

Experiment Number: K03014
Route: Inhalation
Species/Strain: Rat/Sprague-Dawley

Toxicokinetics Data Summary
Compound/Analyte: Alpha-Pinene/Alpha-Pinene
CAS Number: 80-56-8

Request Date: 10/27/2020
Request Time: 2:30:16
Lab: RTI

Male Blood

Treatment Group (ppm)

50^a

100^a

Cmax_pred (ng/mL)	863 ± 92.1	7740 ± 2230
Alpha (hour ⁻¹)	1.06 ± 0.299	4.58 ± 1.35
Alpha_Half-life (hour)	0.656 ± 0.185	0.151 ± 0.0446
Beta (hour ⁻¹)	0.0567 ± 0.0425	0.0541 ± 0.0965
Beta_Half-life (hour)	12.2 ± 9.15	12.8 ± 22.9
k10 (hour ⁻¹)	0.421 ± 0.130	1.75 ± 1.54
k10_Half-life (hour)	1.65 ± 0.508	0.396 ± 0.349
k12 (hour ⁻¹)	0.550 ± 0.235	2.74 ± 1.73
k21 (hour ⁻¹)	0.143 ± 0.108	0.142 ± 0.187
Cl1 (mL/h/kg)	34600 ± 9990	32100 ± 27100
Cl2 (mL/h/kg)	45300 ± 17300	50300 ± 30000
V1 (mL/kg)	82300 ± 8790	18300 ± 5290
V2 (mL/kg)	318000 ± 225000	356000 ± 557000
Vss (mL/kg)	400000 ± 227000	374000 ± 557000
AUC_0-T (h*ng/mL)	2050 ± 592	4420 ± 3730

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50^a

100^a

Cmax_pred (ng/mL)	1340 ± 184	10800 ± 1940
Alpha (hour ⁻¹)	0.987 ± 0.356	2.61 ± 0.623
Alpha_Half-life (hour)	0.702 ± 0.253	0.266 ± 0.0634
Beta (hour ⁻¹)	0.0399 ± 0.0378	0.0405 ± 0.0734
Beta_Half-life (hour)	17.4 ± 16.5	17.1 ± 30.9
k10 (hour ⁻¹)	0.311 ± 0.145	1.25 ± 0.899
k10_Half-life (hour)	2.23 ± 1.04	0.552 ± 0.395
k12 (hour ⁻¹)	0.590 ± 0.291	1.31 ± 0.955
k21 (hour ⁻¹)	0.127 ± 0.114	0.0843 ± 0.119
Cl1 (mL/h/kg)	17900 ± 7980	17600 ± 12300
Cl2 (mL/h/kg)	34000 ± 14800	18400 ± 13000
V1 (mL/kg)	57700 ± 7950	14000 ± 2510
V2 (mL/kg)	269000 ± 222000	218000 ± 387000
Vss (mL/kg)	326000 ± 224000	232000 ± 388000
AUC_0-T (h*ng/mL)	4300 ± 1910	8640 ± 6010

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Male Blood

Treatment Group (ppm)

50^b

100^b

Cmax_obs (ng/mL)

173

220

Tmax_obs (hour)

0.167

0.830

Lambda_z (hour⁻¹)

0.0488

0.0360

Half-life (hour)

14.2

19.2

AUCinf_pred (h*ng/mL)

1260

1820

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Female Blood

Treatment Group (ppm)

	50 ^b	100 ^b
Cmax_obs (ng/mL)	317	498
Tmax_obs (hour)	0.167	0.167
Lambda_z (hour ⁻¹)	0.0552	0.0600
Half-life (hour)	12.6	11.6
AUCinf_pred (h*ng/mL)	1200	1680

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Male Blood

Treatment Group (ppm)

50 °

100 °

Cmax_pred (ng/mL)	181 ± 10.6	221 ± 11.4
Alpha (hour ⁻¹)	1.17 ± 0.308	1.19 ± 0.254
Alpha_Half-life (hour)	0.593 ± 0.156	0.583 ± 0.125
Beta (hour ⁻¹)	0.0637 ± 0.0107	0.0506 ± 0.00804
Beta_Half-life (hour)	10.9 ± 1.82	13.7 ± 2.17
k10 (hour ⁻¹)	0.158 ± 0.0178	0.138 ± 0.0150
k10_Half_life (hour)	4.38 ± 0.493	5.04 ± 0.551
k12 (hour ⁻¹)	0.604 ± 0.176	0.665 ± 0.154
k21 (hour ⁻¹)	0.471 ± 0.146	0.438 ± 0.111
AUC_0-T (h*ng/mL)	1140 ± 106	1610 ± 149

