



Draft Risk Evaluation for 1,1,2-Trichloroethane

Supplemental File Document:

Draft Evaluation of PBPK Model for 1,1,2-Trichloroethane

CASRN 79-00-5

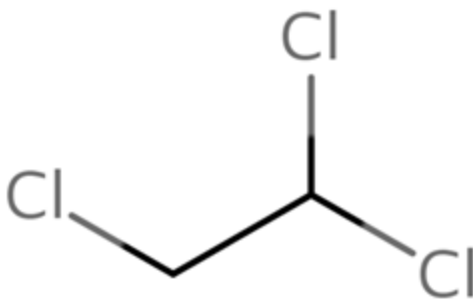


TABLE OF CONTENTS

1	BACKGROUND INFORMATION	4
1.1	Physicochemical Properties	4
1.2	Absorption, Distribution, Metabolism, and Excretion (ADME) and Pharmacodynamic Considerations	4
1.3	Toxicity of 1,1,2-Trichloroethane	5
1.3.1	Summary of 1,1,2-Trichloroethane Toxicity in Animals	5
1.4	1,1,2-Trichloroethane PBPK Models	7
1.5	Model Data	7
2	MODEL PURPOSE	9
3	MATERIALS AND METHODS	10
3.1	Modeling Strategy	10
3.2	Summary of Data for Model Development and Evaluation	10
3.3	Model Development and Structure	12
3.4	Model Parameters	13
3.5	Model Equations	17
3.6	Model Simulations	20
3.7	Software	21
4	MODEL RESULTS	22
4.1	Model Evaluation	22
4.2	Sensitivity, Uncertainty, and Variability Analyses	29
4.2.1	Sensitivity Analysis Results	30
4.3	Model Applicability	43
5	DISCUSSION AND CONCLUSIONS	47
6	LIST OF ELECTRONIC FILES AND SUPPORTING DOCUMENTS	49
	REFERENCES	50

LIST OF TABLES

Table 3-1.	Physiological and Biochemical Parameters for the 1,1,2-Trichloroethane PBPK Model	15
Table 3-2.	State Variables in 1,1,2-Trichloroethane PBPK Model	19
Table 3-3.	Dosing Scenarios for Model Validation Against Data	20
Table 3-4.	Dosing Scenarios for Route-to-Route Extrapolation Studies	20
Table 4-1.	RMSLE and R² Values for Evaluating PBPK Model Goodness of Fit Against Data	27
Table 4-2.	Route-to-route Extrapolation Results	28
Table 4-3.	Locally Influential Parameters for Each Endpoint as They Apply to Applicable Dose Metrics and Grouped by Route and Dose	32
Table 4-4.	Normalized Local Sensitivity Analysis Indices for Developmental, Immunotoxicology, and Acute Neurotoxic Endpoints	36
Table 4-5.	Normalized Local Sensitivity Analysis Indices for the Cancer Endpoint	37
Table 4-6.	Parameter Names and Descriptions – Reference List	38

LIST OF FIGURES

Figure 3-1.	PBPK Model Diagram for Rat and Mouse Adapted from Sapphire Group (2002)	13
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June 2026

77	Figure 4-1. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats	
78	Following Oral Water Gavage.	23
79	Figure 4-2. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats	
80	Following Corn Oil Oral Gavage (Single Day).	23
81	Figure 4-3. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats	
82	Following Corn Oil Oral Gavage (Total Exposure).	24
83	Figure 4-4. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats	
84	Following 100 ppm Inhalation Exposure.	24
85	Figure 4-5. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice Following	
86	100 ppm Inhalation Exposure (Total Duration and Week 4 Only).	25
87	Figure 4-6. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Rats Following	
88	100 ppm Inhalation Exposure (Total Duration and Week 4 Only).	25
89	Figure 4-7. Predicted vs. Observed Blood Concentrations for Mice and Rats Following Inhalation and	
90	Oral Doses of 1,1,2-Trichloroethane.	26
91	Figure 4-8. Predicted vs. Observed Blood Concentrations for Mice and Rats Following Inhalation and	
92	Oral Doses of 1,1,2-Trichloroethane, Grouped by Route of Exposure.	27
93	Figure 4-9. Local Sensitivity Analysis Results for the Cancer Endpoint in Rats (A) and Mice (B) for	
94	Dose Metric Amount Metabolized in the Liver per Liter Liver: Oral and Inhalation	
95	Routes of Exposure.	34
96	Figure 4-10. Local Sensitivity Analysis Results for the Developmental Endpoint (A) and the	
97	Immunotoxicity Endpoint (B) for the Dose Metric Amount Metabolized in the Liver per	
98	Liter Liver: Oral and Inhalation Routes of Exposure.	35
99	Figure 4-11. Local Sensitivity Analysis Results Acute Neurotoxicity Endpoints for Dose Metric of	
100	Maximum Brain Concentration (mg/L): Oral and Inhalation Routes of Exposure.	36
101	Figure 4-12. Local Sensitivity Coefficients for the Oral 1,1,2-Trichloroethane Model for Various Doses	
102	and Dose Metrics.	40
103	Figure 4-13. Local Sensitivity Coefficients for the Inhalation 1,1,2-Trichloroethane Model for Various	
104	Doses and Dose Metrics.	41
105	Figure 4-14. Local Sensitivity Coefficients for the Oral 1,1,2-Trichloroethane Model for Rats:	
106	Comparing Corn Oil and Water Vehicles.	42
107	Figure 4-15. Local Sensitivity Coefficients for the Oral 1,1,2-Trichloroethane Model for Mice:	
108	Comparing Corn Oil and Water Vehicles.	43
109	Figure 4-16. Internal Dose (amount metabolized in the liver) as Function of External Dose.	45
110	Figure 4-17. Internal Dose (maximum brain and blood concentrations) as Function of External Dose. .	46
111		

1 BACKGROUND INFORMATION

1.1 Physicochemical Properties

1,1,2-Trichloroethane is a colorless liquid. The molecular weight is 133.41 g/mol. The solubility in water at 20 degrees Celsius is 4,400 mg/L. The log Kow value (where Kow is the octanol:water partition coefficient) is 2.42. Henry's law constant is $9.1 \times 10^{-4} \text{ atm/m}^3\text{-mol}$.

1.2 Absorption, Distribution, Metabolism, and Excretion (ADME) and Pharmacodynamic Considerations

Absorption

Human studies suggest that 1,1,2-trichloroethane is rapidly absorbed following inhalation. In one experiment, 2-3% of the dose was exhaled within 12 seconds after the subject inhaled a single breath of radiolabeled 1,1,2-trichloroethane and held their breath for 40 seconds. More than 90% of the inhaled dose remained in the body after 50 minutes, indicating extensive systemic uptake ([Morgan et al., 1972, 1970](#)). This high degree of absorption is consistent with the calculated human blood: air PC of 44.2. [Gargas et al. \(1989\)](#) reports a similar measured value of 35.7. Animal studies support these findings. Rats and mice exposed to 100 ppm 1,1,2-trichloroethane for 6 hours/day, 5 days/week over 4 weeks had measurable 1,1,2-trichloroethane concentrations in blood after inhalation exposure ([Sapphire Group, 2002](#)). Reported blood: air PCs include 58.0 in rats ([Gargas et al., 1989](#)). In one study, maximum blood concentrations after 4 weeks were 2.2 ug/mL in rats and 2.1 ug/mL in mice, although data are limited by small sample sizes and restricted time points ([Battelle, 2001](#)).

Oral administration studies demonstrate effective uptake in the GI tract from this route of exposure. Rats given oral gavage doses of 92 mg/kg/d in corn oil or 1.7 mg/kg/d in water for 5 days, and mice given 390 mg/kg/d in corn oil or 10 mg/kg/d in water exhibited the following blood concentrations: peak blood levels in rats were observed on day 1 (up to 17 ug/g) and between days 3 and 5 for mice (8.5-25 ug/g) ([Sapphire Group, 2002](#); [Battelle, 2001](#)). Metabolism studies ([Mitoma et al., 1985](#)) suggest effective uptake from oral exposure. Over 80% of the dose was shown to be metabolized at the near-maximal tolerated oral doses (300 mg/kg in mice and 70 mg/kg in rats).

Dermal studies show that 1,1,2-trichloroethane can also penetrate the skin. In guinea pigs, a single 1.0 mL topical application produced peak blood concentration of approximately 3.7 ug/mL within 30 minutes. Levels then decreased to around 2.5 ug/mL at 1 hour, followed by a plateau, and then rose to 3.7 ug/mL by 6 hours ([Jakobson et al., 1977](#)). This complex absorption profile may reflect an initial barrier effect due to delayed penetration or retention within skin lipids. In mice, 15 minutes after dermal exposure to 0.5 mL, 99.7% of the dose remained in the body and 0.3% was exhaled, resulting in a calculated absorption rate of 130 nmoles/min/cm² ([Tsuruta, 1975](#)). Rapid uptake is attributed to high lipid solubility ([Kronevi et al., 1977](#)).

Distribution

In mice exposed to 1000 ppm 1,1,2-trichloroethane for 1 hour, the distribution of compound was as follows: approximately 600 ug/g distributed in fat, 80 ug/g in kidney and liver, 45-60 ug/g in the blood and brain, and 20-35 ug/g in the heart, lung, and spleen ([Takahara, 1986](#)). Partition coefficient data indicate moderate to high lipid solubility compared with other hydrocarbons, with strong affinity for fat and lipid-rich tissues ([Gargas et al., 1989](#); [Sato and Nakajima, 1979](#); [Morgan et al., 1972](#)). Reported partition coefficient values are: 43 for rat spleen: air, 56 for rat brain: air, 71 for mouse blood: air ([Battelle, 2001](#)). Rat liver: air and fat: air PCs were 73.1 and 1438 respectively ([Gargas et al., 1989](#)).

June 2026

These data indicate preferential distribution and retention in fat, liver, and brain in both animals. Data on oral exposure are more limited. In one study, 1,1,2-trichloroethane localized in the liver following gavage administration in animals and was metabolized and shown to bind to hepatic proteins ([Mitoma et al., 1985](#)), suggesting liver is primary site for metabolism in animals and likely humans.

Metabolism

High performance liquid chromatography identified chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid as primary metabolites in rats and mice given 1,1,2-trichloroethane by oral gavage ([Mitoma et al., 1985](#)). These metabolites were also reported following intraperitoneal injection in mice ([Yllner, 1971](#)). Formation of S-carboxymethylcysteine and thiodiacetic acid occurs through glutathione conjugation of reactive intermediates, while chloroacetic acid is generated by hepatic Cytochrome P450 (CYP450) via oxidative dechlorination ([Yllner, 1971](#)). CYP450 metabolism may also produce free radical intermediates ([Mazzullo et al., 1986](#)). Reactive metabolites such as acyl chlorides and free radicals can bind to proteins and nucleic acids and are considered potential mediators of cytotoxic, mutagenic, and carcinogenic effects ([Mazzullo et al., 1986](#); [Ivanetich and Van den Honert, 1981](#)). Acyl chloride intermediates that conjugate with glutathione form the major urinary metabolites of 1,1,2-trichloroethane, S-carboxymethylcysteine and thiodiacetic acid ([Yllner, 1971](#)).

Metabolic capacity differs between species. Rats and mice metabolized identical proportions (81%) of an oral dose; the absolute amount was higher in mice because their maximum tolerated dose was 4.3% times higher than that of rats ([Mitoma et al., 1985](#)). Metabolic studies indicate the production of chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid as primary metabolites ([Mitoma et al., 1985](#)). These metabolites are mediators of toxicity, suggesting that interspecies metabolism differences affect susceptibility to toxicity. Mice metabolize 1,1,2-trichloroethane at a higher rate than rats, consistent with findings that mice have increased sensitivity ([Mazzullo et al., 1986](#); [Mitoma et al., 1985](#)) and this higher metabolic capacity may increase susceptibility of mice to 1,1,2-trichloroethane-induced carcinogenicity ([Mazzullo et al., 1986](#); [Ivanetich and Van den Honert, 1981](#)). The human metabolic rate relative to rodents is unknown, but pathways are considered to be similar. In related compounds such as TCE and PCE, humans exhibit slower absorption and a lower maximum metabolic rate than rats ([NRC, 2009](#); [Green et al., 1997](#); [Bernauer et al., 1996](#)).

Excretion

In female mice exposed to 250-500 ppm for 4-6 hours, breath analysis confirmed pulmonary elimination ([Battelle, 2001](#)). Tissue half-lives post 1 hour exposure to 1000 ppm 1,1,2-trichloroethane were 625, 122, 43, 39, and 19 minutes in heart, fat, brain, spleen, lungs, kidneys, blood, and liver respectively. Whole body half-life was estimated at 49.3 minutes ([Takahara, 1986](#)). Studies in rodents show excretion pathways in both oral and intraperitoneal administration ([Mitoma et al., 1985](#); [Yllner, 1971](#)). After dosing with radiolabeled compound, 7-10% of 1,1,2-trichloroethane was exhaled unchanged, 3-7% was exhaled as CO₂, 72-87% was excreted as urinary metabolites, approximately 1% was in feces, and 1-3% remained in the carcass after 48 hours. The predominant elimination pathway in humans is expected to be in urine as metabolites. In humans, excretion of inhaled 1,1,2-trichloroethane has been measured in breath and urine ([Morgan et al., 1970](#)). After 1 hour, 2.9% of the inhaled dose was recovered in exhaled air, with a retention curve slope of 0.006. Urinary excretion rate was < 0.01% per minute of administered radioactivity, corresponding to an estimated urinary half-life of approximately 70 minutes ([Morgan et al., 1970](#)).

1.3 Toxicity of 1,1,2-Trichloroethane

1.3.1 Summary of 1,1,2-Trichloroethane Toxicity in Animals

Developmental

June 2026

In a developmental study, body weight decreased of female rats exposed to 111 mg/kg/day in drinking water on days 6–20 of gestation. However, no fetal toxic effects were noticed ([WIL Research, 2005](#)). Lack of developmental effects were also seen in [DuPont \(2006\)](#) and [Seidenberg et al. \(1986\)](#). Since limited studies exist to suggest developmental toxicity of 1,1,2-trichloroethane. MOA of structurally similar compounds (low MW halogenated hydrocarbons) were considered to derive dose metrics. In vitro studies show that chloroform, dichloromethane, and dibromoethane are toxic to developing rat embryos when metabolism is not activated ([Brown-Woodman P et al., 1998](#)). [Fort et al. \(2001\)](#) showed that carbon tetrachloride and chloroform result in greater toxicity and more developmental effects when the metabolic system is activated. These results suggest that a dose metric of the parent compound is insufficient for a developmentally toxic dose metric. Since 1,1,2-trichloroethane toxicity due to metabolic activation is a likely MOA for potential developmental effects, the amount of 1,1,2-trichloroethane metabolized in the liver per liter liver per day is the appropriate internal dose metric for route-to-route extrapolation ([Sapphire Group, 2005](#)).

Immunotoxicology

Male and female mice were exposed to 1,1,2-trichloroethane in drinking water for 90 days to identify potential immunological effects (0, 4.4, 46, and 305 mg/kg/d for male mice and 0, 3.9, 44, and 384 mg/kg/d for female mice) ([White et al., 1985](#)). Humoral immune response was measured by hemagglutination titers (log₂ titers), which were shown to be inversely related to dose, with a decrease of 40 and 45% in females treated at 3.9 and 384 mg/kg/day with a significant correlation occurring at the 44 mg/kg/d dose. Hemagglutination levels were decreased for the males treated at the 46 mg/kg/d group (at which point the change was significant) and the 305 mg/kg/day group (59%) ([Sanders et al., 1985](#)). On the basis of this study, 44 mg/kg/day was chosen as the LOAEL based on decreased hemagglutination titers; 3.9 mg/kg/day was considered the NOAEL. Other measures (quantity of IgM antibody forming cells (AFC) against sheep red blood cells (sRBC), spleen and thymus weight) did not shown to be consistently affected by exposure and/or sex. The mechanisms involved in 1,1,2-trichloroethane-mediated immunotoxicity are not known. When considering the internal dose metric of interest in relation to hemagglutination titer effects, it is noted that because both male and female mice experienced similar affects in hemagglutination titers, their dose metric would be similar. Suicide inhibition occurs in female mice, but not male mice, resulting in higher blood and tissue concentrations in female mice than male mice, but similar overall amounts metabolized. Thus, amount metabolized in the liver is a reasonable metric. The richly-perfused bone marrow is not included in this model and bone marrow: blood PCs have not been measured; Sapphire group suggests that the spleen acts as an appropriate surrogate for bone-marrow since it is rapidly-perfused and non-metabolizing ([Sapphire Group, 2005](#)).

Acute Neurotoxicity

Acute neurotoxicity in Crl:CD (SD) IGS BR rats was evaluated by administering 1,1,2-trichloroethane in corn oil gavage to 12 animals/sex/dose for doses of 0, 55, 95, and 200 mg/kg ([WIL Research, 2004](#)). Note that the PBPK model was developed for F344 rats and not the SD rats from the experiment, however [Sapphire Group \(2004a\)](#) note that physiological and metabolic differences between species are not significant enough to impact model disposition ([Simmons et al., 2002](#)). Originally, the NOAEL was defined as 95 mg/kg, when hypoactivity and habituation disruption was observed, and LOAEL was defined as 200 mg/kg when gait impairment was observed ([WIL Research, 2004](#)). However, the NOAEL and LOAEL have since been updated to be 55 and 95 mg/kg/d. Gait impairment was considered the critical endpoint. Trichloroethane may dampen neuronal activity in the brain by interacting with lipids in the nerve membrane or through GABA_A receptor channels [MacIver \(2009\)](#) which influences motor activity but can also be influenced by peripheral nerve system damage. Mice given single gavage doses of 1,1,2-trichloroethane ≥ 450 mg/kg ([White et al., 1985](#)) were sedated within

June 2026

an hour, a sign of nervous system depression; [Borzelleca \(1983\)](#) found motor impairment in half of the test mice administered 128 mg/kg. Because MOA involves nerve cell interaction from the parent compound, the maximum concentration in the brain was signified as the dose metric in the PBPK model ([Sapphire Group, 2004a](#)).

