Experiment Number: S0559-2 (K00285)
Route: Inhalation
Species/Strain: Rats/Fischer 344

Toxicokinetics Data Summary
Compound: Carbon disulfide/ **Analyte:** Free Carbon disulfide
CAS Number: 75-15-0

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: NIEHS Midwest Research Institute

Male

	Treatment Group (ppm)		
	50 Inhalation Blood[a,c]	**500 Inhalation Blood[b,d]**	**800 Inhalation Blood[b,e]**
Cmax (ug/g)	0.76	10.2	18.9
Alpha Half-life (minute)		3.2	1.3
Beta Half-life (minute)		58.5	84.1
k10 (minute^{-1})	0.07	0.11	0.24
k10 Half-life (minute)	9.3	6.5	2.9
k12 (minute^{-1})		0.96	0.27
k21 (minute^{-1})		0.024	0.018
Cl (mL/min)	0.37	0.26	0.21
V1 (mL)	4.9	2.4	0.86
Vss (mL)	4.9	12.0	13.8
MRT (minute)	13	47	67
AUCinf_pred (ug*min/mL)	137	1960	3890

LEGEND

MODELING SOFTWARE

PCNONLIN

MODELING METHOD & BEST FIT MODEL

[a]PCNONLIN, Statistical Consultants, Lexington, KY, unweighted one-compartment model.

[b]PCNONLIN, Statistical Consultants, Lexington, KY, two-compartment model using an unweighted regression

EXCEPTIONS

[c]V1 represents Vc volume of distribution of the central compartment

[d]Data from both 500 ppm sets (Groups 2 and 3, total n of 12) were combined for toxicokinetic analysis. V1 represents Vc volume of distribution of the central compartment. A is 197 and B is 12.

[e]Data from both sets (Groups 4 and 5, total n of 11 without Rat 1) were combined for toxicokinetic analysis. V1 represents Vc volume of distribution of the central compartment. A is 920 and B is 18.

ANALYTE

Free Carbon disulfide

TK PARAMETERS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
Alpha Half-Life = Half-life for the alpha phase
Beta Half-Life = Half-life for the beta phase
k10 = Elimination rate constant from the central compartment also ke or kelim
k10 Half-life = Half-life for the elimination process from the central compartment
k12 = Distribution rate constant from first to second compartment
k21 = Distribution rate constant from second to first compartment
Cl = Clearance, includes total clearance
V1 = Volume of distribution of the central compartment, includes Vd and V volume of distribution, Vz apparent volume of distribution NCA, Vapp apparent volume of distribution for intravenous studies
Vss = Volume of distribution at steady state
MRT = Mean Residence Time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

50 ppm

Toxicokinetic analyses were performed using the averaged concentrations for the free carbon disulfide determinations. The data was modeled using both the steady state and declining concentration data (i.e., model for intravenous infusion or inhalation profiles). The dose values used in the calculations were set as the nominal carbon disulfide concentration in the atmosphere. The toxicokinetic parameters were calculated using nonlinear regression analysis (PCNONLIN, Statistical Consultants, Lexington, KY). The data from the 50-ppm study did not contain sufficient data points in the elimination phase to fit to a two-compartment model, so an unweighted one-compartment model was used. The lack of data points and relative flatness of the data resulted in a much poorer fit (correlation 0.64).

500 ppm

Toxicokinetic analyses were performed using the averaged concentrations for the free carbon disulfide determinations of set 1 and set 2 rats combined (rat nos 13-24, n equals 12) for 500 ppm exposure. The data was modeled using both the steady state and declining concentration data (i.e., model for intravenous infusion or inhalation profiles). The dose values used in the calculations were set as the nominal carbon disulfide concentration in the atmosphere. The toxicokinetic parameters were calculated using nonlinear regression analysis (PCNONLIN, Statistical Consultants, Lexington, KY). A two-compartment model using an unweighted regression was fit to the data from the 500- and 800-ppm studies with good correlation (0.99).

