilibrium and measurement diminish (Fig. 3.19). This explanation is further supported by the simulation results from constant exposures. The model provided a better prediction of exhaled breath concentrations for both during and post exposure periods for the 90-minute constant than that of the 30-minute constant exposures (Table 3.13, upper sections). The 90-minute constant exposure had a longer exposure and therefore resulted in a continuously increasing body burden as exposure proceeded which was more robust

to the difference between an instantaneous equilibrium and a partial-equilibrium exchange.

The simulation results from the field data that an optimized model using variable inputs results in better predictions of postexposure breath concentration than using constant inputs (section 4.7.1.5.) was examined using the controlled exposure data. There were no statistical differences ($p>.1$) in model predictions for the first 20 minutes postexposure and the entire postexposure breath concentrations between the two inputs for either durations. These findings reveal that the differences in the model predictions of postexposure breath levels between the two inputs are small, and therefore an integrated air concentration can be considered as a simple and relatively accurate exposure input for an optimized PBPK model to predict postexposure breath concentrations.

The body elimination kinetics after the 90-minute variable exposure scenario were found to be somewhat different from that of 90-minute constant exposure (section 4.5). The postexposure breath concentrations of 90-minute variable exposures were mostly over-predicted by both exposure inputs (Fig. 3.21), as most evidenced in the experiments p06206 and p07036. These over-predictions were not found for the data of the other three exposure scenarios (30-minute constant and variable, and 90-minute constant), indicating that the model overestimates Perc body burden under the current 90-minute variable exposure scenario. These results further strengthen the earlier findings that different body elimination kinetics exist between the 90-minute variable and constant exposures, and imply that the current PBPK model may not be sufficient to predict the breath concentrations for highly fluctuating exposure conditions.

4.7.2.3. Comparisons of The Model Prediction Between The Compartment and PBPK Model

Compartment and PBPK models are commonly used to examine or predict the body kinetics after various exposures. Compartment modeling fits the data empirically, therefore is case-specific while PBPK modeling determines the parameters *a priori*, therefore the predictions are based on the exposure input. The prediction of the postexposure breath concentrations of the controlled exposure study from both models were compared to examine the overall model predictions to the data of different exposure conditions. The compartment model provided a good fit to the data due to its empirical nature (Fig. 4.1-Fig. 4.4). Intra-individual variability, which was commonly assumed to be small, was found based on the data from the replicate experiments performed. The PBPK, using a set of "fixed" parameter values" could not account for these variability therefore, may have affected its predictions. Therefore, the prediction of a PBPK model will be improved if case-specific information, such as the parameter values, could be obtained. Alternatively, a PBPK model that incorporates the distributions of the input parameter will provide a range of the output that will account for the variability within and/or between individuals.

4.7.2.4. Intra-individual Differences in Tissue Concentration for Different Exposures

One of the major advantages of using PBPK modeling is being able to predict the distribution of a chemical throughout the body and the amounts or concentrations of a

chemical that reach specific body tissues. Two target tissue concentrations, the maximum Perc concentration in the brain (MCB) and the total amount of Perc metabolized in the liver (AML), were examined to ascertain any differences in Perc concentration or metabolism among the different exposure durations and patterns. The MCB was considered because the health effects from Perc exposures are related to Perc itself, affect the central nervous system and seem to have a threshold (Stewart *et al* 1977; Cai *et al*. 1991). The AML was examined because for many compounds including Perc, carcinogenesis is commonly associated with the metabolites produced, which most often occurs in the liver (Buben and O'Flaherty 1985; Goldsworthy and Popp 1987). The MCB from the 30-minute constant exposure (0.079 mg/L) was higher than that from the 90-minute constant exposure (0.033 mg/L), by more than a factor of two, even though the total exposures were the same (Fig. 3.22). These findings agree with the current hypothesis that exposure durations affect the body kinetics, and support the current regulatory efforts of limiting ceiling exposures (STEL) to protect workers'health even if the total exposure (8-hour TWA) does not exceed the permissible exposure level. The differences in the MCB caused by the different exposure patterns were relatively small (Fig 3.23). The total amounts of Perc reaching the brain were similar for the two exposure durations and patterns.

The AML at the end of the 30-minute constant exposure (0.14 mg) was only 65 % of the AML value at the end of the 90 minutes constant exposure (Fig. 3.24). However, the average rate of metabolism during this period, *i.e.*, AML/exposure duration, for the 30-minute exposure was 0.0047 mg/min., which is higher than that of 90-minute exposure

(0.0024 mg/min.) by nearly a factor of two since the amount of Perc reaching the liver is higher during the 30-minute exposure, and neither amount is sufficient to saturate the enzyme system. Thus, the short-term metabolic burden is a function of exposure concentration rather than total exposure. The fluctuations in exposure concentration for the same exposure duration only resulted in a small difference in the AML.

The AML at about 600 minutes post exposure were almost identical for both exposure durations, with a value of 0.4 mg. This finding indicates that enzyme systems were not saturated under the current exposure levels for either durations. The internal dose attributed from the exposure [297 (mg/m^3) × minute] is 1.1 mg, based on an absorption coefficient of 0.67 and an alveolar ventilation rate of 5.6 l/min, as discussed earlier. Thus, the percent dose metabolized for up to 10 hours following exposure will be ~36% (= 0.4/1.1), which is 20-30 times higher than the values of 1-2% metabolized after higher exposures (>50 ppm, 4-8 hours) reported for occupational exposures, when enzyme systems could become saturated (Monster *et al.* 1979; Ohtsuki *et al.* 1983). A population-based simulation study also predicted a higher percentage, with a median value of 36%, of dose being metabolized after background (1 ppb) environmental exposure (Bois *et al.* 1994) which agrees with the current finding. Risk assessments using a fraction of dose metabolized, calculated directly from the high-level exposure (hundreds of ppm) experiments, would likely underestimate the potential carcinogenic risk at low-level (a few ppm) Perc exposure, by a factor of approximately 20-30.