Carcinogenicity

Osborne-Mendel rats and B6C3F1 mice were exposed to 1,1,2-trichloroethane by daily corn oil gavage (50 animals/sex/species/dose) for 5 days a week. For 20 weeks, low and high-dose rats were exposed to either 35 or 70 mg/kg/day doses followed by 58 weeks of 50 or 100 mg/kg/day daily doses for time-weighted doses of 46 and 92 mg/kg/day. Similarly, low- and high-dose mice were doses with 150 and 300 mg/kg/day for 8 weeks and 200 and 400 mg/kg/day for 70 weeks, resulting in time weighted doses of 196 and 390 mg/kg/day. Exposure was followed by an observation period of 35 weeks for rats or 13 weeks for mice. 20 animals/sex/species were used as controls. [NCI \(1978\)](#) reports that as time went on, rats demonstrated clinical signs that their maximum tolerance dose was achieved. Dose-related increases in hepatocellular carcinomas were observed in male and female mice. The dose metric chosen for cancer route-to-route extrapolation is amount metabolized in the liver per liter liver due to dose-related increases in hepatocellular carcinomas and the liver cancer MOA studies are those that use liver cells in relation to systems that activate P450 2E1. Also, since there was a lack of dose-response in other tissues, the liver-related dose metrics were preferred over blood ([Sapphire Group, 2004a](#)).

1.4 1,1,2-Trichloroethane PBPK Models

The purpose of the 1,1,2-trichloroethane PBPK model is to conduct route-to-route extrapolation for rodents. Because no human parameter data were available to extrapolate animal doses to human doses, this model is only applicable to rodents and not humans. The model described in [Sapphire Group \(2002\)](#) that includes oral and inhalation routes of exposure was used for route-to-route extrapolation as it pertains to immunotoxicity in mice ([Sapphire Group, 2004c](#)), acute neurotoxicity in rats ([Sapphire Group, 2004a](#)), developmental endpoints in rats ([Sapphire Group, 2005](#)) and carcinogenicity in rats and mice ([Sapphire Group, 2004b](#)).

1.5 Model Data

The PBPK model was initially developed by [Sapphire Group \(2002\)](#) and evaluated against data from [Battelle \(2001\)](#) and [WIL Research \(2002\)](#) as described below.

Inhalation studies

36 female F-344 rats and 36 female B6C3F1 mice were exposed by whole body inhalation to 1,1,2-trichloroethane in an inhalation chamber. Groups of three female F344 rats or three female B6C3F1 mice per sample time (36 animals/species) were sacrificed. Blood was collected by [WIL Research \(2002\)](#). They were exposed for six hours per day, 5 days per week, for four consecutive weeks, resulting in 20 exposures. The targeted exposure concentration was 100 ppm. On days 1, 3, and 5 of the 4th week, blood samples were collected at 4, 6, 6.25, and 8 hours after the start of the exposure for three animals, three species, three timepoints. The delay that occurred between removal of animals from the chamber was noted so it could be accounted for in the exposure scenario of the model. Exposure errors are reported in [WIL Research \(2002\)](#) to explain variability in observations on day 1 of collection, in which collection times were delayed 1 hour (On day one, target exposure time and blood sample collection were all delayed one hour such that target times were five, seven, 7.25, and nine hr.). In mice and rats, maximum blood concentrations were 2.1 ug/ml and 2.2 ug/ml, respectively. These blood samples were analyzed at Battelle's Pacific Northwest Laboratory where the [Battelle \(2001\)](#) oral studies were conducted.

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Oral studies

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[Battelle \(2001\)](#) conducted 4 gavage studies. Mice were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 290 mg/kg/day in corn oil for group 1 and 9.5 mg/kg/day in water for group 2. Rats were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 92 mg/kg/day in corn oil for group 1 and 1.7 mg/kg/day in water for group 2. Due to low solubility of 1,1,2-trichloroethane in water, target water concentrations were less than 1 mg/ml because this was the maximum concentration at which 1,1,2-trichloroethane in water was homogenous. Blood samples were taken and animals were sacrificed at 0.5, 1, 2, and 8 hours for the corn oil studies and at 0.1, 0.25, 0.5, and 1 hour for the water gavage studies. Following exposures to the compound in corn oil, the lowest blood levels in mice were at day 1; in rats, the highest blood level was in day 1.

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2 MODEL PURPOSE

The purpose of the 1,1,2-trichloroethane PBPK model is to conduct route-to-route extrapolation for rodents; *i.e.*, to predict the inhalation exposure necessary to reach the equivalent internal doses resulting in the oral exposure for each toxicity study. The model used is described in [Sapphire Group \(2002\)](#). It was subsequently used for route-to-route as it pertains to immunotoxicity in mice ([Sapphire Group, 2004c](#)), acute neurotoxicity in rats ([Sapphire Group, 2004a](#)), developmental endpoints in rats ([Sapphire Group, 2005](#)) and carcinogenicity in rats and mice ([Sapphire Group, 2004b](#)). For route-to-route extrapolation, the PBPK model was used for forward dosimetry (*i.e.*, to predict an internal concentration given an external dose) and also for reverse dosimetry (*i.e.*, to predict an external concentration or dose needed to reach some internal dose metric). Oral-to-inhalation route-to-route extrapolation requires forward dosimetry to generate an internal dose of interest, given an external oral POD. This model allows for simulation of oral dosing via corn oil or water gavage and periodic water drinking, as well as reverse dosimetry to find the external inhaled concentration needed to reach the same internal dose metric as the oral dose. Thus, for the given purpose, the model contributes to refining the route-to-route extrapolation generic assumptions to data-driven approaches. That is, route-to-route equivalence doses or concentrations can be calculated using default assumptions when models or model data are lacking; however, with appropriate PBPK models, these doses can be better characterized.

3 MATERIALS AND METHODS

3.1 Modeling Strategy

The PBPK model was initially developed by ([Sapphire Group, 2002](#)). The model is an expansion of the ([Gargas and Andersen, 1989](#)) 1,1,2-trichloroethane PBPK model which was originally used to determine rat metabolism kinetics of chlorinated ethane using exhaled breath from inhalation exposure. The original model was comprised of the following tissues: adipose, liver, slowly-perfused, richly-perfused. ([Sapphire Group, 2002](#)) modified the model to include brain and spleen compartments to accommodate dosimetric calculations for neurotoxic and immunology endpoint. They evaluated their model goal with accompanying data provided by [Sapphire Group \(2002\)](#). Model parameter for rats and mice were also provided by ([Sapphire Group, 2002](#)). These values were corroborated from literature. This modified model allows for oral dosing via corn oil or water gavage and periodic water drinking. Thus, through reverse dosimetry, this model can find the external inhaled concentration needed to reach the same internal dose metric as the oral dose.

3.2 Summary of Data for Model Development and Evaluation

Evaluation

The [Sapphire Group \(2002\)](#) model was evaluated against data from the inhalation and oral gavage studies by [Battelle \(2001\)](#) and [WIL Research \(2002\)](#). Blood samples from inhalation studies in rodents are from WIL Research Laboratories. Oral gavage studies were performed separately by the HAP Task Force ([Battelle, 2001](#)). The PBPK model and model parameter optimizations generated by [Sapphire Group \(2002\)](#) provided simulations with adequate fit to the data. Thus, there is confidence in the accuracy of the model to predict internal concentrations of 1,1,2-trichloroethane in mice and rats after oral gavage (in water or oil) and inhalation exposures.

Inhalation studies: 36 female F-344 rats and 36 female B6C3F1 mice were exposed by whole body inhalation to 1,1,2-trichloroethane in an inhalation chamber. They were exposed for six hours per day, 5 days per week, for four consecutive weeks, resulting in 20 exposures. The targeted exposure concentration was 100 ppm. On days 1, 3, and 5 of the 4th week, blood samples were collected at 4, 6, 6.25, and 8 hours after the start of the exposure for three animals, three species, three timepoints. A minimum detection limit of 0.1 ppb in air was used. For mice, a single significant difference in blood concentration between days 3 and 5 at hour 8 was found, but it did not affect the overall kinetics significantly, indicating that steady-state (or periodicity) was achieved. In rats, blood levels at 4 hours post exposure showed no significant differences between days 3 and 5, indicating periodicity. While day 1 levels were higher than days 3 and 5, the difference was less than 50%.

Oral studies: [Battelle \(2001\)](#) conducted 4 gavage studies. Mice were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 290 mg/kg/day in corn oil for group 1 and 9.5 mg/kg/day in water for group 2. Blood was collected on days 1, 3, and 5. No statistically significant changes in blood concentrations were found among days 1, 3, and 5 for group 2. Group 1 blood concentrations in day 1 were significantly lower than those on days 3 and 5, indicating a dose-dependent change in disposition. Rats were given 1,1,2-trichloroethane for 1 to 5 days by gavage with target doses of 92 mg/kg/day in corn oil for group 1 and 1.7 mg/kg/day in water for group 2. Blood was collected days 1, 3, and 5. No statistically significant changes in maximum blood concentrations were observed between days 2 and 3 for group 1 and between days 1, 3, and 5 for group 2, indicating periodicity. Due to low solubility of 1,1,2-trichloroethane in water, target water concentrations were less than 1 mg/ml because this was the maximum concentration at which 1,1,2-trichloroethane in water was

June 2026

homogenous. Blood samples were taken and animals were sacrificed at 0.5, 1, 2, and 8 hours for the corn oil studies and at 0.1, 0.25, 0.5, and 1 hour for the water gavage studies.

Determination of PBPK Parameters

Metabolism Studies: [Battelle \(2001\)](#) determined the metabolic rate constants for PBPK model using the data from an experiment in which five female B6C3F1 mice were exposed by whole-body inhalation for 4-6 hours to 1000, 500, and 250 ppm 1,1,2-trichloroethane in an 8.59 L closed chamber. They were then placed within a 2.2 L off-gassing chamber where chamber concentration was measured over time for 9 hours. Overt toxicity was observed during the 1000 ppm exposure with one death and severe lethargy and [Battelle \(2001\)](#) noted that the time-course data for this dose was unusual and not expected and thus not included for parameter estimation. Maximum chamber concentrations were 6 and 17 ppm for mice exposed to 250 and 500 ppm respectively. Note that Michaelis Menten constants were estimated using the exhaled breath technique from [Gargas and Andersen \(1989\)](#), which generally overestimate KM. Compared to findings by [Gargas and Andersen \(1989\)](#) in F344 male rats, female rats exhibit an approximate 30% reduction in binding affinity and a 30% increase in metabolic capacity for saturable metabolic pathways.

Partition coefficients: In collaboration with [Battelle \(2001\)](#) or [WIL Research \(2002\)](#), [Sapphire Group \(2005\)](#) determined the liquid:air and tissue: air PCs for mouse blood and rat brain and rat spleen using the vial equilibrium method described in ([Gargas et al., 1989](#)). Headspace 1,1,2-trichloroethane concentrations were compared to vials of 1,1,2-trichloroethane vapor for blood or vials of 0.75 ml saline for the tissues. PCs for 1,1,2-trichloroethane for mouse blood: air, rat spleen: air, and rat brain: air were 71, 43, and 56 respectively.

Endpoints and Dose Metrics

Developmental: Since 1,1,2-trichloroethane toxicity due to metabolic activation is a likely MOA for potential developmental effects, the amount of 1,1,2-trichloroethane metabolized in the liver per liter liver per day is the appropriate internal dose metric for route-to-route extrapolation ([Sapphire Group, 2005](#)). The modeling strategy proposed by [Sapphire Group \(2005\)](#) exposes rats to 1,1,2-trichloroethane in drinking water, assuming a 12-hour light/dark schedule, where rats consume 80% of their water consumption during the dark period in evenly spaced timepoints. Due to uncertainty in MOA for developmental toxicity, a critical window of exposure time was unknown and route-to-route extrapolations were conducted for the entire window. The model assumes that tissue weights and blood flow in the pregnant rat would be equal between GD 6 and GD 20 so the parameters used were for non-pregnant rats ([Sapphire Group, 2005](#)). A NOAEL of 111 mg/kg/d reported in [WIL Research \(2005\)](#) was used as the oral POD.

Immunotoxicology: On the basis of ([Sanders et al., 1985](#)), 44 mg/kg/day was chosen as the LOAEL based on decreased hemagglutination titers; 3.9 mg/kg/day was considered the NOAEL. The richly-perfused bone marrow is not included in this model and bone marrow: blood PCs have not been measured; Sapphire group suggests that the spleen acts as an appropriate surrogate for bone-marrow since it is rapidly-perfused and non-metabolizing [Sapphire Group \(2005\)](#). However, as discussed above, suicide inhibition occurs in female mice, but not male mice, resulting in higher blood and tissue concentrations in female mice than male mice, while overall amounts metabolized are similar in both male and female mice. Thus, amount metabolized in the liver (*AML*) was chosen as a reasonable metric.

Acute Neurotoxicity: The NOAEL was defined as 55 mg/kg, when hypoactivity and habituation disruption was observed, and LOAEL was defined as 95 mg/kg when gait impairment was observed ([WIL Research, 2004](#)). Because gait impairment is related to nerve activity as impacted by the parent

compound, which is why the maximum brain concentration of 1,1,2-trichloroethane is the dose metric of interest ([Sapphire Group, 2004a](#)).

Carcinogenicity: A LOAEL for rats was not identified since no significant neoplasms increases were observed. The rat oral cancer NOAEL was 92 mg/kg/day for 5 days a week, which averages to a daily average of 65.7 mg/kg/day for 7 days/week. A dose of 46 mg/kg/d (averaging to 32.8 mg/kg/d for 7 days) was also tested in rats. Mice studies also did not produce a NOAEL since liver tumors increased significantly at both the high and low dose experiments. The female and male mice LOAEL is 195 mg/kg/day for 5 days/week, which averages to 139.3 mg/kg/day for 7 days/week. The internal dose metric of interest is amount of 1,1,2-trichloroethane metabolized in the liver per liter liver per day ([Sapphire Group, 2005](#)). A dose of 390 mg/kg/d (averaging to 278.6 mg/kg/d for 7 days) was also tested in mice.

3.3 Model Development and Structure

The 1,1,2-trichloroethane PBPK model contains the basic set of equations for a volatile organic compound (VOC) inhalation model as originally described in the [Ramsey and Andersen \(1984\)](#) styrene PBPK model. This common approach describes the movement of a compound through a mammalian body using sets of mass-balance differential equations to explain the disposition of the compound entering and exiting organs within the body. The [Ramsey and Andersen \(1984\)](#) model is comprised of lung, fat, muscle tissues (or other slowly-perfused tissues), richly-perfused tissues, and liver. Saturable metabolism following Michaelis-Menten kinetics removes the chemical from the liver. Arteries and veins deliver the concentration of compound into and from each tissue. Inhalation of the chemical is represented by a gas exchange compartment. This model structure was then modified by [Gargas and Andersen \(1989\)](#) as a PBPK model for disposition of 1,1,2-trichloroethane and other chlorinated ethanes of male F344 rats. The [Gargas and Andersen \(1989\)](#) rendition incorporated an exhaled breath gas uptake method into their model to be able to estimate kinetic constants for chemical metabolism. [Sapphire Group \(2002\)](#) then expanded and refined the model to include a spleen compartment to accommodate simulation of internal exposure metrics for immunotoxicity endpoints and a brain compartment for neurotoxic effects. A stomach compartment was also included to account for modeling of oral exposure, either by water or corn oil gavage. See Figure 3-1 for the model schematic.

Built upon the previously described 1,1,2-trichloroethane model, [Sapphire Group \(2002\)](#) developed a PBPK model to extrapolate from the oral route of exposure to the inhalation route of exposure for rats and mice. Average anatomical and physiological parameters for rats and mice (body weight, tissue weights, blood flows, respiration rates) were taken from ([Brown et al., 1997](#)). Tissue: blood PCs were calculated from blood: air PCs and tissue: air PCs, which were either measured from experimental data ([Battelle, 2001](#)) or taken from literature ([Gargas et al., 1989](#)). The model can be used for both mice and rats with species-specific parameters. [Sapphire Group \(2002\)](#) determined species-specific enzyme affinity, maximum metabolic rate, and absorption rate parameters using optimization fit to mouse and rat data sets. Of note, absorption studies suggest comparable absorption mechanisms across mice and rat species (similar blood concentrations were reported in both rats and mice following 4 weeks of inhalation exposure in a study conducted by [Battelle \(2001\)](#)). Starting values for stomach absorption rates for corn oil were taken from the [Clewett et al. \(2000\)](#) trichloroethylene model and assumed to be similar. Absorption rates were determined for water or corn oil dosing. 1,1,2-trichloroethane in water was estimated to be absorbed from the stomach at rates of 2.5 h⁻¹ and 1.3 h⁻¹ for mice and rats, respectively; 1,1,2-trichloroethane in corn oil was estimated to be absorbed slower at rates of 0.2 h⁻¹ and 0.45 h⁻¹ for mice and rats, respectively. This reflects the lipophilic nature of 1,1,2-trichloroethane and reflects the altered absorption kinetics from corn oil, leading to slower uptake and more dependence on systemic perfusion for distribution.

June 2026

Species differences in metabolism as shown by the studies mice metabolize 1,1,2-trichloroethane at a higher rate than rats ([Mazzullo et al., 1986](#); [Mitoma et al., 1985](#)) were described using metabolic parameters K_M and V_{MAX} optimized against the kinetic data provided by [Battelle \(2001\)](#) with starting values from [Gargas and Andersen \(1989\)](#). Additionally, the optimized model incorporated suicide inhibition (*i.e.*, enzyme destruction via inactivation by bound, reactive intermediate) to explain reductions in V_{MAX} observed in female mice and drawing from justification in [White et al. \(1985\)](#), the model structure was modified to accommodate a suicide enzyme activation pathway for female mice, since it was found that female mice exposed to 1,1,2-trichloroethane by inhalation or corn oil gavage showed significantly higher blood concentrations on days 3 and 5 compared to day 1.

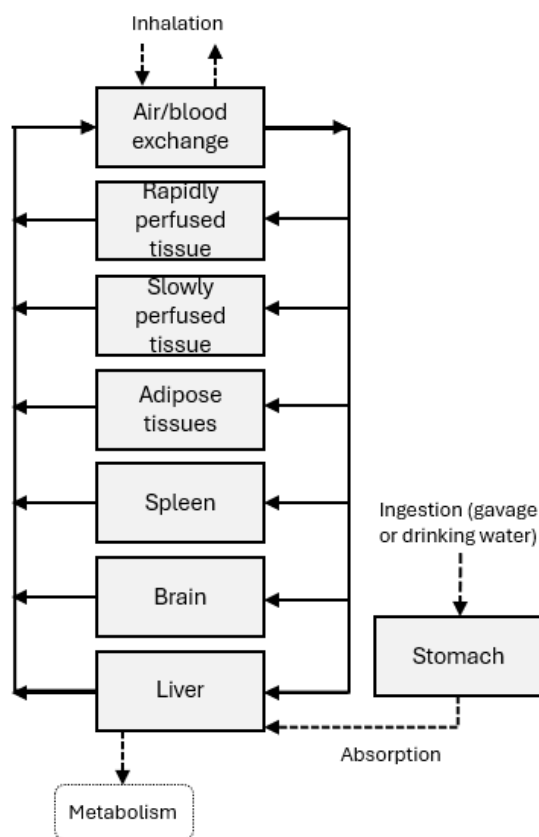


Figure 3-1. PBPK Model Diagram for Rat and Mouse Adapted from [Sapphire Group \(2002\)](#).

