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Revisions to Physiologically-Based Pharmacokinetic Modeling in the Development of Health Protective Levels for Trichloroethylene

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Henry M. Jackson Foundation for the Advancement of Military Medicine

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1.0 SUMMARY

Trichloroethylene (TCE) was commonly used as a solvent by the Department of Defense (DoD), as well as at private sector facilities. Releases to the environment from its past use make TCE one of the most common contaminants encountered at hazardous waste sites. In a joint effort through the TriService Toxicology Consortium, the Air Force Research Laboratory (AFRL) participated in the development of DoD health protective levels for TCE. This participation was at the request for technical support by Mr. John Seibert at the Environment, Safety and Occupational Health Directorate in the Office of the Assistant Secretary of Defense (Energy, Installations and Environment) and funding was from the U.S. Army Corps of Engineers. The work completed by the AFRL was detailed in Covington *et al.* (2019).

The prior work was revised based on a National Academies of Sciences, Engineering, and Medicine (NASEM) review of the occupational exposure limit (OEL) development (NASEM, 2019). Revisions related to the physiologically-based pharmacokinetic modeling portion of the OEL development are reported here. Details for dose metric predictions and human equivalent concentration estimates for which the points of departure did not change based on NASEM recommendations are also included here for completeness. Much of this text is the same as in Covington *et al.* (2019) with additions and modifications made as necessary to reflect the revisions as a result of comments and suggestions from the NASEM review.

2.0 INTRODUCTION

Trichloroethylene (TCE) was commonly used as a solvent by the DoD, as well as at private sector facilities. Releases to the environment from its past use make TCE one of the most common contaminants encountered at hazardous waste sites. In 2011 the United States Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS) program finalized their toxicological review for TCE (USEPA, 2011). The study used for dose response for the developmental endpoint reference concentration (RfC) is controversial; the USEPA used Johnson *et al.* (2003), a rat ingestion study, to develop the RfC for inhaled exposures. There is value, however, in better understanding the physiologically-based pharmacokinetic (PBPK) model used for route-to-route and inter- and intra-species extrapolation and the parameters to which the model is sensitive. The Air Force Research Laboratory (AFRL) previously worked with USEPA to develop a harmonized PBPK model for TCE (Covington *et al.*, 2006; Hack *et al.*, 2006) but it was updated by USEPA for their use in their toxicological review (USEPA, 2011). A more mechanistic understanding of the PBPK model will provide insight into the uncertainty associated with its use by USEPA (2011) to derive a human RfC. This understanding will enhance risk communication efforts to the public and DoD personnel that may be exposed to TCE via the inhalation pathway. It will also be useful to those that may use Johnson *et al.* (2003) to determine values protective of occupational health and enable estimation of the impact that a repeat of this study (DeSesso *et al.*, 2019) may have on the RfC.

A request was made to the AFRL for technical support from the Air Force Civil Engineer Center (AFCEC) and Mr. John Seibert at the Environment, Safety and Occupational Health Directorate in the Office of the Assistant Secretary of Defense (Energy, Installations and Environment) (OASD EI&E) to participate in developing DoD health protective levels for TCE by participating in a joint effort through the TriService Toxicology Consortium (TSTC). The AFRL portion of this work is detailed in Covington *et al.* (2019). These efforts assisted in developing DoD health protective levels for TCE.

Based on a NASEM review of the OEL development (NASEM, 2019), the prior work (Covington *et al.*, 2019) was revised. The purpose of this report is to identify the revisions related to the PBPK modeling portion of the OEL development. Details for dose metric predictions and human equivalent concentration (HEC) estimates for which the point of departure (POD) did not change based on NASEM recommendations are also included here for completeness. Much of this text is the same as in Covington *et al.* (2019) with additions and modifications made as necessary to reflect the resultant revisions based on comments and suggestions from the NASEM review (NASEM, 2019).

3.0 METHODS

Complete tables of model parameters can be found in Appendix A. Model code for this follow-on work was not altered from the code used previously (Covington *et al.*, 2019), but is given again in Appendix B here for easier reference. Script files (*i.e.*, M files) which were not altered from the previous efforts are also presented again here in Appendices C, D, E and F for easier reference.

3.1 Linearity Analysis

One of the comments from reviewers of the prior work was the lack of a linearity analysis with regards to the benchmark dose (BMD) analysis. A linearity analysis can help determine if internal dose metrics should be used for the BMD analysis or if external doses are appropriately representative. This determination is made based on whether the model predictions for the internal dose metric of concern demonstrate a linear relationship with the external doses used to predict these dose metrics. If the model is not linear in the dose range of concern, then the lower limit of the BMD (BMDL) derived from external doses will not appropriately account for biological processes, such as saturable metabolism, and could significantly over- or under-predict a HEC derived from a rodent BMDL. In this case, internal dose metrics should be used to estimate the BMDL in order to adequately account for the non-linear biological processes.

A linearity analysis was conducted for the studies for which BMDLs were used in deriving the HECs in the prior work (see the nine studies in Table 1 for which PODs are in blue text). BMDLs were not estimated for any of the new studies included in this revised work. The linearity analysis was performed by plotting the model-predicted internal dose metric of concern (*e.g.*, peak TCE blood concentration, total metabolized, total metabolized in liver, *etc.*) versus the external dose for various concentrations below the maximum study dose and then fitting a line through the resulting points. The internal dose metric of concern for each study (see Table 5) was specified by Dr. Emily Lent (U.S. Army Public Health Center). Lines were fit to the entire range of points as well as through a subset of points in the region of the BMDL (see Table 1) derived using external dose.

3.2 Prediction of Dose Metrics for OEL Determination

A spreadsheet of PODs for animal studies for which internal dose metrics needed to be simulated was originally sent by Dr. Thomas Sussan (U.S. Army Public Health Center) along with the published studies. These studies are summarized in Table 1. Additional published studies, summarized in Table 2, and updated PODs were sent by Dr. Emily Lent based on suggestions and comments from the NASEM review (NASEM, 2019). Script files (Appendices D and E) were updated or created as necessary for PODs. All simulations in these script files used the mean posterior animal parameters (Appendix A, Tables A1 and A2) and study-specific parameter settings (*e.g.*, body weights, dose, exposure scenario); these were unchanged from the previous work for the originally sent studies. For the new studies, values to be used for body weights not reported in the studies were provided by Dr. Lent and were noted as such in the script files. For longer term exposures, the model was run until steady-state or periodicity was reached rather than for the entire length of the study in order to decrease computational time. Periodicity was assumed to have been reached when both the peak concentrations of interest and the weekly dose metrics were no longer changing from one week to the next.

Table 1. Summary of Originally Selected Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Exposure Duration	Point of Departure ^c
Adams <i>et al.</i> (1951)	Inh	Rat	$\frac{F}{M}$	Kidney	7 hours/day, ~5 days/week for 6 to 8 months	200 ppm
			$\frac{F}{M}$	Liver		
Albee <i>et al.</i> (2006)	Inh	Rat	$\frac{F}{M}$	Neuro	6 hours/day, 5 days/week for 13 weeks	800 ppm
Arito <i>et al.</i> (1994)	Inh	Rat	M	Neuro	8 hours/day, 5 days/week for 6 weeks	18.4 ppm ^d
Bushnell <i>et al.</i> (1997)	Inh	Rat	M	Neuro	1 hour/day for 1 day	1366 ppm ^d
Carney <i>et al.</i> (2006)	Inh	Rat	F	Develop	6 hours/day, 7 days/week from gestational days 6-20	600 ppm
Cosby & Dukelow (1992)	Gav	Mouse	F	Develop	gestational days 1-5, 6-10, or 11-15	240.2 mg/kg/day
Crofton & Zhao (1997)	Inh	Rat	M	Neuro	6 hours/day, 5 days/week for 13 weeks	1367 ppm ^d
Fisher <i>et al.</i> (2001)	Gav	Rat	F	Develop	gestational days 6-15	500 mg/kg/day
George <i>et al.</i> (1986)	Diet	Mouse	M	Repro	1 week premating + 98 days cohabitation + 3 weeks segregation	750 mg/kg/day
Griffin <i>et al.</i> (2000)	DW	Mouse	F	Immuno	4 or 32 weeks	13.4 mg/kg/day ^d
Healy <i>et al.</i> (1982)	Inh	Rat	F	Develop	4 hours/day for gestational days 8-21	100 ppm
Jaspers <i>et al.</i> (1993)	Inh	Rat	M	Neuro	18 hours/day, 5 days/week for 3 weeks	1500 ppm
Kaneko <i>et al.</i> (2000)	Inh	Mouse	M	Immuno	4 hours/day, 6 days/week for 8 weeks	500 ppm

ppm = parts per million; mg/kg/day = milligrams per kilogram of body weight per day

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

^c Green values are no adverse effect levels (NOAELs), red are lowest observed effect levels (LOAELs) and blue are BMDLs.

^d These BMDLs were based on external dose and were revised for this new work (see Table 5) to be based on internal dose.

Table 1 (continued). Summary of Originally Selected Animal Studies

Study Name	Route^a	Species	Sex	Domain^b	Exposure Duration	Point of Departure^c
Kjellstrand <i>et al.</i> (1983)	Inh	Mouse	$\frac{F}{M}$	Liver	continuous for 30 days	37 ppm
Kumar <i>et al.</i> (2000, 2001)	Inh	Rat	M	$\frac{\text{Repro}}{\text{Liver}}$	4 hours/day, 5 days/week for 12 or 24 weeks	376 ppm
Land <i>et al.</i> (1981)	Inh	Mouse	M	Repro	4 hours/day for 5 days	575 ppm ^d
Maltoni <i>et al.</i> (1988)	Inh	Rat	M	Kidney	7 hours/day, 5 days/week for 2 years	221 ppm ^d
Manson <i>et al.</i> (1984)	Gav	Rat	F	Develop	2 weeks before mating + mating + gestation	100 mg/kg/day
Narotsky <i>et al.</i> (1995)	Gav	Rat	F	Develop	gestational days 6-15	36 mg/kg/day ^d
Ramdhan <i>et al.</i> (2010)	Inh	Mouse	M	Liver	8 hours/day for 7 days	546 ppm ^d
Sanders <i>et al.</i> (1982)	DW	Mouse	$\frac{F}{M}$	Immuno	4 or 6 months	18.4 mg/kg/day
Schwetz <i>et al.</i> (1975)	Inh	$\frac{\text{Mouse}}{\text{Rat}}$	F	Develop	7 hours/day for gestational days 6-15	306 ppm
Woolhiser <i>et al.</i> (2006)	Inh	Rat	F	$\frac{\text{Immuno}}{\text{Kidney}} \frac{\text{Liver}}$	6 hours/day, 5 days/week for 4 weeks	$\frac{243 \text{ ppm}^d}{90 \text{ ppm}^d}$ 108 ppm ^d
Wu & Berger (2007)	DW	Rat	F	Repro	2 weeks	66 mg/kg/day

ppm = parts per million; mg/kg/day = milligrams per kilogram of body weight per day

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

^c Green values are no adverse effect levels (NOAELs), red are lowest observed effect levels (LOAELs) and blue are BMDLs.

^d These BMDLs were based on external dose and were revised for this new work (see Table 5) to be based on internal dose.

Table 2. Summary of Newly Selected Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Exposure Duration	Point of Departure ^c
Blossom <i>et al.</i> (2017)	DW	Mouse	F	Develop Immuno	2 weeks premating + mating + gestation + to 8 weeks	2.96 mg/kg/day 2.96 mg/kg/day
Gilbert <i>et al.</i> (2014)	DW	Mouse	F	Immuno	gestation	3.42 mg/kg/day
Isaacson & Taylor (1989)	DW	Rat	F	Develop	2 weeks prior to mating until post-natal day 21 (~8 weeks)	16 mg/kg/day
Zenick <i>et al.</i> (1984)	Gav	Rat	M	Repro	5 days/week for 6 weeks	100 mg/kg/day

mg/kg/day = milligrams per kilogram of body weight per day

^a “DW” is for drinking water and “Gav” is for gavage.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

^c Green values are NOAELs, red are LOAELs and blue are BMDLs.

Details of settings for the simulations are given in Table 3. For studies where the POD was a BMDL, the PBPK model was run for multiple doses rather than a single dose in order to determine internal doses to correspond to external doses. These internal doses were subsequently used to re-estimate BMDLs by Dr. Emily Lent. For the Bushnell *et al.* (1997) study, the dose of 600 ppm was not run as this dose group was dropped by the study investigators so there were no data available for that group for use in BMDL analysis. The doses of 2000 and 2400 ppm were also not run as it appeared that the rats developed a tolerance and the response data for those doses was actually lower than for lower doses and were not included in BMD analysis. The original script files were updated and modified as needed and new script files were created as necessary; all new and modified script files are included in Appendices C, D and E along with those that did not require changes.

Table 3. Summary of Simulation Settings for Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Body Weight (kg)	Dose	Exposure Duration
Adams <i>et al.</i>	Inh	Rat	F	Kidney	0.207	200 ppm	7 hours/day, 5 days/week for 6 weeks (periodicity)
			M		0.349		
			F	Liver	0.207		
			M		0.349		
Albee <i>et al.</i>	Inh	Rat	F	Neuro	0.2	800 ppm	6 hours/day, 5 days/week for 13 weeks
			M		0.4		
Arito <i>et al.</i>	Inh	Rat	M	Neuro	0.375	50 ppm	8 hours/day, 5 day/week for 6 weeks
						100 ppm	
						300 ppm	
Blossom <i>et al.</i>	DW	Mouse	F	Develop Immuno	0.045	2.96 mg/kg/day	5 days (steady state)
Bushnell <i>et al.</i>	Inh	Rat	M	Neuro	0.35	400 ppm	1 hour/day for 1 day
						800 ppm	
						1200 ppm	
						1600 ppm	
Carney <i>et al.</i>	Inh	Rat	F	Develop	0.225	600 ppm	6 hours/day, 7 days/week for 15 days
Cosby & Dukelow	Gav	Mouse	F	Develop	0.022	240.2 mg/kg/day	Daily for 5 days
Crofton & Zhao	Inh	Rat	M	Neuro	0.7	800 ppm	6 hours/day, 5 days/week for 13 weeks
						1600 ppm	
						2400 ppm	
						3200 ppm	
Fisher <i>et al.</i>	Gav	Rat	F	Develop	0.25	500 mg/kg/day	Daily for 10 days
George <i>et al.</i>	Diet	Mouse	M	Repro	0.038	750 mg/kg/day	10 hours/day, 7 days/week for 6 weeks (periodicity)
Gilbert <i>et al.</i>	DW	Mouse	F	Immuno	0.045	3.42 mg/kg/day	5 days (steady state)
Griffin <i>et al.</i>	DW	Mouse	F	Immuno	0.043	21 mg/kg/day	12 days (steady state)
						100 mg/kg/day	
						400 mg/kg/day	

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

Table 3 (continued). Summary of Simulation Settings for Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Body Weight (kg)	Dose	Exposure Duration
Healy <i>et al.</i>	Inh	Rat	F	Develop	0.3	100 ppm	4 hours/day, 7 days/week for 14 days
Isaacson & Taylor	DW	Rat	F	Develop	0.25	16 mg/kg/day	5 days (steady state)
Jaspers <i>et al.</i>	Inh	Rat	M	Neuro	0.24	1500 ppm	18 hours/day, 5 days/week for 3 weeks
Kaneko <i>et al.</i>	Inh	Mouse	M	Immuno	0.047	500 ppm	4 hours/day, 6 days/week for 5 weeks (periodicity)
Kjellstrand <i>et al.</i>	Inh	Mouse	$\frac{F}{M}$	Liver	$\frac{0.035}{0.0362}$	37 ppm	Continuous for 30 days
Kumar <i>et al.</i>	Inh	Rat	M	<u>Repro</u> Liver	0.5	376 ppm	4 hours/day, 5 days/week for 7 weeks (periodicity)
Land <i>et al.</i>	Inh	Mouse	M	Repro	0.026	$\frac{200 \text{ ppm}}{2000 \text{ ppm}}$	4 hours/day for 5 days
Maltoni <i>et al.</i>	Inh	Rat	M	Kidney	0.85	$\frac{100 \text{ ppm}}{300 \text{ ppm}}$ 600 ppm	7 hours/day, 5 days/week for 5 week (periodicity)
Manson <i>et al.</i>	Gav	Rat	F	Develop	0.405	100 mg/kg/day	7 days/week for 3 weeks (periodicity)
Narotsky <i>et al.</i>	Gav	Rat	F	Develop	0.175	$\frac{475 \text{ mg/kg/day}}{633 \text{ mg/kg/day}}$ $\frac{844 \text{ mg/kg/day}}{1125 \text{ mg/kg/day}}$	Daily for 10 days
Ramdhan <i>et al.</i>	Inh	Mouse	M	Liver	0.025	$\frac{1000 \text{ ppm}}{2000 \text{ ppm}}$	8 hours/day for 7 days
Sanders <i>et al.</i>	DW	Mouse	$\frac{F}{M}$	Immuno	$\frac{0.04}{0.049}$	18.4 mg/kg/day	Daily for 13 days (steady state)

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

Table 3 (continued). Summary of Simulation Settings for Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Body Weight (kg)	Dose	Exposure Duration
Schwetz <i>et al.</i>	Inh	<u>Mouse</u> Rat	F	Develop	<u>0.054</u> 0.37	306 ppm	7 hours/day for 10 days
Woolhiser <i>et al.</i>	Inh	Rat	F	Immuno, Kidney & Liver	0.2146	<u>100 ppm</u> <u>300 ppm</u> 1000 ppm	6 hours/day, 5 days/week for 4 weeks
Wu & Berger	DW	Rat	F	Repro	0.2	66 mg/kg/day	Daily for 2 weeks
Zenick <i>et al.</i>	Gav	Rat	M	Repro	0.3947	100 mg/kg/day	Daily for 6 weeks

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

For daily exposures, the dose metrics are the values for last day of exposure; for exposures that were not daily (*i.e.*, 6 hours/day for 5 days/week), the values are for the last week of exposure and are then divided by 7 to get an average daily value. All simulations were checked to ensure that any predicted negative values were within an acceptable tolerance. The dose metrics output and the corresponding units are:

- Peak concentration of TCE in the blood (milligrams per liter or mg/L)
- Area under the curve (AUC) for TCE in the blood (milligrams-hour per liter per day or mg-h/L/d)
- Total amount of TCE metabolized scaled by body weight (milligrams per kg to the 0.75 power per day or mg/kg^{0.75}/d)
- Total amount of TCE metabolized by oxidation scaled by body weight (mg/kg^{0.75}/d)
- Peak concentration of TCE in the liver (mg/L)
- AUC for TCE in the liver (mg-h/L/d)
- Amount of TCE metabolized in the liver scaled by body weight (mg/kg^{0.75}/d)
- Peak concentration of TCE in the kidney (mg/L)
- AUC for TCE in the kidney (mg-h/L/d)
- Amount of TCE metabolized in the kidney scaled by body weight (mg/kg^{0.75}/d)

3.3 Estimation of HECs

The original script files created to fit the external inhalation concentration necessary in the human (*i.e.*, HEC) to match the internal dose metrics predicted from the animal studies were updated as necessary for the changes in animal PODs and to account for the additional studies added; all script files for simulations to estimate HECs are included in Appendix F. The HECs were estimated for both male and female using the same average posterior parameter values

(Appendix A, Tables A3 and A4) as used for the previous work. These simulations were for either continuous inhalation exposure or occupational exposure (*i.e.*, 8 hours/day, 5 days/week) and all simulations were run long enough to reach steady-state or periodicity. As with the animal predictions, all simulations were checked to ensure that any predicted negative values were within an acceptable tolerance.

4.0 RESULTS

4.1 Linearity Analysis

Resulting plots for the linearity analysis for the nine studies with BMDLs as the PODs are shown in Figures 1 through 11. Panel A for each figure shows the entire range of external doses and Panel B shows a subset of the doses that are close to the BMDL from the prior work. Blue squares denote the actual study doses while the red circles denote randomly selected external doses to fill in the external dose range. The solid red line is fit to all of the points while the solid purple line is fit to a subset of points in the range of the BMDL estimated in the prior work using external dose. This external BMDL is also shown in the figures with a vertical blue line while the newly estimated BMDL estimated using internal dose metric values are shown with a green line for comparison. Dotted red and purple lines denote the predicted internal dose metric based on the fit lines for an external dose equivalent to the BMDL derived from external dose.

For the majority of the studies, the relationship between internal dose metric and external dose when including the entire dose range is not linear although some are closer than others. The one exception is the Griffin *et al.* (2000) study. For the remaining studies, however, narrowing the range of doses to those near the BMDL from the prior work do exhibit almost linear relationships. Even though the model is fairly linear in the region of the BMDLs, it was decided to re-estimate the BMDLs using internal dose metric values so as to take full advantage of having a PBPK model.

It should be noted that the BMDLs derived from the internal dose metrics, while close to the fit line within the range of the external dose BMDL for some studies, is much further away for other studies. The newly derived BMDLs using internal dose metric values were estimated using Bayesian BMD analysis while the BMDLs from the prior work did not. Thus it is uncertain how much of the deviation is from deriving the BMDL from internal dose metrics versus external dose and how much is from using Bayesian BMD analysis.

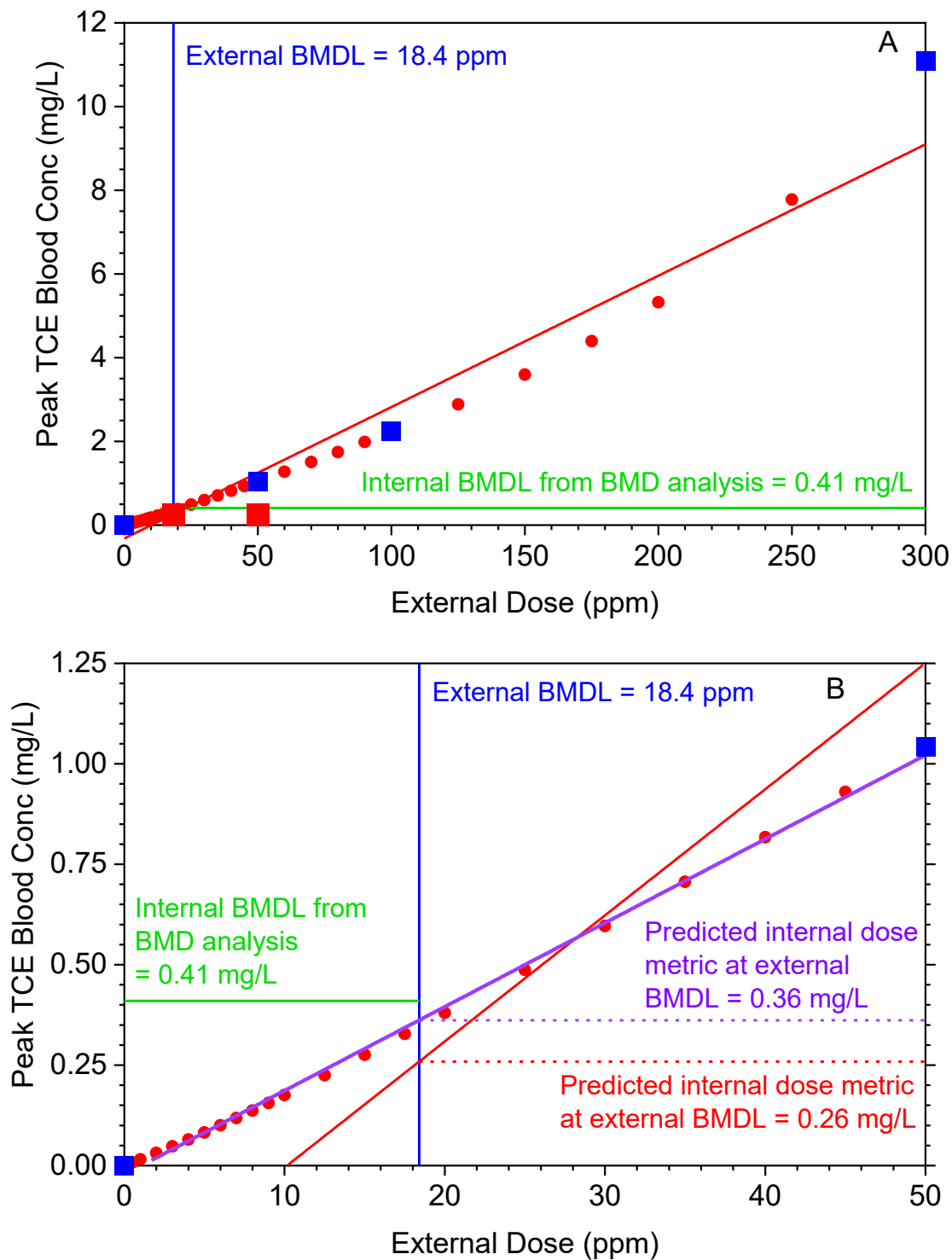


Figure 1. Linearity Analysis Plots for Arito *et al.* (1994). See text above for description of lines and symbols.

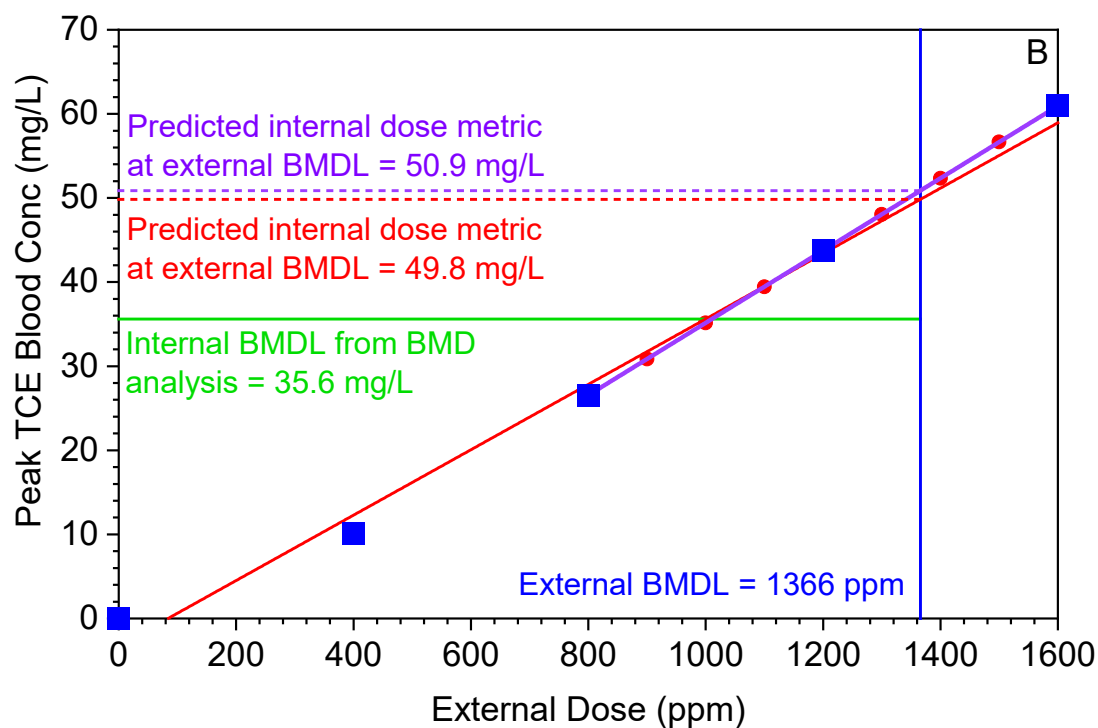
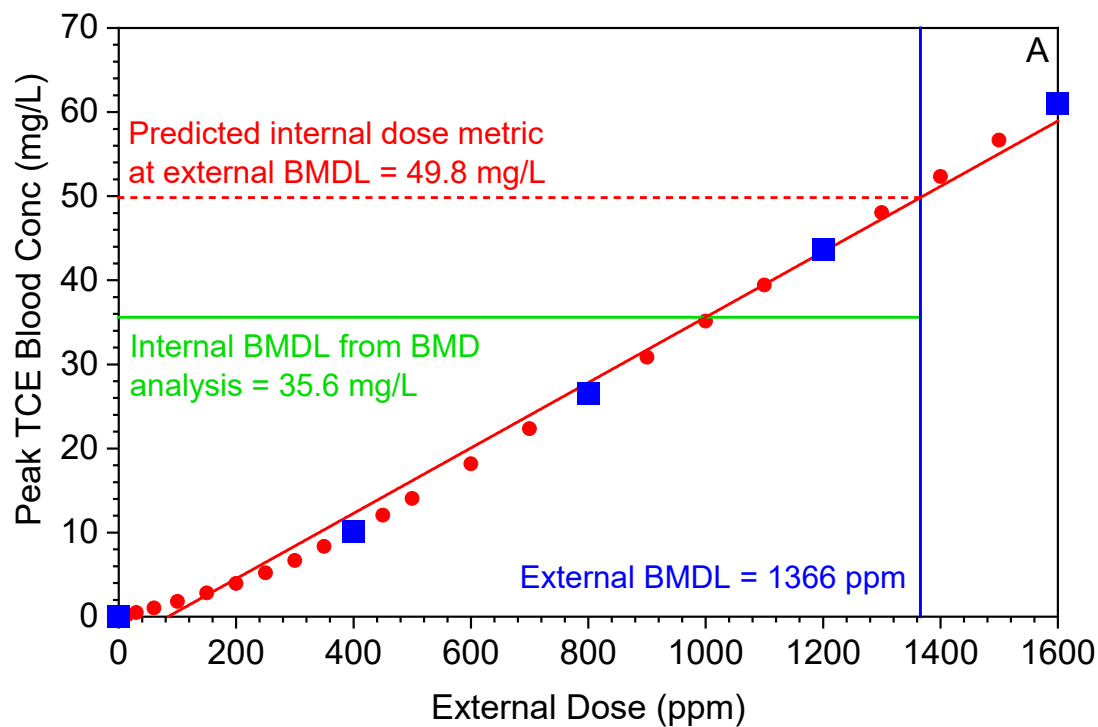


Figure 2. Linearity Analysis Plots for Bushnell *et al.* (1997). See text above for description of lines and symbols.

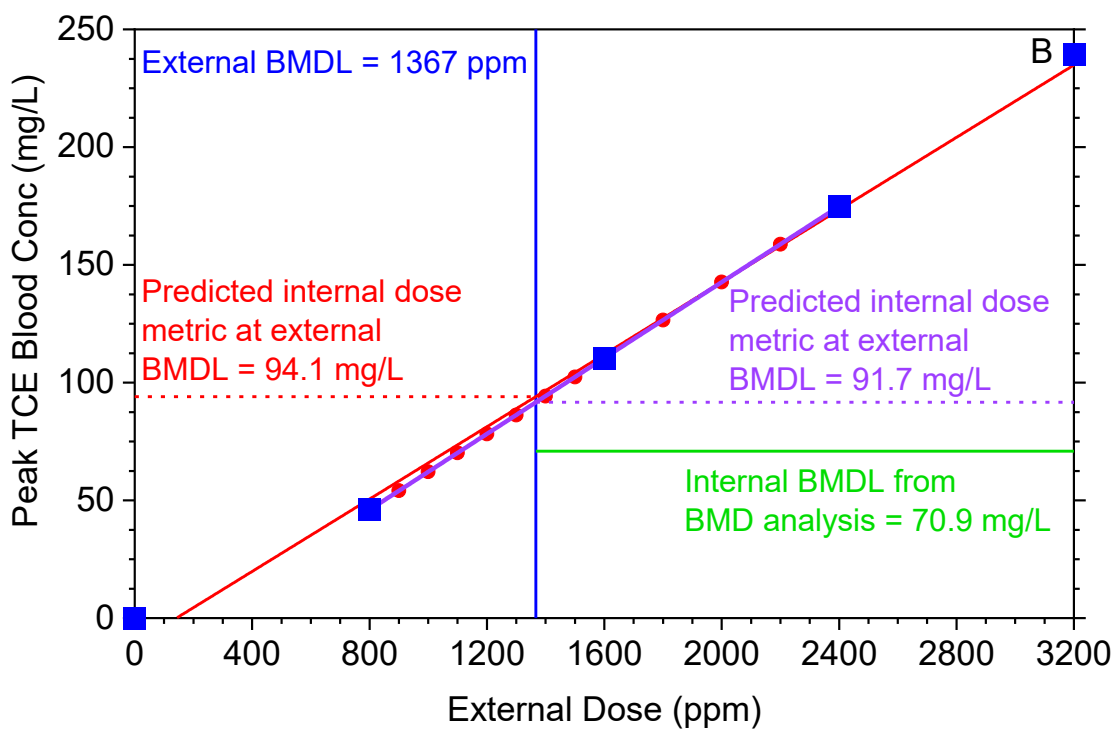
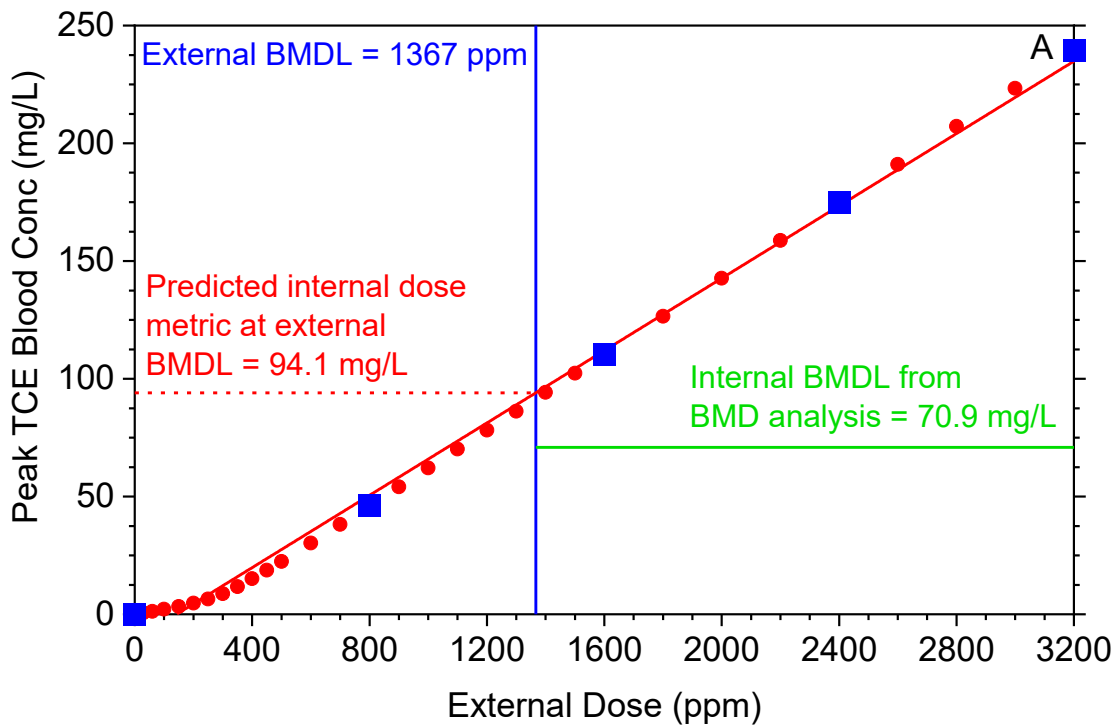


Figure 3. Linearity Analysis Plots for Crofton and Zhao (1997). See text above for description of lines and symbols.

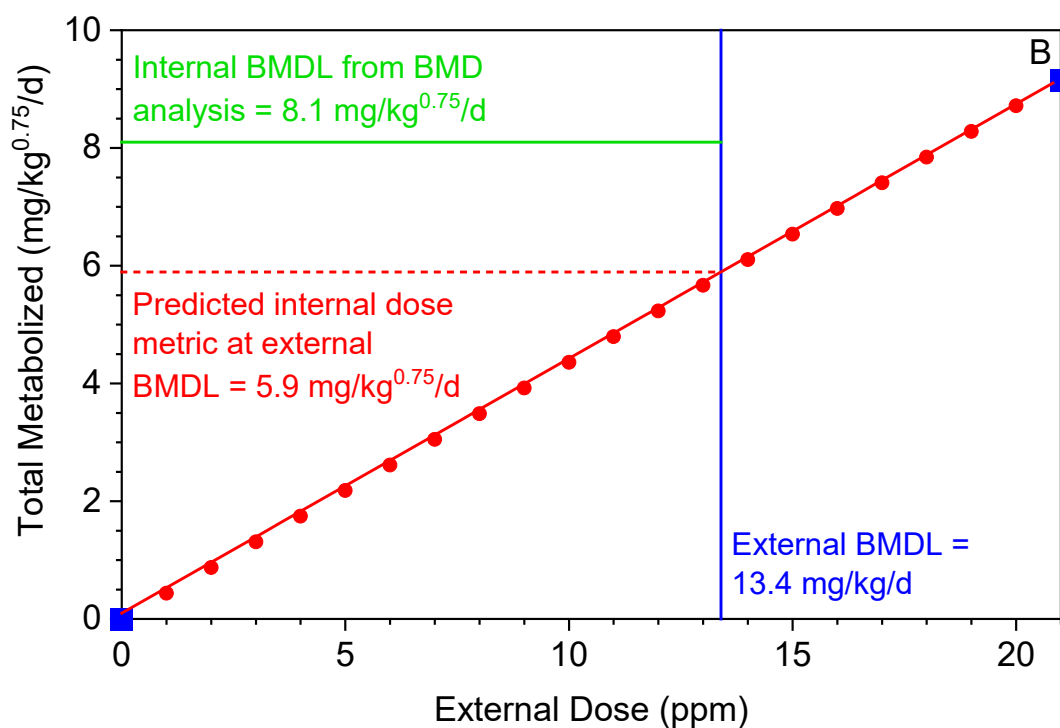
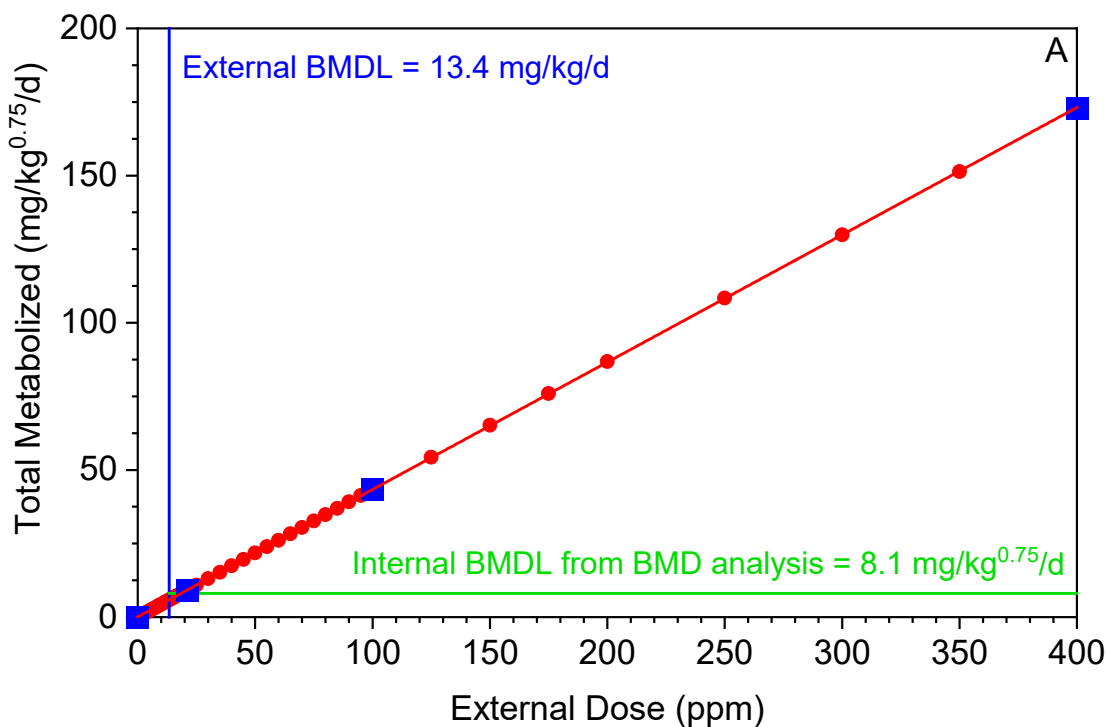


Figure 4. Linearity Analysis Plots for Griffin *et al.* (2000). See text above for description of lines and symbols.

