

Experiment Number: S0594

Route: IV, Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Phenolphthalein / Analyte: Phenolphthalein

CAS Number: 77-09-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: RTI

Male

Treatment Group (mg/kg, ppm)

25 IV Plasma<sup>a,c</sup>

375 Dosed Feed Plasma<sup>b,g</sup>

750 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	210 ± 13	0.0958 ± 0.12	1.05 ± 1.4
AUC_0-T (ug*hr/mL)	56 ± 0.35	0.937 ± 0.15	6.57 ± 1.7

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Treatment Group (ppm)

3000 Dosed Feed Plasma<sup>b,d</sup>

12000 Dosed Feed Plasma<sup>b,g</sup>

50000 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	0.173	0.295 ± 0.37	0.201 ± 0.044
AUC_0-T (ug*hr/mL)	2.69 ± 0.17	3.12 ± 0.51	2.80 ± 0.20

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Female

Treatment Group (mg/kg, ppm)

25 IV Plasma<sup>a,e</sup>

375 Dosed Feed Plasma<sup>b,f</sup>

750 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	166	0.169	0.938 ± 1.5
AUC_0-T (ug*hr/mL)	43 ± 0.69	0.566 ± 0.00	4.23 ± 1.8

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Female

Treatment Group (ppm)

3000 Dosed Feed Plasma<sup>b,g</sup> 12000 Dosed Feed Plasma<sup>b,d</sup> 50000 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	0.454 ± 0.56	0.762	1.85 ± 3.1
AUC_0-T (ug*hr/mL)	2.10 ± 0.65	3.77 ± 1.5	6.13 ± 3.6

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Species/Strain: Rats/F344

CAS Number: 77-09-8

Lab: RTI

Male

Treatment Group (mg/kg, ppm)

25 IV Plasma<sup>a,h</sup>

375 Dosed Feed Plasma<sup>b,g</sup>

750 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	22.4 ± 1.3	31.4 ± 12	39.8 ± 3.4
AUC_0-T (ug*hr/mL)	290 ± 34	540 ± 32	753 ± 21

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CAS Number: 77-09-8

Lab: RTI

Male

Treatment Group (ppm)

3000 Dosed Feed Plasma<sup>b,g</sup>

2000 Dosed Feed Plasma<sup>b,g</sup>

50000 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	108 ± 6.1	261 ± 32	226 ± 50
AUC_0-T (ug*hr/mL)	2115 ± 40	4752 ± 130	4494 ± 128

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Treatment Group (mg/kg, ppm)

25 IV Plasma<sup>a,h</sup>

375 Dosed Feed Plasma<sup>b,g</sup>

750 Dosed Feed Plasma<sup>b,g</sup>

Cmax_obs (ug/mL)	40.4 ± 34	30.2 ± 12	61.1 ± 15
AUC_0-T (ug*hr/mL)	383 ± 22	508 ± 18	984 ± 29

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CAS Number: 77-09-8

Lab: RTI

Female

Treatment Group (ppm)

3000 Dosed Feed Plasma<sup>b,g</sup>    2000 Dosed Feed Plasma<sup>b,g</sup>    50000 Dosed Feed<sup>b,g</sup>

Cmax_obs (ug/mL)	145 ± 12	271 ± 49	231 ± 14
AUC_0-T (ug*hr/mL)	2747 ± 53	4940 ± 92	4352 ± 117

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LEGEND

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MODELING SOFTWARE

Excel, Version 7

MODELING METHOD & BEST FIT MODEL

<sup>a</sup> Excel, Version 7 used to calculate means and standard deviation for C<sub>max</sub>, C<sub>max</sub> steady state and AUC<sub>24-hr</sub> by trapezoidal rule. Due to the extensive enterohepatic recycling of PTH, classical pharmacokinetic models are not applicable to the calculation of clearance, bioavailability, and other pharmacokinetic parameters for PTH.