1,1,2-trichloroethane PBPK model schematic. Solid lines and arrows to the tissues represent arterial blood and arrows from the tissues represent venous blood. Dashed lines represent routes in or out of the body. The oral route of exposure deposits an oral dose into the stomach compartment, which is absorbed into the liver and then distributed in blood. The inhalation route of exposure goes into a gas blood exchange compartment. The chemical is eliminated from the body through exhalation from the air/blood exchange compartment and through hepatic metabolism.

3.4 Model Parameters

Parameter values used in the 1,1,2-trichloroethane model are found in Table 3-1. Generally, anatomical and physiological parameters for rats and mice (*i.e.*, tissue weights and blood flows) are the average values reported in [Brown et al. \(1997\)](#).

The product of the input parameter body weight, B_W , of each individual raised to 0.70 and the input cardiac output constant, Q_C , is the calculated cardiac output (L/hr) of an average individual such that $Q_C = Q_{CC} \times B_W^{0.7}$ (L/hr). Likewise, the calculated pulmonary ventilation rate (L/hr) and blood flow rates (L/hr) are calculated using the cardiac output Q_C (denoted QC in the code) where alveolar ventilation $Q_P = Q_{PC} \times B_W^{0.7}$ (L/hr). [Brown et al. \(1997\)](#) assumes $Q_{CC} = Q_{PC}$.

Each of the input fractional flows (L/hr) are calculated as:

$$\begin{aligned} \text{Blood flow rate to fat:} & Q_F = Q_{FC} Q_C \\ \text{Blood flow rate to liver:} & Q_L = Q_{LC} Q_C \\ \text{Blood flow rate to spleen:} & Q_{SN} = Q_{SNC} Q_C \\ \text{Blood flow rate to brain:} & Q_{BR} = Q_{BRC} Q_C \\ \text{Blood flow rate to slowly perfused tissue:} & Q_S = Q_{SC} Q_C \\ \text{Blood flow rate to rapidly perfused tissue:} & Q_R = Q_{RC} Q_C. \end{aligned}$$

Calculated tissue volumes (L) are calculated using body weight B_W and input fractional tissue volumes to obtain

$$\begin{aligned} \text{Volume of fat:} & V_F = V_{FC} B_W \\ \text{Volume of liver:} & V_L = V_{LC} B_W \\ \text{Volume of spleen:} & V_{SN} = V_{SNC} B_W \\ \text{Volume of brain:} & V_{BR} = V_{BRC} B_W \\ \text{Volume of slowly perfused tissue:} & V_S = V_{SC} B_W \\ \text{Volume of rapidly perfused tissue:} & V_R = V_{RC} B_W. \end{aligned}$$

Partition coefficients were taken from ([Gargas et al., 1989](#)) or measured via [Battelle \(2001\)](#). The tissue: blood PCs are calculated using the input tissue: air partition coefficients divided by P_B , the partition coefficient for the ratio of blood to air, to obtain:

$$\begin{aligned} \text{Fat: blood PC:} & P_F = P_{FA}/P_B \\ \text{Liver: blood PC:} & P_L = P_{LA}/P_B \\ \text{Spleen: blood PC:} & P_{SN} = P_{SNA}/P_B \\ \text{Brain: blood PC:} & P_{BR} = P_{BRA}/P_B \\ \text{Slowly: blood PC:} & P_S = P_{SA}/P_B \\ \text{Rapidly: blood PC:} & P_R = P_{RA}/P_B. \end{aligned}$$

Kinetic parameters for the metabolism of 1,1,2-trichloroethane were determined through optimizing the PBPK model to data. ([Gargas and Andersen, 1989](#)) provided starting values for $V_{\max C}$ ($7.7 \text{ mg/hr}\cdot\text{kg}^{0.7}$) and K_M (0.75 mg/L). $V_{\max}$ was optimized for male F344 rats. K_M was not optimized for the corn oil gavage studies in rats because blood concentrations were generally higher than the nominal value of 0.75 mg/L . The maximum metabolic rate parameter is:

$$\text{Maximum rate of metabolism in the liver (mg/hr):} \quad V_{\max} = V_{\max C} B_W^{0.7}.$$

A study by [White et al. \(1985\)](#) showed that 1,1,2-trichloroethane-exposed female mice had a decrease in CYP450 content and CYP450 2E1 enzyme activity but male mice did not, suggesting suicide inhibition in female mice after oral and inhalation exposure to 1,1,2-trichloroethane. To account for the time-decreasing $V_{\max}$, ([Sapphire Group, 2002](#)) incorporated four inhibition mechanisms per ([Lilly et al., 1998](#)) based on the reactive interaction occurring with the enzyme-substrate complex, the total enzyme

June 2026

present, the free enzyme, or a first order bound intermediate process. Male mice parameters for oral absorption, K_M , and V_{MAX} were assumed to be the same as for female mice.

The initial value for corn oil absorption rate was 1.0 hr^{-1} (Clewett et al., 2000). Sapphire Group (2002) optimized parameters using the PBPK model written in ACSL. They used visual best fit to determine parameters via Log Likelihood Function.

Table 3-1. Physiological and Biochemical Parameters for the 1,1,2-Trichloroethane PBPK Model.

Parameter name and description for the rat and mouse 1,1,2-trichloroethane model. Parameter names in parentheses are the parameter names depicted in the model code, written in MCSim model specification language.

Parameter		Value		Units	Notes	Source
		Mouse	Rat			
B_W (BW)	Body weight	0.03	0.25	kg		
Q_{CC} (QCC)	Cardiac output	14	13	$L\ kg^{-0.7}\ hr^{-1}$		(Brown et al., 1997)
Q_{PC} (QPC)	Alveolar ventilation rate	14	13	$L\ kg^{-0.7}\ hr^{-1}$		$Q_{PC}=Q_{CC}$
Fractional blood flows						
Q_{FC} (QFC)	Flow to fat tissue	0.07	0.07	--	Rat value for mouse	(Brown et al., 1997)
Q_{LC} (QLC)	Flow to liver	0.161	0.183	--		
Q_{SC} (QSC)	Flow to slowly perfused tissue	0.217	0.336	--	Skin and muscle	
Q_{BRC} (QBRC)	Flow to brain	0.033	0.02			
Q_{SNC} (QSNC)	Flow to spleen	0.011	0.011		Rat value used for mouse	(Delp et al., 1991)
Q_{RC} (QRC)	Flow to rapidly perfused tissue	0.508	0.38	--		$Q_R = Q_C - Q_L - Q_F - Q_S - Q_{SN}$
Fractional Tissue Volumes						
V_{FC} (VFC)	Fat tissue	0.07	0.07			(Brown et al., 1997)
V_{LC} (VLC)	Liver tissue	0.0549	0.0366			
V_{RC} (VRC)	Rapidly perfused tissue	0.1958	0.2215		1-(bone + other tissues)	
V_{SC} (VSC)	Slowly perfused tissue	0.5493	0.5946			
V_{SNC} (VSNC)	Spleen	0.0035	0.002			
V_{BRC} (VLBR)	brain	0.0169	0.0057			
Partition Coefficients (tissue to air ratio); Tissue: blood PC = tissue: air PC/blood: air PC						

June 2026

Parameter		Value		Units	Notes	Source
P_B (PB)	Blood to air	71	58	--		Rat: (Gargas et al., 1989) Mouse: Poet (2001)
P_{FA} (PFA)	Fat to air	1438	1438	--		Rat- (Gargas et al., 1989)
P_{LA} (PLA)	Liver to air	73	73	--		Rat - (Gargas et al., 1989)
P_{RA} (PRA)	Rapidly perfused tissue to air	60.7	60.7	--	Average of liver, brain, spleen: air PCs	
P_{SA} (PSA)	Slowly perfused tissue to air	23	23	--		Muscle – (Gargas et al., 1989)
P_{SNA} (PSNA)	Spleen to air	43	43			(Battelle, 2001), rat
P_{BRA} (PBRA)	Brain to air	56.1	56.1			(Battelle, 2001), rat
Metabolism and Absorption						
V_{MAXC} (VMAXC)	Max metabolic rate constant for CYP pathway	17.3	10.2	mg/ hr/ kg ^{0.7}	Optimization to fit corn oil gavage data	(Sapphire Group, 2002)
K_M (KM)	Affinity constant for CYP pathway	0.35	0.54	mg/L	Optimization to fit water gavage	(Sapphire Group, 2002)
KDET	Normal enzyme turnover/resynthesis rate	0.025	NA	hr ⁻¹	Normal CYP P-450 2E1 half-life of 29 hours for rat	(Lilly et al., 1998)
KDBI	Enzyme destruction rate by suicide inhibition through first order inactivation by bound, reactive intermediate	0.0914	NA	hr ⁻¹	Optimized to fit corn oil gavage	(Sapphire Group, 2002)
K_{AS} (KAS)	Absorption rate – water (stomach to liver)	2.5	1.3	hr ⁻¹	optimized	(Sapphire Group, 2002)
	Absorption rate – corn oil (stomach to liver)	0.2	0.45	hr ⁻¹		(Sapphire Group, 2002)

June 2026

3.5 Model Equations

The following equations represent the dynamics for the calculated concentrations (mg/L) where A_j is the amount of chemical for each j tissue. See Table 3-1 for a list of model parameters.

$$\text{Fat tissue: } C_F = A_F/V_F$$

$$\text{Veins leaving fat tissue: } C_{VF} = C_F/P_F$$

$$\text{Liver tissue: } C_L = A_L/V_L$$

$$\text{Veins leaving liver: } C_{VL} = C_L/P_L$$

$$\text{Rapidly perfused tissue: } C_R = A_R/V_R$$

$$\text{Veins leaving rapidly perfused tissue: } C_{VR} = C_R/P_R$$

$$\text{Slowly perfused tissue: } C_S = A_S/V_S$$

$$\text{Veins leaving slowly perfused tissue: } C_{VS} = C_S/P_S$$

$$\text{Spleen tissue: } C_{SN} = A_{SN}/V_{SN}$$

$$\text{Veins leaving Spleen tissue: } C_{VSN} = C_{SN}/P_{SN}$$

$$\text{Brain tissue: } C_{BR} = A_{BR}/V_{BR}$$

$$\text{Veins leaving Brain tissue: } C_{VBR} = C_{BR}/P_{BR}.$$

Venous and arterial blood concentrations are represented as:

$$\text{Venous blood: } C_V = (Q_F C_{VF} + Q_L C_{VL} + Q_S C_{VS} + Q_R C_{VR} + Q_{SN} C_{VSN} + Q_{BR} C_{VBR})/Q_C$$

$$\text{Arterial blood: } C_A = (Q_p C_I + Q_C C_V)/(Q_p/P_B), \text{ where } Q_j \text{ are blood flows to each } j \text{ tissue, } Q_C \text{ is cardiac output, } Q_p \text{ is alveolar ventilation rate, and } P_B \text{ is the blood:air partition coefficient.}$$

The set of ordinary differential equations below models the rates of change of amounts of 1,1,2-trichloroethane (mg/hr) as it travels in the different body tissues.

Equation 3-1. Amount of 1,1,2-trichloroethane in fat (mg).

$$\frac{d}{dt} A_F = Q_F (C_A - C_{VF})$$

Equation 3-2. Amount of 1,1,2-trichloroethane in slowly-perfused tissue (mg).

$$\frac{d}{dt} A_S = Q_S (C_A - C_{VS})$$

Equation 3-3. Amount of 1,1,2-trichloroethane in rapidly-perfused tissue (mg).

$$\frac{d}{dt} A_R = Q_R (C_A - C_{VR})$$

Equation 3-4. Amount of 1,1,2-trichloroethane in spleen (mg).

$$\frac{d}{dt} A_{SN} = Q_{SN} (C_A - C_{VSN})$$

Equation 3-5. Amount of 1,1,2-trichloroethane in brain tissue (mg).

$$\frac{d}{dt} A_{BR} = Q_{BR} (C_A - C_{VBR})$$

Equation 3-6. Amount of 1,1,2-trichloroethane in liver tissue (mg).

$$\frac{d}{dt} A_L = (K_{AS} \cdot A_{ST}) + Q_L (C_A - C_{VL}) - R_{AML}$$

Where R_{AML} is the rate of oxidative metabolism in the liver, shown by Equation 3-7.

Equation 3-7. Rate of rate of oxidative metabolism in the liver (R_{AML})

$$R_{AML} = \frac{V_{\max T} C_{VL}}{K_M + C_{VL}}.$$

Equation 3-8. Amount of 1,1,2-trichloroethane metabolized in the liver (mg).

$$\frac{d}{dt} A_{ML} = \frac{V_{\max T} C_{VL}}{K_M + C_{VL}} = R_{AML}.$$

Equation 3-9. The rate of change of the maximum rate of metabolism of 1,1,2-trichloroethane in the CYP pathway (mg/hr) in the liver.

$$\frac{d}{dt} V_{\max T} = K_{deT}(V_{\max} - V_{\max T}) - K_{dbi} R_{AML}.$$

This model allows 1,1,2-trichloroethane to be ingested orally, which is tracked in the stomach compartment by the amount A_{ST} . An oral dose enters the stomach and the oral dose rate is described as

$\frac{d}{dt} R_{oral} = 0$ and the rate of change of cumulative amount of 1,1,2-trichloroethane taken orally is
 $\frac{d}{dt} A_{inoral} = R_{oral}.$

Equation 3-10. Amount of 1,1,2-trichloroethane in stomach (mg).

$$\frac{d}{dt} A_{ST} = R_{oral} - K_{AS} \cdot A_{ST}.$$

The model also supports inhalation, with concentration in ambient air, or CIN . In the case of the inhalation dose scenario, we can assume a closed chamber with some volume, V_{CH} or an open chamber, which is simulated in the model when the parameter $V_{CH} = 0$. (The chamber volume is effectively infinite for open chamber scenarios.) The concentration of 1,1,2-trichloroethane in inhaled air C_I (mg/L), based on the amount of 1,1,2-trichloroethane in the chamber, A_{CH} such that

$$C_I = \begin{cases} A_{CH}/V_{CH}, & V_{CH} > 0 \\ C_{IN}, & V_{CH} = 0 \end{cases}.$$

The concentration in exhaled air is

$$C_X = C_A/P_B,$$

with the amount of 1,1,2-trichloroethane in exhaled air (mg):

Equation 3-11. Amount of 1,1,2-trichloroethane in Exhaled air per subject

$$\frac{d}{dt} A_X = Q_p C_X.$$

Note that for all subjects in the chamber calculated by the amount in exhaled air for a single subject, A_X (note that the number of subjects is denoted as N_{sub} in the code) so that $A_{XC} = A_X N_{sub}$. Then, the cumulative amount inhaled (mg) for all subjects in the chamber is $A_{INHC} = A_{INH} N_{sub}$.

During a closed chamber experiment, the amount of 1,1,2-trichloroethane in the chamber is described as:

June 2026

Equation 3-12. Amount of 1,1,2-trichloroethane in the closed chamber

$$\frac{d}{dt}A_{\text{ch}} = N_{\text{sub}}Q_p(C_X - C_I).$$

and the rate of change of the cumulative amount of 1,1,2-trichloroethane inhaled is described as:

Equation 3-13. Amount of 1,1,2-trichloroethane Inhaled per subject.

$$\frac{d}{dt}A_{\text{inh}} = Q_p C_{\text{in}}.$$

The rates to describe the area under the curve of the blood concentrations (mg/L/hr) are:

Equation 3-14. Area under venous blood concentration curve

$$\frac{d}{dt}AUC_V = C_V$$

Equation 3-15. Area under arterial blood concentration curve

$$\frac{d}{dt}AUC_A = C_A.$$

Table 3-2. State Variables in 1,1,2-Trichloroethane PBPK Model.

Name	Description
ACH	Amount of 1,1,2-trichloroethane in chamber (mg)
AX	Cumulative amount of 1,1,2-trichloroethane in exhaled air per animal (mg)
AINH	Cumulative amount of 1,1,2-trichloroethane inhaled per animal (mg)
AF	Amount of 1,1,2-trichloroethane in fat (mg)
AS	Amount of 1,1,2-trichloroethane in slowly-perfused tissue (mg)
AR	Amount of 1,1,2-trichloroethane in rapidly-perfused tissue (mg)
ASN	Amount of 1,1,2-trichloroethane in spleen (mg)
ABR	Amount of 1,1,2-trichloroethane in brain (mg)
AL	Amount of 1,1,2-trichloroethane in liver (mg)
AML	Cumulative amount of 1,1,2-trichloroethane metabolized in liver (mg)
VMAXT	Maximum rate of metabolism in liver (mg/hr)
AST	Amount of 1,1,2-trichloroethane in stomach (mg)
AUCV	Area under venous blood concentration curve (mg/L*hr)
AUCA	Area under arterial blood concentration curve (mg/L*hr)
AUCSN	Area under spleen curve (mg/L*hr)
AUCBR	Area under brain curve (mg/L*hr)
AUCL	Area under liver curve (mg/L*hr)
ABFUR	Amount of 1,1,2-trichloroethane in background fur (mg)
CIN	Concentration of 1,1,2-trichloroethane in ambient air
ORALDR	Oral dose rate (mg/hr)
AINORAL	Cumulative amount taken in orally (mg)

June 2026

3.6 Model Simulations

The goal of the combined experimental studies ([WIL Research, 2002](#); [Battelle, 2001](#)) and modeling efforts ([Sapphire Group, 2002](#)) was to develop a PBPK model to support route-to-route extrapolation; specifically, to use studies with an oral exposure of 1,1,2-trichloroethane to assess inhalation risks. In the experimental studies, female rats and mice were exposed to 100 ppm of 1,1,2-trichloroethane via inhalation for 6 hours per day, 5 days per week, over four weeks. Additional groups of female mice and rats received daily oral doses of 1,1,2-trichloroethane administered by gavage either with water or corn oil. Daily oral doses took place for 5 consecutive days with blood sampling occurring on days 1, 3, and 5. Target oral doses for mice were 10 mg/kg (water) and 390 mg/kg (corn oil), while rat target oral doses were 1.7 mg/kg (water) and 92 mg/kg (corn oil). Actual average doses for mice were 9.7 mg/kg (water) and 356.6 mg/kg (corn oil) and actual average doses for rats were 1.6 mg/kg (water) and 94.2 mg/kg (corn oil). See Table 3-3 for the model simulation scenarios.

For studies that conducted drinking water as the dose vehicle, the dosing regimen to model drinking water ingestion habits of rodents was based on 12-hour circadian patterns mice exhibit in drinking water consumption. [Silver et al. \(1991\)](#) found that approximately 80% of water consumption occurs during a 12-hour dark period. The model incorporates this assumption with 21 evenly spaced drinks during the dark phase and 12 evenly spaced drinks during the light phase. Due to the fast half-life of 1,1,2-trichloroethane, this dosing regimen produces the same result as one that assumes continuous oral dosing. The same dosing regime was applied for rats and mice in studies that used periodic drinking water as the oral dosage vehicle. See Table 3-4 for the route-to-route study-specific model specifications.