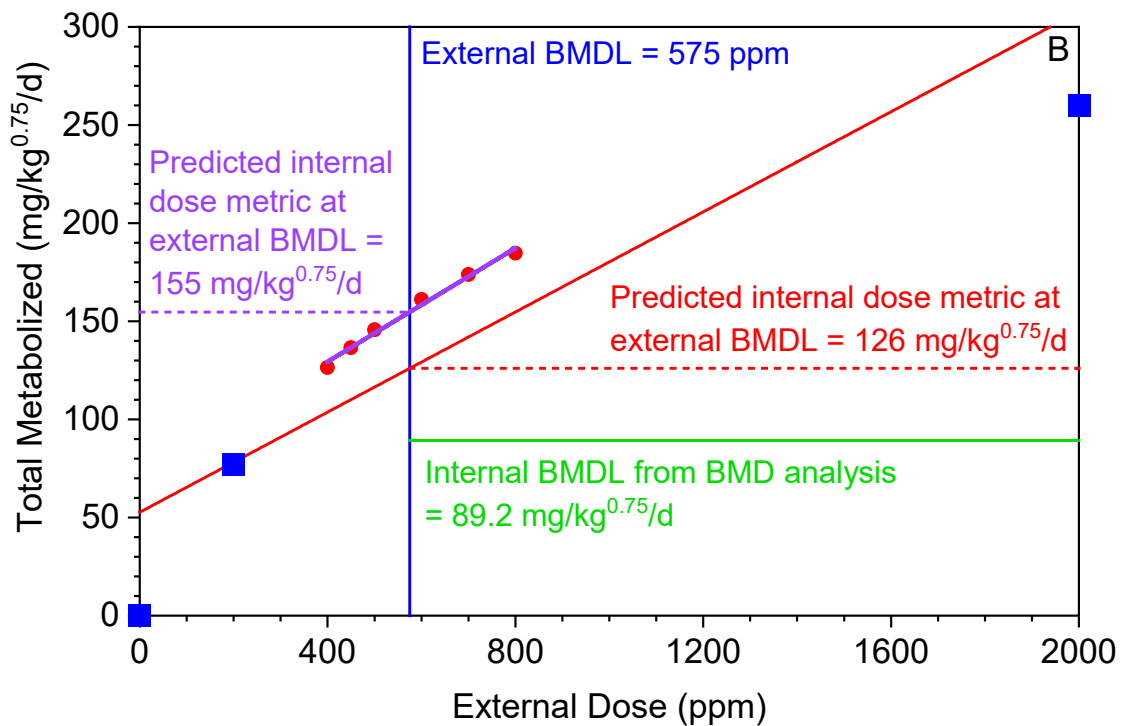
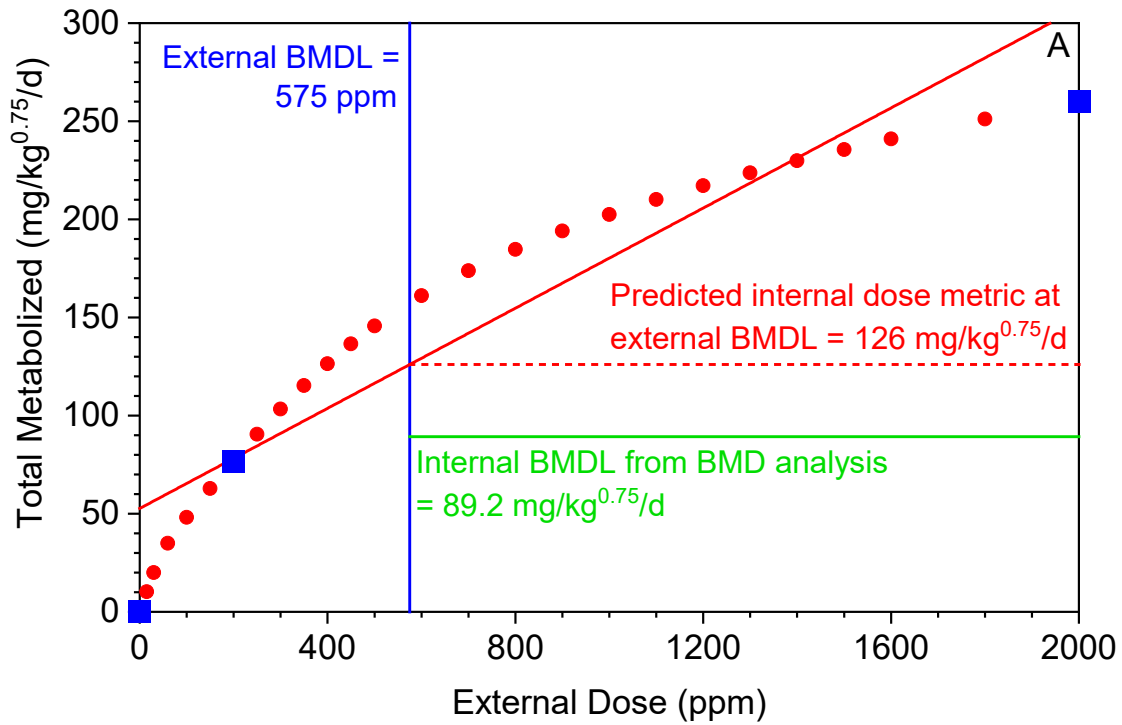


Figure 5. Linearity Analysis Plots for Land *et al.* (1981). See text above for description of lines and symbols.

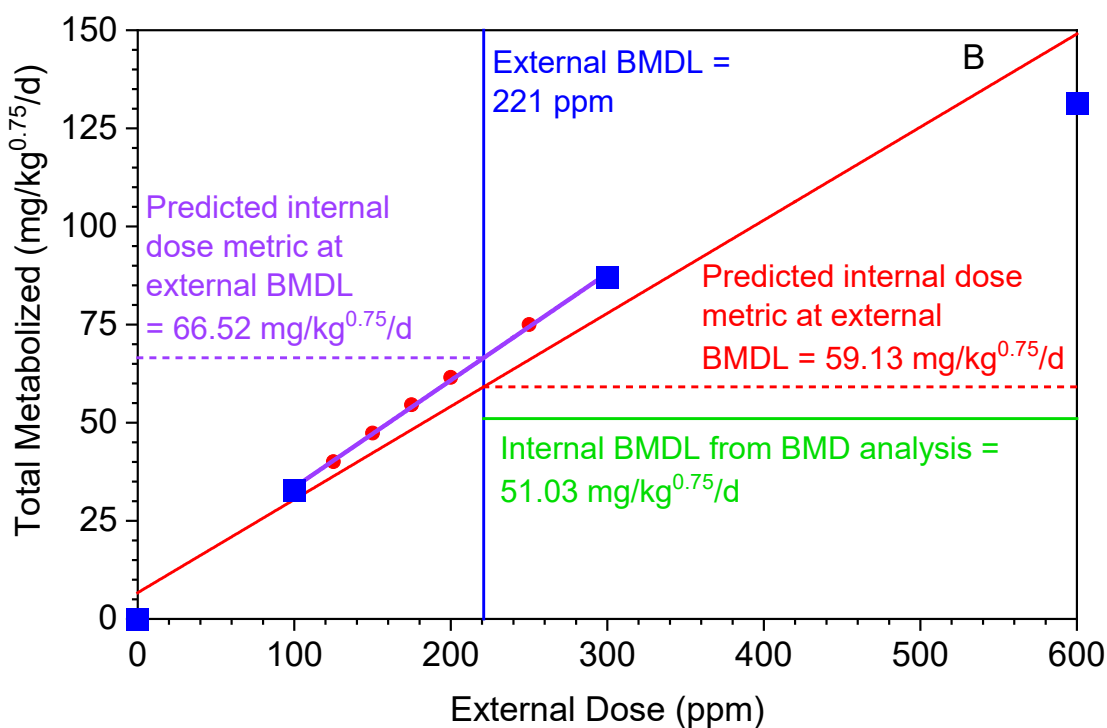
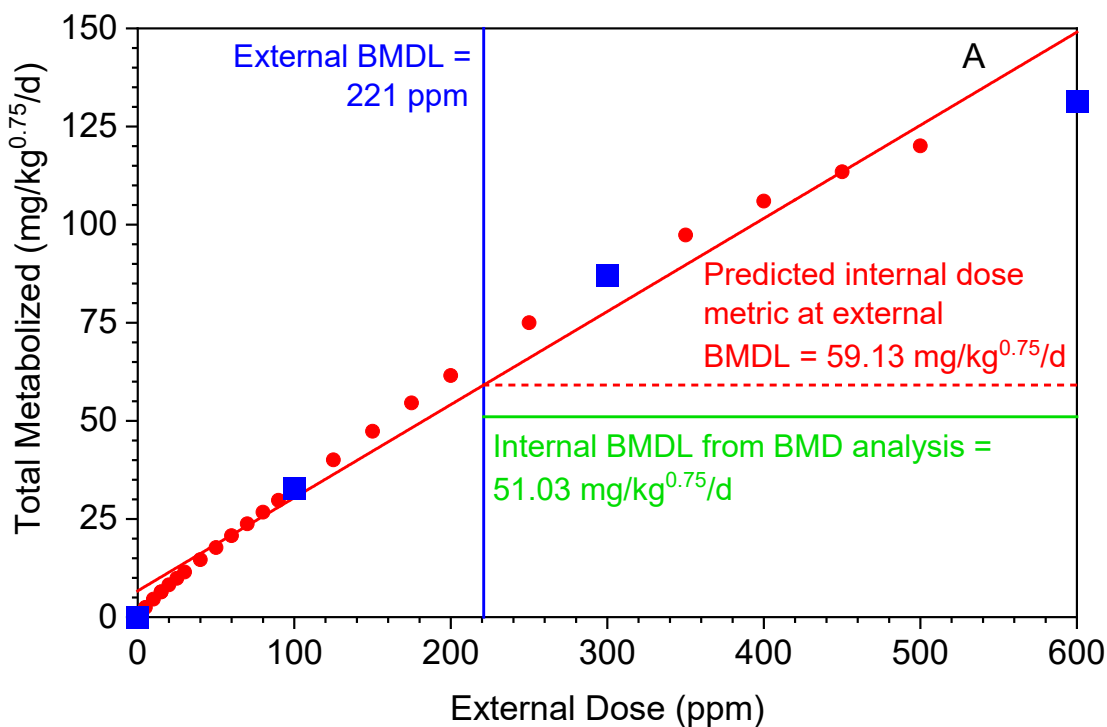


Figure 6. Linearity Analysis Plots for Maltoni *et al.* (1988). See text above for description of lines and symbols.

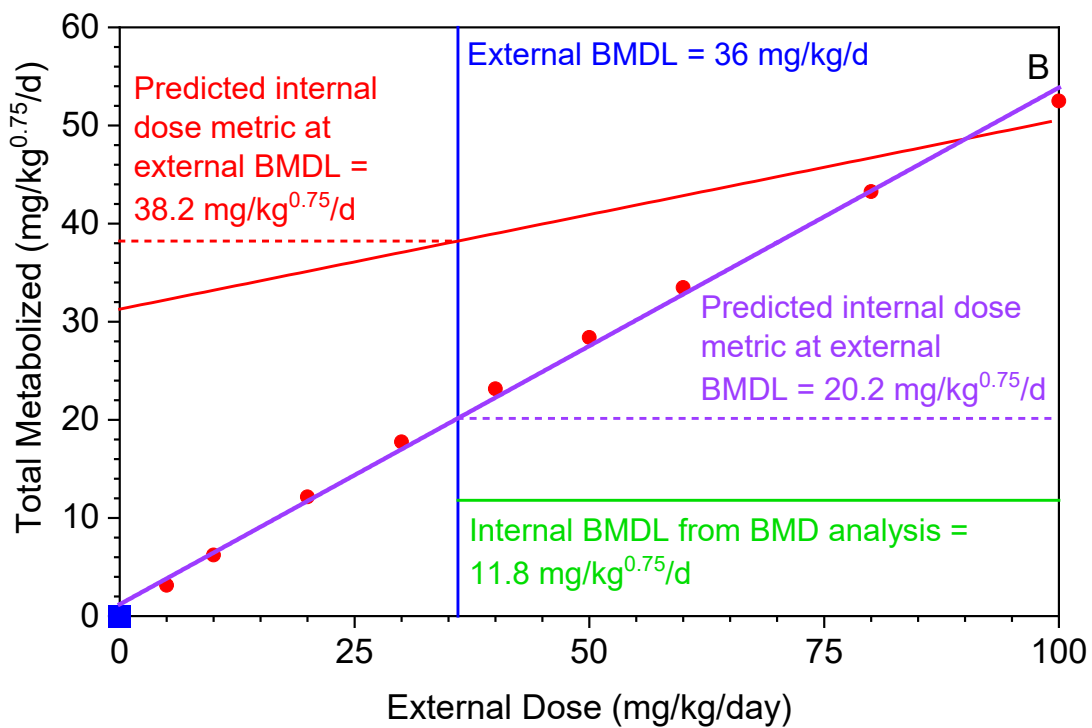
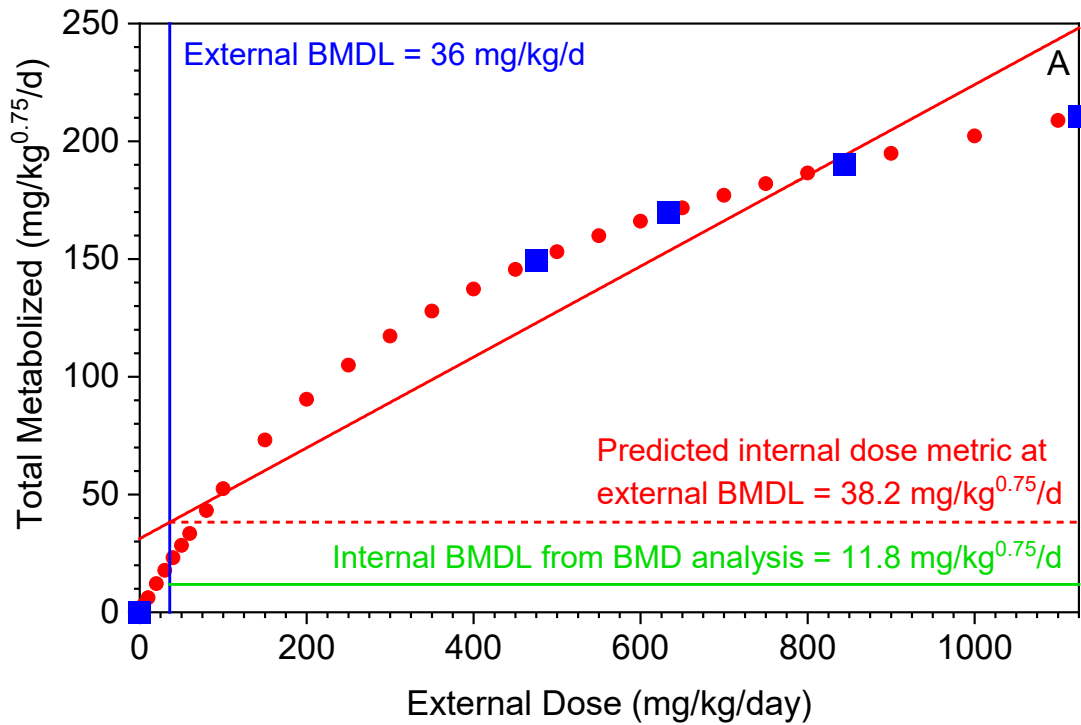


Figure 7. Linearity Analysis Plots for Narotsky *et al.* (1995). See text above for description of lines and symbols.

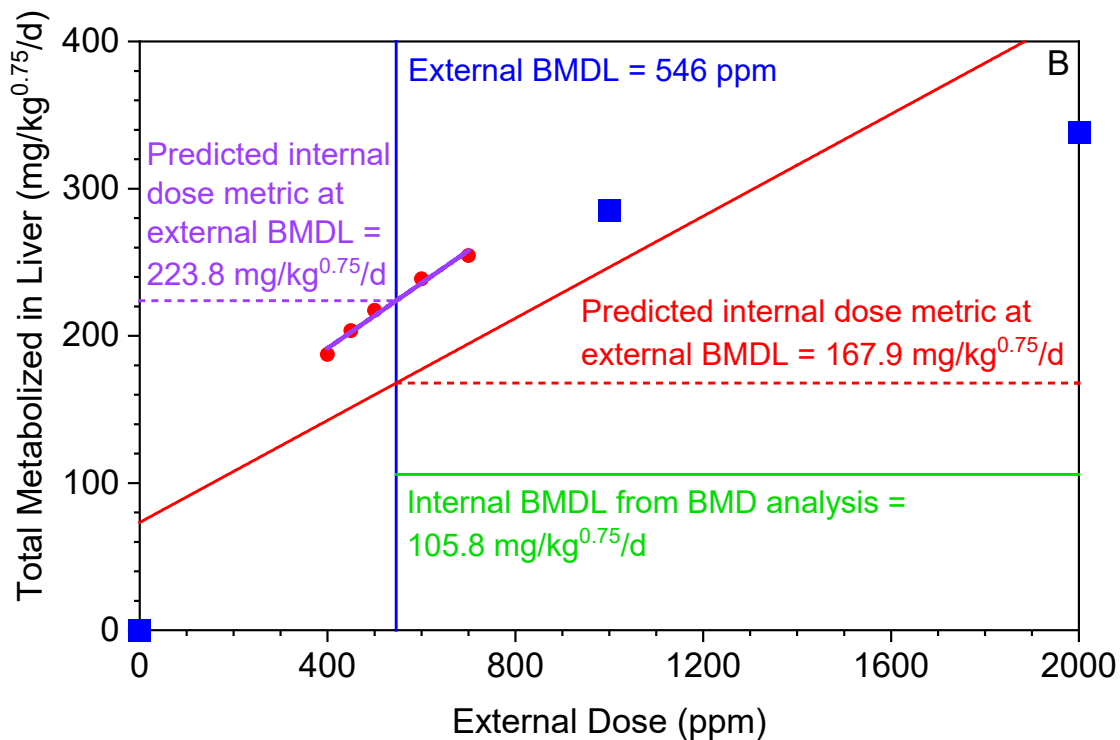
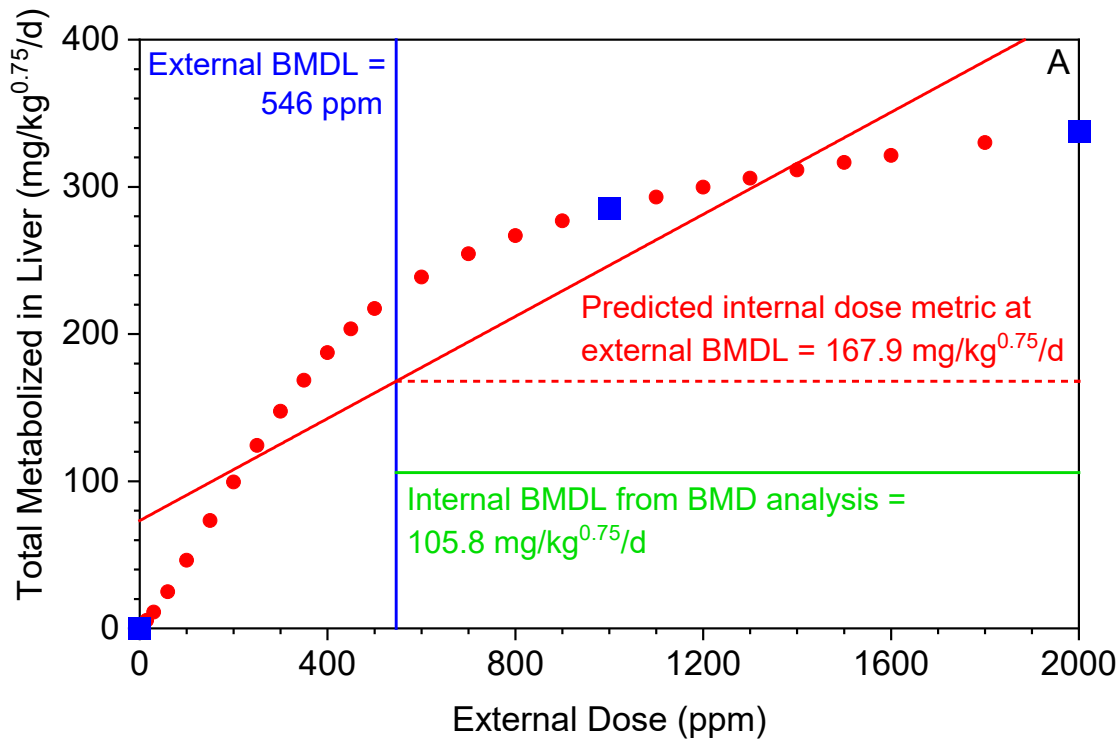


Figure 8. Linearity Analysis Plots for Ramdhan *et al.* (2010). See text above for description of lines and symbols.

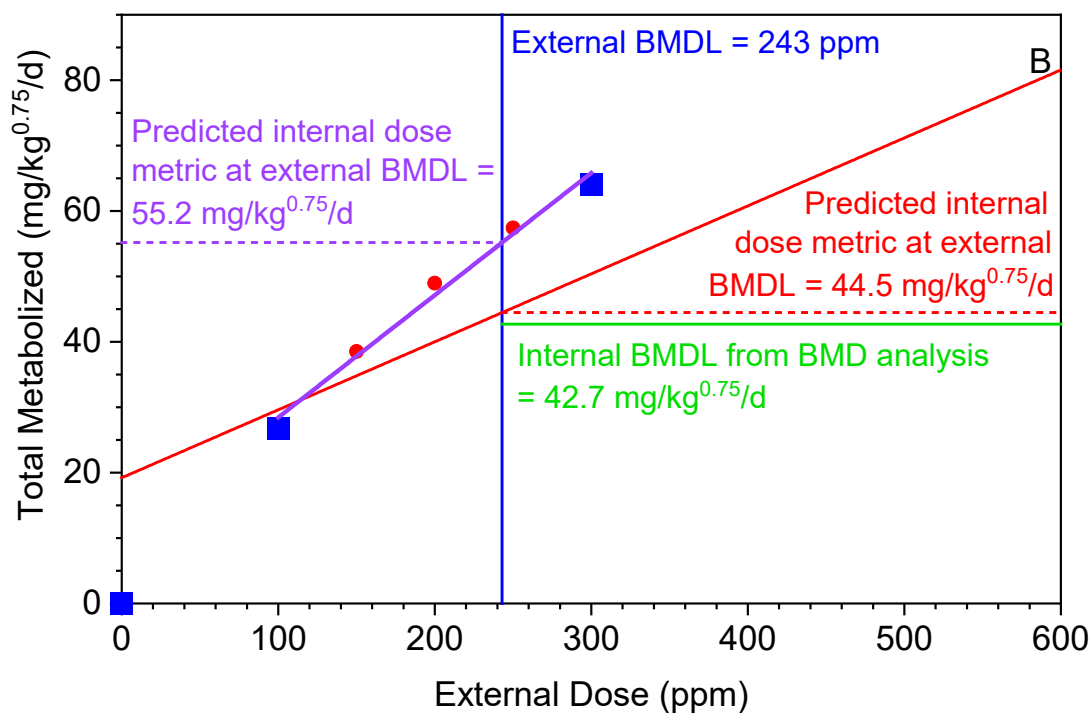
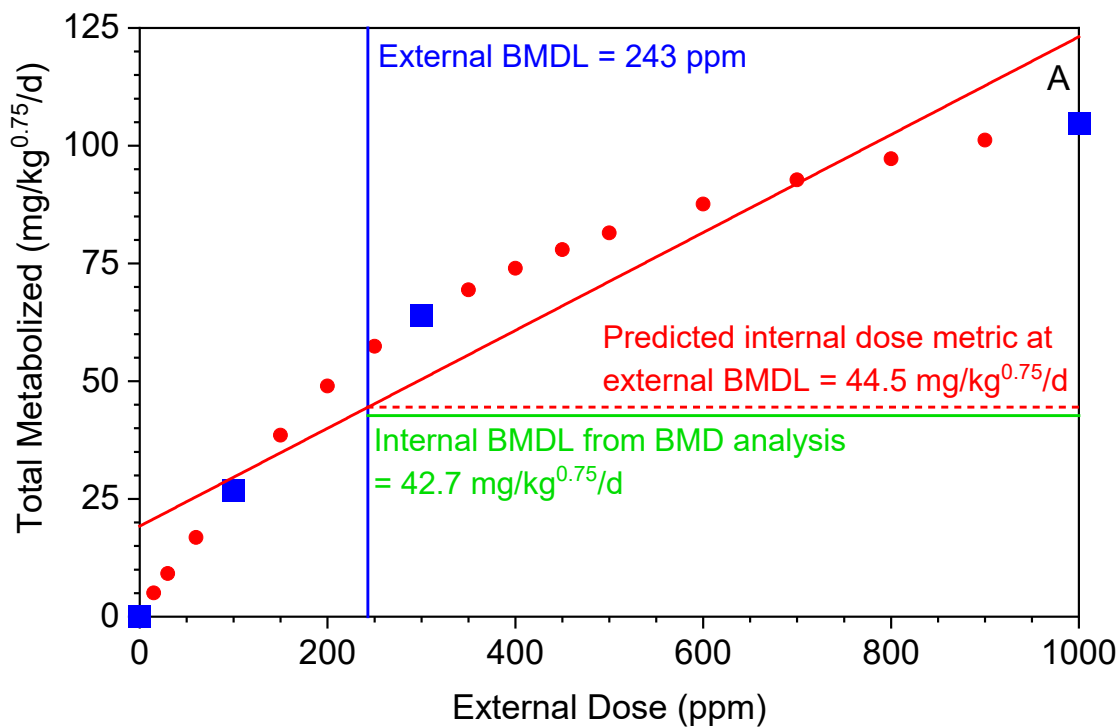


Figure 9. Linearity Analysis Plots for Woolhiser *et al.* (2006) for the Immunological Domain. See text above for description of lines and symbols.

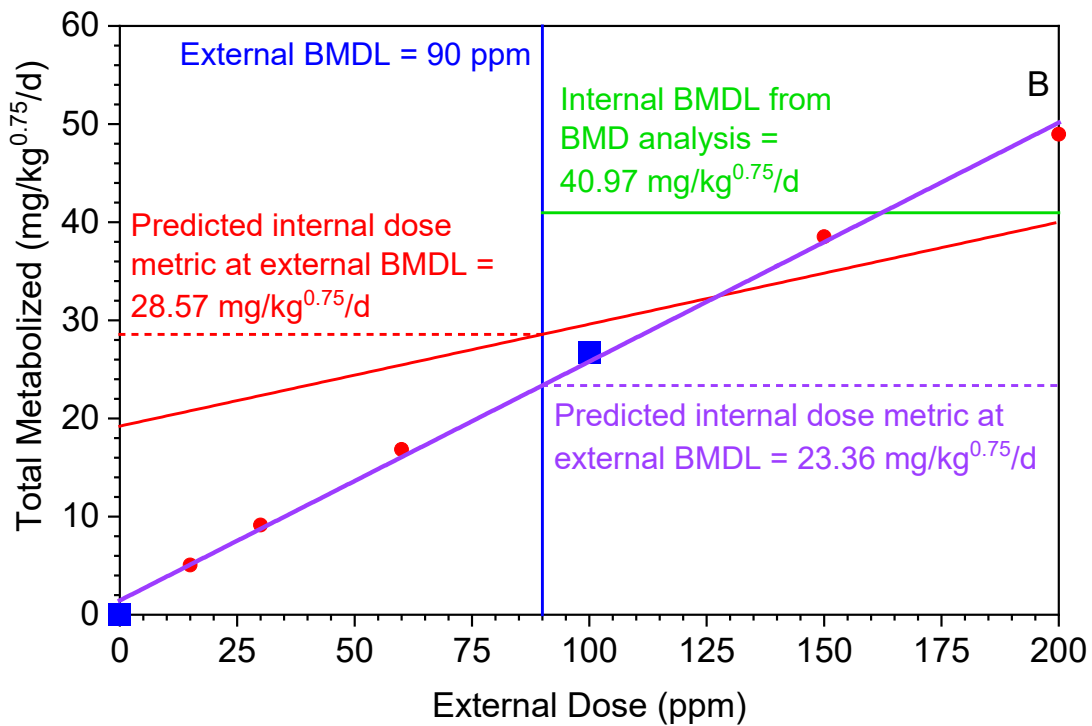
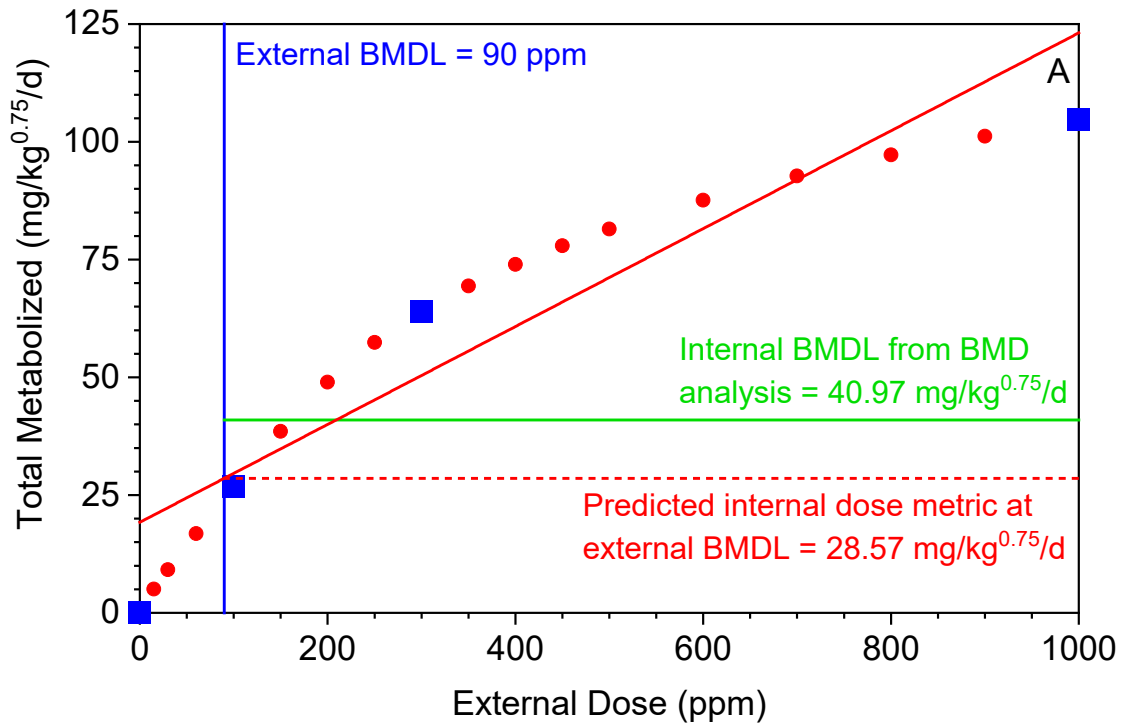


Figure 10. Linearity Analysis Plots for Woolhiser *et al.* (2006) for the Kidney Domain. See text above for description of lines and symbols.

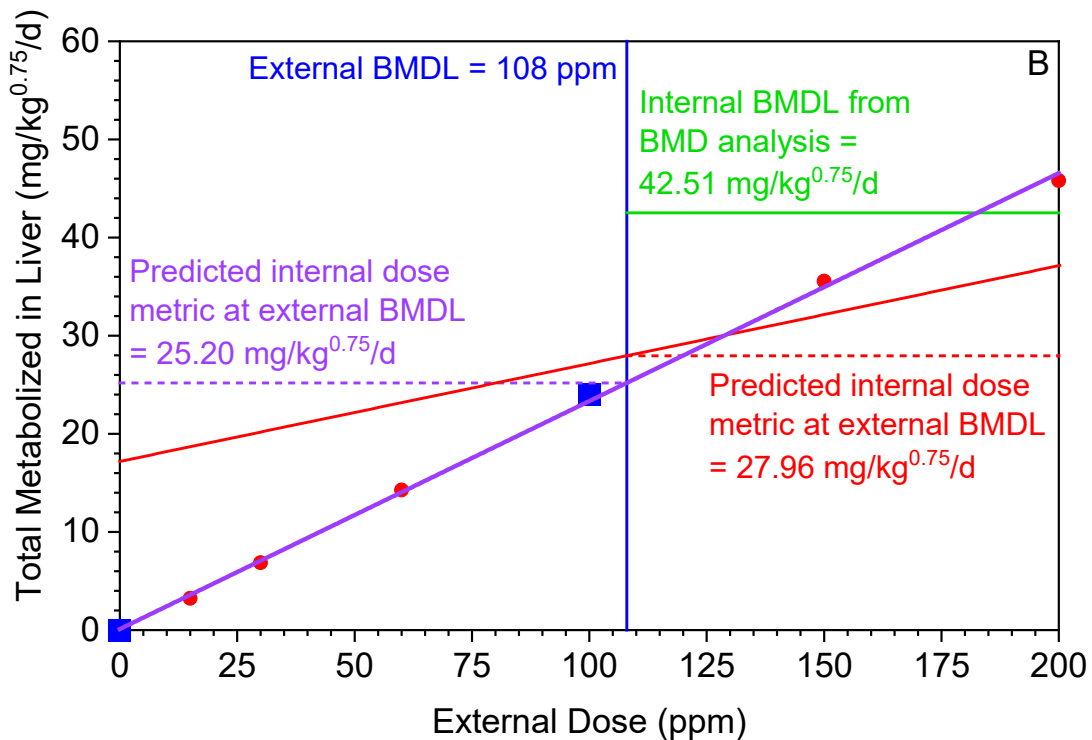
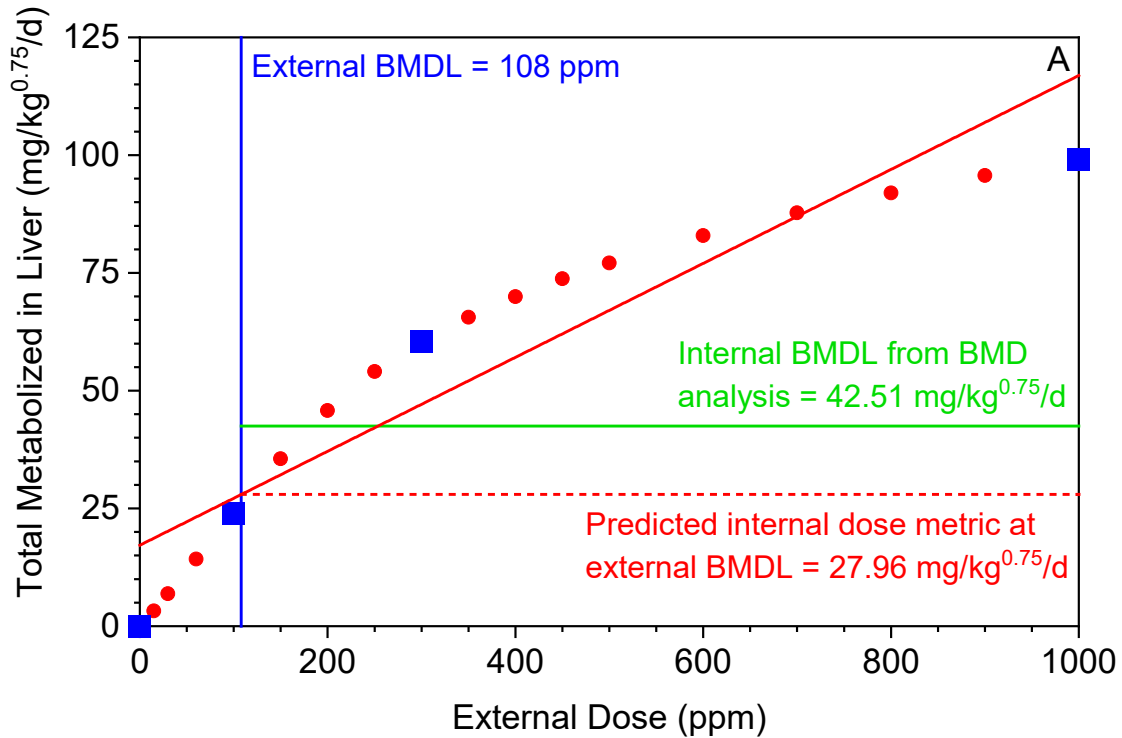


Figure 11. Linearity Analysis Plots for Woolhiser *et al.* (2006) for the Liver Domain. Plots for total metabolized in liver for the liver domain. See text above for description of lines and symbols.

4.2 Prediction of Dose Metrics for OEL Determination

The predicted internal animal dose metrics relevant for the endpoint or endpoints of concern are shown in Table 4, and updated BMDLs based on internal dose are presented in Table 5.

Table 4. Animal Internal Dose Metric Values

Study Name	Route ^a	Species	Sex	Dose	Peak TCE (mg/L)		
					in Blood	in Liver	in Kidney
Adams <i>et al.</i>	Inh	Rat	F	200 ppm	6.034	4.331	7.369
			M		5.360	3.042	6.545
Albee <i>et al.</i>	Inh	Rat	F	800 ppm	55.80		
			M		50.59		
Arito <i>et al.</i>	Inh	Rat	M	50 ppm	1.043		
				100 ppm	2.235		
				300 ppm	11.10		
Blossom <i>et al.</i>	DW	Mouse	F	2.96 mg/kg/day	0.002102		
				400 ppm	10.16		
Bushnell <i>et al.</i>	Inh	Rat	M	800 ppm	26.59		
				1200 ppm	43.73		
				1600 ppm	60.98		
Carney <i>et al.</i>	Inh	Rat	F	600 ppm	37.54		
Cosby & Dukelow	Gav	Mouse	F	240.2 mg/kg/day	14.38		
Crofton & Zhao	Inh	Rat	M	800 ppm	46.10		
				1600 ppm	110.4		
				2400 ppm	174.9		
				3200 ppm	239.5		
Fisher <i>et al.</i>	Gav	Rat	F	500 mg/kg/day	124.1		
George <i>et al.</i>	Diet	Mouse	M	750 mg/kg/day	3.205		
Gilbert <i>et al.</i>	DW	Mouse	F	3.42 mg/kg/day	0.002429		
				21 mg/kg/day	0.01502		
				100 mg/kg/day	0.07413		
Griffin <i>et al.</i>	DW	Mouse	F	400 mg/kg/day	0.3430		
Healy <i>et al.</i>	Inh	Rat	F	100 ppm	2.200		
Isaacson & Taylor	DW	Rat	F	16 mg/kg/day	0.01990		
Jaspers <i>et al.</i>	Inh	Rat	M	1500 ppm	132.5		
Kaneko <i>et al.</i>	Inh	Mouse	M	500 ppm	17.91		
Kjellstrand <i>et al.</i>	Inh	Mouse	F	37 ppm	0.7902	0.3001	
			M		0.7885	0.2973	
Kumar <i>et al.</i>	Inh	Rat	M	376 ppm	13.25	13.26	

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

Table 4 (continued). Animal Internal Dose Metric Values

Study Name	Route ^a	Species	Sex	Dose	Peak TCE (mg/L)		
					in Blood	in Liver	in Kidney
Land <i>et al.</i>	Inh	Mouse	M	200 ppm	6.144		
				2000 ppm	119.1		
Maltoni <i>et al.</i>	Inh	Rat	M	100 ppm	2.106		2.569
				300 ppm	8.508		10.39
				600 ppm	30.29		37.00
Manson <i>et al.</i>	Gav	Rat	F	100 mg/kg/day	23.13		
				475 mg/kg/day	113.2		
Narotsky <i>et al.</i>	Gav	Rat	F	633 mg/kg/day	152.0		
				844 mg/kg/day	203.8		
				1125 mg/kg/day	272.8		
Ramdhan <i>et al.</i>	Inh	Mouse	M	1000 ppm	54.87	94.59	
				2000 ppm	127.7	252.1	
Sanders <i>et al.</i>	DW	Mouse	F	18.4 mg/kg/day	0.01313		
			M		0.01318		
Schwetz <i>et al.</i>	Inh	Mouse	F	306 ppm	9.794		
		Rat			11.35		
Woolhiser <i>et al.</i>	Inh	Rat	F	100 ppm	2.321	0.8550	2.832
				300 ppm	12.49	13.50	15.25
				1000 ppm	72.82	107.2	88.95
Wu & Berger	DW	Rat	F	66 mg/kg/day	0.09164		
Zenick <i>et al.</i>	Gav	Rat	M	100 mg/kg/day	23.06		

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

Table 4 (continued). Animal Internal Dose Metric Values

Study Name	TCE AUC (mg-hour/L/day)			Total Metabolized (mg/kg ^{0.75} /day)			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Adams <i>et al.</i>	28.36	17.77	34.62	56.65	56.59	53.07	0.04146
	25.73	12.76	31.41	58.92	58.85	54.86	0.04805
Albee <i>et al.</i>	222.8			95.52	95.07		
	200.4			112.9	112.5		
Arito <i>et al.</i>	5.947			19.49	19.45		
	12.68			36.32	36.27		
	56.83			90.34	90.21		
Blossom <i>et al.</i>	0.05045			1.306	1.304		
	11.42			22.68	22.64		
Bushnell <i>et al.</i>	31.13			38.71	38.63		
	54.66			51.76	51.62		
	80.79			62.77	62.57		
Carney <i>et al.</i>	203.5			124.0	123.5		
Cosby & Dukelow	10.04			79.98	79.79		
Crofton & Zhao	181.3			127.8	127.4		
	475.6			167.9	166.6		
	790.3			192.2	190.0		
	1114			209.9	206.8		
Fisher <i>et al.</i>	250.1			170.2	169.4		
George <i>et al.</i>	26.28			300.7	300.1		
Gilbert <i>et al.</i>	0.05831			1.508	1.507		
	0.3605			9.150	9.142		
Griffin <i>et al.</i>	1.779			43.50	43.46		
	8.232			172.7	172.5		
Healy <i>et al.</i>	8.918			25.39	25.35		
Isaacson & Taylor	0.4777			11.05	11.04		
Jaspers <i>et al.</i>	1635			241.2	237.7		
Kaneko <i>et al.</i>	60.62			135.1	134.7		
Kjellstrand <i>et al.</i>	18.96	7.202		146.4	146.3	41.62	
	18.92	7.134		146.7	146.6	41.60	
Kumar <i>et al.</i>	34.88	27.56		57.29	57.20	53.85	

Table 4 (continued). Animal Internal Dose Metric Values

Study Name	TCE AUC (mg-hour/L/day)			Total Metabolized (mg/kg ^{0.75} /day)			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Land <i>et al.</i>	24.71			76.96	76.83		
	464.8			260.2	255.6		
Maltoni <i>et al.</i>	10.56		12.87	32.72	32.66		0.05220
	39.94		48.76	87.03	86.92		0.07023
	133.5		163.1	131.4	131.1		0.08818
Manson <i>et al.</i>	20.12			66.10	65.98		
	215.2			149.4	148.8		
Narotsky <i>et al.</i>	325.0			169.9	169.0		
	480.5			190.3	189.0		
	696.7			210.5	208.6		
Ramdhan <i>et al.</i>	415.2	669.2		355.1	351.1	285.5	
	978.5	1851		422.8	413.0	337.9	
Sanders <i>et al.</i>	0.3151			7.868	7.861		
	0.3163			8.295	8.288		
Schwetz <i>et al.</i>	67.89			193.4	193.0		
	71.04			112.9	112.7		
Woolhiser <i>et al.</i>	9.860	3.417	12.03	26.76	26.73	23.98	0.03115
	47.35	43.76	57.83	64.04	63.94	60.44	0.04293
	297.5	415.3	363.4	104.7	104.1	99.00	0.05967
Wu & Berger	2.199			42.90	42.85		
Zenick <i>et al.</i>	14.30			46.89	46.81		

Table 5. BMDLs Based on Internal Dose Metric Values for Animal Studies

Study Name	Route ^a	Species	Sex	Domain ^b	Dose Metric	BMDL
Arito <i>et al.</i>	Inh	Rat	M	Neuro	peak TCE in blood	0.41 mg/L
Bushnell <i>et al.</i>	Inh	Rat	M	Neuro	peak TCE in blood	35.6 mg/L
Crofton & Zhao	Inh	Rat	M	Neuro	peak TCE in blood	70.9 mg/L
Griffin <i>et al.</i>	DW	Mouse	F	Immuno	total metabolized	8.1 mg/kg ^{0.75} /day
Land <i>et al.</i>	Inh	Mouse	M	Repro	total metabolized	89.2 mg/kg ^{0.75} /day
Maltoni <i>et al.</i>	Inh	Rat	M	Kidney	total metabolized	51.03 mg/kg ^{0.75} /day
Narotsky <i>et al.</i>	Gav	Rat	F	Develop	total metabolized	11.8 mg/kg ^{0.75} /day
Ramadhan <i>et al.</i>	Inh	Mouse	M	Liver	total metabolized in liver	105.8 mg/kg ^{0.75} /day
Woolhiser <i>et al.</i>	Inh	Rat	F	Immuno	total metabolized	42.7 mg/kg ^{0.75} /day
				Kidney	total metabolized	40.97 mg/kg ^{0.75} /day
				Liver	total metabolized in liver	42.51 mg/kg ^{0.75} /day

^a “DW” is for drinking water, “Gav” is for gavage, and “Inh” is for inhalation.