These simulation results also suggest that the changes in exposure duration and pattern (for the same total exposure) alter the body kinetics. Shorter exposure duration (or higher

exposure concentration) resulted in higher peak brain concentration and higher short-term metabolic burden than from the same total exposure obtained over a longer tome period. On the other hand, the change in peak brain concentration and metabolic burden caused by different exposure pattern are relatively small. Thus these results are consistent with the early findings from empirically examining the experimental data, and provide a support to the current hypothesis that exposure durations and patterns alter the body kinetics.

Table 4.1 - Summary of Perc kinetic studies, data format and the resulting elimination half-lives.

Study Code[a]	Experiment and Data Layout	# of Compartment used	Half-life Values		
			First	Second	Third
1	1 subject, 2-hour exposure in a dry-cleaning store. Data: from 2 to 10 hours postexposure, hourly, with shorter frequencies during the first three hours	1	21 hr.	-[b]	-
2A	3 subjects, ~4 hours in a hardware store. Data: 3, 8, 18, 28, 38, 53, 68, 98, 128, 173 and 218 min. post exposure.	1	~1.8 hr.	-	-
2B	Same as study 2A	2	~0.1 hr.	~2.7 hr.	-
3	4 subjects, several hours plus 45 minutes to consumer products containing Perc. Data: ~10, 46, 74, 108, 140, 162, 208, 259, 303, 369, 439 and 528 min. post exposure.	3	--[c]	--	~6-8 hr.
4	Same as study 3	3	~10 min.	~1-2 hr.	~6-8 hr.
5A	1 subject, controlled exposures for 30 or 90 min. Data: 0, 2, 4, 8, 12, 18, 28, 43, 73, 133, 253, 373, 493 and 613 min. post exposure.	3	~3 min.	~25 min.	~210 min.
5B	Same as study 5A. Data[d]: 8, 12, 18, 28, 43, 73, 133, 253, 373, 493 and 613 min. post exposure.	3	~10 min.	~60 min.	~220 min.

a study 1: Gordon *et al.* 1988; study 2A and 2B: Raymer *et al.* 1991; study 3: Pellizzari *et al.* 1992; study 4: Wallace *et al.* 1993; study 5 A and 5B: the current study

b not applicable

c not studied

d excluding the first three data points when calculating half-lives

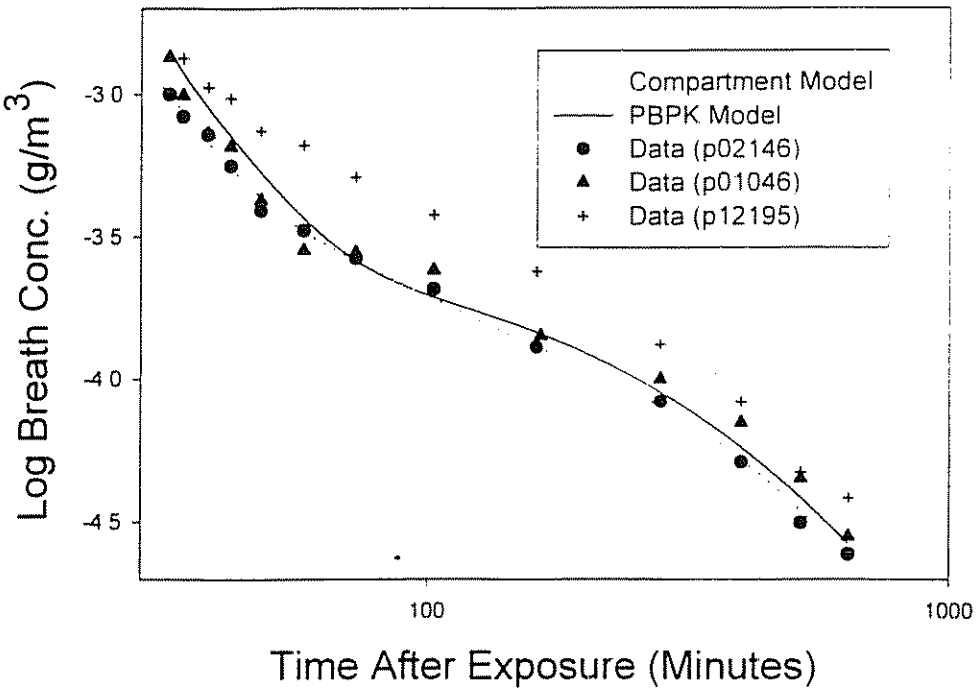

Figure 4.1 - The prediction of postexposure breath concentrations of the 30-minute controlled constant exposures from both the compartment and the optimized PBPK model. Two model predictions were made for experiment p02146 only. The other two experimental data shown are parts of the triplicate experiment, with slightly different exposure intensity, of the 30-minute constant exposure scenario.