Table 3-3. Dosing Scenarios for Model Validation Against Data.

Route of exposure	Duration	Dose	Observation
Oral gavage – water	5 days	9.7 mg/kg – mice 1.6 mg/kg – rats	Concentration in venous blood
Oral gavage – corn oil	5 days	356.6 mg/kg – mice 94.2 mg/kg – rats	
Inhalation	6 hours a day, 5 days a week, 4 weeks	100 ppm	

Table 3-4. Dosing Scenarios for Route-to-Route Extrapolation Studies.

Endpoint	Dosing Scenario	Length of Simulation	Internal dose metric (model variable name)	External Oral Dose	Source
Developmental Rats	12-hour light/dark schedule. 80% of water consumption at night. Water is consumed in even spaces.	GD 6 and GD 20	Amount metabolized in liver per liter liver per day (AML) mg/L/d	NOAEL 111 mg/kg/d	(Sapphire Group, 2005)
Immunotoxicity mice	12-hour light/dark schedule. 80% of water consumption at night. Water is	90 d	Amount metabolized in liver per liter liver per day (AML) mg/L/d	3.9 (NOAEL) 44 (LOAEL)	(Sapphire Group, 2004c)

June 2026

Endpoint	Dosing Scenario	Length of Simulation	Internal dose metric (model variable name)	External Oral Dose	Source
	consumed in even spaces.				
Acute Neurotoxicity	Corn oil gavage	14 d	Maximum concentration in brain (CBrain) mg/L	55 mg/kg/d (NOAEL), 95 mg/kg/d (LOAEL)	(Sapphire Group, 2004a)
Carcinogenicity	Corn oil gavage	5 days a week for 78 weeks	Amount metabolized in liver per liter liver per day (AML) mg/L/d	Mouse: 195 mg/kg/d and 390 mg/kg/d	(Sapphire Group, 2004b)

3.7 Software

All simulations were performed using R version 4.4.0 (R Core Team 2024) on a Dell Precision T7610 with 32 CPUs. The PBPK model was implemented with the MCSim model specification Language ([Bois, 2009](#)) and solutions for differential equation initial value problems involving those models were obtained using the R package “deSolve” ([Soetaert et al., 2010](#)). The original model was written in ACSL Sim 11.8 and ACSL Math 2.5.4.

4 MODEL RESULTS

4.1 Model Evaluation

Oral Simulations for female F344 Rats and female B6C3F1 Mice

The oral data plotted against simulations is from ([Battelle, 2001](#)). Figure 4-1 shows experimental data plotted against simulations of venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average B_W 0.194 kg) were exposed to 9.7 mg/kg/day and rats (average B_W 0.152 kg) were exposed to 1.6 mg/kg/day 1,1,2-trichloroethane as an oral gavage in water once daily for 5 days. The data was collected for 1, 3, and 5 days. The lines are model simulations for the first hour of each day of data collection. Modeling of the water gavage study suggests that peak blood concentrations are achieved quickly (approximately 14 minutes post dose for rats and 5 minutes for mice). Figure 4-2 shows venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average B_W 0.193 kg) were exposed to 365.5 mg/kg/day and rats (average B_W 0.147 kg) were exposed to 94.2 mg/kg/day 1,1,2-trichloroethane as an oral gavage in corn oil once daily for 5 days. Data was collected for 1, 3, and 5 days. The lines are model simulations for the 8 hours of each day of data collection. Figure 4-3 shows the entire simulation over time. For the corn oil gavage study, the model predicts that the maximum blood concentration is reached 46 minutes after dosing for rats, after which point it declines rapidly for about 3 hours post dose when elimination phase slows. For mice, peak concentrations are reached at 83, 159, and 166 minutes post dose for each day.

Inhalation Simulations for female F344 Rats and female B6C3F1 Mice

Figure 4-4 shows venous blood concentrations of mice and rats exposed to 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks. Experimental data from [WIL Research \(2002\)](#). Blood was collected on days 1, 3, and 5 of week 4. The lines are model simulations from the 1st, 3rd, and 5th days of the 4th week, for the 8 hours of each day. The error bars are the standard deviation of the experimental data (n=3 animals). Average B_W was 0.023 kg for mice and 0.16 kg for rats. Limit of detection was 0.013 ug/g. Figure 4-5 shows the total four week duration for mice. Figure 4-6 shows the total four week duration for rats. For both rats and mice, blood concentration peaked at 6 hours.

Goodness of Fit

Figure 4-8 shows a plot predicting the log-transformed observations against the simulated values for both the oral and inhalation studies. Table 4-1 shows the RMSLE and R2 goodness-of-fit values for each scenario.

Route-to-route Prediction Results

See Table 4-2 for a list of the generated external concentrations needed to reach the same internal dose achieved for each oral POD in rats or mice.

June 2026

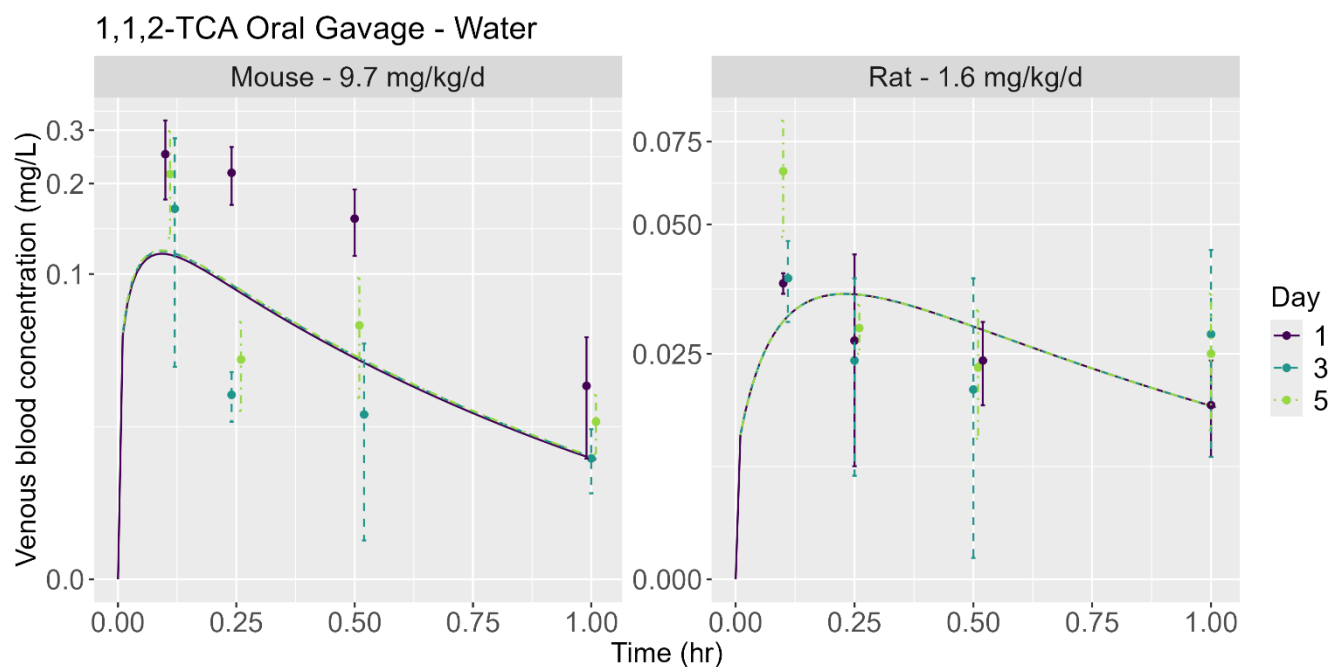


Figure 4-1. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following Oral Water Gavage.

Log-transformed venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average B_W 0.194 kg) were exposed to 9.7 mg/kg/day and rats (average B_W 0.152 kg) were exposed to 1.6 mg/kg/day 1,1,2-trichloroethane as an oral gavage in water once daily for 5 days. Experimental data from (Battelle, 2001). Data was collected for 1, 3, and 5 days. The lines are model simulations for the first hour of each day of data collection. The error bars are the standard deviation of the experimental data (n=3 animals).

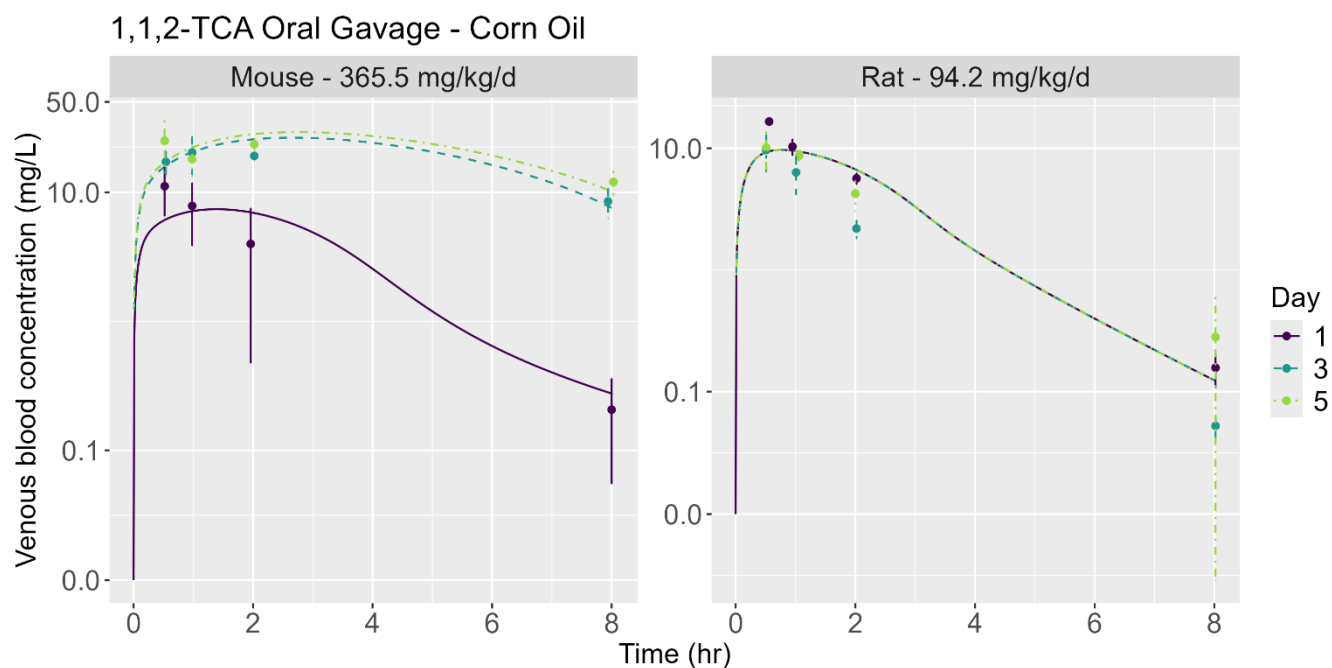


Figure 4-2. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following Corn Oil Oral Gavage (Single Day).

Log-transformed venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average B_W 0.193 kg) were exposed to 365.5 mg/kg/day and rats (average B_W 0.147 kg) were exposed to 94.2 mg/kg/day 1,1,2-

June 2026

trichloroethane as an oral gavage in corn oil once daily for 5 days. Experimental data from (Battelle, 2001). Data was collected for 1, 3, and 5 days. The lines are model simulations for the 8 hours of each day of data collection. The error bars are the standard deviation of the experimental data (n=3 animals).

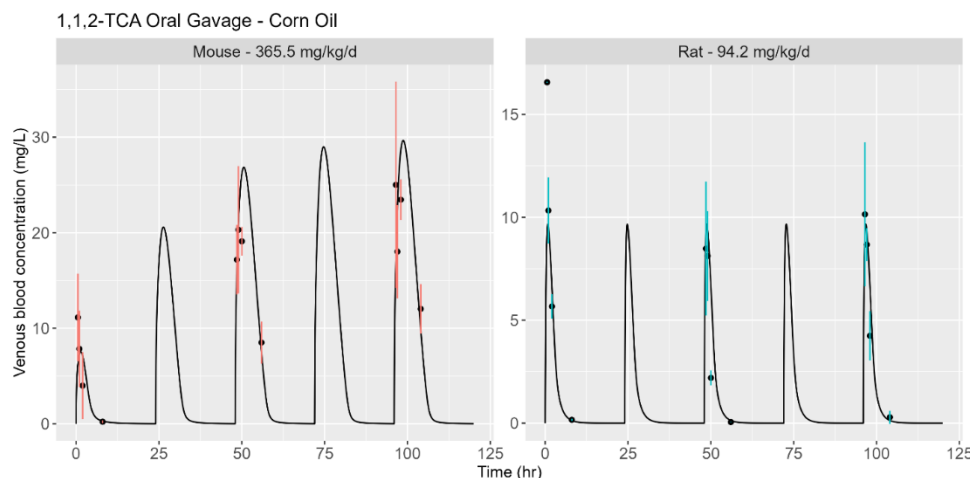


Figure 4-3. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following Corn Oil Oral Gavage (Total Exposure).

Venous blood concentrations (mg/L) of 1,1,2-trichloroethane after mice (average B_W 0.193 kg) were exposed to 365.5 mg/kg/day and rats (average B_W 0.147 kg) were exposed to 94.2 mg/kg/day 1,1,2-trichloroethane as an oral gavage in corn oil once daily for 5 days. Experimental data from (Battelle, 2001). Data was collected for 1, 3, and 5 days. The lines are model simulations for the five day exposure. The error bars are the standard deviation of the experimental data (n=3 animals).

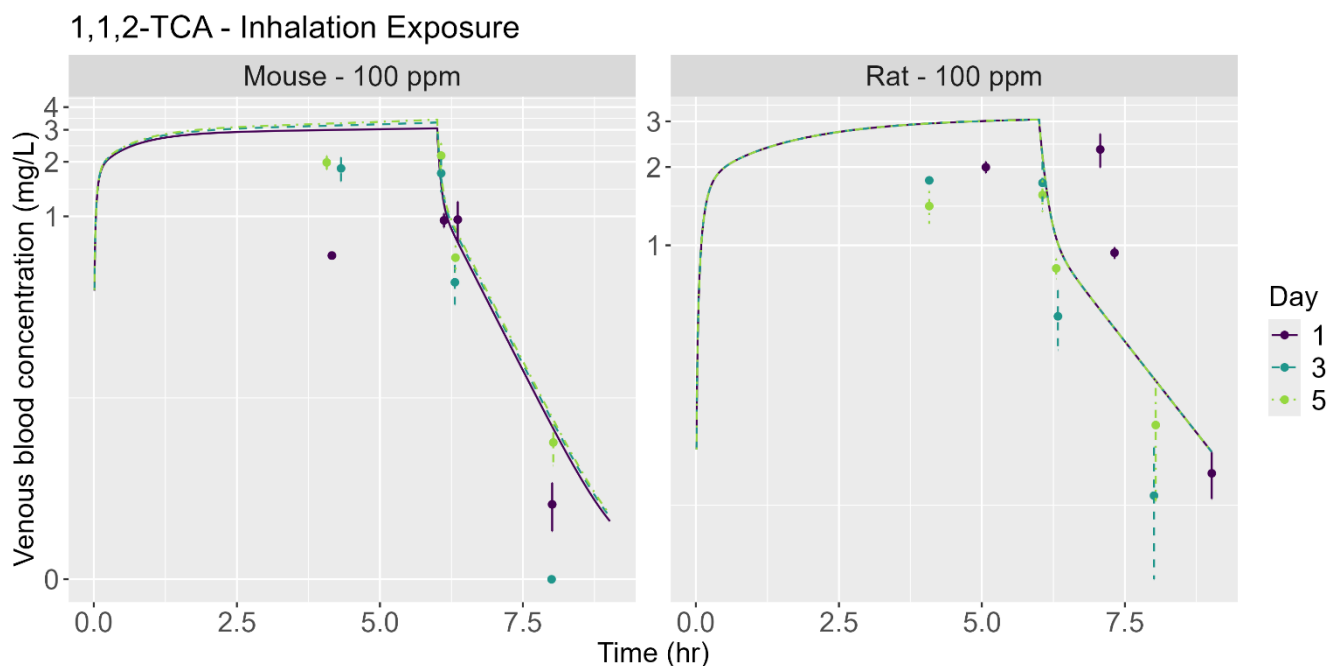


Figure 4-4. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice and Rats Following 100 ppm Inhalation Exposure.

Venous blood concentrations of mice and rats exposed to 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks. Experimental data from WIL Research (2002). Blood was collected on days 1, 3, and 5 of week 4. The lines are model simulations from the 1st, 3rd, and 5th days of the 4th week, for the 8 hours of each

June 2026

day. The error bars are the standard deviation of the experimental data (n=3 animals). Average B_W was 0.023 kg for mice and 0.16 kg for rats. Limit of detection was 0.013 ug/g.

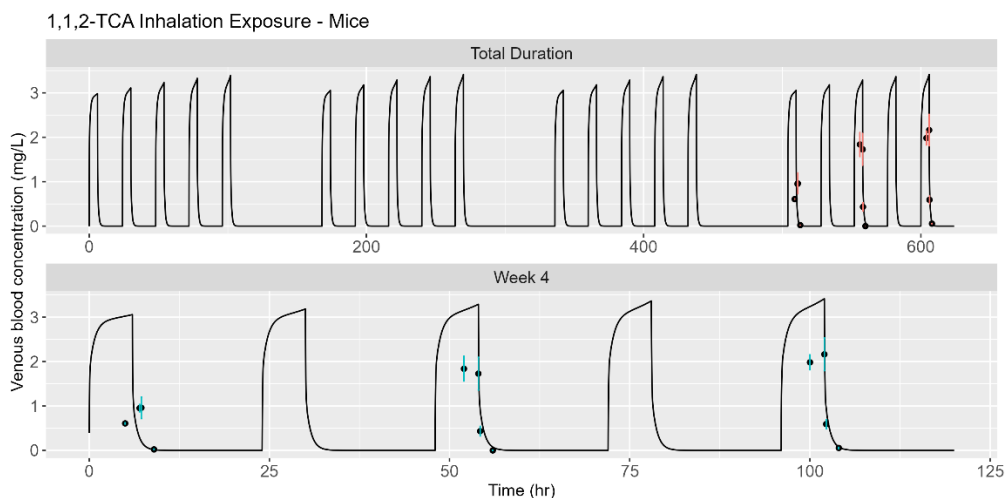


Figure 4-5. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Mice Following 100 ppm Inhalation Exposure (Total Duration and Week 4 Only).