^b “Develop” is for Developmental; “Immuno” is for Immunological; “Neuro” is for Neurological; and “Repro” is for Reproductive.

4.3 Estimation of HECs

The estimated HECs from running the PBPK model are presented in Tables 6, 7, 8 and 9. These HECs represent the external human dose required to achieve an internal dose equivalent to either the rodent internal dose (for PODs that were NOAELs or LOAELs) or the rodent-derived BMDL for each study. In the prior work (Covington *et al.*, 2019), BMDLs were derived from external doses and are, thus, external doses. The model was, therefore, run at the external BMDL dose to predict various internal dose metrics for which HECs were then predicted for each internal dose metric. For the new work described here, the newly derived BMDLs are based on internal dose metric values and, thus, represent an internal value. As such Tables 6 through 9 present a HEC value for only a single internal dose metric when the HEC is based on a BMDL.

Table 6. Estimated HECs (ppm) for Human Male Continuous Inhalation

Study Name	Route	Species	Sex	Domain	Based on Peak TCE		
					in Blood	in Liver	in Kidney
Adams <i>et al.</i>	Inhalation	Rat	F	Kidney & Liver	241.9	209.0	194.3
			M		219.4	182.5	175.7
Albee <i>et al.</i>	Inhalation	Rat	F	Neurological	1349		
			M		1243		
Arito <i>et al.</i>	Inhalation	Rat	M	Neurological	19.43		
Blossom <i>et al.</i>	Drinking water	Mouse	F	Developmental & Immunological	0.1013		
Bushnell <i>et al.</i>	Inhalation	Rat	M	Neurological	934.1		
Carney <i>et al.</i>	Inhalation	Rat	F	Developmental	974.3		
Cosby & Dukelow	Gavage	Mouse	F	Developmental	472.6		
Crofton & Zhao	Inhalation	Rat	M	Neurological	1657		
Fisher <i>et al.</i>	Gavage	Rat	F	Developmental	2735		
George <i>et al.</i>	Diet	Mouse	M	Reproductive	141.0		
Gilbert <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.1171		
Griffin <i>et al.</i>	Drinking water	Mouse	F	Immunological			
Healy <i>et al.</i>	Inhalation	Rat	F	Developmental	99.69		
Isaacson & Taylor	Drinking water	Rat	F	Developmental	0.9586		
Jaspers <i>et al.</i>	Inhalation	Rat	M	Neurological	2905		
Kaneko <i>et al.</i>	Inhalation	Mouse	M	Immunological	555.1		
Kjellstrand <i>et al.</i>	Inhalation	Mouse	F	Liver	37.04	63.15	
			M		36.96	62.78	
Kumar <i>et al.</i>	Inhalation	Rat	M	Reproductive & Liver	444.9	329.2	
Land <i>et al.</i>	Inhalation	Mouse	M	Reproductive			
Maltoni <i>et al.</i>	Inhalation	Rat	M	Kidney			
Manson <i>et al.</i>	Gavage	Rat	F	Developmental	670.7		
Narotsky <i>et al.</i>	Gavage	Rat	F	Developmental			
Ramdhan <i>et al.</i>	Inhalation	Mouse	M	Liver			
Sanders <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.6327		
			M		0.6351		
Schwetz <i>et al.</i>	Inhalation	Mouse	F	Developmental	354.8		
		Rat			396.6		
Woolhiser <i>et al.</i>	Inhalation	Rat	F	Immunological			
				Kidney			
				Liver			
Wu & Berger	Drinking water	Rat	F	Reproductive	4.399		

Zenick <i>et al.</i>	Gavage	Rat	M	Reproductive	669.2		
Table 6 (continued). Estimated HECs (ppm) for Human Male Continuous Inhalation							
Study Name	Based on TCE AUC			Based on Total Metabolized			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Adams <i>et al.</i>	54.86	103.4	42.92	41.38	45.43	48.02	0.8958
	49.90	87.80	39.06	43.11	47.37	49.69	1.041
Albee <i>et al.</i>	340.5			71.61	80.60		
	313.7			85.54	98.76		
Arito <i>et al.</i>							
Blossom <i>et al.</i>	0.1014			0.9025	0.7759		
Bushnell <i>et al.</i>							
Carney <i>et al.</i>	317.4			94.57	111.6		
Cosby & Dukelow	19.82			59.38	66.04		
Crofton & Zhao							
Fisher <i>et al.</i>	371.9			133.8	220.8		
George <i>et al.</i>	50.94			269.3	-- ^a		
Gilbert <i>et al.</i>	0.1171			1.042	1.132		
Griffin <i>et al.</i>				5.647			
Healy <i>et al.</i>	17.64			18.05	19.60		
Isaacson & Taylor	0.9588			7.731	8.389		
Jaspers <i>et al.</i>	1600			201.9	-- ^a		
Kaneko <i>et al.</i>	113.4			103.7	126.6		
Kjellstrand <i>et al.</i>	37.03	63.15		113.2	145.7	37.48	
	36.95	62.77		113.5	146.3	37.46	
Kumar <i>et al.</i>	67.05	125.3		41.87	45.95	48.75	
Land <i>et al.</i>				66.61			
Maltoni <i>et al.</i>				37.11			
Manson <i>et al.</i>	39.25			48.61	53.59		
Narotsky <i>et al.</i>				8.263			
Ramdhan <i>et al.</i>						101.8	
Sanders <i>et al.</i>	0.6327			5.483	5.950		
	0.6351			5.784	6.276		
Schwetz <i>et al.</i>	125.9			154.9	-- ^a		
	131.2			85.54	98.98		
Woolhiser <i>et al.</i>				30.84			
				29.55			
						38.29	
Wu & Berger	4.398			30.99	33.83		
Zenick <i>et al.</i>	28.08			33.99	37.13		

^a Due to saturation of metabolism, the HEC could not be estimated.

Table 7. Estimated HECs (ppm) for Human Male Occupational Inhalation

Study Name	Route	Species	Sex	Domain	Based on Peak TCE		
					in Blood	in Liver	in Kidney
Adams <i>et al.</i>	Inhalation	Rat	F	Kidney & Liver	268.3	231.1	214.3
			M		242.7	201.2	193.3
Albee <i>et al.</i>	Inhalation	Rat	F	Neurological	1625		
			M		1493		
Arito <i>et al.</i>	Inhalation	Rat	M	Neurological	21.15		
Blossom <i>et al.</i>	Drinking water	Mouse	F	Developmental & Immunological	0.1102		
Bushnell <i>et al.</i>	Inhalation	Rat	M	Neurological	1109		
Carney <i>et al.</i>	Inhalation	Rat	F	Developmental	1159		
Cosby & Dukelow	Gavage	Mouse	F	Developmental	540.2		
Crofton & Zhao	Inhalation	Rat	M	Neurological	2007		
Fisher <i>et al.</i>	Gavage	Rat	F	Developmental	3344		
George <i>et al.</i>	Diet	Mouse	M	Reproductive	154.5		
Gilbert <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.1274		
Griffin <i>et al.</i>	Drinking water	Mouse	F	Immunological			
Healy <i>et al.</i>	Inhalation	Rat	F	Developmental	108.9		
Isaacson & Taylor	Drinking water	Rat	F	Developmental	1.043		
Jaspers <i>et al.</i>	Inhalation	Rat	M	Neurological	3554		
Kaneko <i>et al.</i>	Inhalation	Mouse	M	Immunological	640.7		
Kjellstrand <i>et al.</i>	Inhalation	Mouse	F	Liver	40.34	68.87	
			M		40.25	68.46	
Kumar <i>et al.</i>	Inhalation	Rat	M	Reproductive & Liver	506.8	369.8	
Land <i>et al.</i>	Inhalation	Mouse	M	Reproductive			
Maltoni <i>et al.</i>	Inhalation	Rat	M	Kidney			
Manson <i>et al.</i>	Gavage	Rat	F	Developmental	783.0		
Narotsky <i>et al.</i>	Gavage	Rat	F	Developmental			
Ramadhan <i>et al.</i>	Inhalation	Mouse	M	Liver			
Sanders <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.6881		
			M		0.6908		
Schwetz <i>et al.</i>	Inhalation	Mouse	F	Developmental	399.3		
		Rat			448.8		
Woolhiser <i>et al.</i>	Inhalation	Rat	F	Immunological			
				Kidney			
				Liver			

Wu & Berger	Drinking water	Rat	F	Reproductive	4.785
Zenick <i>et al.</i>	Gavage	Rat	M	Reproductive	781.1

Table 7 (continued). Estimated HECs (ppm) for Human Male Occupational Inhalation

Study Name	Based on TCE AUC			Based on Total Metabolized			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Adams <i>et al.</i>	214.6	220.2	170.1	189.1	292.5	292.8	3.914
	196.8	192.7	155.6	197.8	319.9	315.4	4.581
Albee <i>et al.</i>	1157			352.6	919.4		
	1062			439.9	1314		
Arito <i>et al.</i>							
Blossom <i>et al.</i>	0.4256			3.808	3.271		
Bushnell <i>et al.</i>							
Carney <i>et al.</i>	1075			502.3	1613		
Cosby & Dukelow	81.25			282.9	634.2		
Crofton & Zhao							
Fisher <i>et al.</i>	1271			840.8	4221		
George <i>et al.</i>	200.6			2696	-- ^a		
Gilbert <i>et al.</i>	0.4918			4.402	4.779		
Griffin <i>et al.</i>				24.29			
Healy <i>et al.</i>	72.42			79.64	88.97		
Isaacson & Taylor	4.017			33.46	36.50		
Jaspers <i>et al.</i>	6553			1669	-- ^a		
Kaneko <i>et al.</i>	409.6			571.1	1974		
Kjellstrand <i>et al.</i>	149.0	152.1		648.8	2443	183.6	
	148.7	151.5		650.9	2457	183.5	
Kumar <i>et al.</i>	257.2	263.4		191.6	299.7	302.5	
Land <i>et al.</i>				323.5			
Maltoni <i>et al.</i>				168.3			
Manson <i>et al.</i>	157.4			225.7	416.6		
Narotsky <i>et al.</i>				35.81			
Ramdhan <i>et al.</i>						1301	
Sanders <i>et al.</i>	2.653			23.57	25.65		
	2.663			24.89	27.10		
Schwetz <i>et al.</i>	449.1			1068	-- ^a		
	465.9			439.9	1319		
Woolhiser <i>et al.</i>				138.4			
				132.4			
						190.0	

Wu & Berger	18.31	139.1	172.0
Zenick <i>et al.</i>	114.2	153.3	199.0

^a Due to saturation of metabolism, the HEC could not be estimated.

Table 8. Estimated HECs (ppm) for Human Female Continuous Inhalation

Study Name	Route	Species	Sex	Domain	Based on Peak TCE		
					in Blood	in Liver	in Kidney
Adams <i>et al.</i>	Inhalation	Rat	F	Kidney & Liver	237.8	182.0	192.9
			M		216.6	158.4	175.3
Albee <i>et al.</i>	Inhalation	Rat	F	Neurological	1324		
			M		1218		
Arito <i>et al.</i>	Inhalation	Rat	M	Neurological	20.21		
Blossom <i>et al.</i>	Drinking water	Mouse	F	Developmental & Immunological	0.1055		
Bushnell <i>et al.</i>	Inhalation	Rat	M	Neurological	910.4		
Carney <i>et al.</i>	Inhalation	Rat	F	Developmental	950.5		
Cosby & Dukelow	Gavage	Mouse	F	Developmental	456.1		
Crofton & Zhao	Inhalation	Rat	M	Neurological	1631		
Fisher <i>et al.</i>	Gavage	Rat	F	Developmental	2709		
George <i>et al.</i>	Diet	Mouse	M	Reproductive	142.1		
Gilbert <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.1219		
Griffin <i>et al.</i>	Drinking water	Mouse	F	Immunological			
Healy <i>et al.</i>	Inhalation	Rat	F	Developmental	102.0		
Isaacson & Taylor	Drinking water	Rat	F	Developmental	0.9979		
Jaspers <i>et al.</i>	Inhalation	Rat	M	Neurological	2879		
Kaneko <i>et al.</i>	Inhalation	Mouse	M	Immunological	536.0		
Kjellstrand <i>et al.</i>	Inhalation	Mouse	F	Liver	38.45	54.27	
			M		38.37	53.94	
Kumar <i>et al.</i>	Inhalation	Rat	M	Reproductive & Liver	429.6	291.3	
Land <i>et al.</i>	Inhalation	Mouse	M	Reproductive			
Maltoni <i>et al.</i>	Inhalation	Rat	M	Kidney			
Manson <i>et al.</i>	Gavage	Rat	F	Developmental	649.4		
Narotsky <i>et al.</i>	Gavage	Rat	F	Developmental			
Ramdhan <i>et al.</i>	Inhalation	Mouse	M	Liver			
Sanders <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.6587		
			M		0.6612		
Schwetz <i>et al.</i>	Inhalation	Mouse	F	Developmental	344.0		
		Rat			383.5		
Woolhiser <i>et al.</i>	Inhalation	Rat	F	Immunological			

				Kidney	
				Liver	
Wu & Berger	Drinking water	Rat	F	Reproductive	4.578
Zenick <i>et al.</i>	Gavage	Rat	M	Reproductive	647.9

Table 8 (continued). Estimated HECs (ppm) for Human Female Continuous Inhalation

Study Name	Based on TCE AUC			Based on Total Metabolized			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Adams <i>et al.</i>	56.81	89.03	44.64	40.39	44.56	46.79	0.9104
	51.71	75.54	40.65	42.08	46.48	48.44	1.058
Albee <i>et al.</i>	330.5			69.99	80.14		
	305.3			83.74	99.89		
Arito <i>et al.</i>							
Blossom <i>et al.</i>	0.1055			0.8837	0.7594		
Bushnell <i>et al.</i>							
Carney <i>et al.</i>	308.8			92.72	115.2		
Cosby & Dukelow	20.61			57.99	65.16		
Crofton & Zhao							
Fisher <i>et al.</i>	360.1			132.6	-- ^a		
George <i>et al.</i>	52.78			282.7	-- ^a		
Gilbert <i>et al.</i>	0.1219			1.021	1.107		
Griffin <i>et al.</i>				5.525			
Healy <i>et al.</i>	18.34			17.63	19.18		
Isaacson & Taylor	0.9981			7.562	8.208		
Jaspers <i>et al.</i>	1575			205.3	-- ^a		
Kaneko <i>et al.</i>	115.5			101.9	135.9		
Kjellstrand <i>et al.</i>	38.44	54.26		111.5	171.2	36.42	
	38.36	53.94		111.8	172.5	36.40	
Kumar <i>et al.</i>	69.26	108.0		40.87	45.08	47.51	
Land <i>et al.</i>				65.08			
Maltoni <i>et al.</i>				36.23			
Manson <i>et al.</i>	40.73			47.46	52.66		
Narotsky <i>et al.</i>				8.082			
Ramdhan <i>et al.</i>						102.9	
Sanders <i>et al.</i>	0.6586			5.365	5.822		
	0.6611			5.659	6.141		
Schwetz <i>et al.</i>	127.6			154.6	-- ^a		
	132.7			83.74	100.1		
Woolhiser <i>et al.</i>				30.12			
				28.85			

			37.22
Wu & Berger	4.578	30.26	33.13
Zenick <i>et al.</i>	29.18	33.18	36.38

^a Due to saturation of metabolism, the HEC could not be estimated.

Table 9. Estimated HECs (ppm) for Human Female Occupational Inhalation

Study Name	Route	Species	Sex	Domain	Based on Peak TCE		
					in Blood	in Liver	in Kidney
Adams <i>et al.</i>	Inhalation	Rat	F	Kidney & Liver	276.6	209.6	222.5
			M		250.9	181.6	201.5
Albee <i>et al.</i>	Inhalation	Rat	F	Neurological	1700		
			M		1559		
Arito <i>et al.</i>	Inhalation	Rat	M	Neurological	22.78		
Blossom <i>et al.</i>	Drinking water	Mouse	F	Developmental & Immunological	0.1188		
Bushnell <i>et al.</i>	Inhalation	Rat	M	Neurological	1151		
Carney <i>et al.</i>	Inhalation	Rat	F	Developmental	1204		
Cosby & Dukelow	Gavage	Mouse	F	Developmental	551.9		
Crofton & Zhao	Inhalation	Rat	M	Neurological	2106		
Fisher <i>et al.</i>	Gavage	Rat	F	Developmental	3530		
George <i>et al.</i>	Diet	Mouse	M	Reproductive	162.2		
Gilbert <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.1373		
Griffin <i>et al.</i>	Drinking water	Mouse	F	Immunological			
Healy <i>et al.</i>	Inhalation	Rat	F	Developmental	115.7		
Isaacson & Taylor	Drinking water	Rat	F	Developmental	1.124		
Jaspers <i>et al.</i>	Inhalation	Rat	M	Neurological	3753		
Kaneko <i>et al.</i>	Inhalation	Mouse	M	Immunological	656.1		
Kjellstrand <i>et al.</i>	Inhalation	Mouse	F	Liver	43.38	61.30	
			M		43.28	60.94	
Kumar <i>et al.</i>	Inhalation	Rat	M	Reproductive & Liver	517.6	342.6	
Land <i>et al.</i>	Inhalation	Mouse	M	Reproductive			
Maltoni <i>et al.</i>	Inhalation	Rat	M	Kidney			
Manson <i>et al.</i>	Gavage	Rat	F	Developmental	805.2		
Narotsky <i>et al.</i>	Gavage	Rat	F	Developmental			
Ramdhan <i>et al.</i>	Inhalation	Mouse	M	Liver			
Sanders <i>et al.</i>	Drinking water	Mouse	F	Immunological	0.7416		
			M		0.7444		
Schwetz <i>et al.</i>	Inhalation	Mouse	F	Developmental	408.2		
		Rat			458.4		

Woolhiser <i>et al.</i>	Inhalation	Rat	F	Immunological Kidney Liver	
Wu & Berger	Drinking water	Rat	F	Reproductive	5.156
Zenick <i>et al.</i>	Gavage	Rat	M	Reproductive	803.3

**Table 9 (continued). Estimated HECs (ppm) for
Human Female Occupational Inhalation**

Study Name	Based on TCE AUC			Based on Total Metabolized			
	in Blood	in Liver	in Kidney	in Body	in Body by Oxidation	in Liver	in Kidney
Adams <i>et al.</i>	216.9	195.8	173.5	186.5	307.2	307.0	3.962
	199.4	170.7	159.3	195.2	333.7	328.9	4.633
Albee <i>et al.</i>	1158			354.2	839.8		
	1061			445.4	1162		
Arito <i>et al.</i>							
Blossom <i>et al.</i>	0.4430			3.727	3.201		
Bushnell <i>et al.</i>							
Carney <i>et al.</i>	1074			510.7	1420		
Cosby & Dukelow	84.16			282.1	607.1		
Crofton & Zhao							
Fisher <i>et al.</i>	1274			853.1	-- ^a		
George <i>et al.</i>	203.1			2546	-- ^a		
Gilbert <i>et al.</i>	0.5120			4.308	4.675		
Griffin <i>et al.</i>				23.72			
Healy <i>et al.</i>	75.09			77.66	87.45		
Isaacson & Taylor	4.182			32.65	35.68		
Jaspers <i>et al.</i>	6536			1617	-- ^a		
Kaneko <i>et al.</i>	407.6			582.2	1772		
Kjellstrand <i>et al.</i>	152.4	134.0		661.9	2365	189.1	
	152.1	133.4		664.1	2386	189.0	
Kumar <i>et al.</i>	258.6	235.6		188.9	314.3	316.5	
Land <i>et al.</i>				323.9			
Maltoni <i>et al.</i>				165.4			
Manson <i>et al.</i>	160.7			223.6	421.7		
Narotsky <i>et al.</i>				34.94			
Ramdhan <i>et al.</i>						1145	
Sanders <i>et al.</i>	2.762			23.02	25.08		
	2.772			24.30	26.49		
Schwetz <i>et al.</i>	446.3			1070	-- ^a		
	462.8			445.4	1166		

Woolhiser <i>et al.</i>	135.6		
	129.6		
	196.5		
Wu & Berger	19.05	136.3	176.4
Zenick <i>et al.</i>	117.7	150.4	207.4

^a Due to saturation of metabolism, the HEC could not be estimated.

5.0 DISCUSSION AND CONCLUSIONS

The acslX model was used to predict mouse and rat internal dose metrics and the subsequent HECs for continuous or occupational human inhalation exposure. The model appears to run stably (*i.e.*, values within acceptable limits and no unexpected behaviors in predicted blood concentrations) and only had issues in predicting a few HECs. For a few studies, the model was unable to predict HECs based on total metabolism in the body by the oxidative pathway. It is felt that this was due to the predicted saturation of the oxidative metabolic system such that regardless of an increase in dose, an increase in the dose metric could not be achieved. This dose metric, however, was not used in developing the subsequent OELs and, thus, is not considered to be an issue. It is felt that use of the TCE PBPK model allowed for the determination of HECs that were not only more relevant to occupational exposures but also more accurately accounted for differences between pharmacokinetics in animals and humans and differences in absorption between dose routes.

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APPENDIX A: POSTERIOR MODEL PARAMETERS

Table A1. Mean Mouse Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
BW	kg	0.03			0.03
QCC	L/hour/kg ^{0.75}	11.6		1.228	14.24
VPR	unitless	2.5		0.8074	2.019
DRespC	unitless		1.221		1.221
QFatC	unitless	0.07		1.033	0.07231
QGutC	unitless	0.141		1.178	0.1661
QKidC	unitless	0.091		0.9933	0.09039
QLivC	unitless	0.02		1.033	0.02066
QRapC	unitless				0.4370 ^a
QSlwC	unitless	0.217		0.9842	0.2136
VBldC	unitless	0.049		0.9921	0.04861
VFatC	unitless	0.07		1.328	0.09296
VGutC	unitless	0.049		0.9869	0.04836
VKidC	unitless	0.017		1.0	0.0170
VLivC	unitless	0.055		0.8080	0.04444
VPerfC	unitless	0.8897			0.8897
VRapC	unitless	0.1		0.9968	0.09968
VRespC	unitless	0.0007		1.0	0.0007
VRespLumC	unitless	0.004667		1.0	0.004667
VSlwC	unitless				0.5379 ^b
FracPlas	unitless	0.52		0.8718	0.4533
PB	unitless	15		0.9297	13.95
PFat	unitless	36		0.9880	35.57
PGut	unitless	1.9		0.8075	1.534
PKid	unitless	2.1		1.266	2.658
PLiv	unitless	1.7		1.283	2.182
PRap	unitless	1.9		0.9555	1.815
PResp	unitless	2.6		0.9947	2.586
PSlw	unitless	2.4		0.9258	2.222
PRBCPlasTCA	unitless	0.5		2.470	1.235
PBodTCAC	unitless	0.88		0.8875	0.7810
PLivTCAC	unitless	1.18		0.8034	0.9480

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the mouse.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

Table A1 (continued). Mean Mouse Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
PBodTCOH	unitless	1.11		0.8040	0.8924
PLivTCOH	unitless	1.3		1.497	1.946
PBodTCOG	unitless	1.11		0.420	0.4662
PLivTCOG	unitless	1.3		1.015	1.319
PEffDCVG	unitless		0.9871		0.9871
BMaxkDC	unitless	0.88		1.241	1.092
kDissoc	μmole/L	107		1.178	126.0
kAS	/hour		1.798		1.798
kTSD	/hour		5.259		5.259
kAD	/hour		0.2677		0.2677
kTD	/hour	0.0 ^c			0.0 ^c
kASTCA	/hour		3.975		3.975
kASTCOH	/hour		0.730		0.730
VMaxC	mg/hour/kg liver	2700		0.6707	1811
KMC	mg/L	36		0.07288	2.624
Cl	L/hour/kg liver	na			na
FracTCAC	unitless	0.32		0.4870	0.1559
FracOtherC	unitless		0.02371		0.02371
VMaxDCVGC	mg/hour/kg liver	300		2.621	786.4
KMDCVGC	mg/L	na			na
ClDCVG	L/hour/kg liver	1.53		0.3588	0.5490
VMaxKidDCVGC	mg/hour/kg kidney	60		2.573	154.4
KMKidDCVGC	mg/L	na			na
ClKidDCVG	L/hr/kg kidney	0.34		1.216	0.4134
VMaxLungLiv	unitless	0.0701021		2.782	0.1950
KMClara	mg/L		0.01195		0.01195
FracLungSysC	unitless		4.384		4.384
VMaxTCOHC	mg/hour/kg ^{0.75}		1.643		1.643
KMTCOH	mg/L		0.9326		0.9326
CITCOH	L/hour/kg ^{0.75}	na			na
VMaxGlucC	mg/hour/kg ^{0.75}		69.55		69.55
KMGluc	mg/L		30.45		30.45
ClGluc	L/hour/kg ^{0.75}	na			na
kMetTCOHC	kg ^{0.25} /hour		3.367		3.367

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the mouse.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

Table A1 (continued). Mean Mouse Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
kUrnTCAC	L/hour/kg	0.6		0.1096	0.06575
kMetTCAC	kg ^{0.25} /hour		0.6127		0.6127
kBileC	kg ^{0.25} /hour		1.014		1.014
kEHRC	kg ^{0.25} /hour		0.01208		0.01208
kUrnTCOGC	L/hour/kg	0.6		8.593	5.156
kDCVGC	kg ^{0.25} /hour		0.1890		0.1890
FracKidDCVCC	unitless		1.537		1.537
kNATC	kg ^{0.25} /hour		0.1165		0.1165
kKidBioactC	kg ^{0.25} /hour		0.08786		0.08786

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the mouse.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

Table A2. Mean Rat Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
BW	kg	0.3			0.3
QCC	L/hour/kg ^{0.75}	13.3		1.192	15.85
VPR	unitless	1.9		0.6229	1.184
DRespC	unitless		2.553		2.553
QFatC	unitless	0.07		1.187	0.08309
QGutC	unitless	0.153		1.147	0.1755
QKidC	unitless	0.141		1.002	0.1413
QLivC	unitless	0.021		1.032	0.02167
QRapC	unitless				0.2751 ^a
QSlwC	unitless	0.336		0.9028	0.3033
VBldC	unitless	0.074		1.002	0.07415
VFatC	unitless	0.07		0.9720	0.06804
VGutC	unitless	0.032		0.9892	0.03165
VKidC	unitless	0.007		0.9927	0.006949
VLivC	unitless	0.034		0.9844	0.03347
VPerfC	unitless	0.8995			0.8995
VRapC	unitless	0.088		0.9931	0.08739
VRespC	unitless	0.0005		0.9917	0.0004959
VRespLumC	unitless	0.004667		1.005	0.004690
VSlwC	unitless				0.5974 ^b
FracPlas	unitless	0.53		1.042	0.5523
PB	unitless	22		0.8544	18.80
PFat	unitless	27		1.130	30.50
PGut	unitless	1.4		0.8654	1.212
PKid	unitless	1.3		0.9398	1.222
PLiv	unitless	1.5		1.042	1.564
PRap	unitless	1.3		1.079	1.403
PResp	unitless	1		0.9555	0.9555
PSlw	unitless	0.58		1.292	0.7493
PRBCPlasTCA	unitless	0.5		0.9624	0.4812
PBodTCAC	unitless	0.88		1.117	0.9826
PLivTCAC	unitless	1.18		1.282	1.513

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the rat.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

^dValue is set in MCSim input file for the rat from Dr. Chiu.

Table A2 (continued). Mean Rat Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
PBodTCOH	unitless	1.11		0.9510	1.056
PLivTCOH	unitless	1.3		0.9601	1.248
PBodTCOG	unitless	1.11		1.240	1.376
PLivTCOG	unitless	1.3		8.585	11.16
PEffDCVG	unitless	na			na
BMaxkDC	unitless	1.22		0.9516	1.161
kDissoc	μmole/L	275		0.9762	268.5
kAS	/hour		2.721		2.721
kTSD	/hour		4.166		4.166
kAD	/hour		0.1810		0.1810
kTD	/hour	0.0 ^c			0.0 ^c
kASTCA	/hour		1.488		1.488
kASTCOH	/hour		0.6880		0.6880
VMaxC	mg/hour/kg liver	600		0.9528	571.7
KMC	mg/L	21		0.03515	0.7382
Cl	L/hour/kg liver	na			na
FracTCAC	unitless	0.32		0.2488	0.07962
FracOtherC	unitless		0.3097		0.3097
VMaxDCVGC	mg/hour/kg liver	66		11.98	790.5
KMDCVGC	mg/L	na			na
CIDCVG	L/hour/kg liver	0.25		0.3721	0.09302
VMaxKidDCVGC	mg/hour/kg kidney	6		0.2108	1.265
KMKidDCVGC	mg/L	na			na
ClKidDCVG	L/hr/kg kidney	0.026		181.8	4.727
VMaxLungLiv	unitless	0.01435		3.323	0.04768
KMClara	mg/L		0.02078		0.02078
FracLungSysC	unitless		1.981		1.981
VMaxTCOHC	mg/hour/kg ^{0.75}		2.018		2.018
KMTCOH	mg/L		22.42		22.42
CITCOH	L/hour/kg ^{0.75}	na			na
VMaxGlucC	mg/hour/kg ^{0.75}		27.17		27.17
KMGluc	mg/L		5.877		5.877
ClGluc	L/hour/kg ^{0.75}	na			Na
kMetTCOHC	kg ^{0.25} /hour		1.976		1.976

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the rat.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

^dValue is set in MCSim input file for the rat from Dr. Chiu.

Table A2 (continued). Mean Rat Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
kUrnTCAC	L/hour/kg	0.522		0.07186	0.03751
kMetTCAC	kg ^{0.25} /hour		0.3253		0.3253
kBileC	kg ^{0.25} /hour		7.553		7.553
kEHRC	kg ^{0.25} /hour		1.468		1.468
kUrnTCOGC	L/hour/kg	0.522		20.51	10.71
kDCVGC	kg ^{0.25} /hour		22026 ^d		22026 ^d
FracKidDCVCC	unitless		22026 ^d		22026 ^d
kNATC	kg ^{0.25} /hour		0.002089		0.002089
kKidBioactC	kg ^{0.25} /hour		0.006902		0.006902

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the rat.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cSet to zero in the model definition file in the appendix of USEPA (2011).

^dValue is set in MCSim input file for the rat from Dr. Chiu.

Table A3. Mean Human Female Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
BW	kg	60			60
QCC	L/hour/kg ^{0.75}	16		0.8353	13.36
VPR	unitless	0.96		1.526	1.465
DRespC	unitless		0.6080		0.6080
QFatC	unitless	0.085		0.7783	0.06616
QGutC	unitless	0.21		0.7914	0.1662
QKidC	unitless	0.17		1.008	0.1714
QLivC	unitless	0.065		0.5071	0.03296
QRapC	unitless				0.4410 ^a
QSlwC	unitless	0.17		0.7196	0.1223
VBldC	unitless	0.068		1.012	0.06882
VFatC	unitless	0.317		0.7823	0.2480
VGutC	unitless	0.022		1.001	0.02202
VKidC	unitless	0.0046		0.9969	0.004586
VLivC	unitless	0.023		1.044	0.02401
VPerfC	unitless	0.85778			0.85778
VRapC	unitless	0.093		0.9959	0.09262
VRespC	unitless	0.00018		0.9999	0.000180
VRespLumC	unitless	0.002386		1.003	0.002393
VSlwC	unitless				0.3976 ^b
FracPlas	unitless	0.615		1.001	0.6156
PB	unitless	9.5		0.9699	9.214
PFat	unitless	67		0.8515	57.05
PGut	unitless	2.6		1.090	2.834
PKid	unitless	1.6		0.9996	1.599
PLiv	unitless	4.1		0.9890	4.055
PRap	unitless	2.6		0.9256	2.407
PResp	unitless	1.3		1.011	1.314
PSlw	unitless	2.1		1.160	2.435
PRBCPlasTCA	unitless	0.5		0.2888	0.1444
PBodTCAC	unitless	0.52		1.189	0.6182
PLivTCAC	unitless	0.66		1.193	0.7873

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human females.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cNot included in posterior estimations. No TCE oral dosing data so set to zero.

^dSet to zero in the model definition file in the appendix of USEPA 2011.

^eValue is set in MCSim input file for the rat from Dr. Chiu.

Table A3 (continued). Mean Human Female Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
PBodTCOH	unitless	0.91		1.718	1.564
PLivTCOH	unitless	0.59		1.067	0.6294
PBodTCOG	unitless	0.91		0.6819	0.6206
PLivTCOG	unitless	0.59		6.514	3.843
PEffDCVG	unitless		0.01028		0.01028
BMaxkDC	unitless	4.62		0.8813	4.071
kDissoc	μmole/L	182		0.9933	180.8
kAS	/hour	na ^c			na ^c
kTSD	/hour	na ^c			na ^c
kAD	/hour	na ^c			na ^c
kTD	/hour	0.0 ^d			0.0 ^d
kASTCA	/hour		5.270		5.270
kASTCOH	/hour		7.301		7.301
VMaxC	mg/hour/kg liver	255		0.3714	94.70
KMC	mg/L	na			na
Cl	L/hour/kg liver	66		13.05	861.5
FracTCAC	unitless	0.32		0.1278	0.04091
FracOtherC	unitless		0.1072		0.1072
VMaxDCVGC	mg/hour/kg liver	na			na
KMDCVGC	mg/L	2.9		1.247	3.618
CIDCVG	L/hour/kg liver	19		2.779	52.80
VMaxKidDCVGC	mg/hour/kg kidney	na			na
KMKidDCVGC	mg/L	2.7		0.3097	0.8363
ClKidDCVGC	L/hr/kg kidney	230		0.03453	7.941
VMaxLungLiv	unitless	0.02727		3.466	0.09453
KMClara	mg/L		0.2434		0.2434
FracLungSysC	unitless		23.57		23.57
VMaxTCOHC	mg/hour/kg ^{0.75}	na			na
KMTCOH	mg/L		2.271		2.271
CITCOH	L/hour/kg ^{0.75}		0.1766		0.1766
VMaxGlucC	mg/hour/kg ^{0.75}	na			na
KMGluc	mg/L		129.3		129.3
ClGluc	L/hour/kg ^{0.75}		0.2811		0.2811
kMetTCOHC	kg ^{0.25} /hour		0.6991		0.6991

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human females.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cNot included in posterior estimations. No TCE oral dosing data so set to zero.

^dSet to zero in the model definition file in the appendix of USEPA 2011.

^eValue is set in MCSim input file for the rat from Dr. Chiu.

Table A3 (continued). Mean Human Female Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
kUrnTCAC	L/hour/kg	0.108		0.04537	0.004899
kMetTCAC	kg ^{0.25} /hour		0.2755		0.2755
kBileC	kg ^{0.25} /hour		7.243		7.243
KEHRC	kg ^{0.25} /hour		0.1561		0.1561
kUrnTCOGC	L/hour/kg	0.108		16.93	1.828
kDCVGC	kg ^{0.25} /hour		7.171		7.171
FracKidDCVCC	unitless		22026 ^e		22026 ^e
kNATC	kg ^{0.25} /hour		0.0003495		0.0003495
kKidBioactC	kg ^{0.25} /hour		0.06279		0.06279

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human females.

^aCalculated as 1.0 minus the sum of the other fractional tissue blood flows.

^bCalculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cNot included in posterior estimations. No TCE oral dosing data so set to zero.

^dSet to zero in the model definition file in the appendix of USEPA 2011.

^eValue is set in MCSim input file for the rat from Dr. Chiu.

Table A4. Mean Human Male Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
BW	kg	70			70
QCC	L/hour/kg ^{0.75}	16		0.8353	13.36
VPR	unitless	0.96		1.526	1.465
DRespC	unitless		0.6080		0.6080
QFatC	unitless	0.05		0.7783	0.03892
QGutC	unitless	0.19		0.7914	0.1504
QKidC	unitless	0.19		1.008	0.1915
QLivC	unitless	0.065		0.5071	0.03296
QRapC	unitless				0.4279 ^a
QSlwC	unitless	0.22		0.7196	0.1583
VBldC	unitless	0.077		1.012	0.07792
VFatC	unitless	0.199		0.7823	0.1557
VGutC	unitless	0.02		1.001	0.02002
VKidC	unitless	0.0043		0.9969	0.004287
VLivC	unitless	0.025		1.044	0.02610
VPerfC	unitless	0.856			0.8560
VRapC	unitless	0.088		0.9959	0.08764
VRespC	unitless	0.00018		0.9999	0.000180
VRespLumC	unitless	0.002386		1.003	0.002393
VSlwC	unitless				0.4842 ^b
FracPlas	unitless	0.567		1.001	0.5676
PB	unitless	9.5		0.9699	9.214
PFat	unitless	67		0.8515	57.05
PGut	unitless	2.6		1.090	2.834
PKid	unitless	1.6		0.9996	1.599
PLiv	unitless	4.1		0.9890	4.055
PRap	unitless	2.6		0.9256	2.407
PResp	unitless	1.3		1.011	1.314
PSlw	unitless	2.1		1.160	2.435
PRBCPlasTCA	unitless	0.5		0.2888	0.1444
PBodTCAC	unitless	0.52		1.189	0.6182
PLivTCAC	unitless	0.66		1.193	0.7873

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human males.

^a Calculated as 1.0 minus the sum of the other fractional tissue blood flows.

^b Calculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^c Not included in posterior estimations. No TCE oral dosing data so set to zero.

^d Set to zero in the model definition file in the appendix of USEPA (2011).

^e Value is set in MCSim input file for the rat from Dr. Chiu.

Table A4 (continued). Mean Human Male Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
PBodTCOH	unitless	0.91		1.718	1.564
PLivTCOH	unitless	0.59		1.067	0.6294
PBodTCOG	unitless	0.91		0.6819	0.6206
PLivTCOG	unitless	0.59		6.514	3.843
PEffDCVG	unitless		0.01028		0.01028
BMaxkDC	unitless	4.62		0.8813	4.071
kDissoc	μmole/L	182		0.9933	180.8
kAS	/hour	0.0 ^c			0.0 ^c
kTSD	/hour	0.0 ^c			0.0 ^c
kAD	/hour	0.0 ^c			0.0 ^c
kTD	/hour	0.0 ^d			0.0 ^d
kASTCA	/hour		5.270		5.270
kASTCOH	/hour		7.301		7.301
VMaxC	mg/hour/kg liver	255		0.3714	94.70
KMC	mg/L	na			na
Cl	L/hour/kg liver	66		13.05	861.5
FracTCAC	unitless	0.32		0.1278	0.04091
FracOtherC	unitless		0.1072		0.1072
VMaxDCVGC	mg/hour/kg liver	na			na
KMDCVGC	mg/L	2.9		1.247	3.618
CIDCVG	L/hour/kg liver	19		2.779	52.80
VMaxKidDCVGC	mg/hour/kg kidney	na			na
KMKidDCVGC	mg/L	2.7		0.3097	0.8363
ClKidDCVGC	L/hr/kg kidney	230		0.03453	7.941
VMaxLungLiv	unitless	0.02525		3.466	0.08753
KMClara	mg/L		0.2434		0.2434
FracLungSysC	unitless		23.57		23.57
VMaxTCOHC	mg/hour/kg ^{0.75}	na			na
KMTCOH	mg/L		2.271		2.271
CITCOH	L/hour/kg ^{0.75}		0.1766		0.1766
VMaxGlucC	mg/hour/kg ^{0.75}	na			na
KMGluc	mg/L		129.3		129.3
ClGluc	L/hour/kg ^{0.75}		0.2811		0.2811
kMetTCOHC	kg ^{0.25} /hour		0.6991		0.6991

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human males.