<sup>b</sup> Excel, Version 7 used to calculate means and standard deviation for C<sub>max</sub>, C<sub>max</sub> steady state and AUC<sub>24-hr</sub> by trapezoidal rule. To determine AUC<sub>24-hr</sub>, it was assumed that plasma concentrations of PTH and PTH-G in the 10 a.m. sample on day 14 were the same as those in plasma at 10 a.m. on day 15. Mean daily dose is 24.86 mg/kg/day. Due to the extensive enterohepatic recycling of PTH, classical pharmacokinetic models are not applicable to the calculation of clearance, bioavailability, and other pharmacokinetic parameters for PTH.

EXCEPTIONS

<sup>c</sup> C<sub>max</sub> at 2.5 minute timepoint

<sup>d</sup> One sample of the triplicate was below the limit of detection (LOD) of 0.0012 ug/mL. It was assumed that after 14-15 days of continuous exposure to PTH in feed, plasma PTH and PTH-G concentrations were at steady state. (C<sub>max</sub> ss)

<sup>e</sup> One rat was improperly dosed and the data were excluded from the calculation of mean (N is equal to 2) for C<sub>max</sub> 2.5 minute timepoint.

<sup>f</sup> No more than one of three replicates had detectable levels of PTH. SD equals 0. Two samples of the triplicate were below the limit of detection (LOD) of 0.0012 ug/mL. It was assumed that after 14-15 days of continuous exposure to PTH in feed, plasma PTH and PTH-G concentrations were at steady state. (C<sub>max</sub> ss)

<sup>g</sup> It was assumed that after 14-15 days of continuous exposure to PTH in feed, plasma PTH and PTH-G concentrations were at steady state. (C<sub>max</sub> ss)

<sup>h</sup> C<sub>max</sub> at 5 minute timepoint

ANALYTE

Phenolphthalein

Phenolphthalein/Phenolphthalein Glucuronide

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TK PARAMETERS

C<sub>max\_obs</sub> = Observed or Predicted Maximum plasma (or tissue) concentration

AUC<sub>0-T</sub> = Area under the plasma concentration versus time curve, AUC, from time t<sub>i</sub> (initial) to t<sub>f</sub> (final), AUC<sub>last</sub>

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Extracted plasma samples were analyzed by High Performance Liquid Chromatography (HPLC) with a UV detector (230 nm) using bromocresol purple as the internal standard. Plasma PTH concentration at time zero was back extrapolated using the first two timepoints (2.5 and 5 minutes) after dose administration for AUC<sub>24-hr</sub>. Plasma PTH-G concentration at time zero was assumed to be zero. AUC<sub>24-hr</sub> was calculated using the trapezoidal rule for plasma concentrations from time zero to 24 hours.

TK\_INTRAVENTOUS PLASMA

25 mg/kg Male and Female

Animals received a single intravenous dose. Rats were sampled twice. 3 animals/species/sex/dose per timepoint. 15 timepoints 24 rats and 45 mice per group.

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TK\_PARAMETERS PROTOCOL (cont'd)

ANALYSIS METHOD

Extracted plasma samples were analyzed by High Performance Liquid Chromatography (HPLC) with a UV detector (230 nm) using bromocresol purple as the internal standard. Cmax values are mean plus or minus standard deviations with n equal to 3.

TK\_DOSED FEED PLASMA

375 ppm, 750 ppm, 3000 ppm, 12000 ppm, 50000 ppm Male and Female

For multiple dose feed studies, rats and mice received dosed feed for 14-15 days. Plasma samples were collected at 2 hour intervals for 22 hours from 10 a.m. on day 14 through 8 a.m. on day 15. Three animals/species/sex/dose per timepoint (12 timepoints). Mouse Studies C-R and H-R shown as Cr and Hr are repeat studies. Extra animals are included in body weight calculations. Number of animals is 36 except for Study N which had 35 animals.