800 ppm

Toxicokinetic analyses were performed using the averaged concentrations for the free carbon disulfide determinations of set 1 and set 2 rats combined (rat nos 2-6 and 25-30, n equals 11) for 800 ppm exposure. The results from Rat 1 were not included with other values for the 800-ppm study since they were more than 3 standard deviation units from the mean for each time point. The data was modeled using both the steady state and declining concentration data (i.e., model for intravenous infusion or inhalation profiles). The dose values used in the calculations were set as the nominal carbon disulfide concentration in the atmosphere. The toxicokinetic parameters were calculated using nonlinear regression analysis (PCNONLIN, Statistical Consultants, Lexington, KY). A two-compartment model using an unweighted regression was fit to the data from the 500- and 800-ppm studies with good correlation (0.99).

TK PARAMETERS PROTOCOL (cont'd)

TK_INHALATION BLOOD

50 ppm

Six cannulated rats (rat nos 7-12) were exposed once to carbon disulfide at 50 ppm for 180 minutes in nose-only exposure tubes. Blood samples were collected at 10, 20, 30, 60, and 180 minutes at the start of exposure to determine the rapid uptake and elimination time constants and 10 (190), 30 (210), and 90 (270) minutes after the termination of exposure to determine the terminal elimination time constant. Start date is analysis laboratory given start date. Urine samples were not taken so no 2-thiothiazolidine-4-carboxylic acid (TTCA) concentrations, a urinary metabolite of carbon disulfide, were determined. Blood specimens were analyzed for free carbon disulfide with a validated method by analyzing the headspace over the samples using gas chromatography with flame photometric detection with sulfur mode filter using methyl sulfide as the internal standard. The limit of quantitation (LOQ) was 1 or 2 ug/mL, dependent on the data obtained from the standards on each day of analysis.

500 ppm

Two sets of 6 cannulated rats were exposed once to carbon disulfide at 500 ppm for 180 minutes in nose-only exposure tubes. Blood samples were collected from one set of rats (set 1) at 4, 8, 15, 30, 60, and 180 minutes at the start of exposure and 4 (184), 8 (188), and 15 (195) minutes after the termination of exposure to determine the rapid uptake and elimination time constants. Blood was collected from the second set of rats (set 2) 60 and 180 minutes at the start of the exposure and 30 (210), 60 (240), 90 (270), 120 (300), 180 (360), and 240 (420) minutes after the termination of the exposure to determine the terminal elimination time constant. Data from both sets (Groups 2 and 3, total n of 12) were combined for toxicokinetic analysis. Start date is analysis laboratory given start date. Urine samples were not taken so no 2-thiothiazolidine-4-carboxylic acid (TTCA) concentrations, a urinary metabolite of carbon disulfide, were determined. Blood specimens were analyzed for free carbon disulfide with a validated method by analyzing the headspace over the samples using gas chromatography with flame photometric detection with sulfur mode filter using methyl sulfide as the internal standard. The limit of quantitation (LOQ) was 1 or 2 ug/mL, dependent on the data obtained from the standards on each day of analysis.

TK PARAMETERS PROTOCOL (cont'd)

TK_INHALATION BLOOD

800 ppm

Two sets of 6 cannulated rats were exposed once to carbon disulfide at 800 ppm for 180 minutes in nose-only exposure tubes. Blood samples were collected from one set of rats (set 1) at 4, 8, 15, 30, 60, and 180 minutes at the start of exposure and 4 (184), 8 (188), and 15 (195) minutes after the termination of exposure to determine the rapid uptake and elimination time constants. Blood was collected from the second set of rats (set 2) 60 and 180 minutes at the start of the exposure and 30 (210), 60 (240), 90 (270), 120 (300), 180 (360), and 240 (420) minutes after the termination of the exposure to determine the terminal elimination time constant. Data from both sets (Groups 4 and 5, total n of 11 without Rat 1) were combined for toxicokinetic analysis. Start date is analysis laboratory given start date. Urine samples were not taken so no 2-thiothiazolidine-4-carboxylic acid (TTCA) concentrations, a urinary metabolite of carbon disulfide, were determined. Blood specimens were analyzed for free carbon disulfide with a validated method by analyzing the headspace over the samples using gas chromatography with flame photometric detection with sulfur mode filter using methyl sulfide as the internal standard. The limit of quantitation (LOQ) was 1 or 2 ug/mL, dependent on the data obtained from the standards on each day of analysis.