^a Calculated as 1.0 minus the sum of the other fractional tissue blood flows.

^b Calculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cNot included in posterior estimations. No TCE oral dosing data so set to zero.

^dSet to zero in the model definition file in the appendix of USEPA (2011).

^eValue is set in MCSim input file for the rat from Dr. Chiu.

Table A4 (continued). Mean Human Male Posterior Parameters

Parameter	Units	Baseline	Absolute Value	Fractional Increase	Final Value
kUrnTCAC	L/hour/kg	0.108		0.04537	0.004899
kMetTCAC	kg ^{0.25} /hour		0.2755		0.2755
kBileC	kg ^{0.25} /hour		7.243		7.243
kEHRC	kg ^{0.25} /hour		0.1561		0.1561
kUrnTCOGC	L/hour/kg	0.108		16.93	1.828
kDCVGC	kg ^{0.25} /hour		7.171		7.171
FracKidDCVCC	unitless		22026 ^e		22026 ^e
kNATC	kg ^{0.25} /hour		0.0003495		0.0003495
kKidBioactC	kg ^{0.25} /hour		0.06279		0.06279

Notes: Baseline values are from MCSim model code. Absolute values and fractional increases are from the MCSim output file from Dr. Chiu. Calculated posteriors of “na” are parameters not used for the human males.

^a Calculated as 1.0 minus the sum of the other fractional tissue blood flows.

^b Calculated as VPerfC minus the sum of the fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue.

^cNot included in posterior estimations. No TCE oral dosing data so set to zero.

^dSet to zero in the model definition file in the appendix of USEPA (2011).

^eValue is set in MCSim input file for the rat from Dr. Chiu.

APPENDIX B: ACSLX MODEL CODE FOR USEPA (2011) MODEL

```
PROGRAM EPA_2011_TCE_REV.csl
! revised acslX version of model from Appendix A of EPA Toxicological Review of TCE
! (September 2011)

! --- HISTORY OF HACK ET AL. (2006) MODEL
! Model code to correspond to the block diagram version of the harmonized model edited by Deborah
! Keys to incorporate Lapare et al. 1995 data -- Last edited: August 6, 2004
! Translated into MCSim from acslXtreme CSL file by Eric Hack, completed September 15, 2004
! Removed non-essential differential equations (i.e., AUCCBld) for MCMC runs
! Changed QRap and QSlw calculations and added QTot to scale fractional flows back to 1.0 after
! sampling
! Changed QSlw calculation and removed QTot (September 21, 2004)
! Removed diffusion-limited fat uptake (September 24, 2004)

! --- HISTORY OF U.S. EPA (2009) MODEL (Chiu et al., 2009)
! Extensively revised by U.S. EPA June 2007 - June 2008
! Version 1
! Fixed hepatic plasma flow for TCA-submodel to include portal vein (i.e., QGutLivPlas -
! originally was just QLivPlas, which was only hepatic artery)
! Clearer coding and in-line documentation
! Single model for 3 species
! Revised physiological parameters, with discussion of uncertainty and variability
! In vitro data used for default metabolism parameters, with discussion of uncertainty and
! variability
! Added
! TCE blood compartment
! TCE kidney compartment, with GSH metabolism
! DCVG compartment
! Additional outputs available from in vivo data
! IA and PV dosing (for rats)
! Removed DCA compartment

! Version 1.1 -- fixed urinary parameter scaling
! Fixed VBod in kUrnTCOG (should be VBodTCOH)

! Version 1.1.1 -- changed some truncation limits (in comments only)
! Version 1.2
! Removed TB compartment as currently coded
! Added respiratory oxidative metabolism: 3 states: AInhResp, AResp, AExhResp
! Removed clearance from respiratory metabolism

! Version 1.2.1 -- changed oral dosing to be similar to IV
! Version 1.2.2 -- fixed default lung metabolism (additional scaling by lung/liver weight ratio)
! Version 1.2.3 -- fixed FracKidDCVC scaling

! --- Changes made in converting EPA model from MCSim to acslX
! Terms in some equations were rearranged for better readability
! Model changed to not use the parameter "Male" -- calculations didn't differ, only baseline
! values for parameters -- male and female specific M files created and those should be used
! Model changed to use absolute value rather than the baseline value times the fractional
! increase -- values in M files set accordingly (i.e., changed
! PLivTCA=TCAPlas*exp(lnPLivTCAC)*(baseline values) to PLivTCA=TCAPlas*PLivTCAC)
! Replaced "exp(ln*)" with "*" where "*" is the parameter name (i.e., replaced "exp(lnPBodTCAC)"
! with "PBodTCAC") -- "ln" removed from parameter names as appropriate
! Changed code to set measured values for BW, QP, VFatC, PB or Hematocrit in M file rather than
! having separate parameter for it and using IF statements to set
! if Hematocrit measured, in the M file set FracPlas to (1-HematocritMeas) where
! HematocritMeas is the measured value
! if QP is measured, in the M file set QCC to (QPMeas/VPR)/(BW^0.75) where QPMeas is the
! measured value -- not used in any of the M files
! QC used instead of QCNow since code was changed in how it uses measured QP values
! No fractional increase for QSlw since it is calculated in model but it does use a baseline
! value for total volume of perfused tissues so parameter VPerfC defined to be the baseline
! value
```

```

! New parameter defined for initial value for ACh called ACh0 since acslX handles initial values
!   for state parameters differently than MCSim
! Use of "CC" for inhalation concentration for closed chamber changed to be used as a flag to
!   denote closed chamber and concentration set with "CONC"
! AUrnTCA_sat, zAUrnTCA_sat, AUrnTCOG_sat and AUrnTCOGTCOH_sat are not used in any of the M files
!   so these were removed since it was unclear what they should represent and how to recode them
!   for acslX

! Parameter "ConcOn" defined to turn inhalation dosing on and off -- used for acslX
!   implementation of inhalation dosing but not needed for MCSim
! Equation for CInhPPM changed from "ACh/VCh*24450.0/MWTCE" to "(CInh*24450.0)/MWTCE" which would
!   be the same results for closed chamber inhalation it uses CInh which is calculated as
!   separately for open and closed chamber and, by changing the equation this way allows it
!   to work for either closed or open chamber
! Changed equation for AExhExp -- instead of "AExhExp=INTEG(RAExh, 0.0)" used "AExhExp=AExh"
! Code for calculating AUrnTCA_Coll changed to work better in acslX
! Added code for weekly and daily average dosemetrics
! Added parameters Days and TMax for repeated dosing

! Q*Ctmp renamed to Q*C where * is for the tissue (Fat, Gut, Kid, Liv, or Slw)
! DResptmp renamed DRespC
! VRespEffC renamed VRespC
! VRespEfftmp renamed VResp
! ClC renamed Cl (became ClC after removing "exp(ln" from equations)
! ClDCVGC renamed ClDCVG (became ClDCVGC after removing "exp(ln" from equations)
! ClKidDCVGC renamed ClKidDCVG (became ClKidDCVGC after removing "exp(ln" from equations)
! VMaxLungLivC renamed VMaxLungLiv (became VMaxLungLivC after removing "exp(ln" from equations)
! ClTCOHC renamed ClTCOH (became ClTCOHC after removing "exp(ln" from equations)
! ClGlucC renamed ClGluc (became ClGlucC after removing "exp(ln" from equations)
! ExhFactor_Den renamed ExhFac_Den
! CPlasTCAMole and CPlasTCAFreeMole renamed CPlasTCA_uMole and CPlasTCAFree_uMole, respectively,
!   since the units are actually umoles
! RUrnTCA renamed RAUrnTCA
! RUrnTCOG renamed RAUrnTCOG
! RAMetDCVGmole renamed RAMetDCVG_Mole
! ADCVGmol renamed ADCVG_Mole
! CDCVGmol renamed CDCVG_Mole
! AMetDCVG renamed AMetDCVG_Mole
! CVenMole renamed CVen_Mole
! AUrnTCA_collect and zAUrnTCA_collect renamed AUrnTCA_Coll and zAUrnTCA_Coll, respectively
! AUrnTCOGTCOH_collect renamed AUrnTCOGTCOH_Coll

! AUrnTCTotMole renamed AUrnTCTot_Mole
! AUrnNDCVCequiv renamed AUrnNDCVC_Eq

! These parameters weren't used so they are not included in the acslX code (in alphabetical
! order):
!   AUrnTCA_sat, AUrnTCOG_sat, AUrnTCOGTCOH_sat, CDCVGmolLD, CDCVG_NDtmp, CDCVG_ND, MWChlor,
!   QRapC, RUrnNDCVC, RUrnTCOGTCOH, StochChlorTCE, StochTCEGluc, StochDCATCE, TCAUrnSat,
!   TCOGUrnSat, VBldCtmp, VBodCtmp, VBodTCOHCtmp, VFatCtmp, VGutCtmp, VKidCtmp, VLivCtmp,
!   VRapCtmp, VRespEffCtmp, VRespLumCtmp, VSlwCtmp, VPlasCtmp, zAUrnTCA_sat

! Combined the equations for CART and CART_Tmp
! Plot for AUrnTCA_Sat when TCAUrnSat is 1 is the same as the plot for AUrtTCA_Coll when
!   TCAUrnSat is 0 -- same for AUrnTCOG_Sat and AUrnTCOG_Coll
! TCAUrnSat and TCOGUrnSat only set in lines that are commented out so got rid of TCAUrnSat,
!   TCOGUrnSat, AUrnTCA_Sat and AUrnTCOG_Sat
! Added additional code for additional weekly and daily average dosemetrics

! Model runs in mg, L, hrs

INITIAL
  LOGICAL CC
  INTEGER I, J, Species
  DIMENSION ConcList(150), StrtNextList(150), UrnMissList(10)

  CONSTANT BW = 0.0 ! Body weight (kg)
  CONSTANT QCC = 1.0 ! Cardiac output (L/hr/kg^0.75)
  CONSTANT VPR = 1.0 ! Alveolar ventilation-perfusion ratio (unitless)
  CONSTANT DRespC = 1.0 ! Respiratory lumen/tissue diffusive clearance rate (fraction of QP)

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```

! Fractional Blood Flows to Tissues (fraction of cardiac output)
CONSTANT    QFatC = 1.0    ! Fat
CONSTANT    QGutC = 1.0    ! Gut
CONSTANT    QKidC = 1.0    ! Kidney
CONSTANT    QLivC = 1.0    ! Liver
CONSTANT    QRapC = 1.0    ! Rapidly perfused tissues
CONSTANT    QSlwC = 1.0    ! Slowly perfused tissues

! Tissue Volumes (fraction of body weight)
! (Respiratory tissue represents the tracheobronchial region = trachea + bronchial basal +
!   bronchial secretory + bronchiolar)
CONSTANT    VBldC = 1.0    ! Blood
CONSTANT    VFatC = 1.0    ! Fat
CONSTANT    VGutC = 1.0    ! Gut
CONSTANT    VKidC = 1.0    ! Kidney
CONSTANT    VLivC = 1.0    ! Liver
CONSTANT    VPerfC = 1.0    ! Body that is blood perfused
CONSTANT    VRapC = 1.0    ! Rapidly perfused tissues
CONSTANT    VRespC = 1.0    ! Respiratory tissue
CONSTANT    VResplumC = 1.0    ! Respiratory lumen air volume
CONSTANT    VSlwC = 1.0    ! Slowly perfused tissues
CONSTANT    FracPlas = 1.0    ! Fraction of blood that is plasma (1.0 - hematocrit) (unitless)

! Molecular Weights (g/mole = mg/mmmole)
CONSTANT    MWTCE = 131.39    ! TCE
CONSTANT    MWDCVC = 216.1    ! DCVC
CONSTANT    MWTCA = 163.5    ! TCA
CONSTANT    MWTCOH = 149.5    ! TCOH
CONSTANT    MWTCOHgluc = 325.53    ! TCOH-Gluc
CONSTANT    MWNADCVC = 258.8    ! N Acetyl DCVC

! Partition Coefficients for TCE (unitless)
CONSTANT    PB = 1.0    ! Blood/air
CONSTANT    PFat = 1.0    ! Fat/blood
CONSTANT    PGut = 1.0    ! Gut/blood
CONSTANT    PKid = 1.0    ! Kidney/blood
CONSTANT    PLiv = 1.0    ! Liver/blood
CONSTANT    PRap = 1.0    ! Rapidly perfused/blood
CONSTANT    PResp = 1.0    ! Respiratory tissue/air
CONSTANT    PSlw = 1.0    ! Slowly perfused/blood

! Partition Coefficients for TCA (unitless)
CONSTANT    PRBCPlasTCA = 1.0    ! Scaled to species-specific central estimates
CONSTANT    PBodTCAC = 1.0    ! Free body/blood plasma
CONSTANT    PLivTCAC = 1.0    ! Free liver/blood plasma

! Partition Coefficients for TCOH (unitless)
CONSTANT    PBodTCOH = 1.0    ! Body/blood
CONSTANT    PLivTCOH = 1.0    ! Liver/blood

! Partition Coefficients for TCOG (unitless)
CONSTANT    PBodTCOG = 1.0    ! Body/blood
CONSTANT    PLivTCOG = 1.0    ! Liver/blood

! Partition Coefficient for DCVG (unitless)
CONSTANT    PEffDCVG = 1.0    ! Effective PC for the "body" (non-blood) compartment

! Binding Parameters for TCA
CONSTANT    BMaxkDC = 1.0    ! Ratio of max binding conc. to dissociation constant (unitless)
CONSTANT    kDissoc = 1.0    ! Protein/TCA dissociation constant (umole/L)

! Oral Uptake Constants (/hr)
CONSTANT    kAS = 1.4    ! TCE stomach absorption coefficient
CONSTANT    kTSD = 1.4    ! TCE stomach to duodenum transfer coefficient
CONSTANT    kAD = 0.75    ! TCE duodenum absorption coefficient
CONSTANT    kTD = 0.1    ! TCE duodenum-feces transfer coefficient
CONSTANT    kASTCA = 0.75    ! TCA stomach absorption coefficient
CONSTANT    kASTCOH = 0.75    ! TCOH stomach absorption coefficient

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! TCE Metabolism Constants
CONSTANT      VMaxC = 1.0      ! Capacity for hepatic TCE oxidation (mg/hr/kg liver)
CONSTANT      KMC = 1.0       ! Affinity for hepatic TCE oxidation (mg/L)
CONSTANT      Cl = 1.0        ! Ratio of capacity to affinity per kg liver for TCE hepatic
!                               oxidation (L/hr/kg liver)
CONSTANT      FracTCAC = 1.0   ! Fraction of hepatic TCE oxidation to TCA (unitless)
CONSTANT      FracOtherC = 1.0 ! Fraction of hepatic TCE oxidation not to TCA and TCOH
!                               (unitless)
CONSTANT      VMaxDCVGC = 1.0  ! Capacity for hepatic TCE GSH conjugation (mg/hr/kg liver)
CONSTANT      KMDCVGC = 1.0    ! Affinity for hepatic TCE GSH conjugation (mg/L)
CONSTANT      ClDCVG = 1.0     ! Ratio of capacity to affinity per kg liver for TCE GSH
!                               conjugation (L/hr/kg liver)
CONSTANT      VMaxKidDCVGC = 1.0 ! Capacity for renal TCE GSH conjugation (mg/hr/kg kidney)
CONSTANT      KMKidDCVGC = 1.0  ! Affinity for renal TCE GSH conjugation (mg/L)
CONSTANT      ClKidDCVG = 1.0   ! Ratio of capacity to affinity per kg kidney for TCE GSH
!                               conjugation (L/hr/kg kidney)

! TCE Metabolism Constants for Chloral Kinetics in Clara Cells in Lung
CONSTANT      VMaxLungLiv = 1.0 ! Ratio of capacities for lung to liver, scaled central
!                               estimates (unitless)
CONSTANT      KMClara = 1.0     ! Affinity for tracheo-bronchial TCE oxidation but in units of
!                               air concentration (mg/L)
CONSTANT      FracLungSysC = 1.0 ! Fraction of respiratory oxidative metabolism that enters
!                               systemic circulation (unitless)

! TCOH Metabolism Constants
CONSTANT      VMaxTCOHC = 1.0   ! Capacity for hepatic clearance of TCOH to TCA (mg/hr/kg^0.75)
CONSTANT      KMTCOH = 1.0     ! Affinity for hepatic clearance of TCOH to TCA (mg/L)
CONSTANT      ClTCOH = 1.0     ! (L/hr/kg^0.75)
CONSTANT      VMaxGlucC = 1.0   ! Capacity for hepatic glucuronidation of TCOH to TCOG
!                               (mg/hr/kg^0.75)
CONSTANT      KMGluc = 1.0     ! Affinity for hepatic glucuronidation of TCOH to TCOG (mg/L)
CONSTANT      ClGluc = 1.0     ! (L/hr/kg^0.75)
CONSTANT      kMetTCOHC = 1.0   ! Rate constant for hepatic clearance of TCOH to other
!                               (kg^0.25/hr)

! TCA Metabolism and Clearance Rates
CONSTANT      kUrnTCAC = 1.0    ! Rate constant for urinary clearance of TCA in plasma to urine
!                               (L/hr/kg)
CONSTANT      kMetTCAC = 1.0    ! Rate constant for hepatic clearance of TCA to other (kg^0.25/hr)

! TCOG Metabolism and Clearance Rates
CONSTANT      kBileC = 1.0     ! Rate constant for excretion of TCOG in liver to bile (kg^0.25/hr)
CONSTANT      kEHRC = 1.0     ! Lumped rate constant for TCOG in bile to TCOH in liver
!                               (kg^0.25/hr)
CONSTANT      kUrnTCOGC = 1.0  ! Rate constant for excretion of TCOG in urine (L/hr/kg)

! DCVG Metabolism Rates
CONSTANT      kDCVGC = 1.0     ! Rate constant for hepatic clearance of DCVG to DCVC
!                               (kg^0.25/hr)
CONSTANT      FracKidDCVCC = 1.0 ! Fraction of renal TCE GSH conjugation "directly" to DCVC
!                               (i.e., via first pass) (unitless)

! DCVC Metabolism and Clearance Rates (kg^0.25/hr)
CONSTANT      kNATC = 1.0     ! Lumped rate constant for DCVC clearance to urinary NACDCVC
!                               (kg^0.25/hr)
CONSTANT      kKidBioactC = 1.0 ! Rate constant for other bioactivation of DCVC (kg^0.25/hr)

! Closed Chamber Parameters
CONSTANT      CC = .FALSE.    ! Default to open chamber
CONSTANT      NRodents = 1.0  ! Number of rodents in the chamber
CONSTANT      kLossC = 1.0    ! Rate constant for closed chamber air loss (/hr)
CONSTANT      VChC = 1.0     ! Volume of the chamber without animals (L)

! TCE Dosing Parameters
CONSTANT      ConcList = 150*0.0 ! Inhalation exposure concentrations (ppm)
CONSTANT      StrtNextList = 150*0.0 ! Start times for inhalation exposures (hrs)
CONSTANT      TStrt = 1000.0    ! Time to start first inhalation exposure (hrs)
CONSTANT      IVDose = 0.0      ! IV dose (mg/kg/day)
CONSTANT      TChng = 0.003     ! IV infusion duration (hrs)
CONSTANT      Days = 1.0       ! Days of exposure each week

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CONSTANT      TMax = 24.0      ! Maximum length of multiple exposures (hrs)
CONSTANT      PDose = 0.0      ! Oral dose (mg/kg/day)
CONSTANT      Drink = 0.0      ! Drinking water dose (mg/kg/day)
CONSTANT      IADose = 0.0     ! Intraarterial dose (mg/kg)
CONSTANT      PVDose = 0.0     ! Portal vein dose (mg/kg)

! TCA Dosing Parameters
CONSTANT      IVDoseTCA = 0.0   ! IV dose of TCA (mg/kg/day)
CONSTANT      PODoseTCA = 0.0   ! Oral dose of TCA (mg/kg/day)

! TCOH Dosing Parameters
CONSTANT      IVDoseTCOH = 0.0  ! IV dose of TCOH (mg/kg/day)
CONSTANT      PODoseTCOH = 0.0  ! Oral dose of TCOH (mg/kg/day)

! Flags for Species and Urine Collection
CONSTANT      Species = 1       ! 1=human, 2=rat, 3=mouse
CONSTANT      UrnMissList = 10*1000.0 ! Start times for urine collection (hrs)
CONSTANT      TUrN = 0.0        ! Time to start first collection (hrs)

! Simulation Control Parameters
CONSTANT      TStp = 24.0       ! Time to stop simulation (hrs)
CINTERVAL     CINT = 0.01

! Scaled Flow Rates (L/hr)
      QC = QCC * (BW**0.75)
      QP = QC * VPR
      QM = QP / 0.7              ! Minute-volume
      DResp = DRespC * QP

! Blood Flows to Tissues (L/hr)
      QAdjus = QFatC + QGutC + QKidC + QLivC + QRapC + QSlwC
      QFat = (QFatC / QAdjus) * QC
      QGut = (QGutC / QAdjus) * QC
      QKid = (QKidC / QAdjus) * QC
      QLiv = (QLivC / QAdjus) * QC
      QRap = (QRapC / QAdjus) * QC
      QSlw = (QSlwC / QAdjus) * QC
      QC = QFat + QGut + QKid + QLiv + QRap + QSlw
      QGutLiv = QGut + QLiv
      QBod = QC - QGutLiv

! Plasma Flows to Tissues (L/hr)
      QCPlas = FracPlas * QC
      QBodPlas = FracPlas * QBod
      QGutLivPlas = FracPlas * QGutLiv
! Tissue Volumes (L)
      VTotC = VBldC + VFatC + VGutC + VKidC + VLivC + VRapC + VRespC + VSlwC
      VAdjus = VPerfC / VTotC
      VBld = (VBldC * VAdjus) * BW
      VFat = (VFatC * VAdjus) * BW
      VGut = (VGutC * VAdjus) * BW
      VKid = (VKidC * VAdjus) * BW
      VLiv = (VLivC * VAdjus) * BW
      VRap = (VRapC * VAdjus) * BW
      VResp = (VRespC * VAdjus) * BW
      VSlw = (VSlwC * VAdjus) * BW
      VPlas = FracPlas * VBld
      VBod = VFat + VGut + VKid + VRap + VResp + VSlw
      VBodTCOH = VBod + VBld
      VDCVG = VBld + PEffDCVG * (VBod + VLiv)

! Respiratory Tract Air Volumes (L of air)
! (VRespEff is the effective respiratory tissue air volume = V(tissue) * Resp:Air partition
! coefficient
      VRespLum = VRespLumC * BW
      VRespEff = VResp * PResp * PB

```

```

! Stoichiometry
  StochTCATCE = MWTCA / MWTCE
  StochTCATCOH = MWTCA / MWTCOH
  StochTCOHTCE = MWTCOH / MWTCE
  StochGlucTCOH = MWTCOHGluc / MWTCOH
  StochTCOHGluc = MWTCOH / MWTCOHGluc
  StochDCVCTCE = MWDCVC / MWTCE
  StochN = MWNADCVC / MWDCVC

! Partition Coefficients for TCA (unitless)
  TCAPlas = FracPlas + (1.0 - FracPlas) * PRBCPlasTCA
  PBodTCA = TCAPlas * PBodTCAC
  PLivTCA = TCAPlas * PLivTCAC

! Maximum Binding Concentration for TCA (umole/L)
  BMax = kDissoc * BMaxkDC

! TCE Metabolism Constants (scale some parameters differently for humans than for mice and rats)
  VMax = VMaxC * VLiv ! (mg/hr)
  FracOther = FracOtherC / (1.0 + FracOtherC) ! (fraction)
  FracTCA = FracTCAC * (1.0 - FracOther) / (1.0 + FracTCAC) ! (fraction)

IF (Species .EQ. 1) THEN
  KM = VMax / (VLiv * Cl) ! (mg/L)
  VMaxDCVG = VLiv * ClDCVG * KMDCVGC ! (mg/hr)
  KMDCVG = KMDCVGC ! (mg/L)
  VMaxKidDCVG = VKid * ClKidDCVG * KMKidDCVGC ! (mg/hr)
  KMKidDCVG = KMKidDCVGC ! (mg/L)
ELSE
  KM = KMC ! (mg/L)
  VMaxDCVG = VMaxDCVGC * VLiv ! (mg/hr)
  KMDCVG = VMaxDCVG / (VLiv * ClDCVG) ! (mg/L)
  VMaxKidDCVG = VMaxKidDCVGC * VKid ! (mg/hr)
  KMKidDCVG = VMaxKidDCVG / (VKid * ClKidDCVG) ! (mg/L)
ENDIF

! TCE Metabolism Constants for Chloral Kinetics in Lung
  VMaxClara = VMaxLungLiv * VMax ! (mg/hr)
  FracLungSys = FracLungSysC / (1.0 + FracLungSysC) ! (fraction)

! TCOH Metabolism Constants (scale some parameters differently for humans than for mice and rats)
  kMetTCOH = kMetTCOHC / (BW**0.25) ! (/hr)

IF (Species .EQ. 1) THEN
  VMaxTCOH = ClTCOH * KMTCOH * (BW**0.75) ! (mg/hr)
  VMaxGluc = ClGluc * KMGluc * (BW**0.75) ! (mg/hr)
ELSE
  VMaxTCOH = VMaxTCOHC * (BW**0.75) ! (mg/hr)
  VMaxGluc = VMaxGlucC * (BW**0.75) ! (mg/hr)
ENDIF

! TCA Metabolism and Clearance Rates
  kUrnTCA = (kUrnTCAC * BW) / VPlas ! (L/hr)
  kMetTCA = kMetTCAC / (BW**0.25) ! (/hr)

! TCOG Metabolism and Clearance Rates
  kBile = kBileC / (BW**0.25) ! (/hr)
  kEHR = kEHRC / (BW**0.25) ! (/hr)
  kUrnTCOG = kUrnTCOGC * BW / (VBodTCOH * PBodTCOG) ! (L/hr)

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! DCVG Metabolism Rates
      kDCVG = kDCVGC / (BW**0.25)                ! (/hr)
      FracKidDCVC = FracKidDCVCC / (1.0 + FracKidDCVCC)    ! (fraction)

! DCVC Metabolism and Clearance Rates
      kNAT = kNATC / (BW**0.25)                ! (/hr)
      kKidBioact = kKidBioactC / (BW**0.25)      ! (/hr)

! Exposure definition
  IF (CC) THEN
    Rodents = NRodents                ! Closed chamber simulation
    kLoss = kLossC                    ! (/hr)
    VCh = VChC - (Rodents * BW)      ! Calculate net chamber volume (L)
  ELSE
    Rodents = 0.0                    ! Open chamber simulation
    kLoss = 0.0                      ! Turn off chamber losses so concentration is constant (/hr)
    VCh = 1.0                        ! So that VCh drops out of equations (L)
  ENDIF

! Initialize starting value
  UrnMissing = 0.0                    ! Indicator for missing urine collection times
  I = 1
  J = 1
  ACh0 = (ConcList(1) * VCh * MWTCE) / 24450.0    ! Initial amount in chamber (mg)
  Day = 0.5
  Conc = 0.0
  CInh = 0.0
  kDrink = (Drink * BW) / 24.0        ! Ingestion rate via drinking water (mg/hr)
  kIA = 0.0
  kIV = 0.0
  kIVTCA = 0.0
  kIVTCOH = 0.0
  kPV = 0.0
  kStom = 0.0
  kStomTCA = 0.0
  kStomTCOH = 0.0
  AExhExp = 0.0
  AExhPost = 0.0
  ExhFactor = 1.0
  ExhFac_Den = 0.0
  TotDoseBW34 = 0.0
  FracMetab = 0.0
  FracOxMetab = 0.0
  FracMetLiv1 = 0.0
  FracMetLivOther = 0.0
  FracMetGSH = 0.0
  FracBioactKid = 0.0
  FracMetLng = 0.0

! Initialize values for AUC dosemetrics
  PAUCCBld = 0.0
  AUCCBldDM = 0.0
  PAUCCPlasTCA = 0.0
  AUCCPlasTCADM = 0.0
  PAUCCPlasTCAFree = 0.0
  AUCCPlasTCAFreeDM = 0.0
  PAUCCTCOH = 0.0
  AUCCTCOHDM = 0.0
  PAUCCTCOG = 0.0
  AUCCTCOGDM = 0.0
  PAUCTotCTCOH = 0.0
  AUCTotCTCOHDM = 0.0
  PAUCCLiv = 0.0
  AUCCLivDM = 0.0
  PAUCCLivTCA = 0.0
  AUCCLivTCADM = 0.0
  PAUCCLivTCOH = 0.0

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    AUCCLivTCOHDM = 0.0
    PAUCCLivTCOG = 0.0
    AUCCLivTCOGDM = 0.0
    PAUCCKid = 0.0
    AUCCKidDM = 0.0
    PAUCCDCVG_mMole = 0.0
    AUCCDCVG_mMoleDM = 0.0

! Initialize values for metabolism dosemetrics
    PTotMetabBW34 = 0.0
    TotMetabBW34DM = 0.0
    PTotOxMetBW34 = 0.0
    TotOxMetBW34DM = 0.0
    PAMetLiv1VLiv = 0.0
    AMetLiv1VLivDM = 0.0
    PAMetLiv1BW34 = 0.0
    AMetLiv1BW34DM = 0.0
    PAMetLiv1TCAVLiv = 0.0
    AMetLiv1TCAVLivDM = 0.0
    PAMetLiv1TCABW34 = 0.0
    AMetLiv1TCABW34DM = 0.0
    PAMetLiv1TCOHVLiv = 0.0
    AMetLiv1TCOHVLivDM = 0.0
    PAMetLiv1TCOHBW34 = 0.0
    AMetLiv1TCOHBW34DM = 0.0
    PAMetLiv2VLiv = 0.0
    AMetLiv2VLivDM = 0.0
    PAMetLiv2BW34 = 0.0
    AMetLiv2BW34DM = 0.0
    PAMetLivOtherVLiv = 0.0
    AMetLivOtherVLivDM = 0.0
    PAMetLivOtherBW34 = 0.0
    AMetLivOtherBW34DM = 0.0
    PAMetTCAVLiv = 0.0
    AMetTCAVLivDM = 0.0
    PAMetTCABW34 = 0.0
    AMetTCABW34DM = 0.0
    PAMetTCOHTCAVLiv = 0.0
    AMetTCOHTCAVLivDM = 0.0
    PAMetTCOHTCABW34 = 0.0
    AMetTCOHTCABW34DM = 0.0
    PAMetTCOHGlucVLiv = 0.0
    AMetTCOHGlucVLivDM = 0.0
    PAMetTCOHGlucBW34 = 0.0
    AMetTCOHGlucBW34DM = 0.0
    PAMetTCOHOtherVLiv = 0.0
    AMetTCOHOtherVLivDM = 0.0
    PAMetTCOHOtherBW34 = 0.0
    AMetTCOHOtherBW34DM = 0.0
    PAMetKid = 0.0
    AMetKidDM = 0.0
    PAMetKidVKid = 0.0
    AMetKidVKidDM = 0.0
    PAMetKidBW34 = 0.0
    AMetKidBW34DM = 0.0
    PAMetDCVG_mMole = 0.0
    AMetDCVG_mMoleDM = 0.0
    PAMetDCVG_mMoleVKid = 0.0
    AMetDCVG_mMoleVKidDM = 0.0
    PAMetDCVG_mMoleBW34 = 0.0
    AMetDCVG_mMoleBW34DM = 0.0

    SCHEDULE ConcOn .AT. TStrt
    SCHEDULE UrnMissOn .AT. TUrN

END

```

DYNAMIC

ALGORITHM IALG = 2

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DISCRETE DoseOn
  INTERVAL DoseInt = 10000.0                ! Dosing interval (hrs)
  SCHEDULE DoseOff .AT. T + TChng

  IF ((T .LT. TMax) .AND. (Day .LE. Days)) THEN
    kIA = (IADose * BW) / TChng              ! IA infusion rate (mg/hr)
    kIV = (IVDose * BW) / TChng              ! TCE IV infusion rate (mg/hr)
    kPV = (PVDose * BW) / TChng              ! PV infusion rate (mg/hr)
    kIVTCA = (IVDoseTCA * BW) / TChng        ! TCA IV infusion rate (mg/hr)
    kIVTCOH = (IVDoseTCOH * BW) / TChng      ! TCOH IV infusion rate (mg/hr)

    kStom = (PDose * BW) / TChng              ! PO dose rate (into stomach) (mg/hr)
    kStomTCA = (PODoseTCA * BW) / TChng      ! TCA PO dose rate into stomach (mg/hr)
    kStomTCOH = (PODoseTCOH * BW) / TChng    ! TCOH PO dose rate into stomach (mg/hr)
  ENDIF

  IF (Days .GT. 1.0) THEN
    Day = Day + 1.0
    IF (Day .GT. 7.0) Day = 0.5
  ENDIF
END

DISCRETE ConcOn      ! Start inhalation
  SCHEDULE ConcOn .AT. T + StrtNextList(I)
  Conc = ConcList(I)
  I = I + 1
END

DISCRETE DoseOff
  kIA = 0.0
  kIV = 0.0
  kPV = 0.0
  kIVTCA = 0.0
  kIVTCOH = 0.0
  kStom = 0.0
  kStomTCA = 0.0
  kStomTCOH = 0.0
END

DISCRETE UrnMissOn
  SCHEDULE UrnMissOff .AT. T + UrnMissList(J)
  UrnMissing = 1.0
  J = J + 1
END

DISCRETE UrnMissOff
  SCHEDULE UrnMissOn .AT. T + UrnMissList(J)
  UrnMissing = 0.0
  J = J + 1
END

DISCRETE Calc
! Save previous value for calculating daily or weekly dosemetrics
  INTERVAL DMInt = 10000.0                ! Interval for calculating dose metrics (hrs)

! Calculate daily or weekly AUC dosemetrics
  AUCCBldDM = AUCCBld - PAUCCBld
  AUCCPlasTCADM = AUCCPlasTCA - PAUCCPlasTCA
  AUCCPlasTCAFreeDM = AUCCPlasTCAFree - PAUCCPlasTCAFree
  AUCCTCOHDM = AUCCTCOH - PAUCCTCOH
  AUCCTCOGDM = AUCCTCOG - PAUCCTCOG
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AUCTotCTCOHDM = AUCTotCTCOH - PAUCTotCTCOH
AUCCLivDM = AUCCLiv - PAUCCLiv
AUCCLivTCADM = AUCCLivTCA - PAUCCLivTCA
AUCCLivTCOHDm = AUCCLivTCOH - PAUCCLivTCOH
AUCCLivTCOGDM = AUCCLivTCOG - PAUCCLivTCOG
AUCCKidDM = AUCCKid - PAUCCKid
AUCCDCVG_mMoleDM = AUCCDCVG_mMole - PAUCCDCVG_mMole

! Calculate daily or weekly metabolism dosemetrics
TotMetabBW34DM = TotMetabBW34 - PTotMetabBW34
TotOxMetBW34DM = TotOxMetBW34 - PTotOxMetBW34
AMetLiv1VLivDM = AMetLiv1VLiv - PAMetLiv1VLiv
AMetLiv1BW34DM = AMetLiv1BW34 - PAMetLiv1BW34
AMetLiv1TCAVLivDM = AMetLiv1TCAVLiv - PAMetLiv1TCAVLiv
AMetLiv1TCABW34DM = AMetLiv1TCABW34 - PAMetLiv1TCABW34
AMetLiv1TCOHVLivDM = AMetLiv1TCOHVLiv - PAMetLiv1TCOHVLiv
AMetLiv1TCOHBW34DM = AMetLiv1TCOHBW34 - PAMetLiv1TCOHBW34
AMetLiv2VLivDM = AMetLiv2VLiv - PAMetLiv2VLiv
AMetLiv2BW34DM = AMetLiv2BW34 - PAMetLiv2BW34
AMetLivOtherVLivDM = AMetLivOtherVLiv - PAMetLivOtherVLiv
AMetLivOtherBW34DM = AMetLivOtherBW34 - PAMetLivOtherBW34
AMetTCAVLivDM = AMetTCAVLiv - PAMetTCAVLiv
AMetTCABW34DM = AMetTCABW34 - PAMetTCABW34
AMetTCOHTCAVLivDM = AMetTCOHTCAVLiv - PAMetTCOHTCAVLiv
AMetTCOHTCABW34DM = AMetTCOHTCABW34 - PAMetTCOHTCABW34
AMetTCOHGlucVLivDM = AMetTCOHGlucVLiv - PAMetTCOHGlucVLiv
AMetTCOHGlucBW34DM = AMetTCOHGlucBW34 - PAMetTCOHGlucBW34
AMetTCOHOtherVLivDM = AMetTCOHOtherVLiv - PAMetTCOHOtherVLiv
AMetTCOHOtherBW34DM = AMetTCOHOtherBW34 - PAMetTCOHOtherBW34
AMetKidDM = AMetKid - PAMetKid
AMetKidVKidDM = AMetKidVKid - PAMetKidVKid
AMetKidBW34DM = AMetKidBW34 - PAMetKidBW34
AMetDCVG_mMoleDM = AMetDCVG_mMole - PAMetDCVG_mMole
AMetDCVG_mMoleVKidDM = AMetDCVG_mMoleVKid - PAMetDCVG_mMoleVKid
AMetDCVG_mMoleBW34DM = AMetDCVG_mMoleBW34 - PAMetDCVG_mMoleBW34

PAUCCBld = AUCCBld
PAUCCPlasTCA = AUCCPlasTCA
PAUCCPlasTCAFree = AUCCPlasTCAFree
PAUCTCOH = AUCCTCOH
PAUCTCOG = AUCCTCOG
PAUCTotCTCOH = AUCTotCTCOH
PAUCCLiv = AUCCLiv
PAUCCLivTCA = AUCCLivTCA
PAUCCLivTCOH = AUCCLivTCOH
PAUCCLivTCOG = AUCCLivTCOG
PAUCCKid = AUCCKid
PAUCCDCVG_mMole = AUCCDCVG_mMole

PTotMetabBW34 = TotMetabBW34
PTotOxMetBW34 = TotOxMetBW34
PAMetLiv1VLiv = AMetLiv1VLiv
PAMetLiv1BW34 = AMetLiv1BW34
PAMetLiv1TCAVLiv = AMetLiv1TCAVLiv
PAMetLiv1TCABW34 = AMetLiv1TCABW34
PAMetLiv1TCOHVLiv = AMetLiv1TCOHVLiv
PAMetLiv1TCOHBW34 = AMetLiv1TCOHBW34
PAMetLiv2VLiv = AMetLiv2VLiv
PAMetLiv2BW34 = AMetLiv2BW34
PAMetLivOtherVLiv = AMetLivOtherVLiv
PAMetLivOtherBW34 = AMetLivOtherBW34
PAMetTCAVLiv = AMetTCAVLiv
PAMetTCABW34 = AMetTCABW34
PAMetTCOHTCAVLiv = AMetTCOHTCAVLiv
PAMetTCOHTCABW34 = AMetTCOHTCABW34
PAMetTCOHGlucVLiv = AMetTCOHGlucVLiv
PAMetTCOHGlucBW34 = AMetTCOHGlucBW34
PAMetTCOHOtherVLiv = AMetTCOHOtherVLiv
PAMetTCOHOtherBW34 = AMetTCOHOtherBW34
PAMetKid = AMetKid
PAMetKidVKid = AMetKidVKid

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PAMetKidBW34 = AMetKidBW34
PAMetDCVG_mMole = AMetDCVG_mMole
PAMetDCVG_mMoleVKid = AMetDCVG_mMoleVKid
PAMetDCVG_mMoleBW34 = AMetDCVG_mMoleBW34

END

DERIVATIVE

      Hours = T

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

! -----
! ----- TCE Model -----
! -----
! Amount of TCE in inhaled air
      RACH = (Rodents * (QM * CExhResp - QM * ACh / VCh)) - (kLoss * ACh) ! (mg/hr)
      ACh = INTEG(RACH, ACh0) ! (mg)
      CInhPPM = (CInh * 24450.0) / MWTCE ! (ppm)

PROCEDURAL (CInh = CC, ACh, VCh, Conc, MWTCE)
      CInh = Conc * MWTCE / 24450.0 ! (mg/L)
      IF (CC) CInh = ACh / VCh ! (mg/L)
END

! Amount of TCE in inhalation respiratory lumen
      RAInhResp = (QM * CInh + DResp * (CResp - CInhResp) - QM * CInhResp) ! (mg/hr)
      AInhResp = INTEG(RAInhResp, 0.0) ! (mg)
      CInhResp = AInhResp / VRespLum ! (mg/L)

! Amount of TCE in exhalation respiratory lumen
      RAExhResp = (QM * (CInhResp - CExhResp) + QP * (CArt / PB - CInhResp) &
&      + DResp * (CResp - CExhResp)) ! (mg/hr)
      AExhResp = INTEG(RAExhResp, 0.0) ! (mg)
      CExhResp = AExhResp / VRespLum ! (mg/L)

