Experiment Number: S0555
Route: IV, Dermal
Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: DL-Camphor / **Analyte:** DL-Camphor
CAS Number: 21368-68-3

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: RTI

Male

	Treatment Group (mg/kg)				
	6 IV Plasma[a,h]	**50 Dermal Plasma[a,i]**	**200 Dermal Plasma[a,j]**	**200 Dermal Plasma[a,k]**	**200 Dermal Plasma[a,l]**
Beta (minute^{-1})	0.0338	0.0041	0.0043	0.0030	0.0030
Beta Half-life (minute)	185	168	161	230	230
Cl (L/min/kg)	0.0430				
Cl1_F (L/min/kg)		1.93	2.60	2.61	1.83
V1 (L/kg)	11.5	470	602	867	607
MRT (minute)	165	209	237	244	236
AUCinf_pred (ug/mL*mir	156914	20789	63848	76657	92827
F		0.0222	0.0165	0.0165	0.0235

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Male

	Treatment Group (mg/kg)			
	200 Dermal Plasma[b]	**200 Dermal Plasma[c]**	**200 Dermal Plasma[d]**	**400 Dermal Plasma[a,m]**
Beta (minute^{-1})				0.0023
Beta Half-life (minute)				303
k01 (minute-1)	0.100 ± 0.13	0.102 ± 0.12	0.0950 ± 0.11	
k10 (minute^{-1})	0.0110 ± 0.0035	0.0108 ± 0.0036	0.0105 ± 0.0033	
Cl1_F (L/min/kg)				2.01
V1 (L/kg)	2.90 ± 0.68	2.74 ± 0.68	2.53 ± 0.60	880
MRT (minute)				542
AUCinf_pred (ug/mL*min)				172514
F				0.0214

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Female

	Treatment Group (mg/kg)				
	6 IV Plasma[a,n]	**50 Dermal Plasma[a,o]**	**200 Dermal Plasma[a,p]**	**200 Dermal Plasma[a,q]**	**200 Dermal Plasma[a,r]**
Beta (minute^{-1})	0.0059	0.0028	0.0061	0.0051	0.0042
Beta Half-life (minute)	118	246	113	136	164
Cl1_F (L/min/kg)		4.81	7.96	2.44	2.30
Cl (L/min/kg)	0.0544				
V1 (L/kg)	9.25	1710	1295	479	543
MRT (minute)	128	327	178	176	182
AUCinf_pred (ug/mL*mir	123068	8480	21100	82045	72767
F		0.0113	0.00683	0.0223	0.0237

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Female

	Treatment Group (mg/kg)			
	200 Dermal Plasma[e]	**200 Dermal Plasma[f]**	**200 Dermal Plasma[g]**	**400 Dermal Plasma[a,s]**
Beta (minute^{-1})				0.0073
Beta Half-life (minute)				94.4
k01 (minute-1)	0.0957 ± 0.16	0.119 ± 0.14	0.107 ± 0.11	
k10 (minute^{-1})	0.0110 ± 0.0033	0.0103 ± 0.0030	0.0107 ± 0.0030	
Cl1_F (L/min/kg)				6.48
V1 (L/kg)	3.76 ± 0.82	4.24 ± 0.90	3.84 ± 0.79	883
MRT (minute)				120
AUCinf_pred (ug/mL*min)				53694
F				0.00839

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LEGEND

MODELING SOFTWARE

WinNonlin, Version 1.0

MODELING METHOD & BEST FIT MODEL

[a] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Noncompartmental analysis (WinNonlin Models 200 or 201)

[b] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin) with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time. O and Y simultaneously solved iv and single administration mid dose dermal protected, male rats.

[c] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin) with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time. O and AD simultaneously solved iv and single administration mid dose dermal unprotected, male rats.

[d] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin) with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time. O and AG simultaneously solved iv and repeated administraiton mid dose dermal unprotected, male rats.

[e] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin) with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time. P and Z simultaneously solved iv and single administration mid dose dermal protected, female rats.

[f] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time). P and AE simultaneously solved iv and single administration mid dose dermal unprotected, female rats.