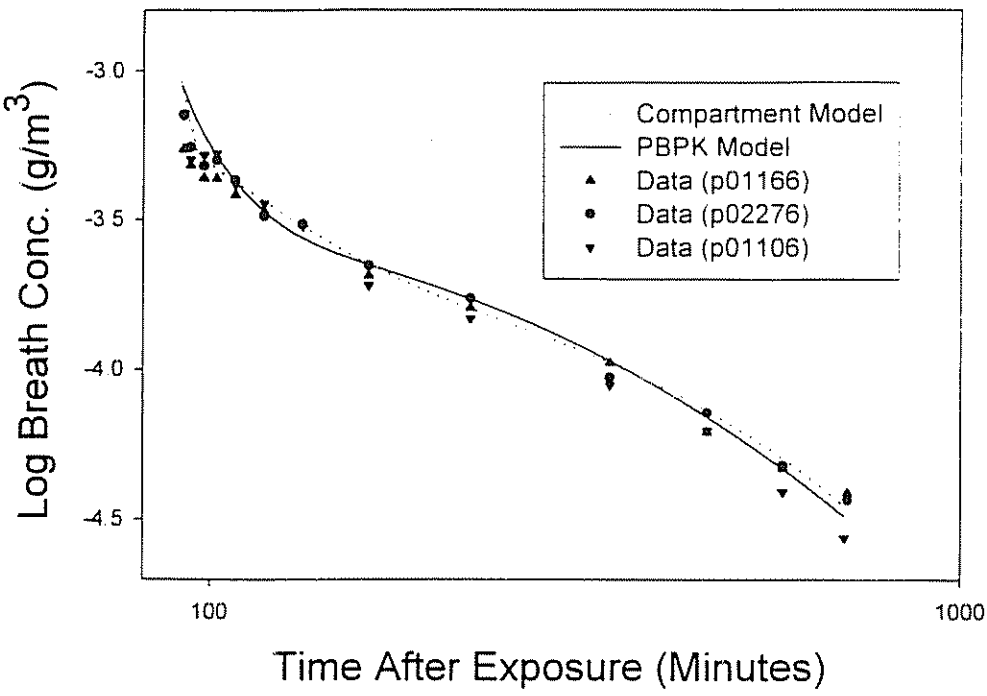

Figure 4.2 - The prediction of postexposure breath concentrations of the 90-minute controlled constant exposures from both the compartment and the optimized PBPK model. Two model predictions were made for experiment p01166 only. The other two experimental data shown are parts of the triplicate experiment, with slightly different exposure intensity, of the 90-minute constant exposure scenario

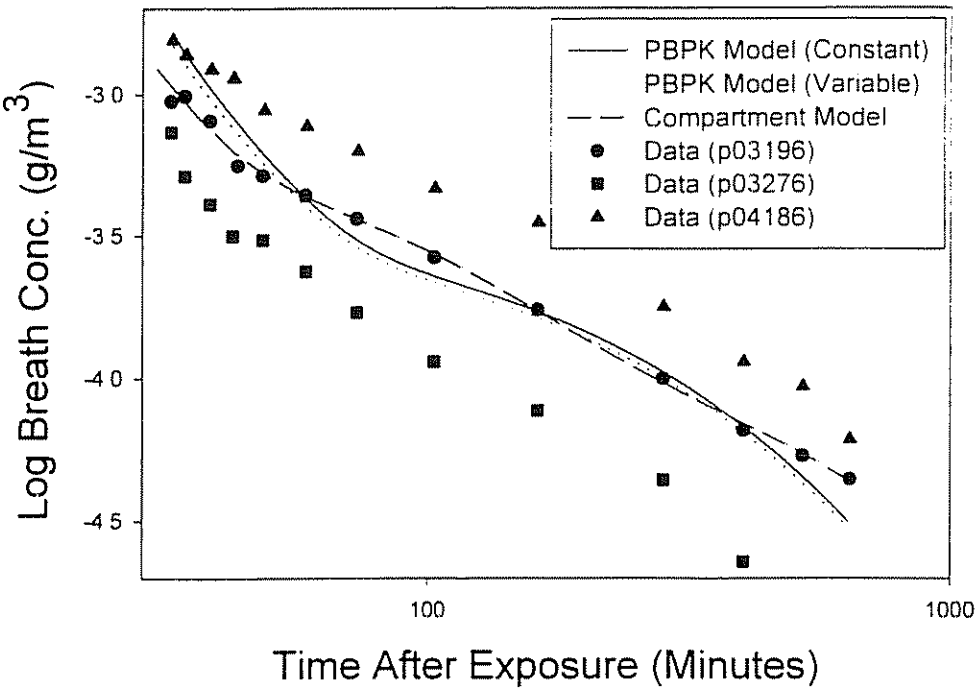

Figure 4.3 - The prediction of postexposure breath concentrations of the 30-minute controlled variable exposures from both the compartment and the optimized PBPK model. Two model predictions were made for experiment p03196 only. The other two experimental data shown are parts of the triplicate experiment, with different exposure intensity, of the 30-minute variable exposure scenario.