! Amount of TCE in the effective respiratory tissue
      RAResp = DResp * (CInhResp + CExhResp - 2.0 * CResp) - RAMetLng ! (mg/hr)
      AResp = INTEG(RAResp, 0.0) ! (mg)
      CResp = AResp / VRespEff ! (mg/L)

! Amount of TCE metabolized in the effective respiratory tissue
      RAMetLng = VMaxClara * CResp / (KMClara + CResp) ! (mg/hr)
      AMetLng = INTEG(RAMetLng, 0.0) ! (mg)
      AMetLngBW34 = AMetLng / (BW**0.75) ! (mg/kg^0.75)
      IF (TotDoseBW34.GT. 0.0) FracMetLng = AMetLngBW34 / TotDoseBW34 ! (unitless)
      AMetLngVResp = AMetLng / VResp ! (mg/L)

! Concentration of TCE in arterial blood
      CArt = (QC * CVen + QP * CInhResp + kIA) / (QC + (QP / PB)) ! (mg/L)
      AUCCBld = INTEG(CArt, 0.0) ! (mg-hr/L)

! Concentration of TCE in alveolar air
      ExhFac_Den = (QP * CArt / PB + (QM - QP) * CInhResp) ! (mg)
      CALv = CArt / PB * ExhFactor ! (unitless)
      CALvPPM = CALv * (24450.0 / MWTCE) ! (ppm)

PROCEDURAL (ExhFactor = QM, CExhResp, ExhFac_Den)
      ExhFactor = 1.0 ! (unitless)
      IF (ExhFac_Den.GT. 0.0) ExhFactor = (QM * CExhResp) / ExhFac_Den ! (unitless)
END

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! Amount of TCE exhaled
  RAExh = QM * CExhResp                                ! (mg/hr)
  AExh = INTEG(RAExh, 0.0)                             ! (mg)
  AExhPost = AExh - AExhExp                             ! (mg)
  IF (Conc .GT. 0.0) AExhExp = AExh                    ! (mg)

! Amount of TCE in fat tissue
  RAFat = QFat * (CArt - CVFat)                         ! (mg/hr)
  AFat = INTEG(RAFat, 0.0)                             ! (mg)
  CFat = AFat / VFat                                    ! (mg/L)
  CVFat = CFat / PFat                                  ! (mg/L)

! Amount of TCE in stomach -- for oral dosing only
  RAStom = kStom - (kAS + kTSD) * AStom                 ! (mg/hr)
  AStom = INTEG(RAStom, 0.0)                           ! (mg)

! Amount of TCE in duodenum -- for oral dosing only
  RADuod = (kTSD * AStom) - (kAD + kTD) * ADuod        ! (mg/hr)
  ADuod = INTEG(RADuod, 0.0)                           ! (mg)

! Amount of TCE excreted in feces
  RAExc = kTD * ADuod                                   ! (mg/hr)
  AExc = INTEG(RAExc, 0.0)                             ! (mg)

! Rate TCE absorbtion
  RAO = (kAS * AStom) + (kAD * ADuod)                  ! (mg/hr)

! Amount of TCE in gut compartment
  RAGut = (QGut * (CArt - CVGut)) + kDrink + RAO       ! (mg/hr)
  AGut = INTEG(RAGut, 0.0)                             ! (mg)
  CGut = AGut / VGut                                    ! (mg/L)
  CVGut = CGut / PGut                                  ! (mg/L)

! Amount of TCE in kidneys
  RAKid = (QKid * (CArt - CVKid)) - RAMetKid            ! (mg/hr)
  AKid = INTEG(RAKid, 0.0)                             ! (mg)
  CKid = AKid / VKid                                    ! (mg/L)
  CVKid = CKid / PKid                                  ! (mg/L)
  AUCCKid = INTEG(CKid, 0.0)                           ! (mg-hr/L)

! Amount of TCE metabolized to DCVG in kidneys
  RAMetKid = (VMaxKidDCVG * CVKid) / (KMKidDCVG + CVKid) ! (mg/hr)
  AMetKid = INTEG(RAMetKid, 0.0)                       ! (mg)
  AMetKidVKid = AMetKid / VKid                         ! (mg/kg)
  AMetKidBW34 = AMetKid / (BW**0.75)                  ! (mg/kg^0.75)

! Amount of TCE in liver
  RALiv = (QLiv * (CArt - CVLiv)) + (QGut * (CVGut - CVLiv)) + kPV - RAMetLiv1 - RAMetLiv2 ! (mg/hr)
  ALiv = INTEG(RALiv, 0.0)                             ! (mg)
  CLiv = ALiv / VLiv                                    ! (mg/L)
  CVLiv = CLiv / PLiv                                   ! (mg/L)
  AUCCLiv = INTEG(CLiv, 0.0)                           ! (mg-hr/L)

! Amount of TCE metabolized to TCA, DCA and TCOH in liver
  RAMetLiv1 = (VMax * CVLiv) / (KM + CVLiv)            ! (mg/hr)
  AMetLiv1 = INTEG(RAMetLiv1, 0.0)                    ! (mg)
  AMetLiv1VLiv = AMetLiv1 / VLiv                      ! (mg/kg)
  AMetLiv1BW34 = AMetLiv1 / (BW**0.75)               ! (mg/kg^0.75)
  IF (TotDoseBW34 .GT. 0.0) FracMetLiv1 = AMetLiv1BW34 / TotDoseBW34 ! (unitless)
  AMetLiv1TCA = FracTCA * AMetLiv1                   ! (mg TCE)
  AMetLiv1TCAVLiv = AMetLiv1TCA / VLiv               ! (mg TCE/kg)

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AMetLiv1TCABW34 = AMetLiv1TCA / (BW**0.75) ! (mg TCE/kg^0.75)
AMetLiv1TCOH = (1.0 - FracOther - FracTCA) * AMetLiv1 ! (mg TCE)
AMetLiv1TCOHVLiv = AMetLiv1TCOH / VLiv ! (mg TCE/kg)
AMetLiv1TCOHBW34 = AMetLiv1TCOH / (BW**0.75) ! (mg TCE/kg^0.75)
AMetLivOther = FracOther * AMetLiv1 ! (mg)
AMetLivOtherVLiv = AMetLivOther / VLiv ! (mg/kg)
AMetLivOtherBW34 = AMetLivOther / (BW**0.75) ! (mg/kg^0.75)
IF (TotDoseBW34 .GT. 0.0) FracMetLivOther = AMetLivOtherBW34 / TotDoseBW34 ! (unitless)

! Amount of TCE metabolized to DCVG in liver
RAMetLiv2 = (VMaxDCVG * CVLiv) / (KMDCVG + CVLiv) ! (mg/hr)
AMetLiv2 = INTEG(RAMetLiv2, 0.0) ! (mg)
AMetLiv2VLiv = AMetLiv2 / VLiv ! (mg/kg)
AMetLiv2BW34 = AMetLiv2 / (BW**0.75) ! (mg/kg^0.75)
AMetGSH = AMetLiv2 + AMetKid ! (mg)
AMetGSHBW34 = AMetGSH / (BW**0.75) ! (mg/kg^0.75)
IF (TotDoseBW34 .GT. 0.0) FracMetGSH = AMetGSHBW34 / TotDoseBW34 ! (unitless)

! Amount of TCE in rapidly perfused tissues
RARap = QRap * (CART - CVRap) ! (mg/hr)
ARap = INTEG(RARap, 0.0) ! (mg)
CRap = ARap / VRap ! (mg/L)
CVRap = CRap / PRap ! (mg/L)
AUCCRap = INTEG(CRap, 0.0) ! (mg-hr/L)
CHrt = CRap ! (mg/L)
CLung = CRap ! (mg/L)
CSpl = CRap ! (mg/L)
CBrn = CRap ! (mg/L)

! Amount of TCE in slowly perfused tissues
RASlw = QSlw * (CART - CVSlw) ! (mg/hr)
ASlw = INTEG(RASlw, 0.0) ! (mg)
CSlw = ASlw / VSlw ! (mg/L)
CVSlw = CSlw / PSlw ! (mg/L)
CMus = CSlw ! (mg/L)

! Concentration of TCE in mixed venous blood (mg/L)
RABld = (QFat*CVFat + QKid*CVKid + QGutLiv*CVLiv + QRap*CVRap + QSlw*CVSlw + kIV) &
& - QC * CVen ! (mg/hr)
ABld = INTEG(RABld, 0.0) ! (mg)
CVen = ABld / VBld ! (mg/L)
CVen_mMole = CVen / MWTCE ! (mmoles/hr)
CBldMix = (CART + CVen) / 2.0 ! (mg/L)

! Total intake of TCE from inhalation
RInhDose = QM * CInh ! (mg/hr)
RetDose = INTEG(RInhDose, 0.0) - AExhExp ! (mg)
IF (ConcList(1) .EQ. 0.0) RetDose = 0.0

! Total intake of TCE from all routes
TotDose = INTEG((kDrink + kIA + kIV + kPV + kStom + RInhDose), 0.0) ! (mg)

! Mass Balance (mg)
TotTissue = AInhResp + AExhResp + AResp + ABld + AFat + AStom + ADuod + AGut + AKid &
& + ALiv + ARap + ASlw
TotMetab = AMetLng + AMetKid + AMetLiv1 + AMetLiv2
MassBalTCE = TotDose - TotTissue - TotMetab - AExc - AExh
TotDoseBW34 = TotDose / (BW**0.75) ! (mg/kg^0.75)
TotMetabBW34 = TotMetab / (BW**0.75) ! (mg/kg^0.75)
IF (TotDoseBW34 .GT. 0.0) FracMetab = TotMetabBW34 / TotDoseBW34 ! (unitless)
TotOxMetBW34 = (AMetLng + AMetLiv1) / (BW**0.75) ! (mg/kg^0.75)
IF (TotDoseBW34 .GT. 0.0) FracOxMetab = TotOxMetBW34 / TotDoseBW34 ! (unitless)

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! -----
! ----- TCA Sub-Model -----
! -----
! Amount of TCA in plasma
  RAPlasTCA = (QBodPlas * CVBodTCA) + (QGutLivPlas * CVLivTCA) + kIVTCA &
&      - (QCPlas * CPlasTCA) - RAUrnTCA      ! (mg/hr)
  APlasTCA = INTEG(RAPlasTCA, 0.0)           ! (mg)
  CPlasTCA = APlasTCA / VPlas                 ! (mg/L)
  CBldTCA = CPlasTCA * TCAPlas                ! (mg/L)
  AUCCPlasTCA = INTEG(CPlasTCA, 0.0)          ! (mg-hr/L)

! Amount of free TCA in plasma
  APlasTCAFree = CPlasTCAFree * VPlas        ! (mg)
  AUCCPlasTCAFree = INTEG(CPlasTCAFree, 0.0)  ! (mg-hr/L)

      A = kDissoc + BMax - ((CPlasTCA / MWTCA) * 1000.0) ! (umoles/L)
      B = 4.0 * kDissoc * ((CPlasTCA / MWTCA) * 1000.0) ! (umoles/L)
PROCEDURAL (CPlasTCAFree = A, B, MWTCA)
  IF (B .LT. (0.01 * (A**2.0))) THEN
    CPlasTCAFree = (0.5 * (B / 2.0 / A)) * MWTCA / 1000.0 ! (mg/L)
  ELSE
    CPlasTCAFree = (0.5 * (SQRT((A**2.0) + B) - A)) * MWTCA / 1000.0 ! (mg/L)
  ENDIF
END

! Concentration of bound TCA in plasma
  CPlasTCABnd = CPlasTCA - CPlasTCAFree      ! (mg/L)

! Amount of TCA in the body
  RABodTCA = QBodPlas * (CPlasTCAFree - CVBodTCAFree) ! (mg/hr)
  ABodTCA = INTEG(RABodTCA, 0.0)                ! (mg)
  CBodTCA = ABodTCA / VBod                      ! (mg/L)
  CVBodTCA = CPlasTCABnd + CVBodTCAFree         ! (mg/L)
  CVBodTCAFree = CBodTCA / PBodTCA              ! (mg/L)
  CKidTCA = CBodTCA                            ! (mg/L)
  CLungTCA = CBodTCA                           ! (mg/L)

! Amount of TCA in stomach -- for oral dosing only
  RASTomTCA = kStomTCA - kASTCA * ASTomTCA      ! (mg/hr)
  ASTomTCA = INTEG(RASTomTCA, 0.0)              ! (mg)

! Amount of TCA in the liver
  RALivTCA = (QGutLivPlas * (CPlasTCAFree - CVLivTCAFree)) + (kASTCA * ASTomTCA) &
&      + (StochTCATCOH * RAMetTCOHTCA) &
&      + (FracTCA * StochTCATCE * (RAMetLiv1 + FracLungSys * RAMetLng)) &
&      - RAMetTCA      ! (mg/hr)
  ALivTCA = INTEG(RALivTCA, 0.0)                ! (mg)
  CLivTCA = ALivTCA / VLiv                      ! (mg/L)
  CVLivTCA = CPlasTCABnd + CVLivTCAFree         ! (mg/L)
  CVLivTCAFree = CLivTCA / PLivTCA              ! (mg/L)
  AUCCLivTCA = INTEG(CLivTCA, 0.0)              ! (mg-hr/L)

! Amount of TCA metabolized in liver
  RAMetTCA = kMetTCA * ALivTCA                  ! (mg/hr)
  AMetTCA = INTEG(RAMetTCA, 0.0)                ! (mg)
  AMetTCAVLiv = AMetTCA / VLiv                  ! (mg TCA/kg)
  AMetTCABW34 = AMetTCA / (BW**0.75)           ! (mg TCA/kg^0.75)

! Amount of TCA in urine
  RAUrnTCA = kUrnTCA * APlasTCAFree            ! (mg/hr)
  AUrnTCA = INTEG(RAUrnTCA, 0.0)               ! (mg)
  RAUrnTCA_Coll = (1.0 - UrnMissing) * RAUrnTCA ! (mg/hr)
  AUrnTCA_Coll = INTEG(RAUrnTCA_Coll, 0.0)      ! (mg)

```

```

! Total intake of TCA from all routes
AOTCA = INTEG((kIVTCA + (kASTCA * ASomTCA)), 0.0) ! (mg)

! Mass Balance (mg)
TotTCAIn = AOTCA + (FracTCA * StochTCATCE * (AMetLiv1 + FracLungSys * AMetLng)) &
& + (StochTCATCOH * AMetTCOHTCA)
TotTissueTCA = APlasTCA + ABodTCA + ALivTCA
MassBalTCA = TotTCAIn - TotTissueTCA - AMetTCA - AUrnTCA
TotTCAInBW = TotTCAIn / BW

! -----
! ----- TCOH Sub-Model -----
! -----

! Concentration of TCOH in blood
CTCOH = (QBod * CVBodTCOH + QGutLiv * CVLivTCOH + kIVTCOH) / QC ! (mg/L)
AUCCTCOH = INTEG(CTCOH, 0.0) ! (mg-hr/L)

! Amount of TCOH in the body
RABodTCOH = QBod * (CTCOH - CVBodTCOH) ! (mg/hr)
ABodTCOH = INTEG(RABodTCOH, 0.0) ! (mg)
CBodTCOH = ABodTCOH / VBodTCOH ! (mg/L)
CVBodTCOH = ABodTCOH / VBodTCOH / PBodTCOH ! (mg/L)
AUCCBodTCOH = INTEG((ABodTCOH / VBodTCOH), 0.0) ! (mg-hr/L)
CKidTCOH = CBodTCOH ! (mg/L)
CLungTCOH = CBodTCOH ! (mg/L)

! Concentration of TCOH-Gluc in the body
CBodTCOGTCOH = StochTCOHGluc * (ABodTCOG / VBodTCOH) ! (mg/L)
CKidTCOGTCOH = CBodTCOGTCOH ! (mg/L)
CLungTCOGTCOH = CBodTCOGTCOH ! (mg/L)

! Amount of TCOH in stomach -- for oral dosing only
RAStomTCOH = kStomTCOH - kASTCOH * ASomTCOH ! (mg/hr)
ASomTCOH = INTEG(RAStomTCOH, 0.0) ! (mg)

! Amount of TCOH in liver
RALivTCOH = (QGutLiv * (CTCOH - CVLivTCOH)) + (kASTCOH * ASomTCOH) &
& + (StochTCOHGluc * RAREcircTCOG) &
& + ((1.0-FracOther-FracTCA) * StochTCOHTCE * (RAMetLiv1 + FracLungSys * RAMetLng)) &
& - RAMetTCOHTCA - RAMetTCOHGluc - RAMetTCOHOther ! (mg/hr)
ALivTCOH = INTEG(RALivTCOH, 0.0) ! (mg)
CLivTCOH = ALivTCOH / VLiv ! (mg/L)
CVLivTCOH = ALivTCOH / VLiv / PLivTCOH ! (mg/L)
AUCCLivTCOH = INTEG((ALivTCOH / VLiv), 0.0) ! (ug-hr/L)

! Concentration of TCOH-Gluc in liver
CLivTCOGTCOH = StochTCOHGluc * (ALivTCOG / VLiv) ! (mg/L)

! Rate of TCOH oxidation to TCA
RAMetTCOHTCA = (VMaxTCOH * CVLivTCOH) / (KMTCOH + CVLivTCOH) ! (mg/hr)
AMetTCOHTCA = INTEG(RAMetTCOHTCA, 0.0) ! (mg)
AMetTCOHTCAVLiv = AMetTCOHTCA / VLiv ! (mg TCOH/kg)
AMetTCOHTCABW34 = AMetTCOHTCA / (BW**0.75) ! (mg TCOH/kg^0.75)

! Amount of TCOH glucuronidation to TCOG
RAMetTCOHGluc = (VMaxGluc * CVLivTCOH) / (KMGluc + CVLivTCOH) ! (mg/hr)
AMetTCOHGluc = INTEG(RAMetTCOHGluc, 0.0) ! (mg)
AMetTCOHGlucVLiv = AMetTCOHGluc / VLiv ! (mg TCOH/kg)
AMetTCOHGlucBW34 = AMetTCOHGluc / (BW**0.75) ! (mg TCOH/kg^0.75)

```

```

! Amount of TCOH metabolized by other routes in liver
RAMetTCOHOther = kMetTCOH * ALivTCOH                                ! (mg/hr)
AMetTCOHOther = INTEG(RAMetTCOHOther, 0.0)                        ! (mg)
AMetTCOHOtherVLiv = AMetTCOHOther / VLiv                          ! (mg TCOH/kg)
AMetTCOHOtherBW34 = AMetTCOHOther / (BW**0.75)                    ! (mg TCOH/kg^0.75)

! Total intake of TCOH from all routes
AOTCOH = INTEG((kIVTCOH + (kASTCOH * ASomTCOH)), 0.0)              ! (mg)

! Mass Balance (mg)
TotTCOHIn = AOTCOH + (StochTCOHGluc * ARecircTCOG) &
& + ((1.0-FracOther-FracTCA) * StochTCOHTCE * (AMetLivl + FracLungSys * AMetLng))
TotTissueTCOH = ABodTCOH + ALivTCOH
TotMetabTCOH = AMetTCOHTCA + AMetTCOHGluc + AMetTCOHOther
MassBalTCOH = TotTCOHIn - TotTissueTCOH - TotMetabTCOH
TotTCOHDose = TotTCOHIn - (StochTCOHGluc * ARecircTCOG)

! -----
! ----- TCOG Sub-Model -----
! -----

! Concentration of TCOH-Gluc in blood
CTCOG = (QBod * CVBodTCOG + QGutLiv * CVLivTCOG) / QC              ! (mg/L)
AUCCTCOG = INTEG(CTCOG, 0.0)                                       ! (mg-hr/L)
CTCOGTCOH = (StochTCOHGluc * CTCOG)                                ! (mg/L)

! Amount of TCOH-Gluc in the body
RABodTCOG = QBod * (CTCOG - CVBodTCOG) - RAUrntCOG                ! (mg/hr)
ABodTCOG = INTEG(RABodTCOG, 0.0)                                    ! (mg)
CVBodTCOG = ABodTCOG / VBodTCOH / PBodTCOG                        ! (mg/L)

! Amount of TCOH-Gluc in liver
RALivTCOG = QGutLiv * (CTCOG - CVLivTCOG) + (StochGlucTCOH * RAMetTCOHGluc) &
& - (kBile * ALivTCOG)                                              ! (mg/hr)
ALivTCOG = INTEG(RALivTCOG, 0.0)                                    ! (mg)
CLivTCOG = ALivTCOG / VLiv                                          ! (mg/L)
CVLivTCOG = ALivTCOG / VLiv / PLivTCOG                             ! (mg/L)
AUCCLivTCOG = INTEG((ALivTCOG / VLiv), 0.0)                        ! (mg-hr/L)

! Amount of TCOH-Gluc excreted into bile
RABileTCOG = (kBile * ALivTCOG) - RAREcircTCOG                    ! (mg/hr)
ABileTCOG = INTEG(RABileTCOG, 0.0)                                  ! (mg)

! Amount of TCOH-Gluc recirculated
RAREcircTCOG = kEHR * ABileTCOG                                    ! (mg/hr)
AREcircTCOG = INTEG(RAREcircTCOG, 0.0)                             ! (mg)

! Amount of TCOH-Gluc excreted in urine
RAUrntCOG = kUrntCOG * ABodTCOG                                    ! (mg/hr)
AUrntCOG = INTEG(RAUrntCOG, 0.0)                                    ! (mg)
AUrntCOGTCOH = StochTCOHGluc * AUrntCOG                            ! (mg)
RAUrntCOG_Coll = (1.0 - UrnMissing) * RAUrntCOG                    ! (mg/hr)
AUrntCOG_Coll = INTEG(RAUrntCOG_Coll, 0.0)                         ! (mg)
AUrntCOGTCOH_Coll = StochTCOHGluc * AUrntCOG_Coll                  ! (mg)

! Total amount of TCA and TCOG in urine
AUrntCTot_mMole = (AUrntTCA / MWTCA) + (AUrntCOGTCOH / MWTCOH)   ! (mmoles)

! Total amount of TCOH-Gluc in tissues
ATCOG = ABodTCOG + ALivTCOG                                        ! (mg)

```

```

! Total concentration of TCOH and TCOH-Gluc
  TotCTCOH = CTCOH + (StochTCOHGluc * CTCOG)          ! (mg/L)
  AUCTotCTCOH = INTEG(TotCTCOH, 0.0)                  ! (mg-hr/L)

! Mass Balance (mg)
  TotTCOGIn = StochGlucTCOH * AMetTCOHGluc
  TotTissueTCOG = ABodTCOG + ALivTCOG + ABileTCOG
  MassBalTCOG = TotTCOGIn - TotTissueTCOG - ARecircTCOG - AUrnTCOG

! ----- DCVC Sub-Model -----
! Amount of DCVC in kidney
  RADCV = FracKidDCVC * StochDCVCTCE * RAMetKid + RAMetDCVG_mMole * MWDCVC &
&      - ((kNat + kKidBioact) * ADCVC)                ! (mg/hr)
  ADCVC = INTEG(RADCV, 0.0)                            ! (mg)
  RABioactDCVC = kKidBioact * ADCVC                    ! (mg/hr)
  ABioactDCVC = INTEG(RABioactDCVC, 0.0)               ! (mg)
  ABioactDCVCVKid = ABioactDCVC / VKid                 ! (mg/L)
  ABioactDCVCBW34 = ABioactDCVC / (BW**0.75)          ! (mg/kg^0.75)
  IF (TotDoseBW34 .GT. 0.0) FracBioactKid = ABioactDCVCBW34 / TotDoseBW34 ! (unitless)

! Amount of DCVC excreted into urine
  RAUrDCVC = kNAT * ADCVC                             ! (mg/hr)
  AUrnDCVC = INTEG(RAUrnDCVC, 0.0)                    ! (mg)

! Amount of N Acetyl DCVC excreted
  AUrnNDCVC_Eq = AUrnNDCVC / StochN                   ! (mg)

! Amount of N Acetyl DCVC excreted
  AUrnNDCVC = StochN * AUrnDCVC                       ! (mg)

! Mass Balance (mg)
  ADCVCIn = (FracKidDCVC * StochDCVCTCE * AMetKid) + (AMetDCVG_mMole * MWDCVC)
  MassBalDCVC = ADCVCIn - ADCVC - ABioactDCVC - AUrnNDCVC_Eq

! ----- DCVG Sub-Model -----
! Amount of DCVG in kidney
  RADCVG_mMole = ((RAMetLiv2 + (1.0 - FracKidDCVC) * RAMetKid) / MWTCE) - RAMetDCVG_mMole
!                                     (mmole/hr)
  ADCVG_mMole = INTEG(RADCVG_mMole, 0.0)              ! (mmole)
  CDCVG_mMole = ADCVG_mMole / VDCVG                   ! (mmole/L)
  AUCCDCVG_mMole = INTEG(CDCVG_mMole, 0.0)            ! (mmole-hr/L)

! Amount of DCVG metabolized
  RAMetDCVG_mMole = kDCVG * ADCVG_mMole               ! (mmole/hr)
  AMetDCVG_mMole = INTEG(RAMetDCVG_mMole, 0.0)        ! (mmole)
  AMetDCVG_mMoleVKid = AMetDCVG_mMole / VDCVG         ! (mmole/kg)
  AMetDCVG_mMoleBW34 = AMetDCVG_mMole / (BW**0.75)   ! (mmole/kg^0.75)

! Mass Balance (mg)
  ADCVGIn = (AMetLiv2 + ((1.0 - FracKidDCVC) * AMetKid)) / MWTCE
  MassBalDCVG = ADCVGIn - ADCVG_mMole - AMetDCVG_mMole

END      ! of Derivative
END      ! of Dynamic

```

```

TERMINAL
! Convert daily or weekly AUC dosemetrics to daily
AUCCBldDM = AUCCBldDM / (DMInt / 24.0)
AUCCPlasTCADM = AUCCPlasTCADM / (DMInt / 24.0)
AUCCPlasTCAFreeDM = AUCCPlasTCAFreeDM / (DMInt / 24.0)
AUCCTCOHDM = AUCCTCOHDM / (DMInt / 24.0)
AUCCTCOGDM = AUCCTCOGDM / (DMInt / 24.0)
AUCTotCTCOHDM = AUCTotCTCOHDM / (DMInt / 24.0)
AUCCLivDM = AUCCLivDM / (DMInt / 24.0)
AUCCLivTCADM = AUCCLivTCADM / (DMInt / 24.0)
AUCCLivTCOHDM = AUCCLivTCOHDM / (DMInt / 24.0)
AUCCLivTCOGDM = AUCCLivTCOGDM / (DMInt / 24.0)
AUCCKidDM = AUCCKidDM / (DMInt / 24.0)
AUCCDCVG_mMoleDM = AUCCDCVG_mMoleDM / (DMInt / 24.0)

! Convert daily or weekly metabolism dosemetrics to daily
TotMetabBW34DM = TotMetabBW34DM / (DMInt / 24.0)
TotOxMetBW34DM = TotOxMetBW34DM / (DMInt / 24.0)
AMetLiv1VLivDM = AMetLiv1VLivDM / (DMInt / 24.0)
AMetLiv1BW34DM = AMetLiv1BW34DM / (DMInt / 24.0)
AMetLiv1TCAVLivDM = AMetLiv1TCAVLivDM / (DMInt / 24.0)
AMetLiv1TCABW34DM = AMetLiv1TCABW34DM / (DMInt / 24.0)
AMetLiv1TCOHVLivDM = AMetLiv1TCOHVLivDM / (DMInt / 24.0)
AMetLiv1TCOHBW34DM = AMetLiv1TCOHBW34DM / (DMInt / 24.0)
AMetLiv2VLivDM = AMetLiv2VLivDM / (DMInt / 24.0)
AMetLiv2BW34DM = AMetLiv2BW34DM / (DMInt / 24.0)
AMetLivOtherVLivDM = AMetLivOtherVLivDM / (DMInt / 24.0)
AMetLivOtherBW34DM = AMetLivOtherBW34DM / (DMInt / 24.0)
AMetTCAVLivDM = AMetTCAVLivDM / (DMInt / 24.0)
AMetTCABW34DM = AMetTCABW34DM / (DMInt / 24.0)
AMetTCOHTCAVLivDM = AMetTCOHTCAVLivDM / (DMInt / 24.0)
AMetTCOHTCABW34DM = AMetTCOHTCABW34DM / (DMInt / 24.0)
AMetTCOHGlucVLivDM = AMetTCOHGlucVLivDM / (DMInt / 24.0)
AMetTCOHGlucBW34DM = AMetTCOHGlucBW34DM / (DMInt / 24.0)
AMetTCOHOtherVLivDM = AMetTCOHOtherVLivDM / (DMInt / 24.0)
AMetTCOHOtherBW34DM = AMetTCOHOtherBW34DM / (DMInt / 24.0)
AMetKidDM = AMetKidDM / (DMInt / 24.0)
AMetKidVKidDM = AMetKidVKidDM / (DMInt / 24.0)
AMetKidBW34DM = AMetKidBW34DM / (DMInt / 24.0)
AMetDCVG_mMoleDM = AMetDCVG_mMoleDM / (DMInt / 24.0)
AMetDCVG_mMoleVKidDM = AMetDCVG_mMoleVKidDM / (DMInt / 24.0)
AMetDCVG_mMoleBW34DM = AMetDCVG_mMoleBW34DM / (DMInt / 24.0)

END                ! End of Terminal
END                ! of Program

```

APPENDIX C: UTILITY M FILES FOR SIMULATIONS

The following M files are called within various M files utilized for this work. As noted in Tables 1 through 4 of the main report, QRapC is calculated as 1.0 minus sum of other blood flows; VSlwC is calculated as VPerfC minus sum of fractional volumes for blood, fat, gut, kidney, liver, rapid and respiratory tissue; and kTD set to zero because it is set in the MCSim model definition file as $kTD=0.0*\exp(\ln kTD)$.

FemalePrior.m

```
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["ACh", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AStom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"], [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "AStomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "AStomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "ARecircTCOG", "AUrnTCOG"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVG_mMole", "AMetDCVG_mMole"], [1.0e-9, 1.0e-9])
% Mean prior parameters for female human
%   DRespC, PEffDCVG, kAS, kTSD, kAD, kASTCA, kASTCOH, FracOtherC, KMClara, FracLungSysC, KMTCOH,
%   CLTCOH, KMGluc, CLGluc, kMetTCOHC, kMetTCAC, kBileC, kEHRC, kDCVGC, kNATC, kKidBioactC from
%   Table 3-39 in report
%   FracKidDCVC from model code (comment from model - "In ".in" files, set to 1, so that all
%   kidney GSH conjugation is assumed to directly produce DCVC (model lacks identifiability
%   otherwise)
SPECIES=1;
BW=60.0; QCC=16.0; VPR=0.96; DRESPC=1.47;
QFATC=0.085; QGUTC=0.21; QKIDC=0.17; QLIVC=0.065; QRAPC=0.3; QSLWC=0.17;
VBLDC=0.068; VFATC=0.317; VGUTC=0.022; VKIDC=0.0046; VLIVC=0.023; VPERFC=0.85778; VRAPC=0.093;
VRESPC=0.00018; VRESPLUMC=0.0023857; VSLWC=0.33; FRACPLAS=0.615;
PB=9.5; PFAT=67; PGUT=2.6; PKID=1.6; PLIV=4.1; PRAP=2.6; PRES=1.3; PSLW=2.1;
PRBCPLASTCA=0.5; PBODTCAC=0.52; PLIVTCAC=0.66;
PBODTCOH=0.91; PLIVTCOH=0.59;
PBODTCOG=0.91; PLIVTCOG=0.59; PEFFDCVG=1.24;
BMAXKDC=4.62; KDISSOC=182.0;
KAS=1.4; KTS=1.4; KAD=0.75; KTD=0.0; KASTCA=0.58; KASTCOH=0.49;
VMAXC=255.0; KMC=1.0; CL=66.0; FRACCTAC=0.32; FRACOTHERC=0.14;
VMAXDCVGC=1.0; KMDCVGC=2.9; CLDCVGC=19.0;
VMAXKIDDCVGC=1.0; KMKIDDCVGC=2.7; CLKIDDCVGC=230.0;
VMAXLUNGLIV=0.027273; KMCLARA=0.019; FRACLUNGSSYS=3.0;
VMAXTCOHC=1.0; KMTCOH=5.0; CLTCOH=0.35;
VMAXGLUCC=1.0; KMGLUC=10.0; CLGLUC=3.0; KMETTCOHC=2.47;
KURNTCAC=0.108; KMETTCAC=0.55;
KBILEC=3.47; KEHRC=0.21; KURNTCOGC=0.108;
KDCVGC=0.127; FRACKIDDCVCC=22026.46579;
KNATC=0.0025; KKIDBIOACTC=0.0064;
```

FemalePost.m

```
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["ACh", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AStom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"], [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "AStomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "AStomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "ARecircTCOG", "AUrnTCOG"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVG_mMole", "AMetDCVG_mMole"], [1.0e-9, 1.0e-9])
```

```
% Mean posterior parameters for female human
SPECIES=1;
BW=60.0; QCC=13.36432; VPR=1.46518; DRESPEC=0.60799;
QFATC=0.066156; QGUTC=0.16619; QKIDC=0.17136; QLIVC=0.032962; QRAPC=0.44100; QSLWC=0.12233;
VBLDC=0.068816; VFATC=0.24799; VGUTC=0.022022; VKIDC=0.0045857; VLIVC=0.024012; VPERFC=0.85778;
VRAPC=0.092619; VRESPEC=0.00017998; VRESPLUMC=0.0023929; VSLWC=0.39756; FRACPLAS=0.61562;
PB=9.21416; PFAT=57.04798; PGUT=2.83403; PKID=1.59940; PLIV=4.05470; PRAP=2.40664;
PRESPEC=1.31422; PSLW=2.43522;
PRBCPLASTCA=0.14440; PBODTCAC=0.61821; PLIVTCAC=0.78732;
PBODTCOH=1.56375; PLIVTCOH=0.62940;
PBODTCOG=0.62057; PLIVTCOG=3.84344; PEFDCVGC=0.010275;
BMAXKDC=4.07143; KDISSOC=180.77365;
KAS=0.0; KTS=0.0; KAD=0.0; KTD=0.0; KASTCA=5.26984; KASTCOH=7.30092;
VMAXC=94.69522; KMC=1.0; CL=861.48250; FRACTCAC=0.040908; FRACOTHERC=0.10721;
VMAXDCVGC=1.0; KMDCVGC=3.61760; CLDCVGC=52.79619;
VMAXKIDDCVGC=1.0; KMKIDDCVGC=0.83632; CLKIDDCVGC=7.94132;
VMAXLUNGLIV=0.094527; KMCLARA=0.24341; FRACLUNGSYS=23.57060;
VMAXTCOH=1.0; KMTCOH=2.27073; CLTCOH=0.17658;
VMAXGLUC=1.0; KMGLUC=129.28251; CLGLUC=0.28111; KMETTCOH=0.69907;
KURNTCAC=0.0048995; KMETTCAC=0.27555;
KBILEC=7.24274; KEHRC=0.15614; KURNTCOGC=1.82828;
KDCVGC=7.17068; FRACKIDDCVCC=22026.46579;
KNATC=0.00034950; KKIDBIOACTC=0.062787;
```

Init.m

```
prepare @All
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-11, 1.0e-11, 1.0e-11])
xerror (["AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw"], [1.0e-8, 1.0e-8, 1.0e-8, 1.0e-8, 1.0e-8, 1.0e-8])
xerror (["ASTom", "ADuod"], [1.0e-8, 1.0e-8])
xerror (["APlasTCA", "ABodTCA", "ALivTCA"], [1.0e-8, 1.0e-8, 1.0e-8])
xerror (["ABodTCOH", "ALivTCOH"], [1.0e-8, 1.0e-8])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG"], [1.0e-8, 1.0e-8, 1.0e-8])
HVDPRN=0;
WESITG=0;
```

MalePrior.m

```
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["ACh", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
[1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ASTom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"], [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "ASTomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
[1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "ASTomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
[1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "AREcircTCOG", "AUrnTCOG"],
[1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC_mMole", "AMetDCVC_mMole"], [1.0e-9, 1.0e-9])
% Mean prior parameters for male human
% DRespC, PEFDCVGC, kAS, kTSD, kAD, kASTCA, kASTCOH, FracOtherC, KMClara, FracLungSysC, KMTCOH,
% ClTCOH, KMGLuc, ClGluc, kMetTCOHC, kMetTCAC, kBileC, KEHRC, kDCVGC, kNATC, kKidBioactC from
% Table 3-39 in report
% FracKidDCVC from model code (comment from model - "In ".in" files, set to 1, so that all
% kidney GSH conjugation is assumed to directly produce DCVC (model lacks identifiability
% otherwise)"
SPECIES=1;
BW=70.0; QCC=16; VPR=0.96; DRESPEC=1.47;
QFATC=0.05; QGUTC=0.19; QKIDC=0.19; QLIVC=0.065; QRAPC=0.285; QSLWC=0.22;
VBLDC=0.077; VFATC=0.199; VGUTC=0.02; VKIDC=0.0043; VLIVC=0.025; VPERFC=0.856; VRAPC=0.088;
VRESPEC=0.00018; VRESPLUMC=0.0023857; VSLWC=0.44252; FRACPLAS=0.567;
PB=9.5; PFAT=67.0; PGUT=2.6; PKID=1.6; PLIV=4.1; PRAP=2.6; PRESPEC=1.3; PSLW=2.1;
PRBCPLASTCA=0.5; PBODTCAC=0.52; PLIVTCAC=0.66;
PBODTCOH=0.91; PLIVTCOH=0.59;
PBODTCOG=0.91; PLIVTCOG=0.59; PEFDCVGC=1.24;
BMAXKDC=4.62; KDISSOC=182.0;
KAS=1.4; KTS=1.4; KAD=0.75; KTD=0.0; KASTCA=0.58; KASTCOH=0.49;
VMAXC=255.0; KMC=1.0; CL=66.0; FRACTCAC=0.32; FRACOTHERC=0.14;
```

```

VMAXDCVGC=1.0; KMDCVGC=2.9; CLDCVG=19.0;
VMAXKIDDCVGC=1.0; KMKIDDCVGC=2.7; CLKIDDCVGC=230.0;
VMAXLUNGLIV=0.025253; KMCLARA=0.019; FRACLUNGSYSYSC=3.0;
VMAXTCOHC=1.0; KMTCOH=5.0; CLTCOH=0.35;
VMAXGLUCC=1.0; KMGLUC=10.0; CLGLUC=3.0; KMETTCOHC=2.47;
KURNTCAC=0.108; KMETTCAC=0.55;
KBILEC=3.47; KEHRC=0.21; KURNTCOGC=0.108;
KDCVGC=0.127; FRACKIDDCVCC=22026.46579;
KNATC=0.0025; KKIDBIOACTC=0.0064;

```

MalePost.m

```

xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["ACh", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AStom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"], [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "ASTomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "ASTomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "ARecircTCOG", "AUrnTCOG"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVG_mMole", "AMetDCVG_mMole"], [1.0e-9, 1.0e-9])
% Mean posterior parameters for male human
SPECIES=1;
BW=70.0; QCC=13.36432; VPR=1.46518; DRESPEC=0.60799;
QFATC=0.038915; QGUTC=0.15037; QKIDC=0.19152; QLIVC=0.032962; QRAPC=0.42793; QSLWC=0.15831;
VBLDC=0.077924; VFATC=0.15568; VGUTC=0.020020; VKIDC=0.0042867; VLIVC=0.026100; VPERFC=0.85600;
VRAPC=0.087639; VRESPEC=0.00017998; VRESPLUMC=0.0023929; VSLWC=0.48417; FRACPLAS=0.56757;
PB=9.21416; PFAT=57.04798; PGUT=2.83403; PKID=1.59940; PLIV=4.05470; PRAP=2.40664;
PRESPEC=1.31422; PSLW=2.43522;
PRBCPLASTCA=0.14440; PBODTCAC=0.61821; PLIVTCAC=0.78732;
PBODTCOH=1.56375; PLIVTCOH=0.62940;
PBODTCOG=0.62057; PLIVTCOG=3.84344; PEFDCVGC=0.010275;
BMAXKDC=4.07143; KDISSOC=180.77365;
KAS=0.0; KTS=0.0; KAD=0.0; KTD=0.0; KASTCA=5.26984; KASTCOH=7.30092;
VMAXC=94.69522; KMC=1.0; CL=861.48250; FRACTCAC=0.040908; FRACOTHERC=0.10721;
VMAXDCVGC=1.0; KMDCVGC=3.61760; CLDCVG=52.79619;
VMAXKIDDCVGC=1.0; KMKIDDCVGC=0.83632; CLKIDDCVGC=7.94132;
VMAXLUNGLIV=0.087525; KMCLARA=0.24341; FRACLUNGSYSYSC=23.57060;
VMAXTCOHC=1.0; KMTCOH=2.27073; CLTCOH=0.17658;
VMAXGLUCC=1.0; KMGLUC=129.28251; CLGLUC=0.28111; KMETTCOHC=0.69907;
KURNTCAC=0.0048995; KMETTCAC=0.27555;
KBILEC=7.24274; KEHRC=0.15614; KURNTCOGC=1.82828;
KDCVGC=7.17068; FRACKIDDCVCC=22026.46579;
KNATC=0.00034950; KKIDBIOACTC=0.062787;

```

MouseLinearityAnalysis.m

```

% Runs to output internal dose metrics for linearity analysis
load @format=model @file=New_EPA
init
ExtDosevsDM = [];
i = 1;