Venous blood concentrations of mice exposed to 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks. Experimental data from (Battelle, 2001). Blood was collected on days 1, 3, and 5 of week 4. The error bars are the standard deviation of the experimental data (n=3 mice per day).

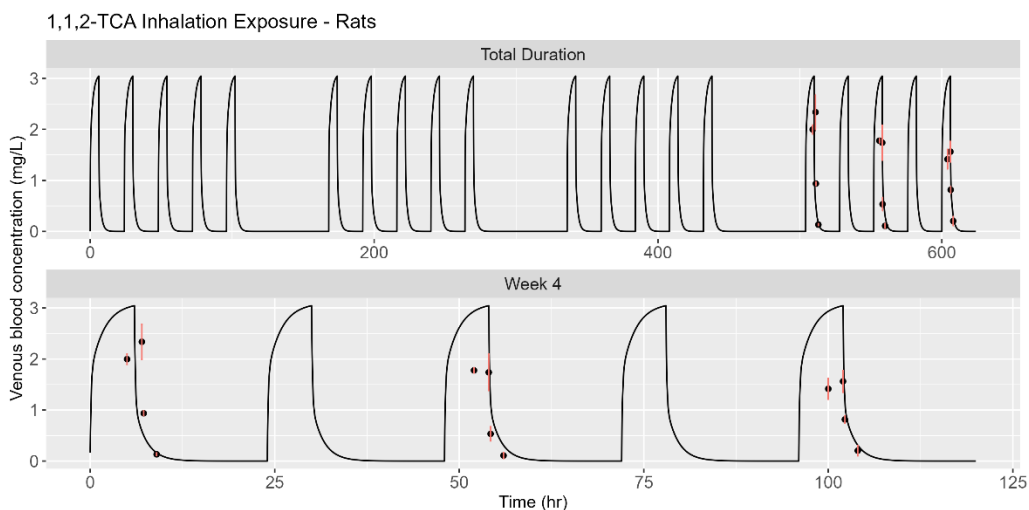


Figure 4-6. Simulated and Observed Blood Concentrations of 1,1,2-Trichloroethane in Rats Following 100 ppm Inhalation Exposure (Total Duration and Week 4 Only).

Venous blood concentrations of rats exposed to 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks. Experimental data from (Battelle, 2001). Blood was collected on days 1, 3, and 5 of week 4. The error bars are the standard deviation of the experimental data (n=3 rats per day). Average B_W was 0.023 kg for mice and 0.16 kg for rats. Limit of detection was 0.013 ug/g.

June 2026

Predictions vs. Observations - 1,1,2-TCA Blood Conc. (mg/L)

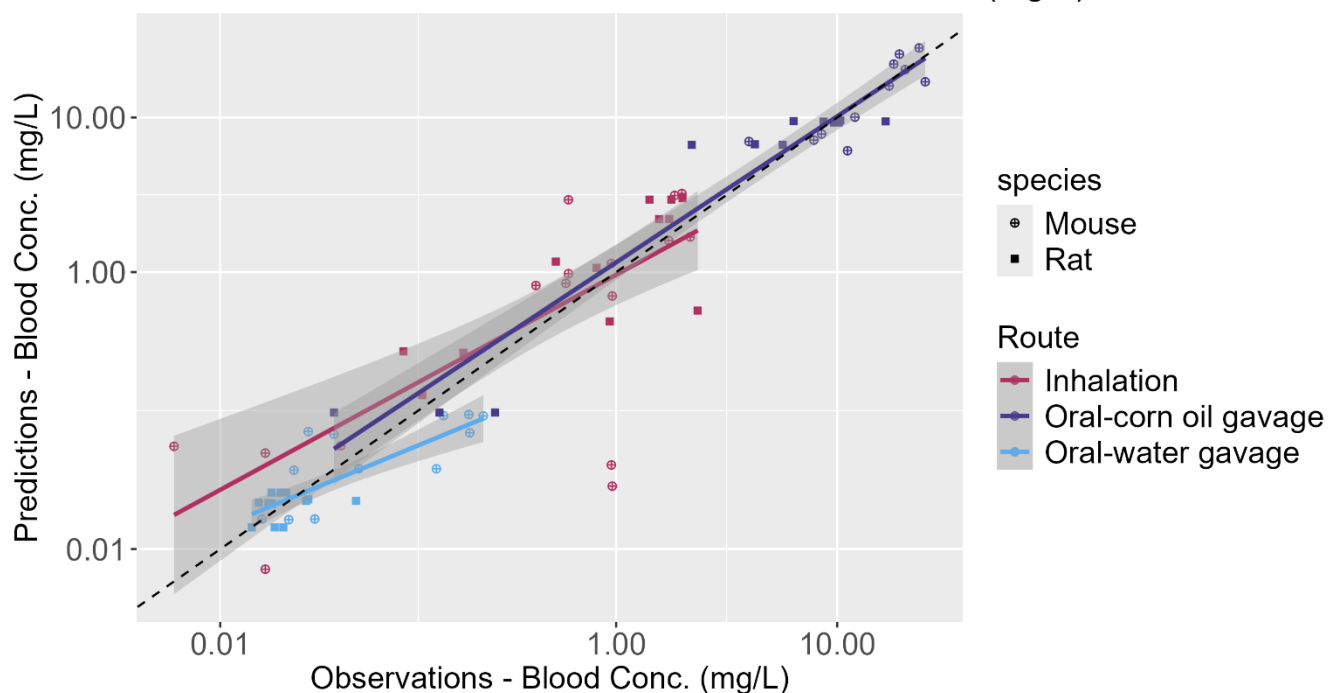


Figure 4-7. Predicted vs. Observed Blood Concentrations for Mice and Rats Following Inhalation and Oral Doses of 1,1,2-Trichloroethane.

Log-transformed observed vs. predicted 1,1,2-trichloroethane venous blood concentration (mg/L), grouped by route of exposure and species. Inhalation exposure in both rats and mice: 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks; blood was collected on days 1, 3, and 5 of week 4. Oral exposure occurred via gavage for 5 days: rats were exposed to 1,1,2-trichloroethane doses of 365.5 mg/kg/day in corn oil or 1.6 mg/kg/day water and mice were exposed to 1,1,2-trichloroethane doses of 94.2 mg/kg/day in corn oil and 9.7 mg/kg/day water. All experimental data is from (Battelle, 2001) and WIL Research (2002). The predictions are simulations from the PBPK model used for each exposure scenario. The dashed line is the identity line; points that fall on this line have been predicted completely while points that fall above the line have over-predicted and points below the line have under predicted.

June 2026

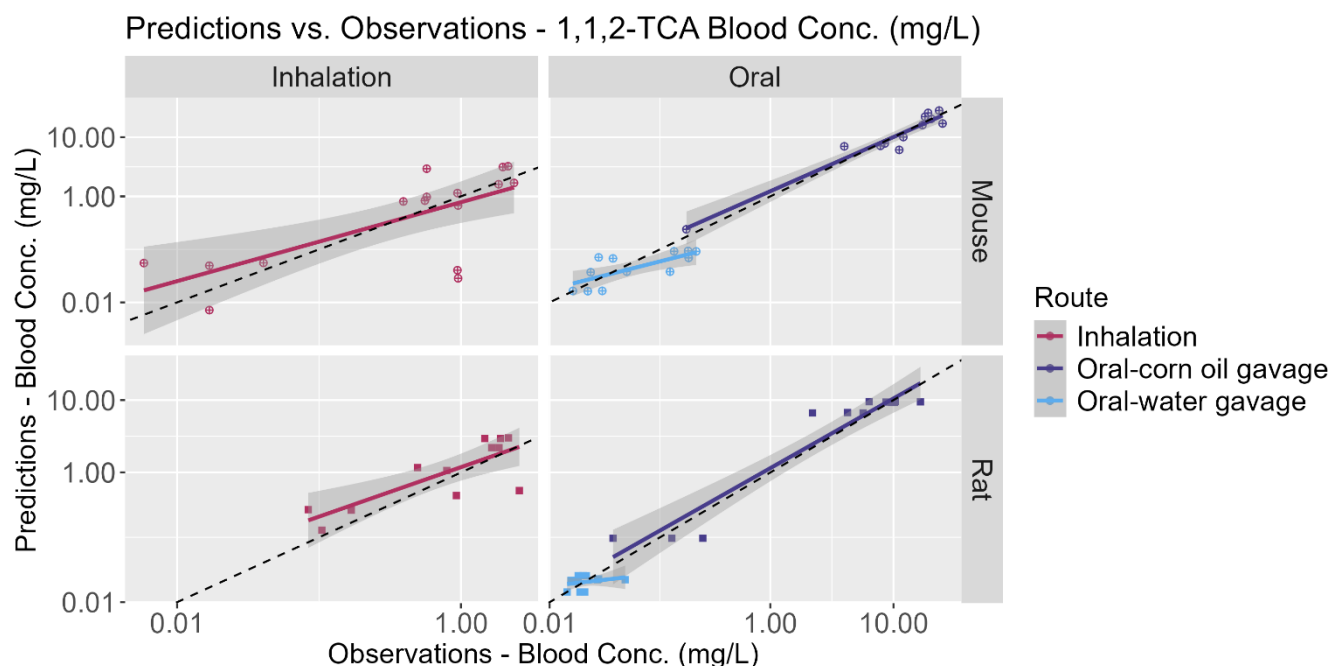


Figure 4-8. Predicted vs. Observed Blood Concentrations for Mice and Rats Following Inhalation and Oral Doses of 1,1,2-Trichloroethane, Grouped by Route of Exposure.

Log-transformed observed vs. predicted 1,1,2-trichloroethane venous blood concentration (mg/L), grouped by route of exposure and species. Inhalation exposure in both rats and mice: 100 ppm 1,1,2-trichloroethane for six hours a day, 5 days a week, for 4 weeks; blood was collected on days 1, 3, and 5 of week 4. Oral exposure occurred via gavage for 5 days: rats were exposed to 1,1,2-trichloroethane doses of 365.5 mg/kg/day in corn oil or 1.6 mg/kg/day water and mice were exposed to 1,1,2-trichloroethane doses of 94.2 mg/kg/day in corn oil and 9.7 mg/kg/day water. All experimental data is from (Battelle, 2001) and WIL Research (2002). The predictions are simulations from the PBPK model used for each exposure scenario. The dashed line is the identity line; points that fall on this line have been predicted completely while points that fall above the line have over-predicted and points below the line have under predicted.

Table 4-1. RMSLE and R^2 Values for Evaluating PBPK Model Goodness of Fit Against Data.

Route	Vehicle (if oral)	Observation	Species	RMSLE		RMSLE – total route	R^2 - total route
Inhalation		Concentration in blood mg(L)	Mouse	0.32	0.19	0.33	0.54
			Rat	0.33			0.44
Oral	Water	Concentration in blood mg(L)	Mouse	0.06	0.24	0.22	0.91
	Corn oil			0.27			
	Water		Rat	0.01			0.83
	Corn oil			0.33			

June 2026

Table 4-2. Route-to-route Extrapolation Results.

Results of route-to-route extrapolation. Inhalation PODs for rodents ($\text{POD}_{\text{inhaled}}$) in mg/m^3 and ppm were generated for each POD_{Oral} ($\text{mg}/\text{kg}/\text{d}$) as they are reported in the dose metrics section above.. Internal doses are either maximum 1,1,2-trichloroethane brain concentration (C_{max} Brain, mg/L), maximum 1,1,2-trichloroethane blood concentration (C_{max} Blood, mg/L), area under the curve blood concentration (AUC blood, $\text{mg}/\text{L}\cdot\text{h}$), and amount metabolized in the liver per liter liver per day (AML, $\text{mg}/\text{L}\cdot\text{d}$).

Endpoint	Internal Dose Metric	Internal Dose Value	Rodent POD_{Oral} $\text{mg}/\text{kg}/\text{d}$	Rodent $\text{POD}_{\text{inhaled}}$ mg/m^3	Rodent $\text{POD}_{\text{inhaled}}$ ppm	Other Notes
Acute neurotoxicity Rat Oral vehicle: corn oil	Cmax Brain	3.71	55	571	105	--
		11.7	95 (NOAEL)	930	171	
		35.9	200 (LOAEL)	1390	255	
	AML	1440	55	120	22.1	
		2280	95 (NOAEL)	190	35	
		3800	200 (LOAEL)	319	58.5	
	Cmax Blood	3.91	55	631	116	
		12.3	95 (NOAEL)	950	175	
		37.8	200 (LOAEL)	1410	260	
	AUC blood	0.347	55	72.4	13.3	
		1.56	95 (NOAEL)	309	56.7	
		7.78	200 (LOAEL)	835	153	
Subchronic Neurotoxicity Rat Oral vehicle: water	Cmax Brain	0.0375	17.1	6.85	1.26	--
		0.149	55.9	27.1	4.98	
		0.274	86 (NOAEL)	49.7	9.13	
		0.339	98.2 (NOAEL)	61.6	11.3	
	AML	466	17.1	38.9	7.15	
		1520	55.9	127	23.4	
		2340	86 (NOAEL)	195	35.9	
		2660	98.2 (NOAEL)	223	41	
Developmental Rat Oral vehicle: water	Cmax Brain	0.0385	17	7.04	1.29	GD 6
		0.0373		6.81	1.25	GD 7-20
	AML	463		38.6	7.09	GD 6-7
		464		38.7	7.11	GD 8-20
	Cmax Brain	0.127	48	23.2	4.26	GD 6
		0.122		22.3	4.10	GD 7-20
	AML	1300		109	20.0	GD 6-7
		1310		109	20.1	GD 8-20
	Cmax Brain	0.446	111 (NOAEL)	80.7	14.8	GD 6
		0.421		76.3	14	GD 7-20

June 2026

Endpoint	Internal Dose Metric	Internal Dose Value	Rodent POD _{Oral} mg/kg/d	Rodent POD _{Inhaled} mg/m ³	Rodent POD _{Inhaled} ppm	Other Notes
	AML	3000		251	46.1	GD 6
		3000		251	46.2	GD 7
		3010		252	46.3	GD 8-20
Immunotoxicity Mouse Oral vehicle: water	AML	68.4	3.9 (NOAEL)	4.11	0.754	--
		771	44 (LOAEL)	46.3	8.51	
		4510	384	289	53.1	
Cancer- Rat Oral vehicle: corn oil	AML	885	32.8	73.9	13.6	--
		1680	65.7	141	25.9	
Cancer – Mouse Oral vehicle: corn oil		2370	195	143	26.3	
		3280	390	199	36.5	
Reproductive - premating Rat Oral vehicle: water	AML	357	13.1	32.8	6.02	P1 m premating
		1110	40.6 (NOAEL)	101	18.6	
		2230	82.2	205	37.7	
		464	17	35.9	6.6	P1 f premating
		1420	52.2	110	20.2	
		2770	102	215	39.5	
		567	20.8	52	9.55	F1 m premating
		1830	67.2	168	30.8	
		4330	162	400	73.5	
		673	24.7	52.2	9.58	F1 f premating
		2240	82.5	174	32	
		4650	173	363	66.6	
Reproductive - gestation Rat Oral vehicle: water	AML	436	16	33.8	6.21	P1 f gestation
		1360	49.9	105	19.4	
		2770	102	215	39.5	
		494	18.1	38.2	7.02	F1 f gestation
		1670	61.5	130	23.8	
		3410	126	265	48.7	

4.2 Sensitivity, Uncertainty, and Variability Analyses

Local sensitivity analysis (LSA) calculates how a model's output (*i.e.*, blood AUC or amount metabolized in liver) changes in response to small perturbations in input parameters. This is done using a one-at-a-time (OAT) method whereby one parameter is changed at a time while others remain at their nominal values; the model output is then compared to the output achieved when all parameters were set

to their nominal values. The rate of change between the nominal output and the output after perturbed parameters indicates a parameter's relative influence. Mathematically, this refers to the first derivative. For a model $x(t) = f(\theta)$ with N number of parameters $\theta = (\theta_1, \theta_2, \dots, \theta_N)$, local sensitivity analysis (LSA) is conducted to compute the sensitivity of an output variable to the j -th parameter; i.e., $S(t) = \frac{dx(t)}{d\theta_j}$. This returns a local sensitivity index, S_j , for each parameter such that $S_j(t) = \frac{dx(t)}{d\theta_j}$. The S_j indicates the parameters to which each observation is most sensitive. Some parameters have different orders of magnitude, in which case normalized sensitivity is calculated. This is represented by $\hat{S}_j(t) = \frac{\theta_j}{x(t)} \cdot \frac{dx(t)}{d\theta_j}$ and expresses the relative change (percentage change in each parameter x_i that results from a 0.1% Change in parameter j). Then the function of maps parameters.

$$\frac{\delta f(\theta)}{d\theta_j} \approx \left(\frac{f(\theta_1, \dots, \theta_j + \Delta, \dots, \theta_N) - f(\theta_1, \dots, \theta_j, \dots, \theta_N)}{\Delta} \right) \cdot \frac{\theta_j}{f(\theta_1, \dots, \theta_j, \dots, \theta_N)}.$$

LSA methods are computationally inexpensive and simple to implement. However, their limitations contribute to uncertainty. The method calculates parameter influence within a narrow scope. Parameters within biological models, such as PBPK models, often have a wide distribution; LSA ignores parameter influence over the entire parameter domain. Global sensitivity analysis (GSA) methods use a probabilistic approach and sample across the entire parameter range; however, if probabilistic information is unknown about the model parameters, then this method is unfeasible.

4.2.1 Sensitivity Analysis Results

Normalized sensitivity analysis (SA) indices are presented for the oral model with oral NOAEL and LOAELs using the dosing regime from Table 3-4 and the corresponding inhalation dose from the route-to-route extrapolation. The normalized indices are presented in Table 4-4 (immunology, neurotoxicity, and developmental endpoints) and Table 4-5 (cancer endpoints). Table 4-3 distills the information and presents only the most influential parameters per endpoint/dose/route. Across both routes of exposure and for the endpoints corresponding to amount metabolized in the liver, the liver volume, enzyme affinity, maximum metabolic capacity, blood-to-air partition coefficient, were the most influential. Note that despite amount metabolized in the liver being sensitive to liver volume, it is not highly influential for route-to-route extrapolation because changes would similarly affect each route by decreasing or increasing the chemical concentration in the liver.

For higher doses, ventilation rate and stomach absorption rate were highly influential. For the endpoint corresponding to maximum brain concentration ($C_{\max \text{ Brain}}$), ventilation rate, maximum metabolic capacity, blood-to-air partitioning and blood-to-brain partitioning were the most influential. Generally, more parameters were influential for the inhalation model than the oral model. That is, multiple parameters contribute to output variation when simulating inhalation whereas relatively few parameters are influential to predict oral disposition. Additionally, the oral model outputs were less sensitive to parameter changes for lower doses. See Table 4-6 for a reference list of model parameters and their descriptions. Most of the influential parameters are physiological or anatomical and their values are supported by data, providing high confidence. Thus, the route-to-route extrapolation results that rely on these influential parameters have correspondingly high levels of confidence.