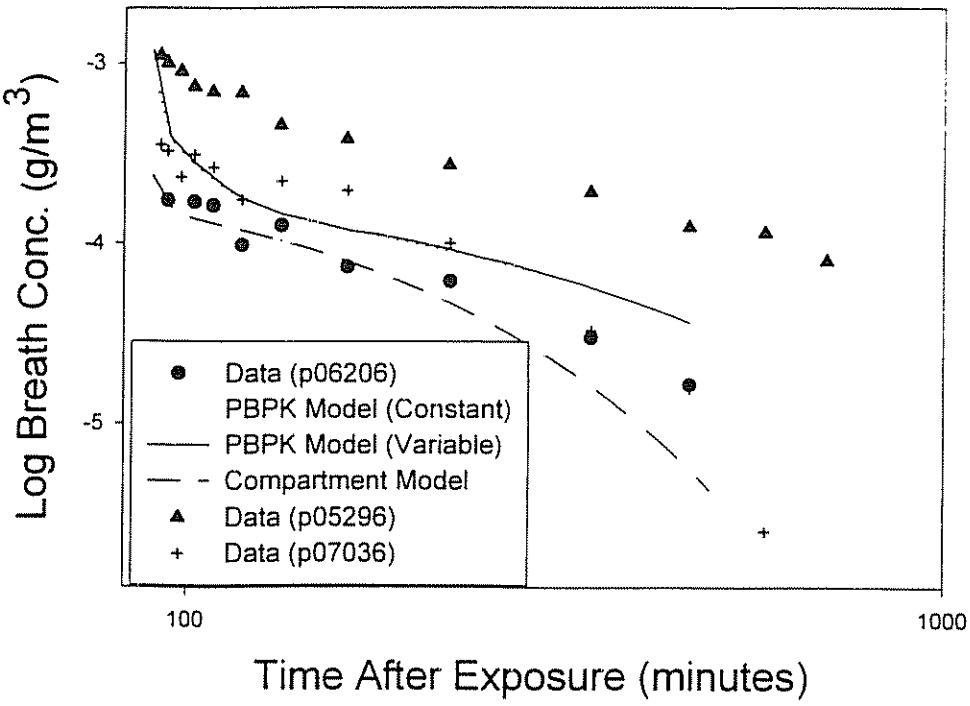

Figure 4.4 - The prediction of postexposure breath concentrations of the 90-minute controlled variable exposures from both the compartment and the optimized PBPK model. Two model predictions were made for experiment p06206 only. The other two experimental data shown are parts of the triplicate experiment, with different exposure intensity, of the 90-minute variable exposure scenario.

5. CONCLUSIONS AND IMPLICATIONS

1) Total exposure measurements, though provide a person's overall exposure, does not account for the differences in body kinetics caused by different exposure duration/concentration which can impact assessments of health risks.
2) It is necessary to know the exposure duration or use breath samples collected several hours after the exposure to estimate the past exposures and internal dose associated with environmental Perc exposures.
3) Elimination half-lives are affected by exposure duration/concentration, and are dependent upon the data used in the calculation, rather than constant values. Therefore elimination half-lives obtained from a specific exposure condition should not be applied to other exposures or individuals.
4) A PBPK model with optimized parameters can effectively predict the postexposure Perc breath concentrations of short-term environmental exposures, and a time-weighted average air concentration is an adequate exposure input for a PBPK model for fluctuating exposure conditions.
5) The PBPK model's assumption of instantaneous equilibrium between alveolar air and alveolar blood may not be valid. This violation particularly affects the model predictions of exhaled breath concentrations at the beginning of exposure and the early postexposure period.
6) Estimates of carcinogenic health risks associated with different Perc exposure levels need to consider the appropriate percentage metabolized for the exposure and dose

presented to the population since the percent dose metabolized in the liver after short-term, low-ppm environmental Perc exposures is 10-20 times higher than that after exposures at high-ppm occupational levels.

7) Finally, it is suggested to shorten the stay in a dry-cleaning store or in a laundromat with dry-cleaning operation, or increase the store's ventilation to reduce the air concentrations to minimize Perc exposures at low-ppm levels.

6. FUTURE RESEARCH

1) A larger study, which include larger numbers of subjects of both genders, will be needed to validate and apply the current findings to the general population
2) Other VOCs with different lipophilicity and metabolic capacity should be studied to test the hypothesis that distribution to the fat tissues plays an important role in determining the elimination kinetics.
3) The validity of the PBPK model's assumption of instantaneous equilibrium between the alveolar air and alveolar blood needs to be further studied. This may be done by examining the improvement of the model prediction after treating blood as a compartment rather than just a carrier.
4) The intra-individual variability needs to be studied and incorporated into PBPK model for developing a population-based PBPK for exposure and risk assessments.

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APPENDIX I

Description of the Controlled Environmental Facility

The Controlled Environment Facility (CEF) is a large stainless steel room in which the air flow, temperature and humidity can be varied and controlled. Low concentrations of the chemical compounds can be maintained in the facility by constant injection of the compounds into the air supply which flows through the volume without recirculation. The room itself is 7.3 ft. high by 13.5 ft. wide by 9 ft. deep for a volume of 887 cubic feet.

The chamber has an operating temperature range of 55^{0} to $80^{0} \pm 1^{0}$F. The relative humidity range is 40 to 80±2% with a 48^{0} F dewpoint limitation in the summer months. The air flow rate through the chamber can vary from 100 to 700 CFM and the chamber can be operated under either a positive or negative pressure of 0.1 inches of water. The air supply passes through a sequence of conditioning processes which include air cooling/heating, humidification/dehumidification, and filtration through carbon and HEPA filters. The air supply enters the chamber through two diffusers in the ceiling and exits through the perforated stainless steel floor to the exhaust vents. All controls are computer interfaced to maintain constant conditions in the chamber.

Perc are injected, at a predetermined rate, using a syringe pump (Model 355, Sage Instruments) into a heated three-neck flask for complete evaporation. The evaporized Perc are diluted by purified air and transported, through a heated tubing to prevent condensation, to the air inlet of the chamber. Perc are thus introduced into the air supply and are well mixed before entering the chamber to achieve a uniform concentration

throughout the chamber. Levels of chemicals in the chamber are continuously monitored to ensure the experimental levels are maintained. The instrumentation which monitors the chemical levels can be interfaced to the instrumentation that injects the chemicals. The injection of the chemicals will be automatically stopped if levels significantly deviate from the experimental conditions. A permanent record of all experimental conditions were maintained.