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Female Blood

Treatment Group (ppm)

50 °

100 °

Cmax_pred (ng/mL)	321 ± 16.9	534 ± 37.1
Alpha (hour ⁻¹)	1.11 ± 0.210	1.01 ± 0.231
Alpha_Half-life (hour)	0.625 ± 0.118	0.686 ± 0.157
Beta (hour ⁻¹)	0.0823 ± 0.0195	0.0805 ± 0.0305
Beta_Half-life (hour)	8.43 ± 1.99	8.61 ± 3.26
k10 (hour ⁻¹)	0.300 ± 0.0350	0.352 ± 0.0583
k10_Half_life (hour)	2.31 ± 0.270	1.97 ± 0.326
k12 (hour ⁻¹)	0.588 ± 0.132	0.508 ± 0.152
k21 (hour ⁻¹)	0.304 ± 0.0930	0.231 ± 0.101
AUC_0-T (h*ng/mL)	1070 ± 107	1520 ± 220

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Male Mammary

Treatment Group (ppm)

50^d

100^d

Cmax_obs (ng/g)	73900	103000
Tmax_obs (hour)	0.250	0.500
Lambda_z (hour ⁻¹)	0.0431	0.0988
Half-life (hour)	16.1	7.02
Cl (g/h/kg)	138	125
AUCinf_pred (h*ng/g)	515000	1130000

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Female Mammary

Treatment Group (ppm)

50^d

100^d

Cmax_obs (ng/g)	135000	245000
Tmax_obs (hour)	0.500	0.500
Lambda_z (hour ⁻¹)	0.0636	0.0329
Half-life (hour)	10.9	21.1
Cl (g/h/kg)	29.1	26.5
AUCinf_pred (h*ng/g)	2650000	5740000

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Male Mammary (lipid adjusted)

Treatment Group (ppm)

50^e

100^e

Cmax_obs (ng/g lipid)	663000	1300000
Tmax_obs (hour)	0.250	0.500
Lambda_z (hour ⁻¹)	0.0802	0.0915
Half-life (hour)	8.64	7.58
Cl (g/h/kg)	15.5	13.4
AUCinf_pred (h*ng/g)	4580000	10600000

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Female Mammary (lipid adjusted)

Treatment Group (ppm)

50^e

100^e

Cmax_obs (ng/g lipid)	1180000	2530000
Tmax_obs (hour)	0.167	0.500
Lambda_z (hour ⁻¹)	0.0393	0.0285
Half-life (hour)	17.6	24.4
Cl (g/h/kg)	2.71	3.37
AUCinf_pred (h*ng/g)	28400000	45100000

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Male Mammary

Treatment Group (ppm)

50^f

100^f

Cmax_obs (ng/g)	6940	8930
Tmax_obs (hour)	0.167	0.250
Lambda_z (hour ⁻¹)	0.0828	0.0633
Half-life (hour)	8.37	11.000
AUCinf_pred (h*ng/g)	44200	63800

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Female Mammary

Treatment Group (ppm)

50^f

100^f

Cmax_obs (ng/g)	9310	14600
Tmax_obs (hour)	0.0830	0.500
Lambda_z (hour ⁻¹)	0.0402	0.0939
Half-life (hour)	17.2	7.38
AUCinf_pred (h*ng/g)	68100	123000

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Male Mammary (lipid adjusted)

Treatment Group (ppm)

50^g

100^g

Cmax_obs (ng/g lipid)	34800	34800
Tmax_obs (hour)	0.0830	0.500
Lambda_z (hour ⁻¹)	0.0855	0.0849
Half-life (hour)	8.10	8.16
AUCinf_pred (h*ng/g)	178000	227000

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Female Mammary (lipid adjusted)

Treatment Group (ppm)

50^g

100^g

Cmax_obs (ng/g)	38300	76600
Tmax_obs (hour)	0.333	0.500
Lambda_z (hour ⁻¹)	0.0778	0.0838
Half-life (hour)	8.90	8.28
AUCinf_pred (h*ng/g)	322000	491000

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LEGEND

MODELING METHOD & BEST FIT MODEL

^a Phoenix WinNonlin (Version 6.4), two-compartment

^b Phoenix WinNonlin (Version 6.4), noncompartmental, Because APO is a metabolite of AP, no parameters calculated from exposure (i.e., clearance, volume, C_{max}/D, AUC/D) are reported. AUC_{inf_pred} is actually the observed value.