Cancer Endpoint: The dose metric of interest is the average cumulative amount of 1,1,2-trichloroethane metabolized in the liver per liter liver per day. Doses were averaged to be given over 7 days a week instead of 5 days a week. Local sensitivity coefficients > 0.1 for the rat and mouse models are depicted in Figure 4-9 (A) for rats and Figure 4-9 (B) for mice. For rats, the oral doses of 32.8 mg/kg/d (low dose) and 65.7 mg/kg/d (high dose) correspond to 13.6 ppm and 25.9 ppm inhaled concentrations, respectively. In mice, the oral doses of 139.3 mg/kg/d (low dose) and 278.6 mg/kg/d (high dose)

June 2026

correspond to 26.8 and 46.2 ppm inhaled concentrations, respectively. For both doses in rats, parameters to which the observation of interest (*AML*) are most sensitive are fractional liver volumes (V_{LC}) for both oral and inhaled routes and ventilation rate (Q_{PC}) for the inhalation route of exposure. The level of parameter influence is dependent on the exposure route. For both species, body weight (B_W) is influential to the inhalation model, but only moderately influential for the low dose oral model. Similarly, maximum metabolic rate (V_{maxC}) is more influential for the high dose and relatively more influential to the oral model than the inhalation model. V_{LC} , Q_{PC} , and B_W have similar patterns in the mouse model; however, V_{maxC} is highly influential for the high oral dose and less influential for the low oral dose. The suicide inhibition parameters are also highly influential for the mouse model. Since the rat model assumes that rats do not have suicide inhibition, this observation is specific only to the mouse model.

Developmental Endpoint: The dose metric of interest is the cumulative amount of 1,1,2-trichloroethane metabolized in the liver per liter liver in rats. Local sensitivity coefficients > 0.1 for the models using the dosing scenarios from Table 3-4 are depicted in Figure 4-10 (A), where the oral NOAEL of 111 mg/kg/d corresponds to a constant inhaled dose of 46.3 ppm. More parameters are influential to the dose metric of interest, *AML*, for the inhalation model than the oral model. Fractional tissue volume is the most influential parameter for the oral model. V_{LC} and Q_{PC} are both highly influential for the inhalation model, followed by B_W , the blood: air PC (P_B), cardiac output (Q_{CC}), and liver flow (Q_{LC}). Less influential are Q_{RC} , Q_{SC} , and V_{MAXC} .

Immunotoxicity Endpoint: The dose metric of interest is the cumulative amount of 1,1,2-trichloroethane metabolized in the liver per liter liver in mice. Local sensitivity coefficients > 0.1 for the models using the dosing scenarios from Table 3-4 are depicted in Figure 4-10 (B). The oral NOAEL and LOAEL values of 3.9 mg/kg/d and 44 mg/kg/d, respectively, correspond to inhaled NOAEL and LOAEL values of 0.754 ppm and 8.51 ppm continuous inhalation. V_{LC} is the only influential parameter for both oral doses; V_{LC} , Q_{PC} , B_W , P_B , Q_{CC} , Q_{LC} , Q_{RC} , and Q_{SC} are all influential for the inhalation route. Metabolic parameters are not influential for these dose levels as they are relatively low.

Acute Neurotoxicity Endpoint: The dose metric of interest is the maximum concentration of 1,1,2-trichloroethane metabolized in the brain ($C_{max,Brain}$) in rats. Local sensitivity coefficients > 0.1 for the models using the dosing scenarios from Table 3-4 are depicted in Figure 4-11. The oral NOAEL and LOAEL values of 95 and 200 mg/kg/d correspond to the continuous inhaled concentrations of 171 and 255 ppm, respectively. Unlike the dose metric *AML*, $C_{max,Brain}$ is highly sensitive to more parameters in the oral model than the inhalation model. For both oral doses, the stomach absorption rate (K_{AS}), the brain: air (P_{BRA}) partition coefficient, and V_{maxC} are the most influential. Q_{CC} and all tissue blood flows are all influential for the oral model; B_W and tissue volumes for slowly-perfused, rapidly-perfused, liver, and fat are influential to the oral model. For the inhalation model. V_{maxC} , Q_{PC} , and P_{BRA} are highly influential and drive the output more than any other parameters. K_M is moderately influential for the NOAEL dose.

June 2026

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925**Table 4-3. Locally Influential Parameters for Each Endpoint as They Apply to Applicable Dose Metrics and Grouped by Route and Dose.**

Endpoint	Route	Dose	Influential parameters	Unique influential parameters, across doses	Unique influential parameters across routes and doses
Developmental – Rat - AML	Oral	NOAEL 111 mg/kg.d	$Q_{PC}, V_{LC}, P_B, V_{MAXC}, K_M$	$V_{LC}, P_B, V_{MAXC}, K_M$	$V_{LC}, P_B, V_{MAXC}, K_M$
	Inhalation	NOAEL 46.3 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B, V_{MAXC}, K_M$		
Immunotoxicity – Mouse - AML	Oral	NOAEL 3.9 mg/kg/d	V_{LC}	V_{LC}	V_{LC}
		LOAEL 44 mg/kg/d	V_{LC}		
	Inhalation	NOAEL 0.75 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B$	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B$	
		LOAEL 8.51 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B$		
Acute Neurotoxicity – Rat – $C_{maxBrain}$	Oral	NOAEL 55 mg/kg/d	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{FC}, Q_{SC}, Q_{RC}, V_{LC}, V_{FC}, V_{SC}, V_{RC}, P_{LA}, P_{FA}, P_{SA}, P_{RA}, P_{BRA}, P_B, V_{MAXC}, K_M, K_{AS}$	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{FC}, Q_{SC}, Q_{RC}, V_{LC}, V_{FC}, V_{SC}, V_{RC}, P_{LA}, P_{FA}, P_{SA}, P^{RA}, P_{BRA}, P_B, V_{MAXC}, K_{AS}$	$Q_{PC}, P_{BRA}, P_B, V_{MAXC}$
		LOAEL 95 mg/kg/d	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{FC}, Q_{SC}, Q_{RC}, V_{LC}, V_{FC}, V_{SC}, V_{RC}, P_{LA}, P_{FA}, P_{SA}, P_{RA}, P_{BRA}, P_B, V_{MAXC}, K_M, K_{AS}$		
	Inhalation	NOAEL 105 ppm	$Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{FC}, Q_{BRC}, Q_{RC}, P_{BRA}, P_B, V_{MAXC}, K_M$	$Q_{PC}, P_{BRA}, P_B, V_{MAXC}, K_M$	
		LOAEL 171 ppm	$Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, P_{BRA}, P_B, V_{MAXC}, K_M$		
Cancer - Rat - AML	Oral	32.8 mg/kg/d	$Q_{PC}, V_{LC}, P_B, V_{MAXC}, K_M, K_{AS}$	$Q_{PC}, V_{LC}, P_B, V_{MAXC}, K_M, K_{AS}$	$Q_{PC}, V_{LC}, P_B, V_{MAXC}, K_M, K_{AS}$
		65.7 mg/kg/d	$B_W, Q_{PC}, Q_{CC}, V_{LC}, V_{FC}, P_{FA}, P_B, V_{MAXC}, K_M, K_{AS}$		
	Inhalation	13.6 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, V_{LC}, V_{FC}, P_{FA}, P_B, V_{MAXC}, K_M, K_{AS}$	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, V_{LC}, V_{FC}, P_{FA}, P_B, V_{MAXC}, K_M, K_{AS}$	
		25.9 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, V_{LC}, V_{FC}, P_{FA}, P_B, V_{MAXC}, K_M, K_{AS}$		

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June 2026

Endpoint	Route	Dose	Influential parameters	Unique influential parameters, across doses	Unique influential parameters across routes and doses
Cancer – Mouse - AML	Oral	139.3 mg/kg/d	$Q_{PC}, V_{LC}, P_B, V_{MAXC}, K_M, K_{det}, K_{dbi}, K_{AS}$	$Q_{PC}, V_{LC}, V_{MAXC}, K_M, K_{det}, K_{dbi}, K_{AS}$	$Q_{PC}, V_{LC}, V_{MAXC}, K_M$
		278.6 mg/kg/d	$B_W, Q_{PC}, V_{LC}, V_{FC}, V_{MAXC}, K_M, K_{det}, K_{dbi}, K_{AS}$		
	Inhalation	26.8 ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B, V_{MAXC}$	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B, V_{MAXC}$	
		462. ppm	$B_W, Q_{PC}, Q_{CC}, Q_{LC}, Q_{SC}, Q_{RC}, V_{LC}, P_B, V_{MAXC}, K_M, K_{det}, K_{dbi}$		

926

June 2026

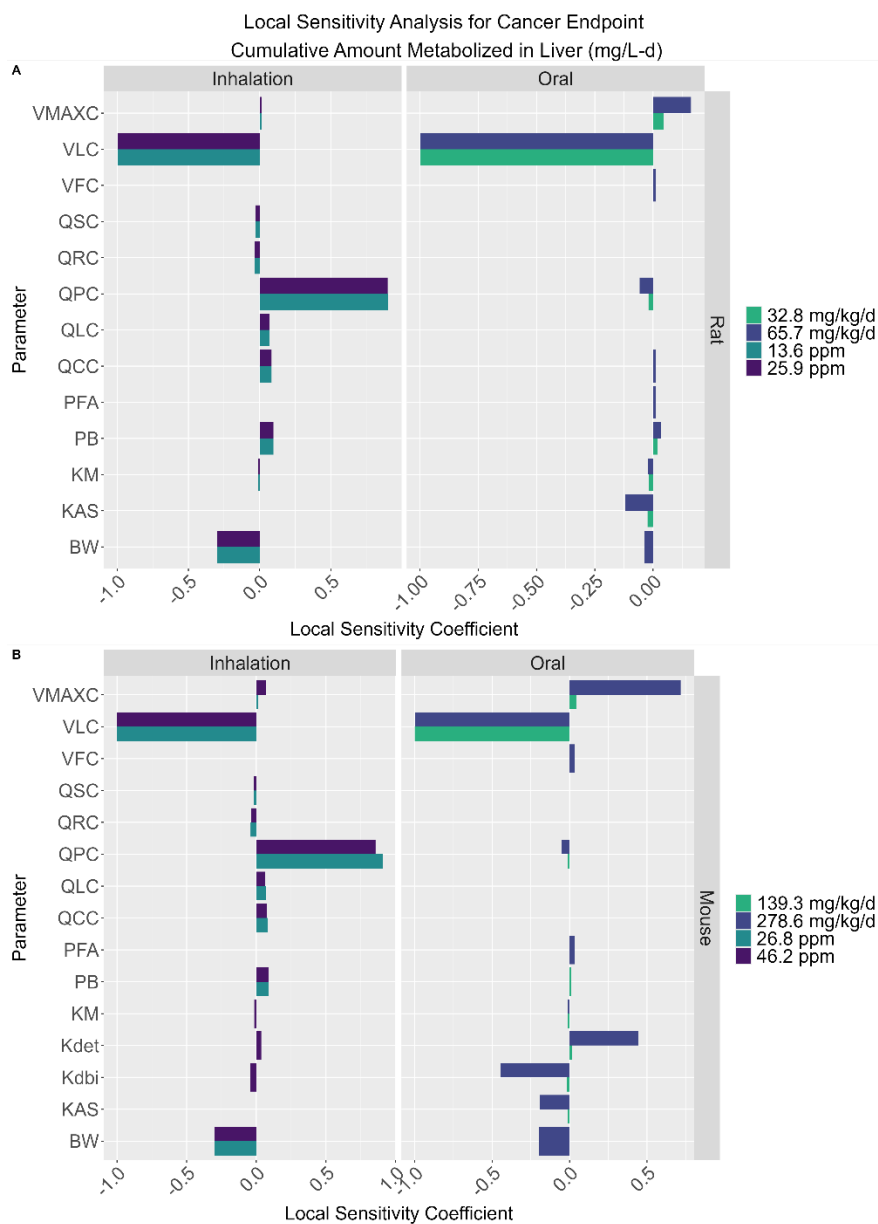


Figure 4-9. Local Sensitivity Analysis Results for the Cancer Endpoint in Rats (A) and Mice (B) for Dose Metric Amount Metabolized in the Liver per Liter Liver: Oral and Inhalation Routes of Exposure.

The dose metric of interest is the cumulative amount of 1,1,2-trichloroethane metabolized in the liver per liter liver. Local sensitivity coefficients > 0.1. SA indices are presented for the oral model with oral NOAEL and LOAELs using the dosing regime from Table x and the corresponding inhalation dose from the route-to-route extrapolation.

June 2026

936

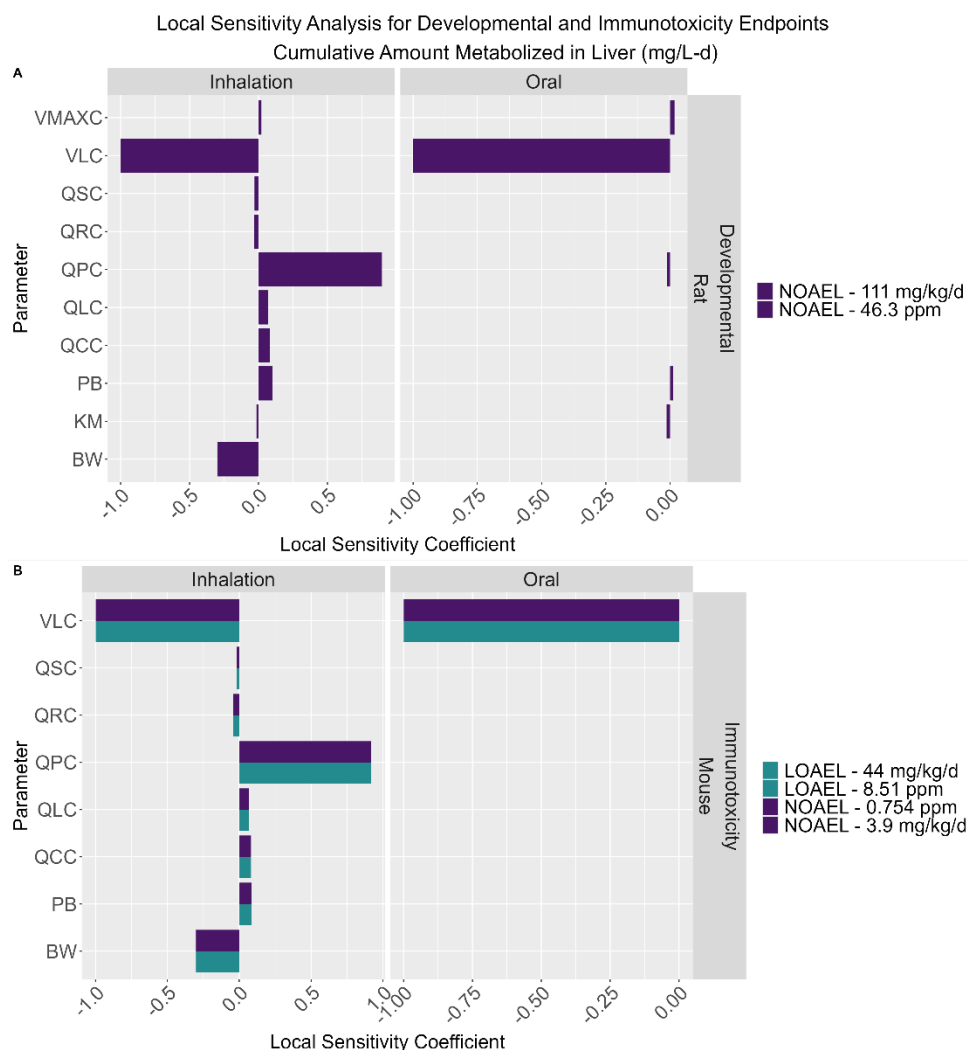


Figure 4-10. Local Sensitivity Analysis Results for the Developmental Endpoint (A) and the Immunotoxicity Endpoint (B) for the Dose Metric Amount Metabolized in the Liver per Liter Liver: Oral and Inhalation Routes of Exposure.

The dose metric of interest is the cumulative amount of 1,1,2-trichloroethane metabolized in the liver per liter liver. Local sensitivity coefficients > 0.1. SA indices are presented for the oral model with oral NOAEL and LOAELs using the dosing regime from Table 3-4 and the corresponding inhalation dose from the R2R extrapolation.

June 2026

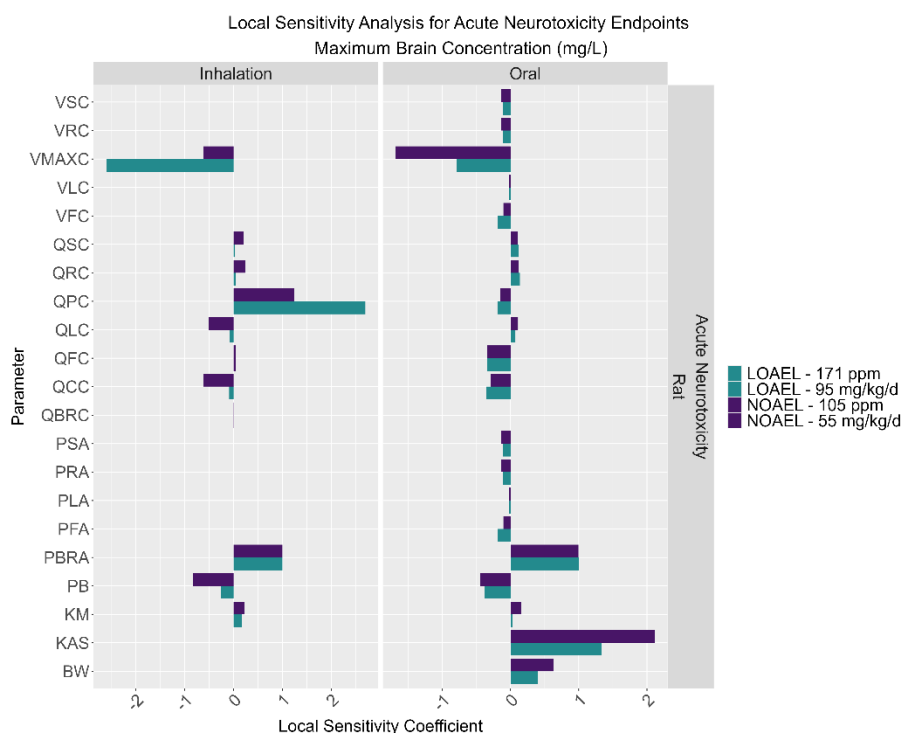


Figure 4-11. Local Sensitivity Analysis Results Acute Neurotoxicity Endpoints for Dose Metric of Maximum Brain Concentration (mg/L): Oral and Inhalation Routes of Exposure.