Subjects enter the chamber through an air lock which has two doors, one which opens to the outer room and the other which opens into the chamber. Each door has a sensor which, when the door is opened, activates a sliding bolt to the other door, preventing it from being opened. When the door is closed, the sensor deactivates the bolt and either door can then be opened. This prevents both doors from being open simultaneously and thus prevents air exchange between the outer room and the chamber. There is a 4 foot wide emergency exit on the front of the chamber which leads directly to the outer room. The latches on the doors are designed to prevent anyone from being locked in the room. Other safety features include a smoke detector, a sprinkler system and battery operated emergency lighting.

Researchers can view subjects participating in human exposure studies through a 4 ft. by 6 ft. two way mirror on the front of the CEF. A two way intercom system allows voice communication and human exposure sessions are videotaped for full documentation. An inertia pad in the floor isolates the body of the chamber from the exercise equipment used to physically stress the subjects. There is a bathroom in the chamber for extended exposure studies.

APPENDIX II

The PBPK Model Parameter Values

Parameter (unit)	Default[a]	Optimized[a]	Default[b]	Optimized[b]
Body Weight (Kg)	70.0	-[c]	77.0[d]	-
Alveolar Ventilation Rate (l/hr)	333.0	-	333.0	-
Cardiac Output Rate (l/hr)	330.0	-	330.0	-
Liver Fraction (Kg/Kg Bwt)	0.034	-	0.031	-
Fat Fraction (Kg/Kg Bwt)	0.23	-	0.30	-
Rapid-Perfused Tissue Fraction (Kg/Kg Bwt)	0.017	-	0.015	-
Slow-Perfused Tissue Fraction (Kg/Kg Bwt)	0.54	-	0.49	-
Skin Fraction (Kg/Kg Bwt)	0.04	-	0.036	-
Brain Fraction (Kg/Kg Bwt)	0.02	-	0.018	-
Liver Flow (l/Hour Cardiac Output)	0.24	-	0.24	-
Fat Flow (l/Hour Cardiac Output)	0.05	-	0.05	-
Rapid-Perfused Tissue Flow (l/Hour Cardiac Output)	0.41	-	0.41	-
Slow-Perfused Tissue Flow (l/Hour Cardiac Output)	0.14	-	0.14	-
Skin Flow (l/Hour Cardiac Output)	0.05	-	0.05	-
Brain Flow (l/Hour Cardiac Output)	0.11	-	0.11	-
Blood Partition Coefficient, PB	10.3	10.86	11.42	7.98
Brain Partition Coefficient, PBR	3.719	-	4.86	-
Liver Partition Coefficient, PL	3.719	1.84	4.86	-
Fat Partition Coefficient, PF	86.6	-	120.6	-
Rapid-Perfused Tissue Partition Coefficient, PR	3.719	2.86	4.86	-
Slow-Perfused Tissue Partition Coefficient, PS	1.058	1.56	2.69	2.35
Skin Partition Coefficient, PSK	26.72	-	26.72	-
Skin Water Coefficient	348.4	-	348.4	-
Skin Air Coefficient	275.2	-	275.2	-
Brain Partition Coefficient	3.719	-	3.719	-
Skin Permeable (cm/hr)	0.125	-	0.125	-
Vmax (mg/min)	0.1128	-	0.166	0.33
Km (mg/l)	4.56	-	2.16	0.716
Surface Area (cm^2)	20000	-	20000	-

a used for evaluating the field exposure data

b used for evaluating the controlled exposure data

c unchanged from default

d increase in subject's body weight, assuming solely fats

APPENDIX III

The Experimental Data

Units: Time in minutes; Air, Average Air and Breath concentration in mg/m^3. Average air concentration are shown inside the brackets. *: data lost or not measured; **: below the method detection limit.

1. Field Study:

	p0310			p0301			p1220	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.24	6.84	1.50	0.24	22.43	4.63	0.24	15.93	3.63
2.24	5.84	1.37	2.24	39.86	9.63	2.24	15.80	3.82
6.24	5.05	1.78	6.24	64.74	18.06	5.24	13.73	3.67
10.24	4.75	1.73	10.24	37.39	13.02	10.24	6.86	2.98
15.24	4.94	1.51	15.24	30.80	10.09	15.24	9.25	3.15
25.24	9.14	2.87	25.24	30.60	9.67	20.24	11.40	3.90
30.24	7.95	3.31	30.24	23.13	8.49	25.24	11.27	4.66
33.24		0.81	33.24		4.32	30.24	7.77	3.05
36.24		0.68	36.24		3.72	33.24		1.30
41.24		0.53	41.24		3.01	36.24		1.14
46.24		0.47	46.24		2.33	41.24		0.89
61.45		0.34	61.45		1.80	46.24		0.76
91.45		0.24	91.45		1.20	56.45		0.60
120.45		0.19	120.45		1.00	74.45		0.53
180.45		0.16	180.45		0.70	123.45		0.35
270.45		0.11	270.45		0.45	178.45		0.24
390.81		0.08	390.81		0.41	280.45		0.15
510.81		0.06	510.81		0.28	412.45		0.09
630.81		0.05	630.81		0.20			
	[5.68]			[32.90]			[9.86]	