^c Phoenix WinNonlin (Version 6.4), two-compartment, Because APO is a metabolite of AP, no parameters calculated from exposure (i.e., clearance, volume, C_{max}/D, AUC/D) are reported.

^d Phoenix WinNonlin (Version 6.4), noncompartmental, Non-lipid adjusted data, concentration is expressed as ng/g mammary tissue

^e Phoenix WinNonlin (Version 6.4), noncompartmental, Concentration (ng/g) for lipid adjusted data is expressed as ng/g lipid in mammary tissue

^f Phoenix WinNonlin (Version 6.4), noncompartmental, Non-lipid adjusted data, concentration is expressed as ng/g mammary tissue. Because APO is a metabolite of AP, no parameters calculated from exposure (i.e., clearance, volume, C_{max}/D, AUC/D) are reported.

^g Phoenix WinNonlin (Version 6.4), noncompartmental, Concentration (ng/g) for lipid adjusted data is expressed as ng/g lipid in mammary tissue. Because APO is a metabolite of AP, no parameters calculated from exposure (i.e., clearance, volume, C_{max}/D, AUC/D) are reported.

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ANALYTE

Alpha-Pinene, Alpha-Pinene oxide

TK PARAMETERS

C_{max} = Observed or Predicted Maximum plasma (or tissue) concentration

T_{max} = Time at which C_{max} predicted or observed occurs

Lambda_z = Non-compartmental analysis (NCA) terminal elimination rate constant, NCA ke or kelim

Half_{life} = Lambda_z Half_{life}, t_{1/2}, the terminal elimination half-life based on non-compartmental analysis

Alpha = Hybrid rate constant of the alpha phase

Alpha_{Half-life} = Half-life for the alpha phase

Beta = Hybrid rate constant of the beta phase

Beta_{Half-life} = Half-life for the beta phase

k₁₀ = Elimination rate constant from the central compartment also ke or kelim

k_{10 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

Cl₁ = Clearance of central compartment, Cl_{app} or apparent clearance for intravenous groups

Cl₂ = Clearance of the secondary compartment

V₁ = Volume of distribution of the central compartment, includes V_d and V volume of distribution, V_z apparent volume of distribution

NCA, V_{app} apparent volume of distribution for intravenous studies

V₂ = Volume of distribution for the peripheral compartment

V_{ss} = Volume of distribution at steady state

AUC_{0-T} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

AUC_{inf} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

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TK PARAMETERS PROTOCOL

Rat Blood and Mammary Tissue

50 ppm Rat Male, 50 ppm Rat Female, 100 ppm Rat Male, 100 ppm Rat Female

Male and female Harlan Sprague Dawley rats were exposed by whole body inhalation for 6 hours plus T90 per day for 7 consecutive days. Dose was calculated for individual animals and the average inhaled dose for the groups in mg/kg (71 and 142 mg/kg for male rats at 50 and 100 ppm, respectively; 77 and 152 mg/kg for female rats at 50 and 100 ppm, respectively). The mg/kg doses are the estimated theoretical inhaled doses and not the doses absorbed from the respiratory tract. Both males and females were 69 days old at first exposure. Body weights ranged 256.2 to 281.8 g for males and 165.8 to 192.7 females at randomization. N = 39 animals/sex/group. Blood and mammary tissues were analyzed for alpha pinene and its metabolite alpha pinene oxide. Animals were fed irradiated NTP-2000 wafer feed available ad libitum, except during exposure. Water was available ad libitum. On Day 0, prior to the start of exposures, whole blood samples were collected from three rats per sex while the animals were under 70% CO₂/30% O₂ anesthesia via the orbital plexus to determine background levels of analyte. Animals were immediately returned to the exposure chamber to continue on study. Beginning on Day 6, whole blood samples were collected from three animals/sex/group via the retro-orbital plexus while under 70% CO₂/30% O₂ anesthesia at the following time points: pre-exposure (0 minutes) and post-exposure times of 5, 10, 15, 20, and 30 minutes, and 1, 2, 4, 8, 12, 24, and 48 hours. Following terminal blood collection, mammary glands were collected. All samples were stored at ultracold temperatures. Alpha pinene and alpha pinene oxide concentrations in blood and mammary glands were determined using validated analytical methods. All variance listed for the parameters is standard error (\pm SE).