[g] WinNonlin, Version 1.0 (Scientific Consulting Inc., 1995), Compartmental models were written to simultaneously solve iv and dermal data sets (WinNonlin) with 1/YHAT weighting, where YHAT is the predicted plasma d,l-camphor concentration at a given time. P and AH simultaneously solved iv and repeated administration mid dose dermal unprotected, female rats.

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EXCEPTIONS

MALE

[h]Beta range is 60-600 minutes, V1 is V beta, F prime, which takes into account the evaporation loss of CAM from the dermal application site, is not applicable for intravenously dosed animals.

[i]Beta range is 180-480 minutes, V1 is V beta, F prime is 0.0742 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[j]Beta range is 20-720 minutes, V1 is V beta, F prime is 0.0552 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[k]Beta range is 120-960 minutes, V1 is V beta, F prime is 0.0550 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[l]Beta range is 120-960 minutes, V1 is V beta, F prime is 0.0783 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[m]Beta range is 10-1440 minutes, V1 is V beta, F prime is 0.0713 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

EXCEPTIONS (cont'd)

FEMALE

[n]Beta range is 15-600 minutes, V1 is V beta, F prime is which into account the evaporation loss of CAM from the dermal application site is not applicable for intravenously dosed animals.

[o]Beta range is 120-240 minutes, V1 is V beta, F prime is 0.0377 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[p]Beta range is 10-360 minutes, V1 is V beta, F prime is 0.0228 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[q]Beta range is 60-480 minutes, V1 is V beta, F prime is 0.0743 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[r]Beta range is 120-720 minutes, V1 is V beta, F prime is 0.0790 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

[s]Beta range is 45-480 minutes, V1 is V beta, F prime is 0.0280 which takes into account the evaporation loss of CAM from the dermal application site. The effective dose (0.30 x administered dose) was used to calculate F prime.

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ANALYTE

DL-Camphor

TK PARAMETERS

Beta = Hybrid rate constant of the beta phase
Beta Half-life = Half-life for the beta phase
k01 = Absorption rate constant, ka
k10 = Elimination rate constant from the central compartment also ke or kelim
Cl = Clearance, includes total clearance
Cl1_F = Apparent clearance of the central compartment, also Cl_F for gavage groups in non-compartmental model
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
MRT = Mean residence time
AUCinf_pred = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity
F = Bioavailability, absolute bioavailability

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TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Each rat provided 1 or 2 plasma samples. Blood was collected for 9-11 time points using 3 rats/dose/sex or 5 rats/dose/sex (for the later dermal time points). The blood samples were analyzed by capillary gas chromatography (GC) with a flame ionization detector (FID).

TK_INTRAVENOUS PLASMA

6 mg/kg Male and Female

Single intravenous doses of d,l-Camphor were administered to the tail vein. For dermal studies, rats were administered a single dermal dose of 0.75 mL/kg body weight of the dosing solution within an approximately 1 inch square, clipped area on the mid dorsal region of the back. Some groups had the site of administration protected (but not occluded) from grooming to prevent oral absorption (Protected), whereas other groups had the site of administration unprotected to more closely mimic the experimental design of the toxicity studies (Unprotected). An additional group had repeated dermal doses once daily for six days, and on the seventh day blood was collected after the seventh final dose. The repeated dose group administration site was unprotected.

TK_DERMAL PLASMA

50 mg/kg, 200 mg/kg, 400 mg/kg Male and Female

Single intravenous doses of d,l-Camphor were administered to the tail vein. For dermal studies, rats were administered a single dermal dose of 0.75 mL/kg body weight of the dosing solution within an approximately 1 inch square, clipped area on the mid dorsal region of the back. Some groups had the site of administration protected (but not occluded) from grooming to prevent oral absorption (Protected), whereas other groups had the site of administration unprotected to more closely mimic the experimental design of the toxicity studies (Unprotected). An additional group had repeated dermal doses once daily for six days, and on the seventh day blood was collected after the seventh final dose. The repeated dose group administration site was unprotected.