	p1229			p0118			p0208	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.24	25.55	6.74	0.24	15.79	3.45	0.24	64.88	13.08
2.24	17.68	5.39	2.24	12.72	3.13	2.24	65.33	15.26
7.24	19.47	6.00	5.24	12.98	3.50	6.24	61.69	16.98
10.24	16.29	5.05	10.24	14.80	3.80	10.24	58.45	15.09
15.24	12.74	4.18	15.24	14.77	5.11	15.24	51.92	17.32
20.24	13.11	4.10	20.24	14.42	5.60	20.24	61.92	19.37
25.24	13.52	4.78	25.24	13.46	5.00	25.24	56.64	19.12
30.24	31.00	8.57	30.24	12.69	4.88	30.24	57.13	21.72
33.24		2.27	33.24		1.70	36.24		6.00
36.24		1.79	36.24		1.44	41.24		5.63
41.24		1.60	41.24		1.33	46.24		4.74
46.45		1.08	48.24		0.86	61.45		3.17
62.45		0.86	63.45		0.71	91.45		2.30
78.45		0.70	91.45		0.47	120.45		1.34
145.45		0.44	176.45		0.33	180.45		1.10
209.45		0.28	266.45		0.23	270.45		0.79
303.81		0.19	376.81		0.11	390.81		0.48
415.81		0.15	461.81		0.09	540.81		0.35
535.81		0.13	587.81		0.01	630.81		0.26
655.81		0.10	707.81		0.02			
	[10.71]			[9.17]			[42.05]	

	p0830			p1202			p1208	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.45	1.11	0.28	0.45	4.56	1.22	0.24	11.44	3.24
3.45	0.84	0.43	3.45	5.21	1.38	2.24	11.55	2.85
6.45	1.11	0.32	6.45	5.44	1.52	5.24	10.05	3.07
11.45	0.85	0.31	11.45	4.29	1.78	10.24	8.18	2.56
16.45	1.15	0.27	16.45	3.79	1.39	15.24	8.02	2.64
23.45	3.01	0.91	21.45	3.95	1.33	22.24	12.13	3.26
30.45	2.04	0.76	26.45	3.26	1.29	30.24	11.78	4.36
33.45		0.28	30.45	*	*	37.24	8.18	2.95
36.45		0.22	33.45		0.64	45.24	26.49	8.18
41.45		0.16	36.45		0.58	47.24		1.87
51.45		0.10	41.45		0.41	50.24		1.71
68.45		0.11	46.45		0.36	55.24		1.32
98.45		0.04	53.45		0.33	65.24		0.99
167.45		0.02	63.45		0.26	81.45		0.71
270.45		0.01	79.45		0.19	118.45		0.55
390.45		0.00	111.45		0.15	197.45		0.29
531.45		0.00	153.45		0.11	295.45		0.24
			243.45		0.10	434.81		0.17
			389.81		0.06	555.81		0.13
			509.81		0.06	674.81		0.10
			689.81		0.04			
	[1.71]			[4.28]			[10.70]	

	p1214			p0124			p1103	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.24	3.81	0.88	0.24	5.70	1.15	0.45	5.24	1.33
2.24	4.08	0.99	2.24	5.12	1.05	2.45	4.89	1.29
5.24	4.59	1.43	5.24	4.37	1.07	5.45	3.81	1.30
10.24	3.95	1.00	10.24	2.62	0.83	10.45	4.22	1.24
15.24	11.13	2.85	15.24	3.40	1.16	17.45	3.38	1.20
23.24	8.91	2.81	22.24	3.20	1.09	24.45	2.58	1.03
30.24	6.01	2.37	29.24	3.40	1.13	31.45	1.73	0.90
37.24	4.61	2.00	35.24	4.38	1.60	38.45	2.22	1.00
45.24	4.62	1.87	40.24	4.93	1.59	45.45	2.35	0.89
47.24		0.93	45.24	4.88	1.53	48.45		0.67
50.24		0.84	48.24		0.47	51.45		0.34
55.24		0.51	51.24		0.36	56.45		0.38
60.24		0.39	56.24		0.30	66.45		0.29
71.24		0.34	61.24		0.14	81.45		0.22
92.24		0.29	73.45		0.20	116.45		0.16
123.45		0.23	103.45		0.15	163.45		0.08
191.45		0.15	141.45		0.13	250.45		0.10
291.45		0.07	256.45		0.03	371.45		0.04
411.45		0.07	346.81		0.03	491.45		0.04
541.81		0.06	436.81		0.02	629.45		0.07
662.81		0.05	556.81		0.04	763.45		0.03
			676.81		0.00			
	[4.73]			[3.04]			[2.64]	

	p1110			p1122			p1129	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.45	0.00	0.03	0.45	2.03	0.53	0.24	1.953	0.61
2.45	0.07	0.06	2.45	2.97	0.80	2.24	1.588	0.48
5.45	0.11	0.05	5.45	5.39	1.48	5.24	0.555	0.34
10.45	0.35	0.14	11.45	2.82	1.11	10.24	0.472	0.24
17.45	0.51	0.17	15.45	1.75	0.78	17.24	0.225	0.20
24.45	0.39	0.15	22.45	11.55	4.10	24.24	0.277	0.20
31.45	0.69	0.28	29.45	1.02	0.83	31.24	0.221	0.22
38.45	0.99	0.44	36.45	1.74	0.91	38.24	0.363	0.24
45.45	0.83	0.33	41.45	0.86	0.63	45.24	0.289	0.24
48.45		0.09	45.45	0.79	0.57	47.24		0.01
51.45		0.07	48.45		0.32	51.45		0.05
56.45		0.03	51.45		0.25	56.45		0.04
66.45		0.03	56.45		0.20	66.45		0.02
81.45		0.00**	61.45		0.17	82.45		0.03
104.45		0.00	75.45		0.13	102.45		0.05
167.45		0.03	103.45		0.12	175.45		0.04
265.45		0.00	173.45		0.09	272.45		0.05
385.45		0.00	275.45		0.01	393.45		0.04
508.45		0.00	386.45		0.00	518.81		0.00
645.45		0.00	446.45		0.00	637.81		0.00
	[0.36]			[2.27]			[0.67]	