% -----
% Griffin JM, Gilbert KM, Lamps LW, Pumford NR. 2000. CD4+ T-cell activation and induction of
% autoimmune hepatitis following trichloroethylene treatment in MRL+/+ mice. Toxicological
% Sciences 57: 345-52.
% Mouse oral drinking water -- 4 or 32 wks
% Run until daily AUC dosemetrics aren't changing (13 days)
NewDose = [1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 11.0 12.0 13.0 14.0 15.0 16.0 17.0 18.0
           19.0 20.0 25.0 30.0 35.0 40.0 45.0 50.0 55.0 60.0 65.0 70.0 75.0 80.0 85.0 90.0 95.0
           100.0 125.0 150.0 175.0 200.0 250.0 300.0 350.0 400.0];
ResetDoses
MousePost
BW=0.043; DRINK=0.5; DMINT=24.0; TSTP=312.0;
start @NoCallback
ExtDosevsDM(i,1) = DRINK;

```

```

ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
for iter = [1 : 44]
    DRINK = NewDose(iter);
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = DRINK;
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Land PC, Owen EL, Linde HW. 1981. Morphologic Changes in Mouse Spermatozoa after
% Exposure to Inhalational Anesthetics during Early Spermatogenesis
% Mouse inhalation -- 4h/d for 5 days
i = i + 2;
NewDose = [30.0 60.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0 700.0 800.0
           900.0 1000.0 1100.0 1200.0 1300.0 1400.0 1500.0 1600.0 1800.0 2000.0];
ResetDoses
MousePost
BW=0.026; TSTRT=0.0; DAYS=5.0; DMINT=24.0; TSTP=120.0;

% THIS LIMIT IS DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR LESS THAN 1 WEEK
% Upper limit for iterations is the total number of days exposed
for iter = [1 : floor(DAYS)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=4.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=20.0;
end

% THESE INDICES ARE DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR LESS THAN 1 WEEK
% Indices are ((2 times (the total number of days exposed )) plus 1)
% AND (2 times (the total number of days exposed))
CONCLIST((2*floor(DAYS))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (24 entries in NewDose)
for iter = [1 : 24]
    for iter2 = [1 : 5]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
end

```

```

end
% THIS INDEX IS DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR LESS THAN 1 WEEK
% Index is ((2 times (the total number of days exposed )) plus 1)
CONCLIST((2*floor(DAYS))+1) = 0.0;
start @NoCallback
i = i + 1;
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Ramdhan DH, Kamijima M, Wang D, Ito Y, Naito H, Yanagiba Y, Hayashi Y, Tanaka N, Aoyama T,
% Gonzalez FJ, Nakajima T. 2010. Differential Response to Trichloroethylene-Induced
% Hepatosteatosi s in Wild-Type and PPAR $\alpha$ -Humanized Mice. Environ Health Perspect 118:1557-1563
% Mouse inhalation -- 8h/d, daily for 7 days
i = i + 2;
NewDose = [30.0 60.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0 700.0 800.0
           900.0 1000.0 1100.0 1200.0 1300.0 1400.0 1500.0 1600.0 1800.0 2000.0];
ResetDoses
MousePost
BW=0.025; TSTRT=0.0; DAYS=7.0; DMINT=24.0; TSTP=168.0;

% THIS LIMIT IS DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR 1 WEEK
% Upper limit for iterations is the total number of days exposed
for iter = [1 : floor(DAYS)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=8.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=16.0;
end

% THESE INDICES ARE DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR 1 WEEK
% Indices are ((2 times (the total number of days exposed )) plus 1)
% AND (2 times (the total number of days exposed))
CONCLIST((2*floor(DAYS))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (24 entries in NewDose)
for iter = [1 : 24]
    for iter2 = [1 : 7]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
end

% THIS INDEX IS DIFFERENT THAN THE OTHERS BECAUSE SIMULATION IS FOR 1 WEEK
% Index is ((2 times (the total number of days exposed )) plus 1)
CONCLIST((2*floor(DAYS))+1) = 0.0;
start @NoCallback
i = i + 1;

```

```

ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
end
save ExtDosevsDM @file='Mouse_Linearity_Output.txt' @format=ascii

MousePrior.m
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-11, 1.0e-11, 1.0e-11])
xerror (["AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw"], [1.0e-8,1.0e-8,1.0e-8,1.0e-8,1.0e-8,1.0e-8])
xerror (["ASTom", "ADuod"], [1.0e-8, 1.0e-8])
xerror (["APlastTCA", "ABodTCA", "ALivTCA"], [1.0e-8, 1.0e-8, 1.0e-8])
xerror (["ABodTCOH", "ALivTCOH"], [1.0e-8, 1.0e-8])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG"], [1.0e-8, 1.0e-8, 1.0e-8])
% Prior parameters for mouse
% DRespC, PEFFDCVG, kAS, kTSD, kAD, kASTCA, kASTCOH, FracOtherC, KMClara, FracLungSysC,
% VMaxTCOHC, KMTCOH, VMaxGlucC, KMGluc, kMetTCOHC, kMetTCAC, kBileC, KEHRC, kDCVGC,
% FracKidDCVCC, kNATC, kKidBioactC from Table 3-37 in report
SPECIES=3;
BW=0.03; QCC=11.6; VPR=2.5; DRESPC=0.00813;
QFATC=0.07; QGUTC=0.141; QKIDC=0.091; QLIVC=0.02; QRAP=0.461; QSLWC=0.217;
VBLDC=0.049; VFATC=0.07; VGUTC=0.049; VKIDC=0.017; VLIVC=0.055; VPERFC=0.8897; VRAPC=0.1;
VRESPC=0.0007; VRESPLUMC=0.0046667; VSLWC=0.549; FRACPLAS=0.52;
PB=15.0; PFAT=36.0; PGUT=1.9; PKID=2.1; PLIV=1.7; PRAP=1.9; PRESP=2.6; PSLW=2.4;
PRBCPLASTCA=0.5; PBODTCAC=0.88; PLIVTCAC=1.18;
PBODTCOH=1.11; PLIVTCOH=1.3;
PBODTCOG=1.11; PLIVTCOG=1.3; PEFFDCVG=1.25;
BMAXKDC=0.88; KDISSOC=107.0;
KAS=1.7; KTS=1.4; KAD=1.2; KTD=0.0; KASTCA=0.63; KASTCOH=0.75
VMAXC=2700.0; KMC=36.0; CL=1.0; FRACTCAC=0.32; FRACOTHERC=0.75;
VMAXDCVGC=300.0; KMDCVGC=1.0; CLDCVG=1.53;
VMAXKIDDCVGC=60.0; KMKIDDCVGC=1.0; CLKIDDCVGC=0.34;
VMAXLUNGLIV=0.070102; KMCLARA=1.5; FRACLUNGSYSC=0.52;
VMAXTCOHC=0.89; KMTCOH=1.4; CLTCOH=1.0;
VMAXGLUCC=1.53; KMGLUC=1.8; CLGLUC=1.0; KMETTCOHC=0.079;
KURNTCAC=0.6; KMETTCAC=0.05;
KBILEC=0.13; KEHRC=0.087; KURNTCOGC=0.6;
KDCVGC=0.1; FRACKIDDCVCC=1.9;
KNATC=0.12; KKIDBIOACTC=0.075;

MousePost.m
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-11, 1.0e-11, 1.0e-11])
xerror (["AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw"], [1.0e-8,1.0e-8,1.0e-8,1.0e-8,1.0e-8,1.0e-8])
xerror (["ASTom", "ADuod"], [1.0e-8, 1.0e-8])
xerror (["APlastTCA", "ABodTCA", "ALivTCA"], [1.0e-8, 1.0e-8, 1.0e-8])
xerror (["ABodTCOH", "ALivTCOH"], [1.0e-8, 1.0e-8])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG"], [1.0e-8, 1.0e-8, 1.0e-8])
% Mean posterior parameters for mouse
SPECIES=3;
BW=0.03; QCC=14.24071; VPR=2.01857; DRESPC=1.22067;
QFATC=0.072310; QGUTC=0.16610; QKIDC=0.090390; QLIVC=0.020660; QRAPC=0.43697; QSLWC=0.21357;
VBLDC=0.048613; VFATC=0.092960; VGUTC=0.048358; VKIDC=0.0170; VLIVC=0.044440; VPERFC=0.88970;
VRAPC=0.099680; VRESPC=0.0007; VRESPLUMC=0.0046667; VSLWC=0.53795; FRACPLAS=0.45334;
PB=13.94569; PFAT=35.56845; PGUT=1.53427; PKID=2.65843; PLIV=2.18153; PRAP=1.81543;
PRESP=2.58620; PSLW=2.22194;
PRBCPLASTCA=1.23485; PBODTCAC=0.78096; PLIVTCAC=0.94801;
PBODTCOH=0.89240; PLIVTCOH=1.94637;
PBODTCOG=0.46620; PLIVTCOG=1.31905; PEFFDCVG=0.98705;
BMAXKDC=1.09173; KDISSOC=126.01851;
KAS=1.79751; KTS=5.25931; KAD=0.26767; KTD=0.0; KASTCA=3.97490; KASTCOH=0.73001;
VMAXC=1810.95037; KMC=2.62353; CL=1.0; FRACTCAC=0.15585; FRACOTHERC=0.023707;

```

```

VMAXDCVGC=786.41329; KMDCVGC=1.0; CLDCVG=0.54896;
VMAXKIDDCVGC=154.35337; KMKIDDCVGC=1.0; CLKIDDCVGC=0.41337;
VMAXLUNGLIV=0.19499; KMCLARA=0.011950; FRACLUNGSYS=4.38417;
VMAXTCOHC=1.64280; KMTCOH=0.93257; CLTCOH=1.0;
VMAXGLUCC=69.54681; KMGLUC=30.44738; CLGLUC=1.0; KMETTCOHC=3.36693;
KURNTCAC=0.065755; KMETTCAC=0.61275;
KBILEC=1.01433; KEHRC=0.012082; KURNTCOGC=5.15607;
KDCVGC=0.1890; FRACKIDDCVCC=1.53664;
KNATC=0.11648; KKIDBIOACTC=0.087861;

```

Output_Check.m

```

% Output parameters to check that all parameters are within range
Params(i,1) = QC;
Params(i,2) = QP;
Params(i,3) = QM;
Params(i,4) = DRESP;
Params(i,5) = QFAT;
Params(i,6) = QGUT;
Params(i,7) = QKID;
Params(i,8) = QLIV;
Params(i,9) = QRAP;
Params(i,10) = QSLW;
Params(i,11) = QGUTLIV;
Params(i,12) = QBOD;
Params(i,13) = QCPLAS;
Params(i,14) = QBODPLAS;
Params(i,15) = QGUTLIVPLAS;
Params(i,16) = VBLD;
Params(i,17) = VFAT;
Params(i,18) = VGUT;
Params(i,19) = VKID;
Params(i,20) = VLIV;
Params(i,21) = VPERFC;
Params(i,22) = VRAP;
Params(i,23) = VRESPLUM;
Params(i,24) = VRESP;
Params(i,25) = VRESPEFF;
Params(i,26) = VSLW;
Params(i,27) = VPLAS;
Params(i,28) = VBOD;
Params(i,29) = VDCVG;
Params(i,30) = TCAPLAS;
Params(i,31) = PBODTCA;
Params(i,32) = PLIVTCA;
Params(i,33) = BMAX;
Params(i,34) = VMAX;
Params(i,35) = KM;
Params(i,36) = FRACOTHER;
Params(i,37) = FRACTCA;
Params(i,38) = VMAXDCVG;
Params(i,39) = KMDCVG;
Params(i,40) = VMAXKIDDCVG;
Params(i,41) = KMKIDDCVG;
Params(i,42) = VMAXCLARA;
Params(i,43) = FRACLUNGSYS;
Params(i,44) = KMETTCOH;
Params(i,45) = VMAXTCOH;
Params(i,46) = VMAXGLUC;
Params(i,47) = KURNTCA;
Params(i,48) = KMETTCA;
Params(i,49) = KBILE;
Params(i,50) = KEHR;
Params(i,51) = KURNTCOG;
Params(i,52) = KDCVG;
Params(i,53) = FRACKIDDCVC;
Params(i,54) = KNAT;
Params(i,55) = KKIDBIOACT;
Params(i,56) = CC;
Params(i,57) = RODENTS;
Params(i,58) = KLOSS;

```

```

Params(i,59) = VCH;
Params(i,60) = ACH0;
Params(i,61) = KDRINK;

TmpCheckOutput = [];
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottissue, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _totmetab, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaltce, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _rinhdose, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _totdose, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _retdose, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ach, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ainhresp, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aexhresp, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aresp, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ametlng, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _cart, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _calv, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _exhfactor, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _exhfac_den, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aexh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aexhpost, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _afat, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _astom, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aduod, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aexc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _rao, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _agut, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _akid, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ametkid, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aliv, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ametliv1, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ametliv2, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _arap, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aslw, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _cven, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottissuetca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaltca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aplastca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _cplastcafree, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aplastcafree, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _cplastcabnd, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _abodtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _astomtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _alivtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _amettca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aurntca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aotca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottcain, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottissuetcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _totmetabtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaltcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ctcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _abodtcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _astomtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _alivtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _amettcohtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _amettcohgluc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _amettcohoth, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aotcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottcohin, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottcohndose, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottissuetcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaltcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ctcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _abodtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _alivtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _abiletcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _arecirtcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aurntcog, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _tottcogin, @Justification = 'begin');

```

```

TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaldcvc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _advcin, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _advc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _abioactdcvc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _aurndcvc, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _massbaldcvg, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _adcvgin, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _adcvg_mmole, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _ametdcvg_mmole, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _cinh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kia, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kiv, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kpv, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kivtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kivtcoh, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kstom, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kstomtca, @Justification = 'begin');
TmpCheckOutput = addcolsj(TmpCheckOutput, _kstomtcoh, @Justification = 'begin');

CheckOutputMax = atrowsj(CheckOutput, max(TmpCheckOutput), @Justification = 'begin');
CheckOutputMin = atrowsj(CheckOutput, min(TmpCheckOutput), @Justification = 'begin');

```

Output_Check_Reset.m

% Output parameters to check that all parameters are reset with each run

```

ParamsReset=[];
ParamsReset(1,1) = BW;
ParamsReset(2,1) = QCC;
ParamsReset(3,1) = VPR;
ParamsReset(4,1) = DRESPEC;
ParamsReset(5,1) = QFATC;
ParamsReset(6,1) = QGUTC;
ParamsReset(7,1) = QKIDC;
ParamsReset(8,1) = QLIVC;
ParamsReset(9,1) = QRAPC;
ParamsReset(10,1) = QSLWC;
ParamsReset(11,1) = VBLDC;
ParamsReset(12,1) = VFATC;
ParamsReset(13,1) = VGUTC;
ParamsReset(14,1) = VKIDC;
ParamsReset(15,1) = VLIVC;
ParamsReset(16,1) = VPERFC;
ParamsReset(17,1) = VRAPC;
ParamsReset(18,1) = VRESPEC;
ParamsReset(19,1) = VRESPLUMC;
ParamsReset(20,1) = VSLWC;
ParamsReset(21,1) = FRACPLAS;
ParamsReset(22,1) = MWTCE;
ParamsReset(23,1) = MWDCVC;
ParamsReset(24,1) = MWTCA;
ParamsReset(25,1) = MWTCOH;
ParamsReset(26,1) = MWTCOHGLUC;
ParamsReset(27,1) = MNWADCVC;
ParamsReset(28,1) = PB;
ParamsReset(29,1) = PFAT;
ParamsReset(30,1) = PGUT;
ParamsReset(31,1) = PKID;
ParamsReset(32,1) = PLIV;
ParamsReset(33,1) = PRAP;
ParamsReset(34,1) = PRESPEC;
ParamsReset(35,1) = PSLW;
ParamsReset(36,1) = PRBCPLASTCA;
ParamsReset(37,1) = PBODTCAC;
ParamsReset(38,1) = PLIVTCAC;
ParamsReset(39,1) = PBODTCOH;
ParamsReset(40,1) = PLIVTCOH;
ParamsReset(41,1) = PBODTCOG;
ParamsReset(42,1) = PLIVTCOG;
ParamsReset(43,1) = PEFDCVG;
ParamsReset(44,1) = BMAXKDC;
ParamsReset(45,1) = KDISSOC;

```

```

ParamsReset(46,1) = KAS;
ParamsReset(47,1) = KTSD;
ParamsReset(48,1) = KAD;
ParamsReset(49,1) = KTD;
ParamsReset(50,1) = KASTCA;
ParamsReset(51,1) = KASTCOH;
ParamsReset(52,1) = VMAXC;
ParamsReset(53,1) = KMC;
ParamsReset(54,1) = CL;
ParamsReset(55,1) = FRAC TCAC;
ParamsReset(56,1) = FRACOTHERC;
ParamsReset(57,1) = VMAXDCVGC;
ParamsReset(58,1) = KMDCVGC;
ParamsReset(59,1) = CLDCVGC;
ParamsReset(60,1) = VMAXKIDDCVGC;
ParamsReset(61,1) = KMKIDDCVGC;
ParamsReset(62,1) = CLKIDDCVGC;
ParamsReset(63,1) = VMAXLUNGLIV;
ParamsReset(64,1) = KMCLARA;
ParamsReset(65,1) = FRACLUNGSYSC;
ParamsReset(66,1) = VMAXTCOHC;
ParamsReset(67,1) = KMTCOH;
ParamsReset(68,1) = CLTCOH;
ParamsReset(69,1) = VMAXGLUCC;
ParamsReset(70,1) = KMGLUC;
ParamsReset(71,1) = CLGLUC;
ParamsReset(72,1) = KMETTCOHC;
ParamsReset(73,1) = KURNTCAC;
ParamsReset(74,1) = KMETTCAC;
ParamsReset(75,1) = KBILEC;
ParamsReset(76,1) = KEHRC;
ParamsReset(77,1) = KURNTCOGC;
ParamsReset(78,1) = KDCVGC;
ParamsReset(79,1) = FRACKIDDCVCC;
ParamsReset(80,1) = KNATC;
ParamsReset(81,1) = KKIDBIOACTC;
ParamsReset(82,1) = CC;
ParamsReset(83,1) = NRODENTS;
ParamsReset(84,1) = KLOSSC;
ParamsReset(85,1) = VCHC;
ParamsReset(86,1) = CONCLIST(1);
ParamsReset(87,1) = STRTNEXTLIST(1);
ParamsReset(88,1) = TSTRT;
ParamsReset(89,1) = IVDOSE;
ParamsReset(90,1) = TCHNG;
ParamsReset(91,1) = DAYS;
ParamsReset(92,1) = TMAX;
ParamsReset(93,1) = PDOSE;
ParamsReset(94,1) = DRINK;
ParamsReset(95,1) = IADOSE;
ParamsReset(96,1) = PVDOSSE;
ParamsReset(97,1) = IVDOSETCA;
ParamsReset(98,1) = PODOSETCA;
ParamsReset(99,1) = IVDOSETCOH;
ParamsReset(100,1) = PODOSETCOH;
ParamsReset(101,1) = SPECIES;
ParamsReset(102,1) = TURN;
ParamsReset(103,1) = URNMISSLIST(1);
ParamsReset(104,1) = URNMISSING;
ParamsReset(105,1) = TSTP;
ParamsReset(106,1) = CINT;
ParamsReset(107,1) = QC;
ParamsReset(108,1) = QP;
ParamsReset(109,1) = QM;
ParamsReset(110,1) = DRESP;
ParamsReset(111,1) = QADJUS;
ParamsReset(112,1) = QFAT;
ParamsReset(113,1) = QGUT;
ParamsReset(114,1) = QKID;
ParamsReset(115,1) = QLIV;
ParamsReset(116,1) = QRAP;

```

```

ParamsReset(117,1) = QSLW;
ParamsReset(118,1) = QGUTLIV;
ParamsReset(119,1) = QBOD;
ParamsReset(120,1) = QCPLAS;
ParamsReset(121,1) = QBODPLAS;
ParamsReset(122,1) = QGUTLIVPLAS;
ParamsReset(123,1) = VTOTC;
ParamsReset(124,1) = VADJUS;
ParamsReset(125,1) = VBLD;
ParamsReset(126,1) = VFAT;
ParamsReset(127,1) = VGUT;
ParamsReset(128,1) = VKID;
ParamsReset(129,1) = VLIV;
ParamsReset(130,1) = VRAP;
ParamsReset(131,1) = VRESP;
ParamsReset(132,1) = VSLW;
ParamsReset(133,1) = VPLAS;
ParamsReset(134,1) = VBOD;
ParamsReset(135,1) = VBODTCOH;
ParamsReset(136,1) = VDCVG;
ParamsReset(137,1) = VRESPLUM;
ParamsReset(138,1) = VRESPEFF;
ParamsReset(139,1) = STOCHTCATCE;
ParamsReset(140,1) = STOCHTCATCOH;
ParamsReset(141,1) = STOCHTCOHTCE;
ParamsReset(142,1) = STOCHGLUCTCOH;
ParamsReset(143,1) = STOCHTCOHLUC;
ParamsReset(144,1) = STOCHDCVCTCE;
ParamsReset(145,1) = STOCHN;
ParamsReset(146,1) = TCAPLAS;
ParamsReset(147,1) = PBODTCA;
ParamsReset(148,1) = PLIVTCA;
ParamsReset(149,1) = BMAX;
ParamsReset(150,1) = VMAX;
ParamsReset(151,1) = FRACOTHER;
ParamsReset(152,1) = FRACTCA;
ParamsReset(153,1) = KM;
ParamsReset(154,1) = VMAXDCVG;
ParamsReset(155,1) = KMDCVG;
ParamsReset(156,1) = VMAXKIDDCVG;
ParamsReset(157,1) = KMKIDDCVG;
ParamsReset(158,1) = VMAXCLARA;
ParamsReset(159,1) = FRACLUNGSYS;
ParamsReset(160,1) = KMETTCOH;
ParamsReset(161,1) = VMAXTCOH;
ParamsReset(162,1) = VMAXGLUC;
ParamsReset(163,1) = KURNTCA;
ParamsReset(164,1) = KMETTCA;
ParamsReset(165,1) = KBILE;
ParamsReset(166,1) = KEHR;
ParamsReset(167,1) = KURNTCOG;
ParamsReset(168,1) = KDCVG;
ParamsReset(169,1) = FRACKIDDCVC;
ParamsReset(170,1) = KNAT;
ParamsReset(171,1) = KKIDBIOACT;
ParamsReset(172,1) = RODENTS;
ParamsReset(173,1) = KLOSS;
ParamsReset(174,1) = VCH;
ParamsReset(175,1) = ACH0;
ParamsReset(176,1) = _day(1,1);
ParamsReset(177,1) = _cinh(1,1);
ParamsReset(178,1) = _kdrink(1,1);
ParamsReset(179,1) = _kia(1,1);
ParamsReset(180,1) = _kiv(1,1);
ParamsReset(181,1) = _kivtca(1,1);
ParamsReset(182,1) = _kivtcoh(1,1);
ParamsReset(183,1) = _kp(1,1);
ParamsReset(184,1) = _kstom(1,1);
ParamsReset(185,1) = _kstomtca(1,1);
ParamsReset(186,1) = _kstomtcoh(1,1);
ParamsReset(187,1) = _aurntca_coll(1,1);

```

```

ParamsReset(188,1) = _aurntcog_coll(1,1);
ParamsReset(189,1) = _paucbld(1,1);
ParamsReset(190,1) = _aucblddm(1,1);
ParamsReset(191,1) = _paucplastca(1,1);
ParamsReset(192,1) = _aucplastcadm(1,1);
ParamsReset(193,1) = _paucplastcafree(1,1);
ParamsReset(194,1) = _aucplastcafreedm(1,1);
ParamsReset(195,1) = _paucctcoh(1,1);
ParamsReset(196,1) = _aucctcohdm(1,1);
ParamsReset(197,1) = _paucctcog(1,1);
ParamsReset(198,1) = _aucctcogdm(1,1);
ParamsReset(199,1) = _pauctotctcoh(1,1);
ParamsReset(200,1) = _auctotctcohdm(1,1);
ParamsReset(201,1) = _pauccliv(1,1);
ParamsReset(202,1) = _aucclivdm(1,1);
ParamsReset(203,1) = _paucclivtca(1,1);
ParamsReset(204,1) = _aucclivtcadm(1,1);
ParamsReset(205,1) = _paucclivtcoh(1,1);
ParamsReset(206,1) = _aucclivtcohdm(1,1);
ParamsReset(207,1) = _paucclivtcog(1,1);
ParamsReset(208,1) = _aucclivtcogdm(1,1);
ParamsReset(209,1) = _pametliviltcavliv(1,1);
ParamsReset(210,1) = _ametliviltcavlivdm(1,1);
ParamsReset(211,1) = _pametliviltcabw34(1,1);
ParamsReset(212,1) = _ametliviltcabw34dm(1,1);
ParamsReset(213,1) = _pametliviltcohvliv(1,1);
ParamsReset(214,1) = _ametliviltcohvlivdm(1,1);
ParamsReset(215,1) = _pametliviltcohbw34(1,1);
ParamsReset(216,1) = _ametliviltcohbw34dm(1,1);
ParamsReset(217,1) = _pametliv2vliv(1,1);
ParamsReset(218,1) = _ametliv2vlivdm(1,1);
ParamsReset(219,1) = _pametliv2bw34(1,1);
ParamsReset(220,1) = _ametliv2bw34dm(1,1);
ParamsReset(221,1) = _pametlivothervliv(1,1);
ParamsReset(222,1) = _ametlivothervlivdm(1,1);
ParamsReset(223,1) = _pametlivotherbw34(1,1);
ParamsReset(224,1) = _ametlivotherbw34dm(1,1);
ParamsReset(225,1) = _pamettcavliv(1,1);
ParamsReset(226,1) = _amettcavlivdm(1,1);
ParamsReset(227,1) = _pamettcabw34(1,1);
ParamsReset(228,1) = _amettcabw34dm(1,1);
ParamsReset(229,1) = _pamettcohtcavliv(1,1);
ParamsReset(230,1) = _amettcohtcavlivdm(1,1);
ParamsReset(231,1) = _pamettcohtcabw34(1,1);
ParamsReset(232,1) = _amettcohtcabw34dm(1,1);
ParamsReset(233,1) = _pamettcohglucvliv(1,1);
ParamsReset(234,1) = _amettcohglucvlivdm(1,1);
ParamsReset(235,1) = _pamettcohglucbw34(1,1);
ParamsReset(236,1) = _amettcohglucbw34dm(1,1);
ParamsReset(237,1) = _pamettcothervliv(1,1);
ParamsReset(238,1) = _amettcothervlivdm(1,1);
ParamsReset(239,1) = _pamettcothervbw34(1,1);
ParamsReset(240,1) = _amettcothervbw34dm(1,1);
ParamsReset(241,1) = _hours(1,1);
ParamsReset(242,1) = _rach(1,1);
ParamsReset(243,1) = _ach(1,1);
ParamsReset(244,1) = _cinhppm(1,1);
ParamsReset(245,1) = _cinh(1,1);
ParamsReset(246,1) = _rainhresp(1,1);
ParamsReset(247,1) = _ainhresp(1,1);
ParamsReset(248,1) = _cinhresp(1,1);
ParamsReset(249,1) = _raexhresp(1,1);
ParamsReset(250,1) = _aexhresp(1,1);
ParamsReset(251,1) = _cexhresp(1,1);
ParamsReset(252,1) = _raresp(1,1);
ParamsReset(253,1) = _aresp(1,1);
ParamsReset(254,1) = _cresp(1,1);
ParamsReset(255,1) = _rametlng(1,1);
ParamsReset(256,1) = _ametlng(1,1);
ParamsReset(257,1) = _ametlngbw34(1,1);
ParamsReset(258,1) = _ametlngvresp(1,1);

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ParamsReset(259,1) = _cart(1,1);
ParamsReset(260,1) = _aucbld(1,1);
ParamsReset(261,1) = _calv(1,1);
ParamsReset(262,1) = _calvppm(1,1);
ParamsReset(263,1) = _exhfac_den(1,1);
ParamsReset(264,1) = _exhfactor(1,1);
ParamsReset(265,1) = _raexh(1,1);
ParamsReset(266,1) = _aexh(1,1);
ParamsReset(267,1) = _aexhpost(1,1);
ParamsReset(268,1) = _aexhexp(1,1);
ParamsReset(269,1) = _rafat(1,1);
ParamsReset(270,1) = _afat(1,1);
ParamsReset(271,1) = _cfat(1,1);
ParamsReset(272,1) = _cvfat(1,1);
ParamsReset(273,1) = _rastom(1,1);
ParamsReset(274,1) = _astom(1,1);
ParamsReset(275,1) = _raduod(1,1);
ParamsReset(276,1) = _aduod(1,1);
ParamsReset(277,1) = _raexc(1,1);
ParamsReset(278,1) = _aexc(1,1);
ParamsReset(279,1) = _rao(1,1);
ParamsReset(280,1) = _ragut(1,1);
ParamsReset(281,1) = _agut(1,1);
ParamsReset(282,1) = _cgut(1,1);
ParamsReset(283,1) = _cvgut(1,1);
ParamsReset(284,1) = _rakid(1,1);
ParamsReset(285,1) = _akid(1,1);
ParamsReset(286,1) = _ckid(1,1);
ParamsReset(287,1) = _cvkid(1,1);
ParamsReset(288,1) = _aucckid(1,1);
ParamsReset(289,1) = _rametkid(1,1);
ParamsReset(290,1) = _ametkid(1,1);
ParamsReset(291,1) = _raliv(1,1);
ParamsReset(292,1) = _aliv(1,1);
ParamsReset(293,1) = _cliv(1,1);
ParamsReset(294,1) = _cvliv(1,1);
ParamsReset(295,1) = _auccliv(1,1);
ParamsReset(296,1) = _rametliv1(1,1);
ParamsReset(297,1) = _ametliv1(1,1);
ParamsReset(298,1) = _ametlivlvliv(1,1);
ParamsReset(299,1) = _ametlivlbw34(1,1);
ParamsReset(300,1) = _ametlivltca(1,1);
ParamsReset(301,1) = _ametlivltcavliv(1,1);
ParamsReset(302,1) = _ametlivltcabw34(1,1);
ParamsReset(303,1) = _ametlivltcoh(1,1);
ParamsReset(304,1) = _ametlivltcohvliv(1,1);
ParamsReset(305,1) = _ametlivltcohbw34(1,1);
ParamsReset(306,1) = _ametlivother(1,1);
ParamsReset(307,1) = _ametlivothervliv(1,1);
ParamsReset(308,1) = _ametlivotherbw34(1,1);
ParamsReset(309,1) = _rametliv2(1,1);
ParamsReset(310,1) = _ametliv2(1,1);
ParamsReset(311,1) = _ametliv2vliv(1,1);
ParamsReset(312,1) = _ametliv2bw34(1,1);
ParamsReset(313,1) = _ametgsh(1,1);
ParamsReset(314,1) = _ametgshbw34(1,1);
ParamsReset(315,1) = _rarap(1,1);
ParamsReset(316,1) = _arap(1,1);
ParamsReset(317,1) = _crap(1,1);
ParamsReset(318,1) = _cvrap(1,1);
ParamsReset(319,1) = _auccrap(1,1);
ParamsReset(320,1) = _chrt(1,1);
ParamsReset(321,1) = _clung(1,1);
ParamsReset(322,1) = _cspl(1,1);
ParamsReset(323,1) = _cbrn(1,1);
ParamsReset(324,1) = _raslw(1,1);
ParamsReset(325,1) = _aslw(1,1);
ParamsReset(326,1) = _cslw(1,1);
ParamsReset(327,1) = _cvslw(1,1);
ParamsReset(328,1) = _cmus(1,1);
ParamsReset(329,1) = _rabld(1,1);

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ParamsReset(330,1) = _abld(1,1);
ParamsReset(331,1) = _cven(1,1);
ParamsReset(332,1) = _cven_mmole(1,1);
ParamsReset(333,1) = _cbldmix(1,1);
ParamsReset(334,1) = _rinhdose(1,1);
ParamsReset(335,1) = _retdose(1,1);
ParamsReset(336,1) = _totdose(1,1);
ParamsReset(337,1) = _tottissue(1,1);
ParamsReset(338,1) = _totmetab(1,1);
ParamsReset(339,1) = _massbaltce(1,1);
ParamsReset(340,1) = _totdosebw34(1,1);
ParamsReset(341,1) = _totmetabbw34(1,1);
ParamsReset(342,1) = _totoxmetbw34(1,1);
ParamsReset(343,1) = _raplastca(1,1);
ParamsReset(344,1) = _aplastca(1,1);
ParamsReset(345,1) = _cplastca(1,1);
ParamsReset(346,1) = _cbldtca(1,1);
ParamsReset(347,1) = _aucplastca(1,1);
ParamsReset(348,1) = _aplastcafree(1,1);
ParamsReset(349,1) = _aucplastcafree(1,1);
ParamsReset(350,1) = _a(1,1);
ParamsReset(351,1) = _b(1,1);
ParamsReset(352,1) = _cplastcafree(1,1);
ParamsReset(353,1) = _cplastcabnd(1,1);
ParamsReset(354,1) = _rabodtca(1,1);
ParamsReset(355,1) = _abodtca(1,1);
ParamsReset(356,1) = _cbodtca(1,1);
ParamsReset(357,1) = _cvbodtca(1,1);
ParamsReset(358,1) = _cvbodtcafree(1,1);
ParamsReset(359,1) = _ckidtca(1,1);
ParamsReset(360,1) = _clungtca(1,1);
ParamsReset(361,1) = _rastomtca(1,1);
ParamsReset(362,1) = _astomtca(1,1);
ParamsReset(363,1) = _ralivtca(1,1);
ParamsReset(364,1) = _alivtca(1,1);
ParamsReset(365,1) = _clivtca(1,1);
ParamsReset(366,1) = _cvlivtca(1,1);
ParamsReset(367,1) = _cvlivtcafree(1,1);
ParamsReset(368,1) = _aucclivtca(1,1);
ParamsReset(369,1) = _ramettca(1,1);
ParamsReset(370,1) = _amettca(1,1);
ParamsReset(371,1) = _amettcavliv(1,1);
ParamsReset(372,1) = _amettcabw34(1,1);
ParamsReset(373,1) = _aurntca(1,1);
ParamsReset(374,1) = _aurntca(1,1);
ParamsReset(375,1) = _aurntca_coll(1,1);
ParamsReset(376,1) = _aotca(1,1);
ParamsReset(377,1) = _tottcain(1,1);
ParamsReset(378,1) = _tottissuetca(1,1);
ParamsReset(379,1) = _massbaltca(1,1);
ParamsReset(380,1) = _tottcainbw(1,1);
ParamsReset(381,1) = _ctcoh(1,1);
ParamsReset(382,1) = _aucctcoh(1,1);
ParamsReset(383,1) = _rabodtcoh(1,1);
ParamsReset(384,1) = _abodtcoh(1,1);
ParamsReset(385,1) = _cbodtcoh(1,1);
ParamsReset(386,1) = _cvbodtcoh(1,1);
ParamsReset(387,1) = _auccbodtcoh(1,1);
ParamsReset(388,1) = _ckidtcoh(1,1);
ParamsReset(389,1) = _clungtcoh(1,1);
ParamsReset(390,1) = _cbodtcogtcoh(1,1);
ParamsReset(391,1) = _ckidtcogtcoh(1,1);
ParamsReset(392,1) = _clungtcogtcoh(1,1);
ParamsReset(393,1) = _rastomtcoh(1,1);
ParamsReset(394,1) = _astomtcoh(1,1);
ParamsReset(395,1) = _ralivtcoh(1,1);
ParamsReset(396,1) = _alivtcoh(1,1);
ParamsReset(397,1) = _clivtcoh(1,1);
ParamsReset(398,1) = _cvlivtcoh(1,1);
ParamsReset(399,1) = _aucclivtcoh(1,1);
ParamsReset(400,1) = _clivtcogtcoh(1,1);

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ParamsReset(401,1) = _ramettcohtca(1,1);
ParamsReset(402,1) = _amettcohtca(1,1);
ParamsReset(403,1) = _amettcohtcavliv(1,1);
ParamsReset(404,1) = _amettcohtcabw34(1,1);
ParamsReset(405,1) = _ramettcohgluc(1,1);
ParamsReset(406,1) = _amettcohgluc(1,1);
ParamsReset(407,1) = _amettcohglucvliv(1,1);
ParamsReset(408,1) = _amettcohglucbw34(1,1);
ParamsReset(409,1) = _ramettcohoother(1,1);
ParamsReset(410,1) = _amettcohoother(1,1);
ParamsReset(411,1) = _amettcohoothervliv(1,1);
ParamsReset(412,1) = _amettcohootherbw34(1,1);
ParamsReset(413,1) = _aotcoh(1,1);
ParamsReset(414,1) = _tottcohin(1,1);
ParamsReset(415,1) = _tottissuetcoh(1,1);
ParamsReset(416,1) = _totmetabtcogh(1,1);
ParamsReset(417,1) = _massbaltcoh(1,1);
ParamsReset(418,1) = _tottcohdose(1,1);
ParamsReset(419,1) = _ctcogh(1,1);
ParamsReset(420,1) = _aucctcogh(1,1);
ParamsReset(421,1) = _ctcogtcogh(1,1);
ParamsReset(422,1) = _rabodtcogh(1,1);
ParamsReset(423,1) = _abodtcogh(1,1);
ParamsReset(424,1) = _cvbodtcogh(1,1);
ParamsReset(425,1) = _ralivtcogh(1,1);
ParamsReset(426,1) = _alivtcogh(1,1);
ParamsReset(427,1) = _cvlivtcogh(1,1);
ParamsReset(428,1) = _aucclivtcogh(1,1);
ParamsReset(429,1) = _rabiletcogh(1,1);
ParamsReset(430,1) = _abiletcogh(1,1);
ParamsReset(431,1) = _rarecirtcogh(1,1);
ParamsReset(432,1) = _arecirtcogh(1,1);
ParamsReset(433,1) = _aurntcogh(1,1);
ParamsReset(434,1) = _aurntcogh(1,1);
ParamsReset(435,1) = _aurntcogtcogh(1,1);
ParamsReset(436,1) = _aurntcogh_coll(1,1);
ParamsReset(437,1) = _aurntcogtcogh_coll(1,1);
ParamsReset(438,1) = _aurntctot_mmole(1,1);
ParamsReset(439,1) = _atcogh(1,1);
ParamsReset(440,1) = _totctcoh(1,1);
ParamsReset(441,1) = _auctotctcoh(1,1);
ParamsReset(442,1) = _tottcogin(1,1);
ParamsReset(443,1) = _tottissuetcogh(1,1);
ParamsReset(444,1) = _massbaltcogh(1,1);
ParamsReset(445,1) = _radcvc(1,1);
ParamsReset(446,1) = _adcvc(1,1);
ParamsReset(447,1) = _rabioactdcvc(1,1);
ParamsReset(448,1) = _abioactdcvc(1,1);
ParamsReset(449,1) = _abioactdcvcvkid(1,1);
ParamsReset(450,1) = _abioactdcvcbw34(1,1);
ParamsReset(451,1) = _aurndcvc(1,1);
ParamsReset(452,1) = _aurndcvc(1,1);
ParamsReset(453,1) = _aurndcvc_eq(1,1);
ParamsReset(454,1) = _aurndcvc(1,1);
ParamsReset(455,1) = _adcvcin(1,1);
ParamsReset(456,1) = _massbaldcvc(1,1);
ParamsReset(457,1) = _radcvg_mmole(1,1);
ParamsReset(458,1) = _adcvg_mmole(1,1);
ParamsReset(459,1) = _cdcvg_mmole(1,1);
ParamsReset(460,1) = _aucdcvg_mmole(1,1);
ParamsReset(461,1) = _rametdcvg_mmole(1,1);
ParamsReset(462,1) = _ametdcvg_mmole(1,1);
ParamsReset(463,1) = _adcvgin(1,1);
ParamsReset(464,1) = _massbaldcvg(1,1);
OutputReset = addcolsj(OutputReset, ParamsReset, @Justification = 'begin');

```

RatLinearityAnalysis.m

```
% Runs to output internal dose metrics for linearity analysis
load @format=model @file=New_EPA
init
ExtDosevsDM = [];
i = 1;

% -----
% Arito H, Takahashi M, Ishikawa T. 1994. Effect of subchronic inhalation exposure to low-level
% trichloroethylene on heart rate and wakefulness-sleep in freely moving rats. Japanese
% Journal of Industrial Health 36:1-8.
% Rat inhalation -- 8h/d, 5d/w for 2, 4 or 6w
% Simulation for 2 weeks
NewDose = [1.0 2.0 3.0 4.0 5.0 6.0 7.0 8.0 9.0 10.0 12.5 15.0 17.5 20.0 25.0 30.0 35.0 40.0
           45.0 50.0 60.0 70.0 80.0 90.0 100.0 125.0 150.0 175.0 200.0 250.0 300.0];

ResetDoses
RatPost
BW=0.375; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=336.0;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=0.5;
    STRTNEXTLIST(j)=8.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=16.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1), (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=64.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (31 entries in NewDose)
for iter = [1 : 31]
    for iter2 = [1 : 10]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
    % Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
    % (NumWks))) plus 1),
    CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = CONCLIST(1);
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
```

```

end
% Simulation for 4 weeks
i = i + 2;
TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=672.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=0.5;
    STRTNEXTLIST(j)=8.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=16.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=64.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (31 entries in NewDose)
for iter = [1 : 31]
    for iter2 = [1 : 20]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
    % Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
    % (NumWks))) plus 1)
    CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = CONCLIST(1);
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% Simulation for 6 weeks
i = i + 2;
TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=1008.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;

```