The dose metric of interest is the maximum concentration of 1,1,2-trichloroethane in the brain. Local sensitivity coefficients > 0.1. SA indices are presented for the oral model with oral NOAEL and LOAELs using the dosing regime from Table 3-4 and the corresponding inhalation dose from the R2R extrapolation.

Table 4-4. Normalized Local Sensitivity Analysis Indices for Developmental, Immunotoxicology, and Acute Neurotoxic Endpoints.

Parameter	Developmental - Rat		Immunotoxicity - Mouse				Acute Neurotoxicity - Rat			
	Oral	Inhalation	Oral		Inhalation		Oral		Inhalation	
	NOAEL 111 mg/kg.d	NOAEL 46.3 ppm	NOAEL 3.9 mg/kg/d	LOAEL 44 mg/kg/d	NOAEL 0.75 ppm	LOAEL 8.51 ppm	NOAEL 55 mg/kg/d	LOAEL 95 mg/kg/d	NOAEL 105 ppm	NOAEL 171 ppm
BW	< 0.01	-0.3	< 0.01	< 0.01	-0.3	-0.3	0.63	0.4	< 0.01	< 0.01
QPC	-0.012	0.89	< 0.01	< 0.01	0.92	0.92	-0.15	-0.19	1.2	2.7
QCC	< 0.01	0.084	< 0.01	< 0.01	0.081	0.081	-0.29	-0.35	-0.62	-0.092
QLC	< 0.01	0.069	< 0.01	< 0.01	0.068	0.068	0.11	0.073	-0.51	-0.075
QFC	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.35	-0.35	0.043	< 0.01
QSC	< 0.01	-0.028	< 0.01	< 0.01	-0.018	-0.018	0.11	0.12	0.21	0.031
QSNC	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
QBRC	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	0.012	< 0.01
QRC	< 0.01	-0.032	< 0.01	< 0.01	-0.041	-0.041	0.12	0.14	0.24	0.035
VLC	-1	-1	-1	-1	-1	-1	-0.019	-0.02	< 0.01	< 0.01
VFC	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.11	-0.18	< 0.01	< 0.01
VSC	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.14	-0.11	< 0.01	< 0.01

June 2026

Parameter	Developmental - Rat		Immunotoxicity - Mouse				Acute Neurotoxicity - Rat			
	Oral	Inhalation	Oral		Inhalation		Oral		Inhalation	
	NOAEL 111 mg/kg/d	NOAEL 46.3 ppm	NOAEL 3.9 mg/kg/d	LOAEL 44 mg/kg/d	NOAEL 0.75 ppm	LOAEL 8.51 ppm	NOAEL 55 mg/kg/d	LOAEL 95 mg/kg/d	NOAEL 105 ppm	NOAEL 171 ppm
V _{SNC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
V _{BRC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
V _{RC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.14	-0.11	< 0.01	< 0.01
P _{LA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.019	-0.02	< 0.01	< 0.01
P _{FA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.11	-0.18	< 0.01	< 0.01
P _{SA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.14	-0.11	< 0.01	< 0.01
P _{RA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-0.14	-0.11	< 0.01	< 0.01
P _{SNA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P _{BRA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	1	1	1	1
P _B	0.012	0.099	< 0.01	< 0.01	0.085	0.086	-0.45	-0.38	-0.84	-0.27
V _{MAXC}	0.017	0.021	< 0.01	< 0.01	< 0.01	< 0.01	-1.7	-0.79	-0.62	-2.6
K _M	-0.013	-0.015	< 0.01	< 0.01	< 0.01	< 0.01	0.16	0.027	0.22	0.17
K _{FC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
K _{det}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
K _{dbi}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
K _{AS}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	2.1	1.3	< 0.01	< 0.01
K _{si}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Table 4-5. Normalized Local Sensitivity Analysis Indices for the Cancer Endpoint.

Parameter	Cancer - Rat				Cancer - Mouse			
	Oral		Inhalation		Oral		Inhalation	
	32.8 mg/kg/d	65.7 mg/kg/d	13.6 ppm	25.9 ppm	139.3 mg/kg/d	278.6 mg/kg/d	26.8 ppm	462. ppm
B _W	< 0.01	-0.036	-0.3	-0.3	< 0.01	-0.2	-0.3	-0.3
Q _{PC}	-0.02	-0.057	0.9	0.9	-0.011	-0.051	0.91	0.85
Q _{CC}	< 0.01	0.014	0.085	0.085	< 0.01	< 0.01	0.081	0.076
Q _{LC}	< 0.01	< 0.01	0.069	0.069	< 0.01	< 0.01	0.068	0.064
Q _{FC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Q _{SC}	< 0.01	< 0.01	-0.029	-0.028	< 0.01	< 0.01	-0.018	-0.017
Q _{SNC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Q _{BRC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Q _{RC}	< 0.01	< 0.01	-0.032	-0.032	< 0.01	< 0.01	-0.041	-0.039
V _{LC}	-1	-1	-1	-1	-1	-1	-1	-1
V _{FC}	< 0.01	0.013	< 0.01	< 0.01	< 0.01	0.034	< 0.01	< 0.01

June 2026

Parameter	Cancer - Rat				Cancer - Mouse			
	Oral		Inhalation		Oral		Inhalation	
	32.8 mg/kg/d	65.7 mg/kg/d	13.6 ppm	25.9 ppm	139.3 mg/kg/d	278.6 mg/kg/d	26.8 ppm	462. ppm
V_{SC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
V_{SNC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
V_{BRC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
V_{RC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_{LA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_{FA}	< 0.01	0.013	< 0.01	< 0.01	< 0.01	0.034	< 0.01	< 0.01
P_{SA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_{RA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_{SNA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_{BRA}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
P_B	0.018	0.035	0.097	0.097	0.011	< 0.01	0.087	0.091
V_{MAXC}	0.044	0.16	0.013	0.015	0.043	0.72	0.011	0.07
K_M	-0.019	-0.021	-0.012	-0.013	-0.011	-0.011	< 0.01	-0.015
K_{FC}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
K_{det}	< 0.01	< 0.01	< 0.01	< 0.01	0.017	0.44	< 0.01	0.035
K_{dbi}	< 0.01	< 0.01	< 0.01	< 0.01	-0.016	-0.44	< 0.01	-0.043
K_{AS}	-0.024	-0.12	< 0.01	< 0.01	-0.013	-0.19	< 0.01	< 0.01
K_{si}	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Table 4-6. Parameter Names and Descriptions – Reference List.

Parameter Name	Description	Parameter Name	Description
B_W	Body weight	P_B	Blood to air ratio
Q_{CC}	Cardiac output	P_{FA}	Fat to air ratio
Q_{PC}	Alveolar ventilation rate	P_{LA}	Liver to air ratio
Q_{FC}	Flow to fat tissue	P_{RA}	Rapidly perfused tissue to air ratio
Q_{LC}	Flow to liver	P_{SA}	Slowly perfused tissue to air ratio
Q_{SC}	Flow to slowly perfused tissue	P_{SNA}	Spleen to air
Q_{BRC}	Flow to brain	P_{BRA}	Brain to air
Q_{SNC}	Flow to spleen	V_{MAXC}	Max metabolic rate constant for CYP pathway
Q_{RC}	Flow to rapidly perfused tissue	K_M	Affinity constant for CYP pathway
V_{FC}	Fat tissue	K_{DET}	Normal enzyme turnover/resynthesis rate

June 2026

Parameter Name	Description	Parameter Name	Description
V_{LC}	Liver tissue	K_{DBI}	Enzyme destruction by suicide inhibition through first order inactivation by bound, reactive intermediate
V_{RC}	Rapidly perfused tissue	K_{AS}	Absorption rate – water oil (stomach to liver)
V_{SC}	Slowly perfused tissue		
V_{SNC}	Spleen		
V_{BRC}	brain		

Generalized Results

Local sensitivity analysis was also conducted to identify key parameters for generic dosing scenarios to compare the impact of dose, exposure route, and oral vehicle across multiple model outputs: *AML*, blood AUC, and maximum brain concentration ($C_{\max Brain}$). The results revealed that most influential parameters are physiological and anatomical, the values of which are well-known and documented, which improves model confidence.

Comparison of Routes: See Figure 4-12 for LSA results for the oral model. The oral model simulates daily oral gavages in water of 1,1,2-trichloroethane for 2 weeks for female mice and female rats across various doses: 1, 10, 100, and 500 mg/kg/d. At low oral doses, liver volume (V_{LC}) is highly influential for *AML*. At the highest dose, V_{MAX} is just as influential as V_{LC} , indicating that when metabolism is not saturated, the capacity of the liver to process the absorbed compound is determined by systemic and tissue concentrations. Metabolic parameters V_{MAX} and K_M are both highly influential for blood AUC and $C_{\max Brain}$ because they influence systemic kinetics; at higher doses, K_M becomes less influential because metabolic saturation is being approached. In mice, the rates of enzyme destruction ARE particularly influential for high doses. Blood: air and brain: air partitioning is influential to maximum brain concentration, indicating the relevance of perfusion limits.

The inhalation model simulates constant inhalation concentrations of 1, 10, 100, and 500 ppm 1,1,2-trichloroethane to mice and rats for 1 week. This range was chosen to ensure steady state concentrations. Normalized LSA indices are shown in Figure 4-13. Generally, a broader set of parameters exhibited relatively high sensitivity indices compared to the oral scenarios. Tissue blood flow rates were among the most important determinants for blood AUC and $C_{\max Brain}$ across lower exposure concentrations, reflecting the dependence of inhaled chemical uptake on perfusion-driven processes. Blood: air partitioning effects exchange of the compound between alveolar air and blood as is highly influential. For the 500 ppm inhaled dose scenario, model output is highly driven by tissue partitioning. Overall, more parameters influence inhalation scenarios than oral scenarios; this is consistent with the kinetics of inhalation exposure compared with the limiting absorption and first-pass metabolism kinetics of oral dosing.

Oral Vehicle: The oral vehicle (corn oil gavage or periodic water drinking) also influences the model and ascribed kinetics. Normalized LSA indices were calculated for rats (Figure 4-14) and mice (Figure 4-15) exposed to 3 weeks of either corn oil gavage or continuous/periodic water consumption of 1,1,2-trichloroethane, for 1, 10, 100, and 500 mg/kg/day doses. The outputs of interest were again *AML*, blood AUC, and maximum brain concentration. In both rats and mice dosed with corn oil, parameters related to hepatic and systemic blood flow (liver, slowly-perfused, and rapidly-perfused) exhibited higher LSA indices for both *AML* and blood AUC endpoints, compared to water dosing. This suggests that corn oil

June 2026

administration alters absorption kinetics, leading to slower uptake and more dependence on systemic perfusion for distribution. Fat blood flow and volume under corn oil dosing are also more influential, reflecting lipophilic partitioning. Water dosing produces generally similar results, but lacks the same influence for fat parameters. Also, V_{MAX} is relatively more influential for blood AUC and brain concentrations after water dosing than for corn oil, particularly for higher doses. This implies that when absorption is more rapid in water, the extent of metabolic capacity plays a role in determining systemic concentrations.

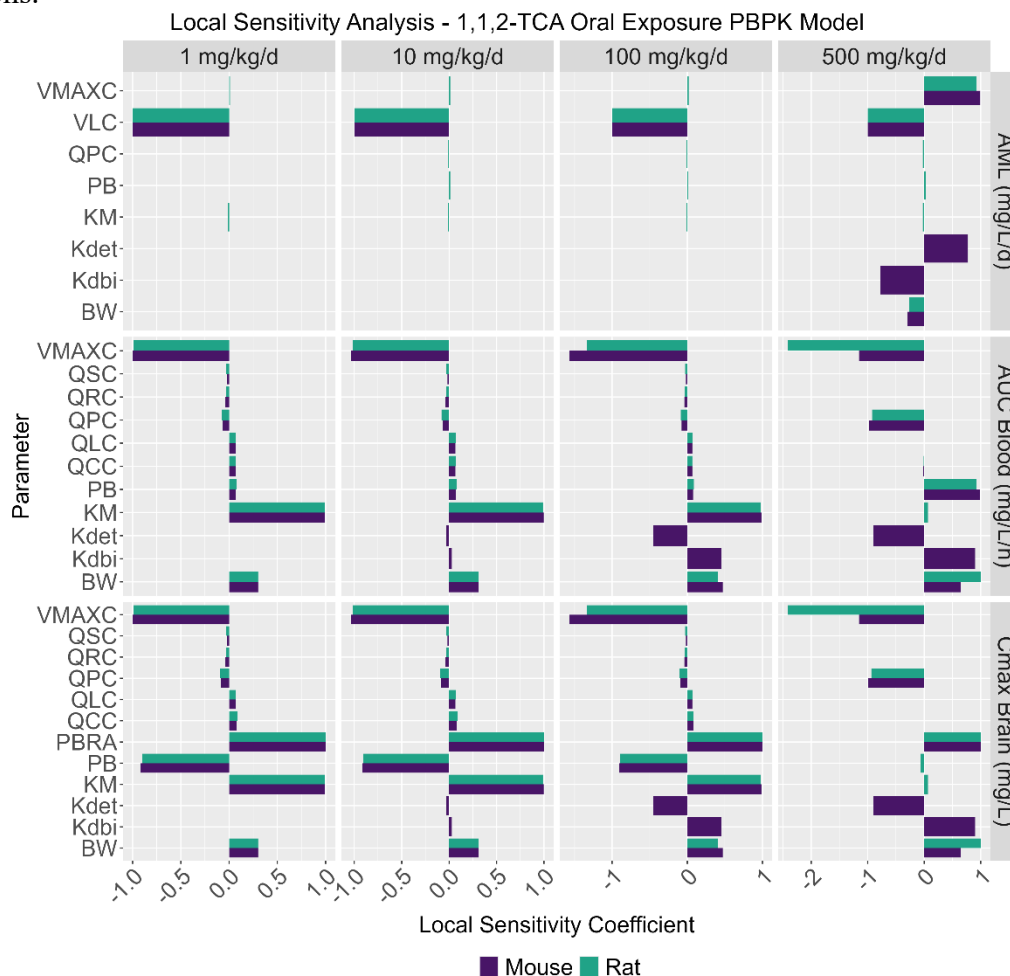


Figure 4-12. Local Sensitivity Coefficients for the Oral 1,1,2-Trichloroethane Model for Various Doses and Dose Metrics.

Dosing regimen assumes single daily bolus doses are given to rats and mice for 2 weeks at 1, 10, 100, and 500 mg/kg/d. The SA indices are reported for the following dose metrics: AML , AUC_{blood} , $C_{max Brain}$.

June 2026



Figure 4-13. Local Sensitivity Coefficients for the Inhalation 1,1,2-Trichloroethane Model for Various Doses and Dose Metrics.

Dosing regimen assumes rats and mice are exposed to continuous exposures of 1, 10, 100, and 500 ppm. The SA indices are reported for the following dose metrics: *AML*, AUC blood, $C_{\max \text{ Brain}}$.

June 2026

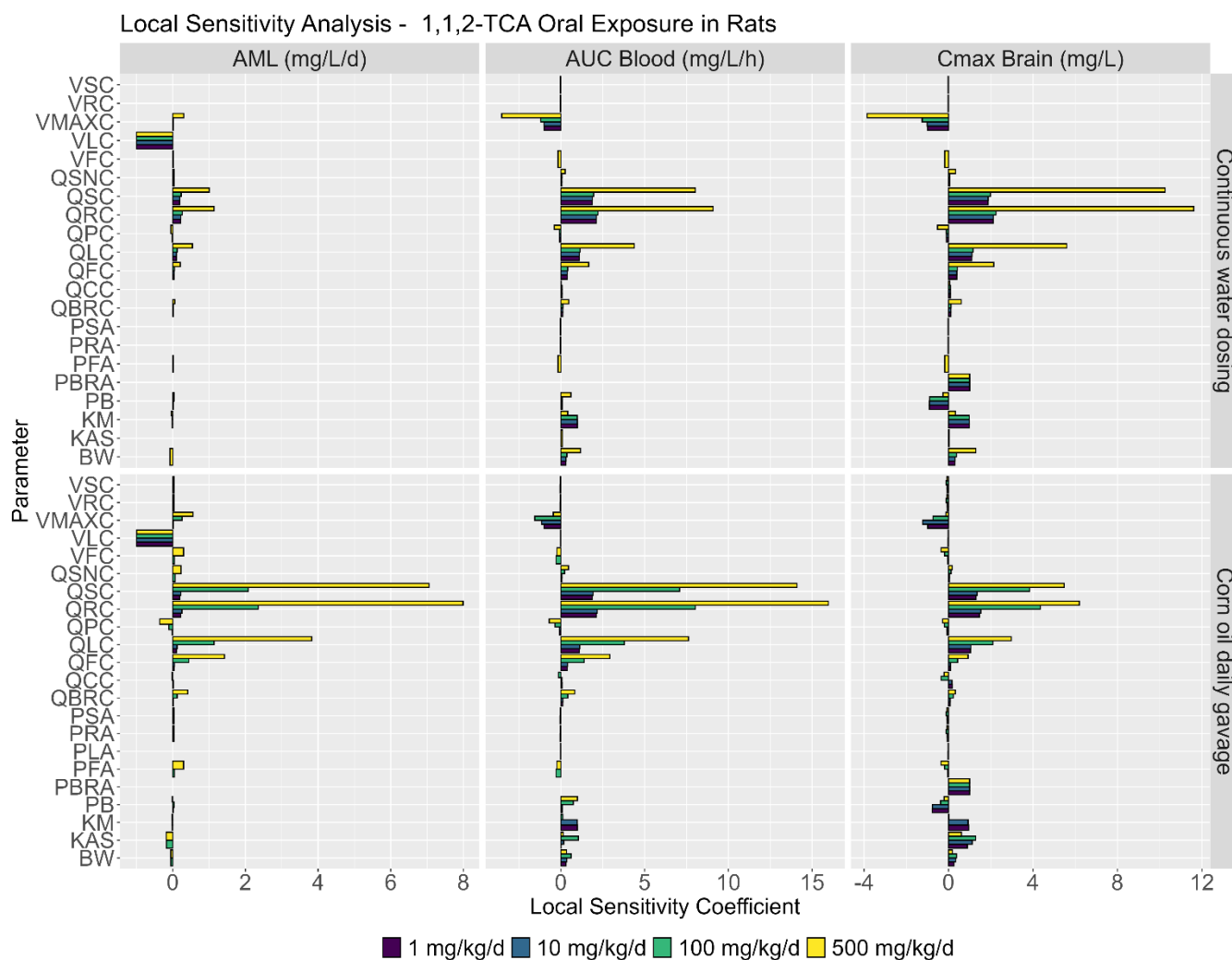
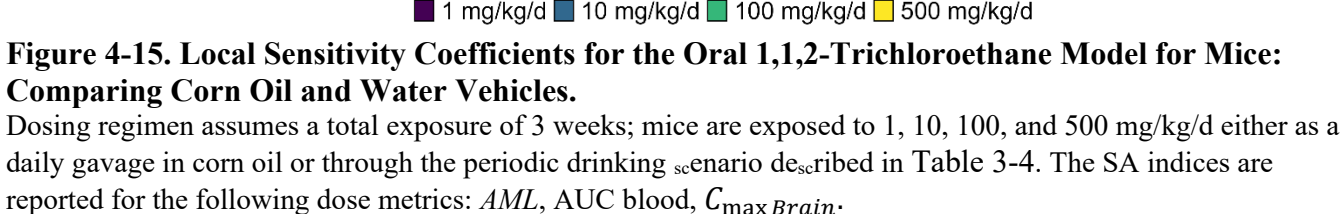


Figure 4-14. Local Sensitivity Coefficients for the Oral 1,1,2-Trichloroethane Model for Rats: Comparing Corn Oil and Water Vehicles.