	p0106			p0131			p0216	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.24	2.93	0.65	0.24	0.51	0.12	0.24	13.07	2.96
2.24	3.68	0.84	2.24	0.36	0.11	2.24	12.16	2.93
5.24	4.56	1.19	5.24	0.00	0.06	5.24	11.22	3.18
10.24	2.70	0.93	10.24	6.17	1.33	10.24	8.55	2.85
17.24	3.32	0.10	17.24	2.14	0.96	17.24	12.96	3.41
24.24	2.52	1.02	24.24	4.09	1.33	24.24	10.91	3.41
31.24	2.50	0.95	31.24	3.63	1.04	31.24	8.13	3.18
38.24	1.66	0.81	38.24	1.57	0.87	28.24	6.31	2.83
45.24	1.33	0.66	45.24	0.22	0.52	45.24	5.28	2.55
52.24	1.02	0.57	50.24	3.62	1.09	52.24	5.43	2.58
60.24	0.92	0.54	55.24	1.25	0.72	60.24	4.79	2.33
63.24		0.24	60.24	1.21	0.70	63.24		1.15
66.24		0.23	63.24		0.60	66.24		1.01
71.24		0.18	66.24		0.35	71.24		0.86
77.45		0.12	71.24		0.18	76.24		0.66
90.24		0.10	76.24		0.12	91.45		0.53
121.24		0.09	91.45		0.12	120.45		0.46
178.45		0.09	125.45		0.08	150.45		0.35
238.45		0.06	150.45		0.05	210.45		0.22
328.45		0.04	210.45		0.02	300.81		0.17
448.81		0.04	312.81		0.02	420.81		0.14
568.81		0.04	420.81		0.05	540.81		0.12
678.81		0.04	540.81		0.02	660.81		0.06
			660.81		0.00			
	[1.81]			**[2.13]**			**[6.86]**	

	p0322			p1020			p1117	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.24	10.46	2.00	0.45	0.74	0.25	0.45	2.75	0.56
2.24	9.58	2.61	3.45	0.68	0.25	3.45	1.87	0.54
5.24	8.80	2.26	6.45	0.78	0.34	6.45	3.24	0.92
10.24	7.33	2.49	11.45	1.24	0.52	11.45	5.80	1.77
17.24	5.08	1.88	18.45	1.34	0.57	16.45	5.24	1.76
24.24	3.82	1.73	25.45	0.12	0.24	23.45	3.59	1.38
31.24	8.10	2.25	32.45	0.16	0.21	30.45	3.03	1.28
38.24	6.10	2.00	39.45	0.16	0.18	37.45	2.34	1.05
45.24	4.64	1.90	46.45	0.49	0.23	44.45	11.77	3.16
52.24	3.24	1.53	53.45	0.22	0.19	52.45	5.00	2.38
60.24	6.17	1.97	60.45	0.14	0.15	60.45	2.07	1.24
63.24		0.91	63.45		0.10	63.45		0.73
66.24		0.62	66.45		0.12	66.45		0.63
71.24		0.49	71.45		0.09	71.45		0.48
76.24		0.39	81.45		0.08	81.45		0.45
91.45		0.35	93.45		0.09	96.45		0.21
121.45		0.20	155.45		0.06	139.45		0.15
150.45		0.15	245.45		0.06	185.45		0.07
210.45		0.05	335.45		0.04	281.45		0.07
314.81		0.06	458.45		0.04	402.45		0.08
420.81		0.06	609.45		0.01	523.45		0.07
540.81		0.03	747.45		0.00	684.81		0.01
660.81		0.02						
	[4.41]			**[0.43]**			**[3.64]**	

	p0329	
Time	Air	Breath
0.24	2.42	0.37
2.24	3.10	0.71
5.24	4.37	1.03
10.24	3.18	0.91
17.24	5.97	1.57
24.24	7.60	1.87
31.24	5.19	1.47
38.24	2.75	1.21
45.24	1.79	0.97
52.24	3.34	1.29
60.24	2.22	1.08
63.24		0.40
66.24		0.33
71.24		0.36
95.45		0.33
121.45		0.14
150.45		0.12
210.45		0.13
300.45		0.18
443.8		0.05
540.8		0.00
660.8		0.00
	[2.60]	

2. CEF Study

	p12195			p01046			p02146	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.12	11.38	2.48	0.12	10.33	3.07	0.12	10.08	1.80
2.12	11.11	3.17	2.12	11.26	3.19	2.12	10.07	2.21
4.12	10.95	3.29	4.12	11.90	3.23	4.12	9.43	2.65
6.12	11.94	3.54	6.12	11.87	3.45	6.12	9.63	2.89
11.12	10.81	3.76	11.12	11.68	3.72	11.12	10.23	2.49
17.12	11.37	4.27	17.12	9.44	3.08	17.12	9.42	2.86
23.12	9.51	4.25	23.12	10.14	3.18	23.12	9.32	2.48
29.87	11.61	4.22	29.87	10.31	3.31	29.87	10.15	3.38
32.12		1.17	32.12		1.35	32.12		1.00
34.12		1.34	34.12		0.99	34.12		0.83
38.12		1.06	38.12		0.73	38.12		0.72
42.12		0.97	42.12		0.65	42.12		0.56
48.12		0.74	48.12		0.42	48.12		0.39
58.12		0.66	58.24		0.28	58.12		0.33
73.24		0.51	73.24		0.28	73.24		0.26
103.45		0.38	103.45		0.24	103.45		0.21
163.45		0.24	166.45		0.14	163.45		0.13
283.8		0.13	283.8		0.10	283.8		0.08
403.8		0.08	403.8		0.07	403.8		0.05
523.8		0.05	523.8		0.04	523.8		0.03
643.8		0.04	643.8		0.03	643.8		0.02
	[11.50]			**[10.54]**			**[9.70]**	