```

% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=0.5;
    STRTNEXTLIST(j)=8.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=16.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=64.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (31 entries in NewDose)
for iter = [1 : 31]
    for iter2 = [1 : 30]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
    % Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
    % (NumWks))) plus 1)
    CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
    CONCLIST(61) = 0.0;
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = CONCLIST(1);
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Bushnell PJ. 1997. Concentration-time relationships for the effects of inhaled
% trichloroethylene on signal detection behavior in rats. Fundamental and Applied Toxicology
% 36:30-38.
% Rat inhalation -- 1h/d for 1d
% Simulation for 1 day
NewDose = [30.0 60.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0 700.0 800.0
          900.0 1000.0 1100.0 1200.0 1300.0 1400.0 1500.0 1600.0 1700.0 1800.0 1900.0 2000.0
          2200.0 2400.0];
i = i + 2;
ResetDoses
RatPost
BW=0.35; TSTRT=0.0; DMINT=24.0; TSTP=24.0;

```

```

CONCLIST=[15.0 0.0 0.0];
STRTNEXTLIST=[1.0 100.0];
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (28 entries in NewDose)
for iter = [1 : 28]
    CONCLIST(1) = NewDose(iter);
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = CONCLIST(1);
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Crofton KM and Zhao X. 1997. The Ototoxicity of Trichloroethylene: Extrapolation and Relevance
%   of High-Concentration, Short-Duration Animal Exposure Data. FUNDAMENTAL AND APPLIED
%   TOXICOLOGY 38, 101-106.
% Rat inhalation -- 6h/d, 5d/w for 1d, 1w, 4w or 13w (1d and 1w not run because effects were not
%   seen at these times)

% Simulation for 4 weeks
NewDose = [30.0 60.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0 700.0 800.0
900.0 1000.0 1100.0 1200.0 1300.0 1400.0 1500.0 1600.0 1800.0 2000.0 2200.0 2400.0 2600.0 2800.0
3000.0 3200.0];
i = i + 2;
ResetDoses
RatPost
BW=0.700; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=672.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
%   weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=6.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
%   (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;

```

```

ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (30 entries in NewDose)
for iter = [1 : 30]
    for iter2 = [1 : 20]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
    % Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
    % (NumWks))) plus 1)
    CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = CONCLIST(1);
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% Simulation for 13 weeks
i = i + 2;
TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2184.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=6.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;

```

```

% Upper limit for iterations is the number of different doses to run (30 entries in NewDose)
for iter = [1 : 30]
    for iter2 = [1 : 65]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
% Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
start @NoCallback
i = i + 1;
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Maltoni C, Lefemine G, Coiti G, Perino G. 1988. Long-term carcinogenicity bioassays on
% trichloroethylene administered by inhalation to sprague-dawley rats and swiss and B6C3F1
% mice. Annals of the New York Academy of Sciences. 534: 316-342.
% Rat inhalation -- 7h/d, 5d/w for 2y
% Run until weekly AUC dosemetrics aren't changing (7 weeks)
NewDose = [5.0 10.0 15.0 20.0 25.0 30.0 40.0 50.0 60.0 70.0 80.0 90.0 100.0 125.0 150.0 175.0
            200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0];
i = i + 2;
ResetDoses
RatPost
BW=0.85; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=1176.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=7.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=17.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=65.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;

```

```

% Upper limit for iterations is the number of different doses to run (24 entries in NewDose)
for iter = [1 : 24]
    for iter2 = [1 : 35]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
% Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
start @NoCallback
i = i + 1;
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
end

% -----
% Narotsky MG, Weller EA, Chinchilli VM, Kavlock RJ. Nonadditive Developmental Toxicity in
% Mixtures of Trichloroethylene, Di(2-ethylhexyl) Phthalate, and Heptachlor in a 5 x 5 x 5
% Design. Fundam. Appl. Toxicol. 27, 203-216.
% Rat oral gavage -- once per day for E6-15
% Simulation for 10 days
NewDose = [10.0 20.0 30.0 40.0 50.0 60.0 80.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0
           500.0 550.0 600.0 650.0 700.0 750.0 800.0 900.0 1000.0 1100.0 1125.0];
i = i + 2;
ResetDoses
RatPost
BW=0.175; PDOSE=5.0; TCHNG=0.017; DAYS=7.0; TMAX=240.0; DOSEINT=24.0; DMINT=24.0; TSTP=240.0;
start @NoCallback
ExtDosevsDM(i,1) = PDOSE;
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
for iter = [1 : 26]
    PDOSE = NewDose(iter);
    start @NoCallback
    i = i + 1;
    ExtDosevsDM(i,1) = PDOSE;
    ExtDosevsDM(i,2) = max(_cart);
    ExtDosevsDM(i,3) = AUCCBLDDM;
    ExtDosevsDM(i,4) = TOTMETABBW34DM;
    ExtDosevsDM(i,5) = TOTOXMETBW34DM;
    ExtDosevsDM(i,6) = max(_cliv);
    ExtDosevsDM(i,7) = AUCCLIVDM;
    ExtDosevsDM(i,8) = AMETLIV1BW34DM;
    ExtDosevsDM(i,9) = max(_ckid);
    ExtDosevsDM(i,10) = AUCCKIDDM;
    ExtDosevsDM(i,11) = AMETKIDBW34DM;
end
end

```

```

% -----
% Woolhiser MR, Krieger SM, Thomas J., Hotchkiss JA. 2006. Trichloroethylene (TCE):
% immunotoxicity potential in CD rats following a 4-week vapor inhalation exposure. Midland,
% MI: The Dow Chemical Company. Study ID: 031020
% Rat inhalation -- 6h/d, 5d/w for 4w
% Simulation for 4 weeks
NewDose = [30.0 60.0 100.0 150.0 200.0 250.0 300.0 350.0 400.0 450.0 500.0 600.0 700.0 800.0
          900.0 1000.0];

i = i + 2;
ResetDoses
RatPost
BW=0.2146; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=672.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=15.0;
    STRTNEXTLIST(j)=6.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
% Upper limit for iterations is the number of different doses to run (16 entries in NewDose)
for iter = [1 : 16]
    for iter2 = [1 : 20]
        j=(2 * iter2) - 1;
        CONCLIST(j)=NewDose(iter);
        CONCLIST(j+1) = 0.0;
    end
end
% Index is ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
start @NoCallback
i = i + 1;
ExtDosevsDM(i,1) = CONCLIST(1);
ExtDosevsDM(i,2) = max(_cart);
ExtDosevsDM(i,3) = AUCCBLDDM;
ExtDosevsDM(i,4) = TOTMETABBW34DM;
ExtDosevsDM(i,5) = TOTOXMETBW34DM;
ExtDosevsDM(i,6) = max(_cliv);
ExtDosevsDM(i,7) = AUCCLIVDM;
ExtDosevsDM(i,8) = AMETLIV1BW34DM;
ExtDosevsDM(i,9) = max(_ckid);
ExtDosevsDM(i,10) = AUCCKIDDM;
ExtDosevsDM(i,11) = AMETKIDBW34DM;
end
save ExtDosevsDM @file='Rat_Linearity_Output.txt' @format=ascii

```

RatPrior.m

```
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["AFat", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ASTom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"], [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "ASTomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "ASTomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "AREcircTCOG", "AUrnTCOG"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVG_mMole", "AMetDCVG_mMole"], [1.0e-9, 1.0e-9])
% Prior parameters for rat
%   DRespC, kAS, kTSD, kAD, kASTCA, FracOtherC, KMClara, FracLungSysC, VMaxTCOHC, KMTCOH,
%   VMaxGlucC, KMGluc, kMetTCOHC, kMetTCAC, kBileC, kEHRC, kNATC, kKidBioactC from Table 3-38
%   in report
%   kASTCOH from Table A-12
SPECIES=2;
BW=0.3; QCC=13.3; VPR=1.9; DRESPC=0.99;
QFATC=0.07; QGUTC=0.153; QKIDC=0.141; QLIVC=0.021; QRAP=0.279; QSLWC=0.336;
VBLDC=0.074; VFATC=0.07; VGUTC=0.032; VKIDC=0.007; VLIVC=0.034; VPERFC=0.8995; VRAPC=0.088;
VRESPC=0.0005; VRESPLUMC=0.0046667; VSLWC=0.594; FRACPLAS=0.53;
PB=22.0; PFAT=27.0; PGUT=1.4; PKID=1.3; PLIV=1.5; PRAP=1.3; PRESP=1.0; PSLW=0.58;
PRBCPLASTCA=0.5; PBODTCAC=0.88; PLIVTCAC=1.18;
PBODTCOH=1.11; PLIVTCOH=1.3;
PBODTCOG=1.11; PLIVTCOG=1.3; PEFDCVGC=1.0;
BMAXKDC=1.22; KDISSOC=275.0;
KAS=0.73; KTS=1.4; KAD=0.96; KTD=0.0; KASTCA=0.83; KASTCOH=0.69;
VMAXC=600.0; KMC=21.0; CL=1.0; FRACOTHC=0.32; FRACOTHC=0.028;
VMAXDCVGC=66.0; KMDCVGC=1.0; CLDCVGC=0.25;
VMAXKIDDCVGC=6.0; KMKIDDCVGC=1.0; CLKIDDCVGC=0.026;
VMAXLUNGLIV=0.014347; KMCLARA=0.016; FRACLUNGSSYS=4.6;
VMAXTCOHC=1.9; KMTCOH=1.0; CLTCOH=1.0;
VMAXGLUCC=67.0; KMGLUC=31.0; CLGLUC=1.0; KMETTCOHC=3.1;
KURNTCAC=0.522; KMETTCAC=0.56;
KBILEC=1.0; KEHRC=0.0096; KURNTCOGC=0.522;
KDCVGC=22206.46579; FRACKIDDCVCC=22206.46579;
KNATC=0.11; KKIDBIOACTC=0.09;
```

RatPost.m

```
xerror (["AInhResp", "AExhResp", "AResp"], [1.0e-13, 1.0e-13, 1.0e-13])
xerror (["AFat", "AExh", "AFat", "AGut", "AKid", "ALiv", "ARap", "ASlw", "ABld"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ASTom", "ADuod", "AExc"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["AMetLng", "AMetKid", "AMetLiv1", "AMetLiv2"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["APlasTCA", "ABodTCA", "ASTomTCA", "ALivTCA", "AMetTCA", "AUrnTCA"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOH", "ASTomTCOH", "ALivTCOH", "AMetTCOHTCA", "AMetTCOHGluc", "AMetTCOHOther"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ABodTCOG", "ALivTCOG", "ABileTCOG", "AREcircTCOG", "AUrnTCOG"],
        [1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVC", "ABioactDCVC", "AUrnDCVC"], [1.0e-9, 1.0e-9, 1.0e-9])
xerror (["ADCVG_mMole", "AMetDCVG_mMole"], [1.0e-9, 1.0e-9])
% Mean posterior parameters for rat
SPECIES=2;
BW=0.3; QCC=15.84833; VPR=1.18359; DRESPC=2.55308;
QFATC=0.083090; QGUTC=0.17549; QKIDC=0.14128; QLIVC=0.021672; QRAPC=0.27512; QSLWC=0.30334;
VBLDC=0.074148; VFATC=0.068040; VGUTC=0.031654; VKIDC=0.0069489; VLIVC=0.033470;
VPERFC=0.89950; VRAPC=0.087393; VRESPC=0.00049585; VRESPLUMC=0.0046900; VSLWC=0.59735;
FRACPLAS=0.55226;
PB=18.79597; PFAT=30.50031; PGUT=1.21152; PKID=1.22174; PLIV=1.56356; PRAP=1.40279;
PRESP=0.95547; PSLW=0.74929;
PRBCPLASTCA=0.48121; PBODTCAC=0.98262; PLIVTCAC=1.51333;
PBODTCOH=1.05556; PLIVTCOH=1.24815;
PBODTCOG=1.37638; PLIVTCOG=11.16032; PEFDCVGC=1.0;
BMAXKDC=1.16098; KDISSOC=268.46783;
```

```

KAS=2.72100; KTS=4.16618; KAD=0.18105; KTD=0.0; KASTCA=1.48750; KASTCOH=0.68805;
VMAXC=571.68015; KMC=0.73825; CL=1.0; FRACTCAC=0.079624; FRACOTHC=0.30975;
VMAXDCVGC=790.49137; KMDCVGC=1.0; CLDCVG=0.093015;
VMAXKIDDCVGC=1.26460; KMKIDDCVGC=1.0; CLKIDDCVG=4.72724;
VMAXLUNGLIV=0.047682; KMCLARA=0.020775; FRACLUNGSYSC=1.98080;
VMAXTCOHC=2.01819; KMTCOH=22.42104; CLTCOH=1.0;
VMAXGLUCC=27.16692; KMGLUC=5.87673; CLGLUC=1.0; KMETTCOHC=1.97605;
KURNTCAC=0.037512; KMETTCAC=0.32530;
KBILEC=7.55342; KEHRC=1.46756; KURNTCOGC=10.70716;
KDCVGC=22026.46579; FRACKIDDCVCC=22026.46579;
KNATC=0.0020891; KKIDBIOACTC=0.0069016;

```

ResetDoses.m

```

% Setting concentration parameters with loop because lines were longer than 510 characters and
% were too long

CC=0; NRODENTS=1.0; KLOSSC=0.0; VCHC=1.0;
for iter = [1 : 150]
    CONCLIST(iter) = 0.0;
    STRTNEXTLIST(iter)=0.0;
end
STRTNEXTLIST(1)=50000.0;
IVDOSE=0.0; TCHNG=1.0; DAYS=1.0; TMAX=24.0;
PDOSE=0.0; DRINK=0.0; IADOSE=0.0; PVDSE=0.0;
IVDOSETCA=0.0; PODOSETCA=0.0;
IVDOSETCOH=0.0; PODOSETCOH=0.0;
URNMISLIST=[100000.0 100000.0 100000.0 100000.0 100000.0 100000.0 100000.0 100000.0
100000.0];
CINT=0.01; DOSEINT=100000.0;

```

RunDMs.m

```

load @format=model @file=EPA_2011_TCE_REV
init

% Mouse
CheckOutputMax=[]; CheckOutputMin=[]; DMOutput=[]; Params=[]; i=0;
Blossom2017_MouseDM
Cosby92_MouseDM
George85_MouseDM
Gilbert2014_MouseDM
Griffin00_MouseDM
Kaneko00_MouseDM
Kjellstrand83_MouseDM
Land81_MouseDM
Ramadhan10_MouseDM
Sanders82_MouseDM
Schwetz75_MouseDM
save CheckOutputMax @file='CheckOutputMax_MouseDMs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_MouseDMs.txt' @format=ascii
save DMOutput @file='MouseDMs.txt' @format=ascii
save Params @file='Params_MouseDMs.txt' @format=ascii

% Rat
CheckOutputMax=[]; CheckOutputMin=[]; DMOutput=[]; Params=[]; i=0;
Adams51_RatDM
Albee06_RatDM
Arito94_RatDM
Bushnell97_RatDM
Carney06_RatDM
Crofton97_RatDM
Fisher01_RatDM
Healy82_RatDM
Isaacson89_RatDM
Jaspers93_RatDM
Kumar00a_01a_RatDM
Maltoni88_RatDM
Manson84_RatDM
Narotsky95_RatDM
Schwetz75_RatDM

```

```

Woolhiser06_RatDM
Wu07_RatDM
Zenick84_RatDM
save CheckOutputMax @file='CheckOutputMax_RatDMs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_RatDMs.txt' @format=ascii
save DMOutput @file='RatDMs.txt' @format=ascii
save Params @file='Params_RatDMs.txt' @format=ascii

```

RunHECs.m

```

load @format=model @file=EPA_2011_TCE_REV
init
% Human
Male_Fit_HECs_ContInh
Male_Fit_HECs_OccInh
Female_Fit_HECs_ContInh
Female_Fit_HECs_OccInh

```

SaveDMs.m

```

DMOutput(i,1) = max(_cart);
DMOutput(i,2) = AUCCBLDDM;
DMOutput(i,3) = TOTMETABBW34DM;
DMOutput(i,4) = TOTOXMETBW34DM;
DMOutput(i,5) = max(_cliv);
DMOutput(i,6) = AUCCLIVDM;
DMOutput(i,7) = AMETLIV1BW34DM;
DMOutput(i,8) = max(_ckid);
DMOutput(i,9) = AUCCKIDDM;
DMOutput(i,10) = AMETKIDBW34DM;

```

APPENDIX D: M FILES FOR MOUSE DOSE METRICS

The following are M files for generating mouse dose metric values.

MouseDms_for_BMD.m

```
% Runs to output internal dose metrics for BMD analysis based

load @format=model @file=EPA_2011_TCE_REV
init
CheckOutputMax=[]; CheckOutputMin=[]; DMOutput=[]; Params=[];

% -----
% Griffin JM, Gilbert KM, Lamps LW, Pumford NR. 2000. CD4+ T-cell activation and induction of
% autoimmune hepatitis following trichloroethylene treatment in MRL+/+ mice. Toxicological
% Sciences 57: 345-52.
% MRL+/+ autoimmune prone mice, female, n = 8
% 0.1 mg/mL TCE in drinking water or 21 mg/kg-dy TCE (NOAEL, POD) for 32 wk
% LOAEL: 0.5 mg/mL or 100 mg/kg-dy
% Critical Effect: Liver lymphocyte infiltration (Table 2)
% Also tested: 0, 2.5 mg/mL (400 mg/kg-dy) TCE in drinking water
% Body weights were not different between groups
% Mice were 4 wk old at purchase; assuming a 2 wk acclimation period, mice were 38 wk at
% study end
% A growth chart for MRL mice was not found. A comparison was found (10-week-old
% female C57BL/6 weighed 20.1+/-0.5 g, MRL/MpJ weighed an average of 31.7+/-0.4 g)
% Thuret S, Thallmair M, Horky LL, Gage FH. 2012. Enhanced Functional Recovery in
% MRL/MpJ Mice after Spinal Cord Dorsal Hemisection. PLoS ONE 7(2):
% e30904. doi:10.1371/journal.pone.0030904
% At 270 days, female C57BL/6 weigh 27 g (Hilltop Labs), so the MRL females may
% weigh 43 g
% http://www.hilltoplabs.com/public/c57growth.html
% Mouse oral drinking water -- 4 or 32 wks
% Run until daily AUC dosemetrics aren't changing (13 days)
ResetDoses
MousePost
BW=0.043; DRINK=21.0; DMINT=24.0; TSTP=288.0; CINT=0.1;
i = 1;
start @NoCallback
plot(t, _cart);
SaveDms
Output_Check
DRINK=100.0;
i = i + 1;
start @NoCallback
SaveDms
Output_Check
DRINK=400.0;
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Check for steady state (13 days)
DRINK=21.0; TSTP=312.0;
i = i + 1;
start @NoCallback
SaveDms
Output_Check
DRINK=100.0;
i = i + 1;
start @NoCallback
SaveDms
Output_Check
DRINK=400.0;
i = i + 1;
start @NoCallback
SaveDms
Output_Check
```

```

% -----
% Land PC, Owen EL, Linde HW. 1981. Morphologic Changes in Mouse Spermatozoa after
% Exposure to Inhalational Anesthetics during Early Spermatogenesis
% (C57Bl x C3H)F1 mice (n = 5)
% Inhalation of 200 ppm TCE (NOAEL, POD) for 4 hr/dy, 5 dy
% LOAEL (abnormal epididymal sperm, euthanized 28 dy after 1st exposure) 2000 ppm (n = 10)
% Also tested: 0 ppm
% Mice obtained at 8-10 wk old and exposed at 11 wk old; should be about 26 g
% RAO GN, HASEMAN JK, GRUMBEIN S, CRAWFORD DD, EUSTIS SL. 1990. Growth, Body Weight,
% Survival, and Tumor Trends in (C57BL/6 X C3H/HeN) F1 (B6C3F1) Mice During a
% Nine-Year Period. TOXICOLOGIC PATHOLOGY. 18(1): 71-77.
% Mouse inhalation -- 4h/d for 5 days
ResetDoses
MousePost
BW=0.026; TSTRT=0.0; DAYS=5.0; DMINT=24.0; TSTP=120.0; CINT=0.1;
CONCLIST=[200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 0.0];
STRTNEXTLIST=[4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 100.0];
start @NoCallback
i = i + 1;
start @NoCallback
plot(_t, _cart);
SaveDMS
Output_Check
CONCLIST=[2000.0 0.0 2000.0 0.0 2000.0 0.0 2000.0 0.0 2000.0 0.0 0.0];
STRTNEXTLIST=[4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
start @NoCallback
SaveDMS
Output_Check

% -----
% Ramdhan DH, Kamijima M, Wang D, Ito Y, Naito H, Yanagiba Y, Hayashi Y, Tanaka N, Aoyama T,
% Gonzalez FJ, Nakajima T. 2010. Differential Response to Trichloroethylene-Induced
% Hepatosteatois in Wild-Type and PPAR $\alpha$ -Humanized Mice. Environ Health Perspect 118:1557-1563
% Wild type PPAR $\alpha$  mice, male (n = 6)
% Inhalation of 1000 ppm TCE (LOAEL, POD) for 8 hr/dy, 7 dy
% Critical Effect: increased ALT
% Also tested: 0, 2000 ppm
% NOTE: Ppara $\alpha$ -null and hPPAR $\alpha$  mice were also tested; only wild type results were
% highlighted in the journal article copies received for this project so only
% HEC from wild type data are predicted
% BW for wild type mice exposed to 1000 ppm was listed as 25.0 +/- 2.3 g in Table 1
% Mouse inhalation -- 8h/d, daily for 7 days
ResetDoses
MousePost
BW=0.025; TSTRT=0.0; DAYS=7.0; DMINT=24.0; TSTP=168.0;
CONCLIST=[1000.0 0.0 1000.0 0.0 1000.0 0.0 1000.0 0.0 1000.0 0.0 1000.0 0.0 0.0];
STRTNEXTLIST=[8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 100.0];
i = i + 1;
start @NoCallback
plot(_t, _cart);
SaveDMS
Output_Check
CONCLIST=[2000.0 0.0 2000.0 0.0 2000.0 0.0 2000.0 0.0 2000.0 0.0 2000.0 0.0 0.0];
STRTNEXTLIST=[8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 16.0 8.0 100.0];
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
save CheckOutputMax @file='CheckOutputMax_MouseDMS.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_MouseDMS.txt' @format=ascii
save DMOutput @file='Mouse_DMS_for_BMD.txt' @format=ascii
save Params @file='Params_MouseDMS.txt' @format=ascii

```

Blossom2017_MouseDM.m

```
% Blossom SJ, Melnyk SB, Li M, Wessinger WD and Cooney CA. 2017. Inflammatory and oxidative
% stress-related effects associated with neurotoxicity are maintained after
% exclusively prenatal trichloroethylene exposure. NeuroToxicology 59:164-174.
% MRL +/- female mice
% 0, 0.01 or 0.1 mg/mL TCE in drinking water (0, 2.96 or (29.6 or 26.56) mg/kg/d) from 2 weeks
% prior to mating until the end of pregnancy
% Water also contained 1% Alkamuls EL-620, an emulsifier consisting of ethoxylated castor oil, a
% reagent used to solubilize the TCE
% POD=LOAEL of 2.96 mg/kg/d for developmental effects and NOAEL of 2.96 mg/kg/d for immune
% effects
% Critical Effect: Developmental effect of increased locomotor activity and
% Immuno effect of increased splenic central memory CD4+
% Body weights given for dams are 0.047, 0.045 and 0.045 kg for the 3 dose groups -- used a
% BW of 0.045 since both dosed groups had this average BW
% Females
% Run until daily dosemetrics aren't changing (5 days)
ResetDoses
MousePost
BW=0.045; DRINK=2.96; DMINT=24.0; TSTP=120.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Cosby92_MouseDM.m

```
% Cosby NC, Dukelow WR. Toxicology of maternally ingested trichloroethylene
% (TCE) on embryonal and fetal development in mice and of TCE metabolites on
% in vitro fertilization. Fundam Appl Toxicol. 1992 Aug;19(2):268-74.
% C57BL/6 X DBA/2 (B6D2F1) mice, female, n = 11 with litters
% Oral gavage of 240.2 mg/kg TCE (NOAEL, POD) daily for 5 dy (GD1-5, GD6-10, or GD11-15)
% Doses assumed to take 1 minute (0.017 hr)
% Doses based upon 1/10 and 1/100 of the LD50 value of 2402 mg/kg body weight
% Critical Effect: Litter size/viability, pup size/gross development
% Also tested: 0, 24.02 mg/kg
% Females were 6-8 wk at study start. Mean values for weight of female litter-bearing
% mice were not significantly different across treatment doses for any treatment
% group (data not shown).
% Mice are 8-10 wk at the end of the study. Since the mice are dosed by bw, size of
% mouse does not change the dose. As there are no adverse effects recorded, no
% particular exposure time is more important than another.
% The mice will be ~20-23 g during pregnancy (using the high end of the female curve due
% to pregnancy). The simulation will be run for 22 g.
% https://www.criver.com/products-services/find-model/b6d2f1-bdf1-mouse?region=3611
ResetDoses
MousePost
BW=0.022; PDOSE=240.2; TCHNG=0.017; DAYS=5.0; TMAX=120.0; DOSEINT=24.0; DMINT=24.0; TSTP=120.0;
CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

George85_MouseDM.m

```
% George JD, Reel JR, Myers CB, Lawton AD, Lamb JC. 1985. Trichloroethylene: Reproduction and
% Fertility Assessment in CD-1 Mice When Administered in the Feed. Research Triangle
% Park NC: National Toxicology Program, National Institute of Environmental Health
% Sciences. NTP-86-068
% CD-1 mice, male and female, n = 8/sex
% 0.3% TCE in diet or 375 mg/kg-dy TCE (NOAEL, POD) for 15 wk
% LOAEL: 0.6% or 750 mg/kg-dy
% Critical Effect: Decreased sperm motility
% Continuous breeding study (1 wk pre-dosing, 14 wks breeding, 3 wk segregation)
% Also tested: 0, 0.15% TCE in food (0, 187.5 mg/kg) (page 20)
% Male mouse weight in the 750 mg/kg-dy dose group was 37.79 +/- 0.62 g and was not
% different from controls (39.19 +/- 0.55) (Table 6); it is assumed that the
% 375 mg/kg-dy group would be similar in weight (assuming 38 g)
% Assume it takes them 10 hours to consume their food (dark hours) as lights were on 0500
% to 1900 hours
% Run until weekly AUC dosemetrics aren't changing (6 weeks)
ResetDoses
MousePost
BW=0.038; PDOSE=750.0; TCHNG=10.0; DAYS=7.0; TMAX=1008.0; DOSEINT=24.0; DMINT=168.0;
TSTP=1008.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Gilbert2014_MouseDM.m

```
% Gilbert KM, Woodruff W and Blossom SJ. 2014. Differential immunotoxicity induced by two
% different windows of developmental trichloroethylene exposure. Autoimmune Diseases, Article
% ID 982073, 12 pages, http://dx.doi.org/10.1155/2014/982073
% MRL +/- female mice
% 0, 0.01 or 0.1 mg/mL TCE in drinking water (0, 3.42 or 34.2 mg/kg/d OR 0, 2.96 and 26.56
% like Blossom?) from the start of gestation until the end of pregnancy
% Water also contained 1% Alkamuls EL-620, an emulsifier consisting of ethoxylated castor oil, a
% reagent used to solubilize the TCE
% POD=NOAEL of 3.42 mg/kg/d
% Critical Effect: Spleen cellularity
% Body weights were not given so assumed they were same as those given in Blossom et al 2017
% (0.047, 0.045 and 0.045 kg for the 3 dose groups) so used a BW of 0.045 kg since that
% was the average BW for the dosed groups
% Females
% Run until daily dosemetrics aren't changing (5 days)
ResetDoses
MousePost
BW=0.045; DRINK=3.42; DMINT=24.0; TSTP=120.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Kaneko00_MouseDM.m

```
% Kaneko T, Saegusa M, Tasaka K, Sato A. 2000. Immunotoxicity of Trichloroethylene:
%   a Study with MRL-lpr/lpr Mice. J. Appl. Toxicol. 20, 471-475
% MRL-lpr/lpr male mice, n = 5
% Inhalation of 500 ppm TCE (LOAEL, POD) for 4 hr/dy, 6 dy/wk, 8 wk
% Effect: B cell function in MRL mice was used b/c the histology was not quantified
%   and the T cell staining lacks clear relevance and shows an effect at only one dose.
% Also tested: 0, 1000, 2000 ppm
% Mice were ~46-48 g at study finish (not statistically different between groups)
%   (Figure 1) - Using middle number (47 g)
% Run until weekly AUC dosemetrics aren't changing (5 weeks)
ResetDoses
MousePost
BW=0.047; TSTRT=0.0; DMINT=168.0; TSTP=840.0;
CONCLIST=[500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0
0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0
500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0
0.0 500.0 0.0 500.0 0.0 500.0 0.0 500.0 0.0 0.0];
STRTNEXTLIST=[4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 44.0 4.0 20.0 4.0 20.0 4.0 20.0
4.0 20.0 4.0 20.0 4.0 44.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 44.0
4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 44.0 4.0 20.0 4.0 20.0 4.0 20.0
4.0 20.0 4.0 20.0 4.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDms
Output_Check
```

Kjellstrand83_MouseDM.m

```
% Kjellstrand P, Holmquist B, Aim P, Kanje M, Romare S, Jonsson I, Mansson L, Bjerkemo M.
%   1983. Trichloroethylene: Further Studies of the Effects on Body and Organ
%   Weights and Plasma Butyrylcholinesterase Activity in Mice. Acta pharmacol. et
%   toxicol. 1983, 53, 375-384.
% White NMRI mice, 20 male and 20 female (see Table 1)
% Inhalation of 37 ppm TCE (LOAEL, POD) for 24 hr/dy, 7 dy/wk, 30 dy
%   Critical effect: Relative liver weight increase (see Table 3)
% Also tested: 75, 150, 300 ppm continuous; intermittent exposures also tested
% Female ending BW = 35.0 +/- 1.3 g (Table 2)
ResetDoses
MousePost
BW=0.035; CONCLIST(1)=37.0; STRTNEXTLIST(1)=800.0; TSTRT=0.0; DMINT=24.0; TSTP=720.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDms
Output_Check
% Male ending BW = 36.2 +/- 1.0 g (Table 2)
ResetDoses
MousePost
BW=0.0362; CONCLIST(1)=37.0; STRTNEXTLIST(1)=800.0; TSTRT=0.0; DMINT=24.0; TSTP=720.0;
CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDms
Output_Check
```

Sanders82_MouseDM.m

```
% Sanders VM, Tucker AN, White KL, Kauffmann BM, Hallett P, Carchman RA, Borzelleca JF,
% Munson AE. 1982. Humoral and cell-mediated immune status in mice exposed to
% trichloroethylene in the drinking water. Toxicol. Appl. Pharmacol. 62: 358-68.

% CD-1 mice, female and male, n = 12-20 for each sex
% 0.1 mg/mL TCE in drinking water or 18.4 mg/kg-dy TCE (LOAEL, POD) for 4 mo
% NOTE: A second group was exposed for 6 mo but the cell mediated response at the
% LOAEL was only significant in the 4 mo group (Table 6)
% Critical Effect: Cell-mediated SRBC response (Table 6) and bone marrow stem cells
% (Table 8)
% Also tested: 0, 1.0, 2.5, 5.0 mg/mL (0, 216.7, 393, 660.2 mg/kg-dy) TCE in drinking
% water for 4 or 6 months
% Simulation is for last week of study
% Effects on BW and starting ages or BW were not mentioned
% Assuming the mice are approximately 5 mo old for the 4 mo exposures
% At 15 wk, female CD-1 rats would be 40 g at the top of the range and may indicate
% their size at 20 wk
% At 15 wk, male CD-1 rats would be 49 g at the top of the range and may indicate
% their size at 20 wk
% https://www.criver.com/products-services/find-model/cd-1-igs-mouse?region=3611
% Females
% Run until daily AUC dosemetrics aren't changing (13 days)
ResetDoses
MousePost
BW=0.040; DRINK=18.4; DMINT=24.0; TSTP=312.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
% Males
% Run until daily AUC dosemetrics aren't changing
ResetDoses
MousePost
BW=0.049; DRINK=18.4; DMINT=24.0; TSTP=312.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Schwetz75_MouseDM.m

```
% Schwetz BA, Leong BKJ, Gehring PJ. 1975. The effect of maternally inhaled
% trichloroethylene, perchloroethylene, methyl chloroform, and methylene
% chloride on embryonal and fetal development in mice and rats. Toxicology
% and Applied Pharmacology. 32:84-96.

% Swiss-Webster female mice, n = 12
% Inhalation of 306 ppm TCE (NOAEL, POD) for 7 hr/dy, GD 6-15 (10 days)
% No effect on fetal development
% Tables 5-6
% Also tested: 0 ppm, also tested mice (see additional m file)
% Mice were 25-30 g prior to pregnancy; Mice exposed to TCE did not have decreased body
% weight as the rats did
% Ending mouse weights are not given but liver weight was 2.8 +/- 0.3 g in TCE group and
% relative liver weight was 0.052 +/- 0.006 g LW/g BW (Table 2)
% Therefore BW was ~54 g in this group
ResetDoses
MousePost
BW=0.054; TSTRT=0.0; DMINT=24.0; TSTP=240.0;
CONCLIST=[306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0
0.0 306.0 0.0 0.0];
STRTNEXTLIST=[7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0
7.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

APPENDIX E: M FILES FOR RAT DOSE METRICS

The following are M files for generating rat dose metric values.

RatDms_for_BMD.m

```
% Runs to output internal dose metrics for BMD analysis based
load @format=model @file=EPA_2011_TCE_REV
init
CheckOutputMax=[]; CheckOutputMin=[]; DMOOutput=[]; Params=[];

% -----
% Arito H, Takahashi M, Ishikawa T. 1994. Effect of subchronic inhalation exposure to low-level
% trichloroethylene on heart rate and wakefulness-sleep in freely moving rats. Japanese
% Journal of Industrial Health 36:1-8.
% JCL-Wistar rats, 20 male (4 groups of 5 exposed to each concentration)
% Inhalation of 50 ppm TCE (LOAEL, POD) for 8 hr/dy, 5 dy/wk, 2,4,6 wk
% Critical effect: Decreased wakefulness
% Also tested: 100 & 300 ppm
% Body weights are not specified
% Rats were 4 wk at receipt, 9 wk at EEG/EMG/ECG implant, 11 wk (most likely) at study start, and
% 17 wk at end
% Rats would be about 375 g (M) at 17 weeks
% Estimate based on website growth curve:
% http://www.clea-japan.com/en/animals/animal_e/e_03.html
% Male ending BW = 375 g
% Rat inhalation -- 8h/d, 5d/w for 2, 4 or 6w (Arito study)
% Only 6 wk exposures were run as the data used for BMD were for 6 wks

% Simulation for 6 weeks
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=50.0;
    STRTNEXTLIST(j)=8.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=16.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=64.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
i = 1;
start @NoCallback
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=100.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=300.0;
end
```

```

i = i + 1;
start @NoCallback
SaveDMS
Output_Check

% -----
% Bushnell PJ. 1997. Concentration-time relationships for the effects of inhaled
% trichloroethylene on signal detection behavior in rats. Fundamental and Applied Toxicology
% 36:30-38.
% Long-Evans rats, 11 male
% Inhalation of 800 ppm TCE (NOAEL, POD) for 1 hr/dy (see Figure 1 of article)
% LOAEL (sensitivity to light stimulus, visual learning) 1200 ppm
% Also tested: 400, 600, 1600, 2000, 2400 ppm
% Animals are exposed 3 times a week. All animals are exposed to air, then 3 different
% concentrations on 4 consecutive days of a week (0, 400, 800, 1600 ppm; 60, 1200, 2000 ppm;
% 1200 2400, 2400 ppm).
% 600, 2000 and 2400 ppm doses were not run -- 600 ppm dose group was dropped by Bushnell et al.
% such that there were no data for that dose for BMD analysis; 2000 and 2400 ppm doses were
% not run as it appeared that the rats developed a tolerance and the response for those doses
% was actually lower than for lower doses and were not included in BMD analysis
% Ending BW = 350 g (controlled by measured diet)
% Rat inhalation -- 1h/d for 1d
% Simulation for 1 day
ResetDoses
RatPost
BW=0.35; TSTRT=0.0; DAYS=1.0; DMINT=24.0; TSTP=24.0;
CONCLIST=[400.0 0.0 0.0];
STRTNEXTLIST=[1.0 100.0];
i = i + 1;
start @NoCallback
plot(_t, _cart);
SaveDMS
Output_Check
CONCLIST=[800.0 0.0 0.0];
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
CONCLIST=[1200.0 0.0 0.0];
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
CONCLIST=[1600.0 0.0 0.0];
i = i + 1;
start @NoCallback
SaveDMS
Output_Check

% -----
% Crofton KM and Zhao X. 1997. The Ototoxicity of Trichloroethylene: Extrapolation and Relevance
% of High-Concentration, Short-Duration Animal Exposure Data. FUNDAMENTAL AND APPLIED
% TOXICOLOGY 38, 101-106.
% Long Evan rats, 10-12 male
% Inhalation of 1600 ppm TCE (NOAEL, POD) for 6 hr/dy, 5 dy/wk, 13 wk
% LOAEL (shift in auditory threshold, 13 wk group) 2400 ppm
% Also tested: 800, 3200 ppm; All concentrations tested for 1 dy, 1 wk, 4 wk, 13 wk
% Rats were received at 60 dy of age (8.5 wk) and would have been 23 wks at study finish,
% including a 2 wk quarantine/acclimation period
% Rats would be about 300 g at 8 wk and 700 g at 23 wk (675 g at 21 wk, no acclimation)
% Tordoff MG, Alarcon LK, Lawler MP. 2008. Preferences of 14 rat strains for
% 17 taste compounds. Physiol Behav. 2008 October 20; 95(3): 308-332.
% Rat inhalation -- 6h/d, 5d/w for 1d, or 1, 4 or 13w
% Only 13 wk exposures were run as the data used for BMD were for 13 wks
% Simulation for 13 weeks
ResetDoses
RatPost
BW=0.700; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2184.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;

```

```

% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=800.0;
    STRTNEXTLIST(j)=6.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
i = i + 1;
start @NoCallback
plot(_t, _cart);
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=1600.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=2400.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=3200.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check

% -----
% Maltoni C, Lefemine G, Coiti G, Perino G. 1988. Long-term carcinogenicity bioassays on
% trichloroethylene administered by inhalation to sprague-dawley rats and swiss and B6C3F1
% mice. Annals of the New York Academy of Sciences. 534: 316-342.
% Sprague-Dawley rats, 15 male and 15 female
% Inhalation of 300 ppm TCE (NOAEL, POD) for 7 hr/dy, 5 dy/wk, 104 wk
% LOAEL (meganucleocytosis of kidney, Table 20) 600 ppm
% Also tested: 100 ppm
% Rats were 12-13 wk at start of experiment; this strain of male rat appears to max out at 850 g
% Tordoff MG, Alarcon LK, Lawler MP. 2008. Preferences of 14 rat strains for
% 17 taste compounds. Physiol Behav. 2008 October 20; 95(3): 308-332.
% Simulating the last week of exposures
% NOTE: These POD simulations for HEC predictions are for non-cancer endpoints. This study
% contains cancer endpoints as well. Further, the study was performed in two strains of mice
% also. However, the non-cancer POD for this study was found in the male rats only.

```

```

% Rat inhalation -- 7h/d, 5d/w for 2 yrs
% Run until weekly AUC dosemetrics aren't changing (6 weeks)
ResetDoses
RatPost
BW=0.85; TSTP=0.0; DAYS=5.0; DMINT=168.0; TSTP=840.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=100.0;
    STRTNEXTLIST(j)=7.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=17.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=65.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
i = i + 1;
start @NoCallback
plot(t, _cart);
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=300.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=600.0;
end
i = i + 1;
start @NoCallback
SaveDms
Output_Check
% Check for steady state (6 weeks)
TSTP=1008.0;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=100.0;
    STRTNEXTLIST(j)=7.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=17.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=65.0;
end

```

```

% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
%   (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
%   weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=300.0;
end
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
%   weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=600.0;
end
i = i + 1;
start @NoCallback
SaveDMS
Output_Check

% -----
% Narotsky MG, Weller EA, Chinchilli VM, Kavlock RJ. Nonadditive Developmental Toxicity in
%   Mixtures of Trichloroethylene, Di(2-ethylhexyl) Phthalate, and Heptachlor in a 5 x 5 x 5
%   Design. Fundam. Appl. Toxicol. 27, 203-216.
% F-344 rats, female, n = 7-12
% Oral gavage of 844 mg/kg TCE (NOAEL, POD) daily on GD6-15 (10 dy)
%   Doses assumed to take 1 minute (0.017 hr)
% LOAEL: 1125 mg/kg-dy
% Critical Effect: Litter resorptions (Table 3a)
% Also tested: 0, 475, 633 mg/kg-dy TCE (corn oil)
% Timed pregnant females were purchased at 90 dy old
% Doses were the same daily and were based on GD6 BW (~96 dy or ~14 wk)
% Weight gain data were given (Table 5) but no data were presented on actual BW
% F-344 females at 14 wk weigh ~175 g at 14 wk (high end of range due to pregnancy);
%   This weight is what the dose was calculated on, not the ending pregnancy wt
%   Charles River Laboratories 2018 Catalog
% Rat oral gavage -- once per day for E6-15
% Simulation for 10 days
ResetDoses
RatPost
BW=0.175; PDOSE=475.0; TCHNG=0.017; DAYS=7.0; TMAX=240.0; DOSEINT=24.0; DMINT=24.0; TSTP=240.0;
i = i + 1;
start @NoCallback
plot(_t, _cart);
SaveDMS
Output_Check
PDOSE=633.0;
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
PDOSE=844.0;
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
PDOSE=1125.0;
i = i + 1;
start @NoCallback
SaveDMS
Output_Check

```