Dosing regimen assumes a total exposure of 3 weeks; rats are exposed to 1, 10, 100, and 500 mg/kg/d either as a daily gavage in corn oil or through the periodic drinking scenario described in Table 3-4. The SA indices are reported for the following dose metrics: AML , AUC blood, $C_{max Brain}$.



The [Sapphire Group \(2002\)](#) model was able to simulate experimental data for oral and inhalation exposure routes. Given its goodness of fit for both routes of exposure, it can also reasonably recapitulate an inhalation dose necessary to reach an internal tissue concentration achieved by an external oral dose for female mice and rats for corn oil gavage or drinking water dosing. The model also captures differences in 1,1,2-trichloroethane metabolism between mice and rats. The current model includes two routes of exposure, oral and inhalation; adding dermal exposure route to the current model would require modifications to the model equations and/or increased uncertainty in the predictions.

A high oral dose that causes saturation may correspond to a much lower equivalent inhalation concentration than linear scaling would suggest. Figure 4-16 shows the internal dose, amount

June 2026

metabolized in the liver, as a function of the external dose or concentration for the mouse model using simulations to mirror the cancer study exposures (1,1,2-trichloroethane administered via oral gavage in corn oil for 5 days a week over 53 weeks). It is noticeable that for oral doses, the relationship is linear for lower doses and becomes less linear as the dose increases, however, corresponding inhaled doses for each oral dose have a more linear pattern. The inhaled dose necessary to reach the internal dose of interest does not cause saturation in the liver. An orally administered chemical absorbed by the gut goes directly to the liver for first pass metabolism, before reaching systemic distribution. The nonlinear relationship between oral dose and internal dose at higher doses indicates that the metabolism is saturable. At low doses, hepatic metabolism is first order. At higher doses, liver enzymes approach V_{max} and additional dose is not cleared proportionally. That is, the maximum metabolic capacity has been reached, leading to a disproportionately higher internal exposure as dose increases. When inhaled, the chemical enters systemic circulation directly, driven by ventilation rates and bypassing first-pass liver metabolism. The chemical reaches liver more gradually so instantaneous concentration in the liver is typically lower than after a bolus oral dose. A linear concentration-internal dose relationship suggests that uptake and clearance remain linear (unsaturated).

Figure 4-17 shows the relationship between external dose or external concentration and blood AUC, maximum blood concentration, and maximum brain concentration. Maximum brain and blood concentrations are linear for low doses and increase dramatically and nonlinearly for higher doses. The distinction between oral doses that cause non-linear internal responses and inhaled concentrations that cause non-linear internal responses is clearer; generally, the linear oral doses correspond to inhaled concentrations that also produce linear responses.

June 2026

Internal Dose as a Function of External Dose
(1,1,2-TCA Metabolized in Liver per Liter Liver mg/L-d)

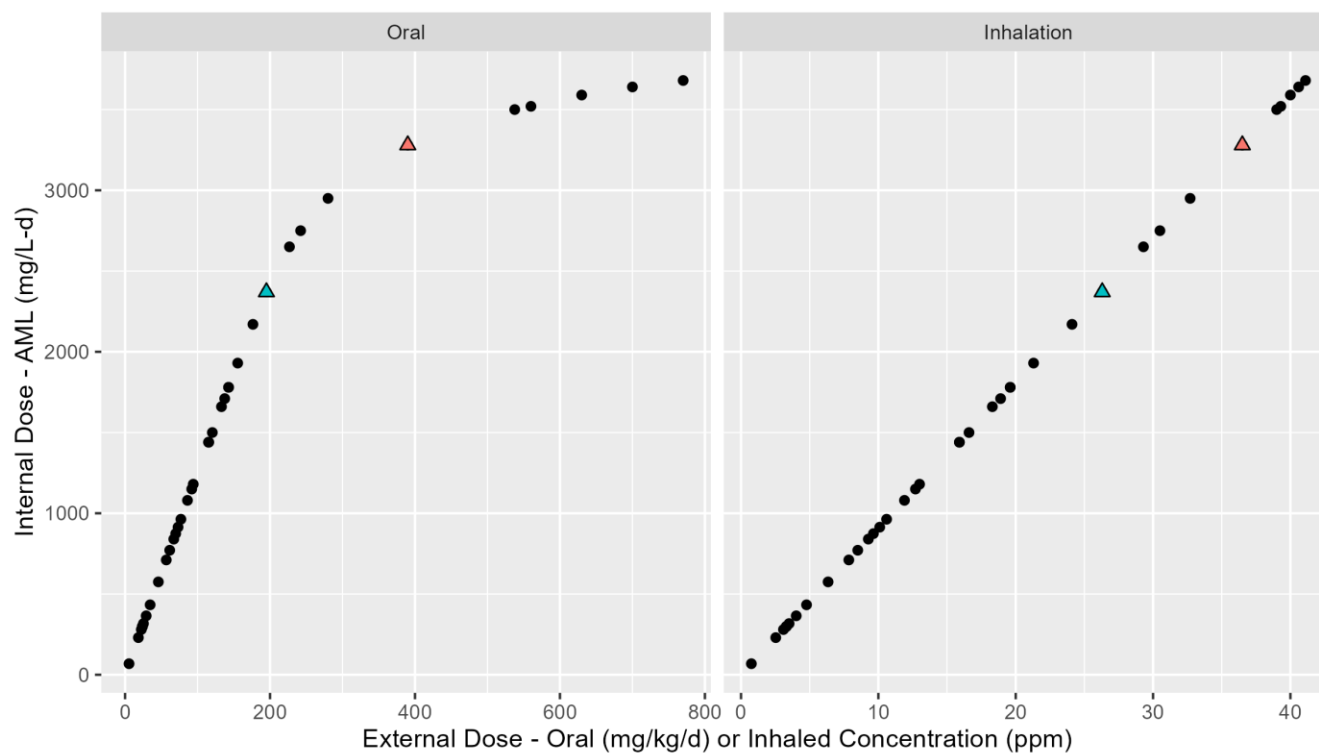
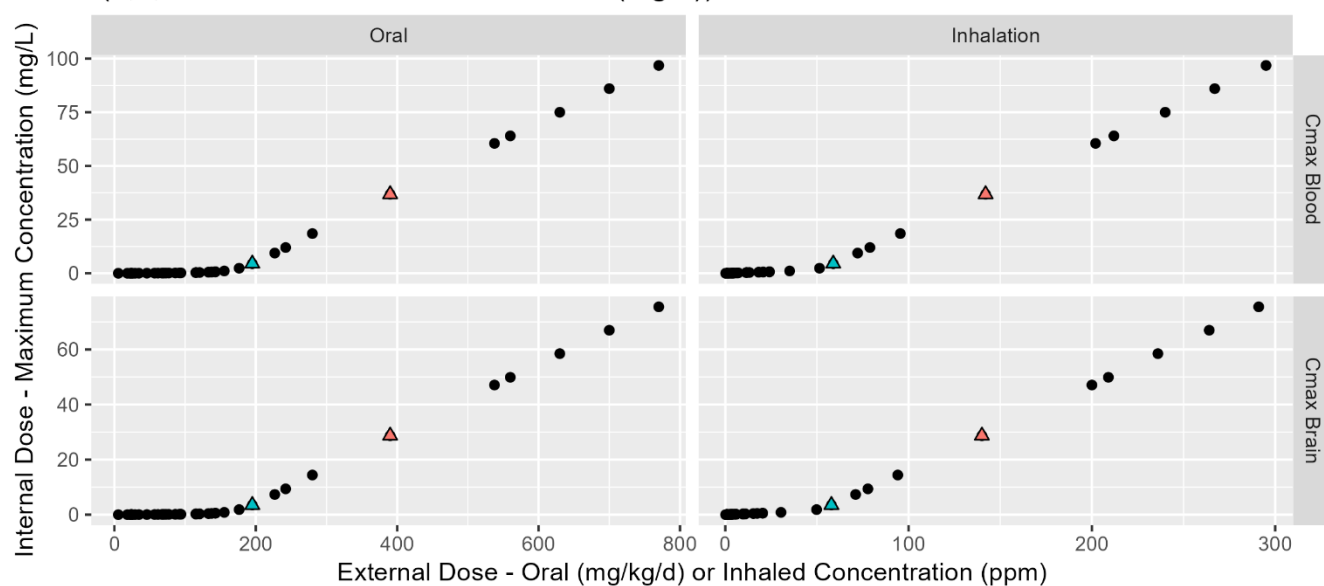


Figure 4-16. Internal Dose (amount metabolized in the liver) as Function of External Dose.

External doses of 1,1,2-trichloroethane plotted as a function of corresponding internal dose (*AML*), for mice exposed to oral doses of 1,1,2-trichloroethane via corn-oil oral gavage for 5 days a week over 53 weeks. Inhaled concentrations (right panel) are the corresponding concentrations for each oral dose (left panel) that generated the same internal dose. Notice that for inhalation, the external concentration continues to be linear beyond when the oral dose produced linear results. The red triangle represents the highest oral dose given in the cancer study (390 mg/kg/d) and its corresponding inhaled POD; the teal triangle represents the lower dose in the cancer study (195 mg/kg/d).

June 2026

Internal Dose as a Function of External Dose (1,1,2-TCA Maximum Concentrations (mg/L))



(1,1,2-TCA Blood AUC (mg/L-h))

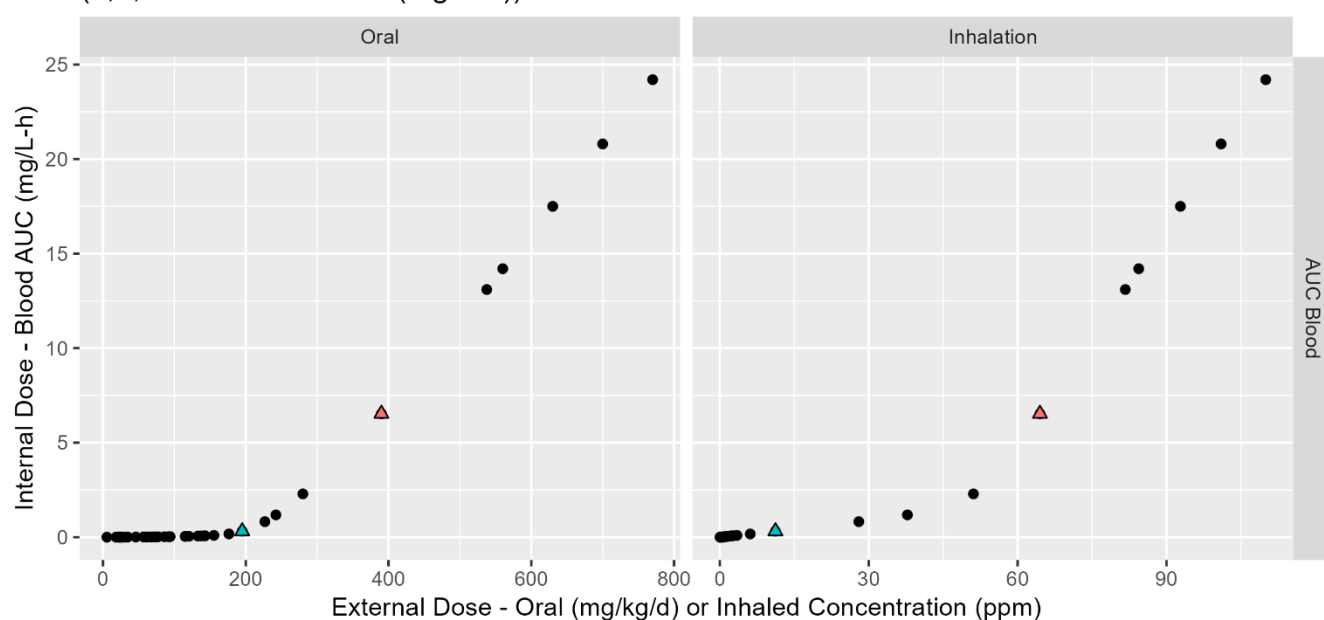


Figure 4-17. Internal Dose (maximum brain and blood concentrations) as Function of External Dose.

Internal doses of 1,1,2-trichloroethane plotted as a function of corresponding external dose (blood AUC or maximum brain or maximum blood concentrations), mice exposed to 1,1,2-trichloroethane oral gavage in corn oil for 5 days a week over 53 weeks. Inhaled concentrations (right panel) are the corresponding concentrations for each oral dose (left column) that generated the same internal dose. . The red triangle represents the highest oral dose given in the cancer study (390 mg/kg/d) and its corresponding inhaled POD; the teal triangle represents the lower dose in the cancer study (195 mg/kg/d).

5 DISCUSSION AND CONCLUSIONS

Confidence in a model for route-to-route extrapolation depends on several factors. Model-specific confidence relies on 1) how driving parameters in a specific route of exposure, such as absorption, are estimated (whether through experimental measurements or computational methods); and 2) general PBPK model and parameter uncertainty given the purpose of route to route extrapolation. Sensitivity analysis was conducted to characterize PBPK model and parameter uncertainty. In general, the amount metabolized in the liver was determined by the amount to which the animal was exposed and physiological parameters, which are generally known. The tissue and blood concentrations are sensitive to the metabolic rate constants and oral absorption rate constants, indicating that estimation conducted by [Sapphire Group \(2002\)](#) is appropriate for determining the values of these particular parameters. Just as importantly, is the confidence in estimated PODs for systemic effects from source toxicity studies as well as confidence in the assumptions used for extrapolation and the pharmacokinetics describing ADME from both exposures. Given reasonable confidence in these factors provides a relative advantage for the PBPK model compared to the default approach, which compares calculated bioavailable doses between the two routes without being able to account for realistic exposure scenarios and effects of ADME factors on target tissue exposure and their changes over time. Because the PBPK model accounts for these elements, this mechanistic approach can increase confidence in route to route extrapolation compared to the default approach. [Sapphire Group \(2002\)](#) modified an existing 1,1,2-trichloroethane inhalation PBPK model that had been originally created to estimate metabolic parameters in rats. To support the purpose of route to route extrapolation, additional modifications were made, adding an oral absorption route of exposure and validating the model with data collected in [Battelle \(2001\)](#) and [WIL Research \(2002\)](#) for repeated exposure of rats and mice to 1,1,2-trichloroethane. This model was further verified for the existing risk evaluation to describe ADME of 1,1,2-trichloroethane for inhalation and oral exposures and route-to-route extrapolation. Given that 1,1,2-trichloroethane MOA evidence supports the relevance of using the amount of the parent compound metabolized in the liver or the maximum brain concentration as internal dose metrics, which are supported by this model, the model was considered suitable for use to predict internal doses or external doses of 1,1,2-trichloroethane. In addition, the model allows to simulate various relevant internal dose metrics to support different toxicity studies with different routes of exposure, as well as to support sex and species-specific differences among mice and rats. Sensitivity analysis revealed that most influential parameters are physiological and anatomical, the values of which are well known and certain. Chemical-specific parameters, such as maximum metabolic rate, are highly influential, but were able to be captured by the model to predict species differences in metabolism, which increases confidence. Metabolic parameters were estimated from robust in vivo data sets that included different doses and routes of exposure, providing more confidence in these parameters.

PK data for female F344 rats exposed to repeated doses of 1,1,2-trichloroethane (approximately 100 ppm inhalation doses, 92 mg/kg/d corn oil gavage or 1.7 mg/kg/d water gavage) were comparable across days 1, 3, and 5 of exposure. The model effectively simulates the 8-hour data point from the corn oil gavage studies. However, the elimination phase is difficult to define on days 3 and 5 due to minimal concentration changes over the first two hours post dosing.

Sex-related differences in CYP2E1-mediated clearance have important implications for cross-route extrapolation and for determining the proper dose metric in assessments. The majority of 1,1,2-trichloroethane is metabolically cleared, so a reduction in V_{MAX} prolongs internal parent concentrations without drastically changing the total amount metabolized within a 24-hour period. That is, metabolic capacity will be similar between male and females, but females may sustain higher systemic exposures, such as concentration in brain or blood.

June 2026

In B6C3F1 mice, repeated inhalation exposure (100 ppm for 6 h/day) and corn oil gavage led to increased blood levels on days 3 and 5, relative to day 1; concentrations on days 3 and 5 were nearly identical. Notably, the inhalation phase commenced after a 3 week exposure regime, implying potential metabolic activity recovery over the 2 day rest period. Also, the lower dose given in water does not have this same behavior. Aniline hydroxylase activity, a marker for CYP2E1, and total P450 content declined as a function of dose in female mice who consumed 1,1,2-trichloroethane in drinking water for 90 days for 44 and 384 mg/kg/d doses ([White et al., 1985](#)); these declines are not observed in male mice, however. CYP2E1 helps mediate small halogenated and non-halogenated hydrocarbon metabolism ([Nakajima, 1997](#)). At higher exposure levels, hepatic aniline hydroxylase activity dropped to almost 50% of that in untreated controls ([White et al., 1985](#)). Utilizing SI, the [Sapphire Group \(2002\)](#) model was able to generate predictions for mice dosed with corn oil gavage where V_{MAX} is time dependent and V_{MAX} decreases 30-50% after the first 3 days dosing (i.e., suppression of CYP activity). The noted day-one PK behavior seen in mice is captured by the PBPK model.

The 1,1,2-PODs from route-to-route extrapolation were able to be generated for 1,1,2-trichloroethane. The described 1,1,2-trichloroethane model was developed and evaluated with confidence given the species and routes of exposure.

1170 **6 LIST OF ELECTRONIC FILES AND SUPPORTING DOCUMENTS**

1171 R Scripts that were used for local sensitivity analysis and calculation of the model residuals are included
1172 in “Draft PBPK Model Code and Data for 1,1,2-Trichloroethane.zip,” attached to this report.

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