	p01166			p02276			p01106	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.12	3.43	0.95	0.12	3.95	0.74	0.12	3.82	0.74
2.12	3.55	1.02	2.12	4.50	0.99	2.12	3.32	0.93
4.12	3.54	1.00	4.12	3.81	1.19	4.12	3.04	0.79
6.12	4.08	1.13	6.12	4.55	1.20	6.12	3.93	0.87
11.12	3.39	1.16	11.12	4.60	1.34	11.12	3.72	1.01
20.12	4.43	1.47	20.12	4.27	1.21	20.12	3.30	1.07
30.12	4.60	1.75	30.12	4.32	1.29	30.12	3.75	1.33
45.12	4.88	1.77	45.12	3.86	1.71	45.12	3.54	1.25
60.12	4.50	1.71	60.12	4.28	0.53	60.12	3.35	1.31
75.12	4.90	1.86	75.12	3.94	0.92	75.12	3.83	1.55
82.12	4.48	1.77	82.12	5.77	1.64	82.12	4.18	1.80
89.87	4.26	2.25	89.87	7.03	1.55	89.87	3.90	1.99
92.12		0.71	92.12		0.54	92.12		0.71
94.12		0.55	94.12		0.48	94.12		0.50
98.12		0.48	98.12		0.44	98.12		0.52
102.24		0.50	102.24		0.43	102.24		0.53
108.24		0.43	108.24		0.38	108.24		0.42
118.24		0.32	118.24		0.34	118.24		0.36
133.45		0.30	133.45		0.30	133.45		0.30
163.45		0.22	163.45		0.21	163.45		0.19
223.8		0.17	223.8		0.16	223.8		0.15
343.8		0.09	343.8		0.11	343.8		0.09
463.8		0.07	463.8		0.06	463.8		0.06
583.8		0.05	583.8		0.05	583.8		0.04
710.8		0.04	710.8		0.04	703.8		0.03
	[4.29]			**[4.40]**			**[3.53]**	

	p03196			p03276			p04186	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.12	21.61	4.81	0.12	12.08	2.56	0.12	27.39	5.84
2.12	23.09	5.94	3.12	11.99	3.02	2.12	30.42	7.39
4.87	20.00	6.09	4.87	12.76	3.34	4.87	28.32	7.41
7.12	*	0.60	7.12	*	*	7.12	*	0.71
10.12	20.26	5.19	10.12	11.54	2.81	10.12	29.88	7.22
14.87	21.53	7.21	14.87	11.29	3.50	14.87	31.16	8.64
17.12	*	0.99	19.12	*	0.41	17.12	*	1.41
20.12	11.69	3.53	20.12	4.94	1.76	20.12	17.55	5.30
29.87	11.07	3.89	29.87	5.40	1.65	29.87	17.40	7.37
32.24		0.94	32.24		0.74	32.24		1.55
34.24		0.99	34.24		0.51	34.24		1.38
38.24		0.81	38.24		0.41	38.24		1.23
43.24		0.56	42.24		0.32	42.24		1.14
48.45		0.52	48.45		0.31	48.45		0.88
58.45		0.44	58.45		0.24	58.45		0.78
73.45		0.36	73.45		0.18	73.45		0.63
103.45		0.27	103.45		0.12	103.45		0.46
163.45		0.17	163.45		0.08	163.45		0.35
283.8		0.10	283.8		0.05	283.8		0.18
403.8		0.07	403.8		0.02	403.8		0.11
523.8		0.05	523.8		0.02	523.8		0.09
643.8		0.04	643.8		0.01	643.8		0.06
	[11.40]			**[5.52]**			**[15.63]**	

	p05296			p06206			p07036	
Time	Air	Breath	Time	Air	Breath	Time	Air	Breath
0.12	6.27	2.23	0.12	3.22	0.69	0.12	6.00	0.64
2.12	9.93	2.30	2.12	2.94	0.56	2.12	7.11	1.28
4.12	11.69	2.80	4.12	3.43	0.87	4.12	7.27	1.59
9.87	11.41	3.72	9.87	3.43	1.02	9.87	6.37	1.65
25.12	10.05	4.04	25.12	4.19	0.68	25.12	0.00	0.00
45.12	12.80	4.24	45.12	4.03	1.40	45.12	7.13	1.81
64.87	9.62	4.99	64.87	3.01	1.00	64.87	7.92	2.62
80.12	13.01	3.04	80.12	3.62	1.04	80.12	7.19	2.11
89.87	12.93	4.05	89.87	3.34	1.41	89.87	6.55	2.38
92.12		1.10	92.12		0.00	92.12		0.35
94.24		1.00	94.24		0.17	94.12		0.33
98.12		0.90	98.12		0.00	98.12		0.23
102.24		0.74	102.24		0.17	102.24		0.31
108.24		0.69	108.24		0.16	108.24		0.26
118.24		0.69	118.24		0.10	118.24		0.18
133.45		0.46	133.45		0.13	133.45		0.22
163.45		0.38	163.45		0.07	163.45		0.20
223.81		0.27	223.81		0.06	223.81		0.10
343.81		0.19	343.81		0.03	343.81		0.03
463.81		0.12	463.81		0.02	463.81		0.02
583.81		0.11	583.81		0.00	583.81		0.00
703.81		0.08	703.81		0	703.81		0.00
	[7.62]			[2.29]			[4.72]	

Curriculum Vita

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