```

% -----
% Woolhiser MR, Krieger SM, Thomas J., Hotchkiss JA. 2006. Trichloroethylene (TCE):
% immunotoxicity potential in CD rats following a 4-week vapor inhalation exposure. Midland,
% MI: The Dow Chemical Company. Study ID: 031020
% Sprague-Dawley rats, female, n =
% Inhalation of 300 ppm TCE (NOAEL, POD) for 6 hr/dy, 5 dy/wk, 4 wk
% LOAEL 1000 ppm
% Increased relative kidney & liver weight; Decreased PFC response (plaque
% forming cell assay) - Tables 10, 19
% Also tested: 100 ppm
% Rats were 214.6 g at end (300 ppm group, Table 6)
% Simulations are for the final week of exposure
% Rat inhalation -- 6h/d, 5d/w for 4w
% Simulation for 4 weeks
ResetDoses
RatPost
BW=0.2146; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=672.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=100.0;
    STRTNEXTLIST(j)=6.0;
    CONCLIST(j+1) = 0.0;
    STRTNEXTLIST(j+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j=iter*10;
    STRTNEXTLIST(j)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
i = i + 1;
start @NoCallback
plot(t, _cart);
SaveDMS
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=300.0;
end
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    j=(2 * iter) - 1;
    CONCLIST(j)=1000.0;
end
i = i + 1;
start @NoCallback
SaveDMS
Output_Check
save CheckOutputMax @file='CheckOutputMax_RatDMS.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_RatDMS.txt' @format=ascii
save DMOutput @file='Rat_DMS_for_BMD.txt' @format=ascii
save Params @file='Params_RatDMS.txt' @format=ascii

```

Adams51_RatDM.m

```
% Adams EM, Spencer HC, Rowe VK, McCollister DD, Irish DD. 1951. Vapor toxicity of
%   trichloroethylene determined by experiments on laboratory animals. AMA Archives of
%   Industrial Hygiene and Occupational Medicine 4:469-481.
% Wistar origin rats, 15 male and 15 female
% Inhalation of 200 ppm TCE (NOAEL, POD) for 7 hr/dy, ~5 dy/wk,
%   as many as 151 exposures in 205 days (29.3 wk, 6.7 mo) (Table 5)
% LOAEL (increased relative liver & kidney wt) 400 ppm, 7 hr/dy, ~5 dy/wk,
%   as many as 173 exposures in 242 days (34.6 wk, 8 mo) (Table 3)
% Also tested: 100 ppm
% Female ending BW = 207 g (Table 5)
% Run until weekly AUC dosemetrics aren't changing (6 weeks)
ResetDoses
RatPost
BW=0.207; TSTRT=0.0; DMINT=168.0; TSTP=1008.0; CINT=0.1;
CONCLIST=[200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0
0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0
200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0
0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 0.0];
STRTNEXTLIST=[7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0
7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0
7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0 7.0
7.0 17.0 7.0 17.0 7.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check

% Male ending BW = 349 g (Table 5)
% Run until weekly AUC dosemetrics aren't changing (6 weeks)
ResetDoses
RatPost
BW=0.349; TSTRT=0.0; DMINT=168.0; TSTP=1008.0; CINT=0.1;
CONCLIST=[200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0
0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0
200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0
0.0 200.0 0.0 200.0 0.0 200.0 0.0 200.0 0.0 0.0];
STRTNEXTLIST=[7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0
7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0
7.0 17.0 7.0 65.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 65.0 7.0 17.0
7.0 17.0 7.0 17.0 7.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

Albee06_RatDM.m

```
% Albee RR, Spencer PJ, Johnson KA, Bradley GJ, Marable BR. 2006. Lack of trigeminal
%   nerve toxicity in rats exposed to trichloroethylene vapor for 13 weeks.
%   International Journal of Toxicology 25:531-540.
% Fischer-344 rats, 10 male and 10 female
% Inhalation of 800 ppm TCE (NOAEL, POD) for 6 hr/dy, 5 dy/wk, 13 wk
% LOAEL (hearing loss, loss of hair cells) 2500 ppm
% Also tested: 250 ppm
% Body weights are not specified; only that they were not different between groups
%   Rats were 14 wk at receipt, 16 wk (most likely) at study start, and 29 wk at end
% Rats would be about 275 g (M) and 175 g (F) at study start
%   Based on 2018 Charles River catalog
% Estimated 29 wk weight is 400 g (M) and 200 g (F)
%   (4 wk F344 rats, 25 wk on feeding study, Fig 1)
% Rao GN, Morris RW, Seely JC. 2001 Beneficial effects of NTP-2000 diet on growth,
%   survival, and kidney and heart diseases of Fischer 344 rats in chronic studies
%   Toxicological Sciences 63:245-255.
% Female ending BW = 200 g (estimated from Rao et al. 2001)
```

```

% Run for 13 weeks
ResetDoses
RatPost
BW=0.2; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2184.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    il=(2 * iter) - 1;
    CONCLIST(il)=800.0;
    STRTNEXTLIST(il)=6.0;
    CONCLIST(il+1) = 0.0;
    STRTNEXTLIST(il+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    jl=iter*10;
    STRTNEXTLIST(jl)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDms
Output_Check

% Male ending BW = 400 g (estimated from Rao et al. 2001)
% Run for 13 weeks
ResetDoses
RatPost
BW=0.4; TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2184.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    il = (2 * iter) - 1;
    CONCLIST(il)=800.0;
    STRTNEXTLIST(il)=6.0;
    CONCLIST(il+1) = 0.0;
    STRTNEXTLIST(il+1)=18.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    jl=iter*10;
    STRTNEXTLIST(jl)=66.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDms
Output_Check

```

Carney06_RatDM.m

```
% Carney, E.W., Thorsrud, B.A., Dugard, P.H. and Zablony, C.L. 2006. Developmental toxicity
% studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and
% perchloroethylene. Birth Defects Res B Dev Reprod Toxicol 77(5): 405-12.
% Crl:CD rats (Sprague-Dawley), 27 female
% Developmental study to look for cardiac defects
% Inhalation of 600 ppm TCE (NOAEL, POD) for 6 hr/dy, 7 dy/wk, GD6-20 (15 days)
% Also tested: 50, 150 ppm
% Body weights are not specified; According to the Charles River 2018 catalog,
% young adult female SD rats are about 200 g with the high end of the range
% at 225 g. Since these are pregnant, 225 g was chosen.
% Timed pregnant female ending BW = 225 g (estimated from CRL catalog)
ResetDoses
RatPost
BW=0.225; TSTRT=0.0; DMINT=24.0; TSTP=360.0;
CONCLIST=[600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0
0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 600.0 0.0 0.0];
STRTNEXTLIST=[6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0
6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Fisher01_RatDM.m

```
% Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon KL, Goodyear CD, Sudberry GL,
% Warren DA, Latendresse JR, Graeter LJ. 2001. Trichloroethylene, Trichloroacetic
% Acid, and Dichloroacetic Acid: Do They Affect Fetal Rat Heart Development?
% International Journal of Toxicology, 20:257-267.
% Sprague Dawley rats, female, n = 20 litters
% Oral gavage of 500 mg/kg TCE (NOAEL, POD) daily for 10 dy (GD6-15)
% Doses assumed to take 1 minute (0.017 hr)
% Critical Effect: Cardiovascular malformation
% Also tested: 0 mg/kg TCE (2 groups, water or soybean oil); 300 mg/kg TCA, 300 mg/kg DCA
% or 15 mg/kg retinoic acid groups were included in the study
% Males and females were purchased at 9 wk and 200-300 g at study start. They were 11 wk
% at study start
% Rats were approximately 13 wk at study end.
% Maternal body weight gain for TCE- and RA-treated rats during gestation was not
% significantly different from the control soybean oil vehicle; TCE rats had gained
% almost 20 g at study end
% SD females should weigh about 225 g at this age (middle of range), making them 245-250 g
% when pregnant and at the top end of the weight range for this strain (250 g)
% From: Charles River 2018 catalog
ResetDoses
RatPost
BW=0.250; PDOSE=500.0; TCHNG=0.017; DAYS=7.0; TMAX=240.0; DOSEINT=24.0; DMINT=24.0; TSTP=240.0;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check
```

Healy82_RatDM.m

```
% Healy TEJ, Poole TR and Hopper A. 1982. Rat fetal development and maternal exposure to
% trichloroethylene 100 ppm. Br. J. Anaesth. 54, 337-341.
% Wistar origin rats, 32 female (31 control), GD 8-21
% Inhalation of 100 ppm TCE (LOAEL, POD) for 4 hr/dy, 7 dy/wk, 14 dy
% Increased resorptions, decreased fetal weight
% Also tested: 0 ppm
% Body weights were 200-300 g at breeding. These rats are approximately 11 weeks old
% according to the Charles River 2018 catalog. Three weeks later (14 wk) they
% would weigh 210-330 g. Taking the middle value at start (250 g) and adding 20 g
% growth and 30 g of babies, you get 300 g at study end.
ResetDoses
RatPost
BW=0.300; TSTRT=0.0; DMINT=24.0; TSTP=336.0;
```

```

CONCLIST=[100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0
          0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 100.0 0.0 0.0];
STRTNEXTLIST=[4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0
              4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check

```

Isaacson89_RatDM.m

```

% Isaacson LG and Taylor DH. 1989. Maternal exposure to 1,1,2-trichloroethylene affects myelin
%   in the hippocampal formation of the developing rat. Brain Research 488:403-407.
% Sprague-Dawley female (n=6 for each dose group) were given TCE (0, 4.0 or 8.1 mg/d OR 0, 16 or
%   32 mg/kg/d) in drinking water starting 2 weeks prior to breeding until the end of lactation
%   (PD21)
% POD=LOAEL of 16.0 mg/kg/d
% Critical Effect: Decreased myelination
% Used body weight of 0.25 per Emily Lent's email (appears to be what EPA used)
% Females
% Run until daily dosemetrics aren't changing (5 days)
ResetDoses
RatPost
BW=0.25; DRINK=16.0; DMINT=24.0; TSTP=120.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check

```

Jaspers93_RatDM.m

```

% Jaspers RMA, Muijsers H, Lammers JHCM and Kulig BM. 1993. Mid-frequency hearing loss and
%   reduction of acoustic startle responding in rats following trichloroethylene exposure.
%   Neurotoxicology and Teratology, Vol. 15, pp. 407-412.
% Wistar-derived Wag-Rij/MBL strain rats, 12, assumed male but not specified
% Inhalation of 1500 ppm TCE (NOAEL, POD) for 18 hr/dy, 5 dy/wk, 3 wk
% LOAEL (auditory threshold shift) 3000 ppm
% Also tested: 0 ppm
% BW = 180 +/- 10 g (about 11 weeks old) at receipt
%   Figure 1 shows BW change over time; At last week of exposure, rats weighed
%   ~250, ~240, ~225 for exposure groups 0, 1500, 3000 ppm, respectively. BW
%   differences were significant. 240 g was used for the NOAEL POD simulation
ResetDoses
RatPost
BW=0.240; TSTRT=0.0; DMINT=168.0; TSTP=504.0; CINT=0.1;
CONCLIST=[1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0
          0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0 1500.0 0.0
          0.0];
STRTNEXTLIST=[18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 54.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0
              18.0 54.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 6.0 18.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMs
Output_Check

```

Kumar00a_01a_RatDM.m

```
% Kumar P, Prasad AK, Dutta KK. 2000. Steroidogenic alterations in testes and sera of
% rats exposed to trichloroethylene (TCE) by inhalation. Human & Experimental
% Toxicology (2000) 19, 117-121
% Wistar origin rats, 12-13 male
% Inhalation of 376 ppm TCE (LOAEL, POD) for 4 hr/dy, 5 dy/wk, 12 or 24 wk
% Critical effect: Decreased sperm count & motility
% Also tested: 0 ppm
% A smaller rat would inhale a relatively higher total amount of TCE. Therefore
% the simulation will model the last week of the 12 wk exposure.
% BW at receipt: 50 +/- 5 g
% The Charles River Laboratory 2018 catalog indicates that these rats would be just
% weaned and about 3 weeks old
% Rats were bred in house; they would not have needed quarantine and there was no mention
% of acclimation. The rats would be 15 weeks of age
% The rats would be approximately 500 g according to Tordoff et al. 2008
% Tordoff MG, Alarcon LK, Lawler MP. 2008. Preferences of 14 rat strains for
% 17 taste compounds. Physiol Behav. 2008 October 20; 95(3): 308-332.

% Kumar P, Prasad AK, Maji BK, Mani U, Dutta KK. 2001. Hepatotoxic alterations induced
% by inhalation of trichloroethylene (TCE) in rats. Biomedical and Environmental
% Sciences 14, 325-332.
% Wistar rats, 6 male
% Inhalation of 376 +/- 1.76 ppm TCE (LOAEL, POD) for 4 hr/dy, 5 dy/wk,
% 8, 12, or 24 wk
% Critical effect: Liver weight (significant increase but data not shown), enlarged
% fatty hepatocytes (via histology but no statistics); All effects evident at 8 wk
% and more progressive at 12 and 24 wk
% Also tested: 0 ppm

% Simulating the last week of the 8 wk exposure; Younger rats will inhale comparatively
% more TCE than larger due to higher respiratory rates
% BW was 130 +/- 10 g at study start; Animals bred in-house, so no quarantine was
% necessary; Acclimation was not mentioned in the study
% Rats were about 5 weeks at study start (Charles River Laboratories 2018 catalog)
% Rats would be 13 weeks at study end and approximately 400 g according to Tordoff et al.
% Tordoff MG, Alarcon LK, Lawler MP. 2008. Preferences of 14 rat strains for
% 17 taste compounds. Physiol Behav. 2008 October 20; 95(3): 308-332.

% Ending BW = 530 g
% Run until weekly AUC dosemetrics aren't changing (7 weeks)
ResetDoses
RatPost
BW=0.5; TSTRT=0.0; DMINT=168.0; TSTP=1176.0; CINT=0.1;
CONCLIST=[376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0
0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0
376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0
0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0 376.0 0.0
376.0 0.0 0.0];
STRTNEXTLIST=[4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 68.0 4.0 20.0 4.0 20.0 4.0 20.0
4.0 68.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 68.0 4.0 20.0 4.0 20.0
4.0 20.0 4.0 68.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 68.0 4.0 20.0 4.0 20.0
4.0 20.0 4.0 20.0 4.0 68.0 4.0 20.0 4.0 20.0 4.0 20.0 4.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

Manson84_RatDM.m

```
% Manson JM, Murphy M, Richdale N, Smith MK. 1984. Effects of oral exposure to
% trichloroethylene on female reproductive function. Toxicology. 32: 229-42.
% Long-Evans rats, female, n = 23
% Oral gavage of 100 mg/kg TCE (NOAEL, POD) 5 dy/wk for 3 wk, 7 dy/wk for 3 wk
% Doses assumed to take 1 minute (0.017 hr)
% Simulating last week of gestation (7 dy/wk)
% LOAEL: 1000 mg/kg-dy
% Critical Effect: Neonatal+Postnatal death
% Also tested: 0, 10 mg/kg-dy TCE (corn oil)
% Males and females were purchased at 80-100 dy. There was a 2 wk quarantine.
% Body weights in the 100 mg/kg-dy group on GD22 were 405 +/- 7.4 g (Table 1).
% NOTE: BW were significantly decreased in the 1000 mg/kg-dy group.
% Run until weekly AUC dosemetrics aren't changing (3 weeks)
ResetDoses
RatPost
BW=0.405; PDOSE=100.0; TCHNG=0.017; DAYS=7.0; TMAX=504.0; DOSEINT=24.0; DMINT=168.0;
TSTP=504.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

Schwetz75_RatDM.m

```
% Schwetz BA, Leong BKJ, Gehring PJ. 1975. The effect of maternally inhaled
% trichloroethylene, perchloroethylene, methyl chloroform, and methylene
% chloride on embryonal and fetal development in mice and rats. Toxicology
% and Applied Pharmacology. 32:84-96.
% Sprague-Dawley female rats, n = 18
% Inhalation of 306 ppm TCE (NOAEL, POD) for 7 hr/dy, GD 6-15 (10 days)
% No effect on fetal development
% Tables 5-6
% Also tested: 0 ppm, also tested mice (see additional m file)
% Rats were ~250 g prior to pregnancy; Rats exposed to TCE weighed 4-5% less than
% controls (statistically significant; not really biologically significant)
% Ending rat weights are not given but liver weight was 13.7 +/- 1.4 g in TCE group and
% relative liver weight was 0.037 +/- 0.004 g LW/g BW (Table 2)
% Therefore BW was ~370 g in this group
ResetDoses
RatPost
BW=0.370; TSTRT=0.0; DMINT=24.0; TSTP=240.0;
CONCLIST=[306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0 0.0 306.0
0.0 306.0 0.0 0.0];
STRTNEXTLIST=[7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0 7.0 17.0
7.0 100.0];
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

Wu07_RatDM.m

```
% Wu KL, Berger T. 2007. Trichloroethylene metabolism in the rat ovary reduces oocyte
%      fertilizability. Chemico-Biological Interactions 170 (2007) 20-30.
% Simonson albino rats, a Sprague-Dawley derived strain, female, n = 12-20
% 0.45% in drinking water or 66 mg/kg-dy TCE (LOAEL, POD) for 2 wk
% Critical Effect: In vitro fertilization by oocytes from exposed females less successful
% Also tested: 0 mg/kg-dy (3% Tween vehicle control) in drinking
%      water for 4 or 5 dy or 2 wk
% Simulation is for whole study
% Female rats were between 28 and 45 days old at receipt (using 37 dy); Assuming a 2 wk
%      acclimation; Therefore the rats were ~51 dy at start and 65 dy (~9 wk) at finish
%      (in vitro fertilization collection)
% BW was not mentioned in the results but no effect was seen on liver wt
% Growth data on Simonson albino rats were not found; Sprague-Dawley females are
%      approximately 200 g at that age (mid-range)
%      Charles River Laboratories 2018 catalog
```

```
ResetDoses
RatPost
BW=0.200; DRINK=66.0; DMINT=24.0; TSTP=336.0;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

Zenick84_RatDM.m

```
% Zenick H, Blackburn K, Hope E. Richdale N, and Smith MK. 1984. Effects of trichloroethylene
%      exposure on male reproductive function in rats. Toxicology 31:237-250.
% Long-Evans hooded male rats ~100 days of age at dosing (10 males/group)
% Oral gavage of TCE (0, 10, 100 or 1000 mg/kg BW) in 0.5 mL corn oil, 30-45 minutes before
%      dark cycle, daily for 5 d/wk for 6 weeks
%      Doses assumed to take 1 minute (0.017 hr)
% POD=NOAEL of 100 mg/kg
% Critical Effect: Temporarily impaired copulation
% Baseline body weights were 402, 392, 395 and 397 g for the 4 dose groups (average of 3 groups
%      getting TCE is 394.6667 g -- average of 4 groups is 396.5 g)
% Run for 6 weeks (length of study)
ResetDoses
RatPost
BW=0.39467; PDOSE=100.0; TCHNG=0.017; DAYS=5.0; TMAX=1010.0; DOSEINT=24.0; DMINT=168.0;
TSTP=1008.0; CINT=0.1;
start @NoCallback
plot(_t, _cart);
i = i + 1;
SaveDMS
Output_Check
```

APPENDIX F: M FILES FOR HUMAN EQUIVALENT CONCENTRATIONS

The following are M files for generating the HECs to correspond to the mouse and rat dose metrics. Values for “Target” in FitHumanDMs.m are the mouse or rat dose metric values from running the RunDMs.m file.

Female_Fit_DMs_ContInh.m

```
% Fit female human continuous inhalation doses to animal internal dosemetrics
load @format=model @file=EPA_2011_TCE_REV
Init
CheckOutputMax=[]; CheckOutputMin=[]; DMOOutput=[]; Params=[]; i=0;
% Set parameters for simulations
FitDoses = []; j = 0; Sex = 'Female';
ResetDoses
FemalePost
ConcFit = 'ContInh';
CONCLIST=[10.0 0.0]; STRTNEXTLIST=[10000.0]; TSTRT=0.0; DMINT=24.0; TSTP=1344.0; CINT=0.1;
FitHumanHECs
% Save the results of the dose fitting
save FitDoses @file='FitDoses_Female_ContInh_HECs.txt' @format=ascii
save CheckOutputMax @file='CheckOutputMax_FemaleContHECs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_FemaleContHECs.txt' @format=ascii
save Params @file='Params_FemaleContHECs.txt' @format=ascii
```

Female_Fit_DMs_OccInh.m

```
% Fit female human occupational (8 hr/d, 5 d/w) inhalation doses to animal internal dosemetrics
load @format=model @file=EPA_2011_TCE_REV
Init
CheckOutputMax=[]; CheckOutputMin=[]; DMOOutput=[]; Params=[]; i=0;
% Set parameters for simulations
FitDoses = []; j = 0; Sex = 'Female';
ResetDoses
FemalePost
ConcFit = 'OccInh';
TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2352.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    i1=(2 * iter) - 1;
    CONCLIST(i1)=10.0;
    STRTNEXTLIST(i1)=8.0;
    CONCLIST(i1+1) = 0.0;
    STRTNEXTLIST(i1+1)=16.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j1=iter*10;
    STRTNEXTLIST(j1)=64.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
FitHumanHECs
% Save the results of the dose fitting
save FitDoses @file='FitDoses_Female_OccInh_HECs.txt' @format=ascii
save CheckOutputMax @file='CheckOutputMax_FemaleOccHECs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_FemaleOccHECs.txt' @format=ascii
save Params @file='Params_FemaleOccHECs.txt' @format=ascii
```

Male_Fit_DMs_ContInh.m

```
% Fit male human continuous inhalation doses to animal internal dosemetrics
load @format=model @file=EPA_2011_TCE_REV
Init
CheckOutputMax=[]; CheckOutputMin=[]; DMOutput=[]; Params=[]; i=0;
% Set parameters for simulations
FitDoses = []; j = 0; Sex = 'Male ';
ResetDoses
MalePost
ConcFit = 'ContInh';
CONCLIST=[10.0 0.0]; STRTNEXTLIST=[10000.0]; TSTRT=0.0; DMINT=24.0; TSTP=1344.0; CINT=0.1;
FitHumanHECs
% Save the results of the dose fitting
save FitDoses @file='FitDoses_Male_ContInh_HECs.txt' @format=ascii
save CheckOutputMax @file='CheckOutputMax_MaleContHECs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_MaleContHECs.txt' @format=ascii
save Params @file='Params_MaleContHECs.txt' @format=ascii
```

Male_Fit_DMs_OccInh.m

```
% Fit male human occupational (8 hr/d, 5 d/w) inhalation doses to animal internal dosemetrics
load @format=model @file= EPA_2011_TCE_REV
Init
CheckOutputMax=[]; CheckOutputMin=[]; DMOutput=[]; Params=[]; i=0;
% Set parameters for simulations
FitDoses = []; j = 0; Sex = 'Male ';
ResetDoses
MalePost
ConcFit = 'OccInh ';
TSTRT=0.0; DAYS=5.0; DMINT=168.0; TSTP=2352.0; CINT=0.1;
NumWks = TSTP / 24.0 / 7.0;
% Upper limit for iterations is the number of days exposed per week (DAYS) times the number of
% weeks (NumWks)
for iter = [1 : floor(DAYS*NumWks)]
    i1=(2 * iter) - 1;
    CONCLIST(i1)=10.0;
    STRTNEXTLIST(i1)=8.0;
    CONCLIST(i1+1) = 0.0;
    STRTNEXTLIST(i1+1)=16.0;
end
% Upper limit for iterations is the number of weeks (NumWks) minus 1
for iter = [1 : floor(NumWks-1)]
    j1=iter*10;
    STRTNEXTLIST(j1)=64.0;
end
% Indices are ((2 times (the number of days exposed per week (DAYS) times the number of weeks
% (NumWks))) plus 1)
% AND (2 times (the number of days exposed per week (DAYS) times the number of weeks (NumWks)))
CONCLIST((2*floor(DAYS*NumWks))+1) = 0.0;
STRTNEXTLIST(2*floor(DAYS*NumWks))=100.0;
FitHumanHECs
% Save the results of the dose fitting
save FitDoses @file='FitDoses_Male_OccInh_HECs.txt' @format=ascii
save CheckOutputMax @file='CheckOutputMax_MaleOccHECs.txt' @format=ascii
save CheckOutputMin @file='CheckOutputMin_MaleOccHECs.txt' @format=ascii
save Params @file='Params_MaleOccHECs.txt' @format=ascii
```

FitHumanHECs.m

```
% Fits to all dose metrics (for BMDLs, didn't have all of the dose metrics)

% Blossom 2017 -- Mouse
% max(_cart)
    TargetParam='MaxCART          '; Target=0.002102; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=0.05045; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=1.306; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=1.034; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Cosby 1992 -- Mouse
% max(_cart)
    TargetParam='MaxCART          '; Target=14.38; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=10.04; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=79.98; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
```

```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=79.79; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% George 1985 -- Mouse
% max(_cart)
    TargetParam='MaxCART'; Target=3.205; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=26.28; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=300.7; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
%% Commented out because metabolism was saturated and dose would be larger than 30,000 ppm
%% TotOxMetBW34DM
% TargetParam='TotOxMetBW34DM'; Target=300.1; Tolerance=Target/1000000.0;
% start @NoCallback
% Fit_Dose
% FitDoses(i,10) = CONCLIST(1);
% FitDoses(i,11) = Target;
% FitDoses(i,12) = TOTOXMETBW34DM;
% Output_Check
% save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Gilbert 2014 -- Mouse
% max(_cart)
    TargetParam='MaxCART'; Target=0.002429; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=0.05831; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=1.508; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=1.507; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Griffin 2000 -- Mouse
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=8.1; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Kaneko 2000 -- Mouse
% max(_cart)
    TargetParam='MaxCART'; Target=17.91; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=60.62; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=135.1; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=134.7; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% Kjellstrand 1983b -- Mouse -- Female
% max(_cart)
    TargetParam='MaxCART          '; Target=0.7902; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=18.96; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=146.4; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=146.3; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_cliv)
    TargetParam='MaxCLiv          '; Target=0.3001; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,13) = CONCLIST(1);
    FitDoses(i,14) = Target;
    FitDoses(i,15) = max(_cliv);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCLivDM
    TargetParam='AUCCLivDM        '; Target=7.202; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,16) = CONCLIST(1);
    FitDoses(i,17) = Target;
    FitDoses(i,18) = AUCCLIVDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=41.62; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% Kjellstrand 1983b -- Mouse -- Male
% max(_cart)
    TargetParam='MaxCART          '; Target=0.7885; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=18.92; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=146.7; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=146.6; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_cliv)
    TargetParam='MaxCLiv          '; Target=0.2973; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,13) = CONCLIST(1);
    FitDoses(i,14) = Target;
    FitDoses(i,15) = max(_cliv);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCLivDM
    TargetParam='AUCCLivDM        '; Target=7.134; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,16) = CONCLIST(1);
    FitDoses(i,17) = Target;
    FitDoses(i,18) = AUCCLIVDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=41.60; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% Land 1981 -- Mouse
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=89.2; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Ramdhan 2010 -- Mouse
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=105.8; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Sanders 1982 -- Mouse -- Female
% max(_cart)
    TargetParam='MaxCArt'; Target=0.01313; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=0.3151; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=7.868; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=7.861; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% Sanders 1982 -- Mouse -- Male
% max(_cart)
    TargetParam='MaxCART          '; Target=0.01318; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=0.3163; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=8.295; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=8.288; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Schwetz 1975 -- Mouse
% max(_cart)
    TargetParam='MaxCART          '; Target=9.794; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=67.89; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=193.4; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

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```

%% Commented out because metabolism was saturated and dose would be larger than 30,000 ppm
%% TotOxMetBW34DM
%   TargetParam='TotOxMetBW34DM';   Target=193.0;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,10) = CONCLIST(1);
%   FitDoses(i,11) = Target;
%   FitDoses(i,12) = TOTOXMETBW34DM;
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Adams 1951 -- Rat -- Female
% max(_cart)
%   TargetParam='MaxCART           ';   Target=6.034;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   i = i + 1;
%   FitDoses(i,1) = CONCLIST(1);
%   FitDoses(i,2) = Target;
%   FitDoses(i,3) = max(_cart);
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
%   TargetParam='AUCCBldDM         ';   Target=28.36;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,4) = CONCLIST(1);
%   FitDoses(i,5) = Target;
%   FitDoses(i,6) = AUCCBLDDM;
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
%   TargetParam='TotMetabBW34DM';   Target=56.65;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,7) = CONCLIST(1);
%   FitDoses(i,8) = Target;
%   FitDoses(i,9) = TOTMETABBW34DM;
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
%   TargetParam='TotOxMetBW34DM';   Target=56.59;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,10) = CONCLIST(1);
%   FitDoses(i,11) = Target;
%   FitDoses(i,12) = TOTOXMETBW34DM;
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_cliv)
%   TargetParam='MaxCLiv           ';   Target=4.331;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,13) = CONCLIST(1);
%   FitDoses(i,14) = Target;
%   FitDoses(i,15) = max(_cliv);
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCLivDM
%   TargetParam='AUCCLivDM         ';   Target=17.77;   Tolerance=Target/1000000.0;
%   start @NoCallback
%   Fit_Dose
%   FitDoses(i,16) = CONCLIST(1);
%   FitDoses(i,17) = Target;
%   FitDoses(i,18) = AUCCLIVDM;
%   Output_Check
%   save FitDoses @file='FitDoses_HECs.txt' @format=ascii

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```

% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=53.07; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_ckid)
    TargetParam='MaxCKid'; Target=7.369; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,22) = CONCLIST(1);
    FitDoses(i,23) = Target;
    FitDoses(i,24) = max(_ckid);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCKidDM
    TargetParam='AUCCKidDM'; Target=34.62; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,25) = CONCLIST(1);
    FitDoses(i,26) = Target;
    FitDoses(i,27) = AUCCKIDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetKidBW34DM
    TargetParam='AMetKidBW34DM'; Target=0.04146; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,28) = CONCLIST(1);
    FitDoses(i,29) = Target;
    FitDoses(i,30) = AMETKIDBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Adams 1951 -- Rat -- Male
% max(_cart)
    TargetParam='MaxCART'; Target=5.360; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=25.73; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=58.92; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

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```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=58.85; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_cliv)
    TargetParam='MaxCLiv'; Target=3.042; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,13) = CONCLIST(1);
    FitDoses(i,14) = Target;
    FitDoses(i,15) = max(_cliv);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCLivDM
    TargetParam='AUCCLivDM'; Target=12.76; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,16) = CONCLIST(1);
    FitDoses(i,17) = Target;
    FitDoses(i,18) = AUCCLIVDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=54.86; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_ckid)
    TargetParam='MaxCKid'; Target=6.545; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,22) = CONCLIST(1);
    FitDoses(i,23) = Target;
    FitDoses(i,24) = max(_ckid);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCKidDM
    TargetParam='AUCCKidDM'; Target=31.41; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,25) = CONCLIST(1);
    FitDoses(i,26) = Target;
    FitDoses(i,27) = AUCCKIDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetKidBW34DM
    TargetParam='AMetKidBW34DM'; Target=0.04805; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,28) = CONCLIST(1);
    FitDoses(i,29) = Target;
    FitDoses(i,30) = AMETKIDBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% Albee 2006 -- Rat -- Female
% max(_cart)
    TargetParam='MaxCART          '; Target=55.80; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=222.8; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=95.52; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=95.07; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Albee 2006 -- Rat -- Male
% max(_cart)
    TargetParam='MaxCART          '; Target=50.59; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=200.4; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=112.9; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=112.5; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Arito 1994 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=0.410; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Bushnell 1997 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=35.6; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Carney 2006 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=37.54; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=203.5; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=124.0; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=123.5; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Crofton 1997 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=70.9; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Fisher 2001 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=124.1; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=250.1; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=170.2; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% TotOxMetBW34DM
    if (Sex == 'Male ')
        TargetParam='TotOxMetBW34DM'; Target=169.4; Tolerance=Target/1000000.0;
        start @NoCallback
        Fit_Dose
        FitDoses(i,10) = CONCLIST(1);
        FitDoses(i,11) = Target;
        FitDoses(i,12) = TOTOXMETBW34DM;
        Output_Check
        save FitDoses @file='FitDoses_HECs.txt' @format=ascii
    end
end

```

```

% Healy 1982 -- Rat
% max(_cart)
    TargetParam='MaxCART          '; Target=2.200; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=8.918; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=25.39; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=25.35; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Isaacson 1989 -- Rat
% max(_cart)
    TargetParam='MaxCART          '; Target=0.01990; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM        '; Target=0.4777; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=11.05; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=11.04; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Jaspers 1993 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=132.5; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=1635.0; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=241.2; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
%% Commented out because metabolism was saturated and dose would be larger than 30,000 ppm
%% TotOxMetBW34DM
% TargetParam='TotOxMetBW34DM'; Target=237.7; Tolerance=Target/1000000.0;
% start @NoCallback
% Fit_Dose
% FitDoses(i,10) = CONCLIST(1);
% FitDoses(i,11) = Target;
% FitDoses(i,12) = TOTOXMETBW34DM;
% Output_Check
% save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Kumar 2000a & Kumar 2001a -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=13.25; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=34.88; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=57.29; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=57.20; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% max(_cliv)
    TargetParam='MaxCLiv'; Target=13.26; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,13) = CONCLIST(1);
    FitDoses(i,14) = Target;
    FitDoses(i,15) = max(_cliv);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCLivDM
    TargetParam='AUCCLivDM'; Target=27.56; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,16) = CONCLIST(1);
    FitDoses(i,17) = Target;
    FitDoses(i,18) = AUCCLIVDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=53.85; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Maltoni 1988 -- Rat
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=51.03; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Manson 1984 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=23.13; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% AUCCBldDM
    TargetParam='AUCCBldDM      '; Target=20.12; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=66.10; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=65.98; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Narotsky 1995 -- Rat
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=11.8; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Schwetz 1975 -- Rat
% max(_cart)
    TargetParam='MaxCART      '; Target=11.35; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM      '; Target=71.04; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=112.9; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=112.7; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Woolhiser 2006 -- Rat -- Immuno
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=42.7; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Woolhiser 2006 -- Rat -- kidney
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=40.97; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Woolhiser 2006 -- Rat -- liver
% AMetLiv1BW34DM
    TargetParam='AMetLiv1BW34DM'; Target=42.51; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,19) = CONCLIST(1);
    FitDoses(i,20) = Target;
    FitDoses(i,21) = AMETLIV1BW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Wu 2007 -- Rat
% max(_cart)
    TargetParam='MaxCart'; Target=0.09164; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=2.199; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

```

% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=42.90; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=42.85; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

% Zenick 1984 -- Rat
% max(_cart)
    TargetParam='MaxCART'; Target=23.06; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    i = i + 1;
    FitDoses(i,1) = CONCLIST(1);
    FitDoses(i,2) = Target;
    FitDoses(i,3) = max(_cart);
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% AUCCBldDM
    TargetParam='AUCCBldDM'; Target=14.30; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,4) = CONCLIST(1);
    FitDoses(i,5) = Target;
    FitDoses(i,6) = AUCCBLDDM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotMetabBW34DM
    TargetParam='TotMetabBW34DM'; Target=46.89; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,7) = CONCLIST(1);
    FitDoses(i,8) = Target;
    FitDoses(i,9) = TOTMETABBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii
% TotOxMetBW34DM
    TargetParam='TotOxMetBW34DM'; Target=46.81; Tolerance=Target/1000000.0;
    start @NoCallback
    Fit_Dose
    FitDoses(i,10) = CONCLIST(1);
    FitDoses(i,11) = Target;
    FitDoses(i,12) = TOTOXMETBW34DM;
    Output_Check
    save FitDoses @file='FitDoses_HECs.txt' @format=ascii

```

Fit_Dose.m

```
% Dose fitting algorithm -- uses ratios

if (TargetParam == 'MaxCART      ')
    EndPt = max(_cart);
else
    if (TargetParam == 'AUCCBLDDM  ')
        EndPt = AUCCBLDDM;
    else
        if (TargetParam == 'MaxCLiv      ')
            EndPt = max(_cliv);
        else
            if (TargetParam == 'AUCCLivDM      ')
                EndPt = AUCCLIVDM;
            else
                if (TargetParam == 'TotMetabBW34DM')
                    EndPt = TOTMETABBW34DM;
                else
                    if (TargetParam == 'TotOxMetBW34DM')
                        EndPt = TOTOXMETBW34DM;
                    else
                        if (TargetParam == 'AMetLiv1BW34DM')
                            EndPt = AMETLIV1BW34DM;
                        else
                            if (TargetParam == 'MaxCKid      ')
                                EndPt = max(_ckid);
                            else
                                if (TargetParam == 'AUCCKidDM      ')
                                    EndPt = AUCCKIDDM;
                                else
                                    if (TargetParam == 'AMetKidBW34DM ')
                                        EndPt = AMETKIDBW34DM;
                                    end
                                end
                            end
                        end
                    end
                end
            end
        end
    end
end

NumAttempt = 0;
while abs(EndPt-Target) > Tolerance
    if (ConcFit == 'ContInh')
        CONCLIST(1) = CONCLIST(1) * (Target / EndPt);
    else
        TmpConc = CONCLIST(1) * (Target / EndPt);

%       Upper limit for iterations is the number of days exposed per week (DAYS) times the
%       number of weeks (NumWks)
        for iter = [1 : floor(DAYS*NumWks)]
            i1 = (2 * iter) - 1;
            CONCLIST(i1) = TmpConc;
        end
    end

    start @NoCallback
    NumAttempt = NumAttempt + 1;
    CONCLIST(1)

    if (TargetParam == 'MaxCART      ')
        max(_cart)
        EndPt = max(_cart);
    else
        if (TargetParam == 'AUCCBLDDM  ')
            AUCCBLDDM
            EndPt = AUCCBLDDM;
        else
```

```

        if (TargetParam == 'MaxCLiv      ')
            max(_cliv)
            EndPt = max(_cliv);
        else
            if (TargetParam == 'AUCCLivDM      ')
                AUCCLIVDM
                EndPt = AUCCLIVDM;
            else
                if (TargetParam == 'TotMetabBW34DM')
                    TOTMETABBW34DM
                    EndPt = TOTMETABBW34DM;
                else
                    if (TargetParam == 'TotOxMetBW34DM')
                        TOTOXMETBW34DM
                        EndPt = TOTOXMETBW34DM;
                    else
                        if (TargetParam == 'AMetLiv1BW34DM')
                            AMETLIV1BW34DM
                            EndPt = AMETLIV1BW34DM;
                        else
                            if (TargetParam == 'MaxCKid      ')
                                max(_ckid)
                                EndPt = max(_ckid);
                            else
                                if (TargetParam == 'AUCCKidDM      ')
                                    AUCCKIDDM
                                    EndPt = AUCCKIDDM;
                                else
                                    if (TargetParam == 'AMetKidBW34DM ')
                                        AMETKIDBW34DM
                                        EndPt = AMETKIDBW34DM;
                                    end
                                end
                            end
                        end
                    end
                end
            end
        end
    end
end

if (NumAttempt > 15)
    Fit_Dose_Alt
    break;
end
end

```

Fit_Dose_Alt.m

```

% Alternate dose fitting algorithm -- uses interval halving

% Find doses that bound the target endpoint value
CurrentConc = CONCLIST(1);
if (EndPt < Target)
    while EndPt < Target
        PLowConc = CurrentConc;
        CurrentConc = 1.1 * CurrentConc;

        if (ConcFit == 'ContInh')
            CONCLIST(1) = CurrentConc;
        else
            % Upper limit for iterations is the number of days exposed per week (DAYS) times the
            % number of weeks (NumWks)
            for iter = [1 : floor(DAYS*NumWks)]
                i1 = (2 * iter) - 1;
                CONCLIST(i1) = CurrentConc;
            end
        end
    end
end

```


LIST OF ABBREVIATIONS AND ACRONYMS

AFCEC	Air Force Civil Engineer Center
AFRL	Air Force Research Laboratory
AUC	area under the curve
BMD	benchmark dose
BMDL	lower limit of the benchmark dose
DoD	Department of Defense
DW	drinking water
Gav	gavage
HEC	human equivalent concentration
Inh	inhalation
IRIS	Integrated Risk Information System
LOAEL	lowest observed adverse effect level
mg-h/L/d	milligrams-hour per liter per day
mg/kg/day	milligrams per kilogram of body weight per day
mg/kg ^{0.75} /d	milligrams per kilogram of body weight to the 0.75 power per day
mg/L	milligrams per liter
NASEM	National Academies of Sciences, Engineering, and Medicine
NOAEL	no observed adverse effect level
OASD EI&E	Office of the Assistant Secretary of Defense (Energy, Installations and Environment)
OEL	occupational exposure limit
PBPK	physiologically-based pharmacokinetic
POD	point of departure
ppm	parts per million
RfC	reference concentration
TCE	trichloroethylene
TSTC	TriService Toxicology Consortium
USEPA	United States Environmental Protection Agency