Experiment Number: S0555
Route: IV, Dermal
Species/Strain: Mouse/B6C3F1

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)				
	50 IV Plasma[a,f]	**200 Dermal Plasma[a,g]**	**500 Dermal Plasma[a,h]**	**500 Dermal Plasma[a,i]**	**500 Dermal Plasma[a,j]**
Beta (minute^{-1})	0.0337	0.0105	0.0076	0.0304	0.0091
Beta Half-life (minute)	20.5	66.0	91.5	22.8	75.8
Cl (L/min/kg)	0.121				
Cl1_F (L/min/kg)		15.1	17.7	23.7	22.2
V1 (L/kg)	3.59	1438	2333	780	2434
MRT (minute)	16.6	104	140	38.7	115
AUCinf_pred (ug/mL*mir	391079	11457	23924	16944	18878
F		0.00803	0.00686	0.00511	0.00545

Experiment Number: S0555
Route: IV, Dermal
Species/Strain: Mouse/B6C3F1

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)			
	500 Dermal Plasma[b]	**500 Dermal Plasma[c]**	**500 Dermal Plasma[d]**	**1000 Dermal Plasma[a,k]**
Beta (minute^{-1})				0.0062
Beta Half-life (minute)				112
k01 (minute-1)	0.0100 ± 0.0045	0.0571 ± 0.037	0.0120 ± 0.0066	
k10 (minute^{-1})	0.0593 ± 0.0044	0.0664 ± 0.0066	0.0610 ± 0.0050	
Cl1_F (L/min/kg)				15.6
V1 (L/kg)	2.02 ± 0.16	1.89 ± 0.21	1.99 ± 0.18	2522
MRT (minute)				188
AUCinf_pred (ug/mL*mir				59483
F				0.00777

Experiment Number: S0555
Route: IV, Dermal
Species/Strain: Mouse/B6C3F1

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

Female

	Treatment Group (mg/kg)		
	50 IV Plasma[a,l]	**200 Dermal Plasma[a,m]**	**500 Dermal Plasma[a,n]**
Beta (minute^{-1})	0.0335	0.0053	0.0062
Beta Half-life (minute)	20.7	131	112
Cl (L/min/kg)	0.152		
Cl1_F (L/min/kg)	16.6	24.2	
V1 (L/kg)	4.52	3129	3933
MRT (minute)	17.4	226	190
AUCinf_pred (ug/mL*min)	309567	10782	17863
F		0.00913	0.00625

Experiment Number: S0555
Route: IV, Dermal
Species/Strain: Mouse/B6C3F1

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

Female

	Treatment Group (mg/kg)	
	500 Dermal Plasma[e]	**1000 Dermal Plasma[a,o]**
Beta (minute^{-1})		0.0067
Beta Half-life (minute)		104
k01 (minute^{-1})	0.100 ± 0.0046	
k10 (minute^{-1})	0.0571 ± 0.0043	
Cl1_F (L/min/kg)	22.5	
V1 (L/kg)	2.59 ± 0.21	3368
MRT (minute)		142
AUCinf_pred (ug/mL*min)		42010
F		0.00674

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. M and S simultaneously solved iv and single administration mid dose dermal protected, male mice.

[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. M and AC simultaneously solved iv and single administration mid dose dermal unprotected, male mice.

[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. M and AF simultaneously solved iv and repeated administration mid dose dermal unprotected, male mice.

[e] 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. N and T simultaneously solved iv and single administration mid dose dermal protected, female mice.

EXCEPTIONS

MALE

[f]Beta range is 60-180 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.

[g]Beta range is 10-300 minutes, V1 is V beta, F prime is 0.0268 which 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.

[h]Beta range is 10-360 minutes, V1 is V beta, F prime is 0.0229 which 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.

[i]Beta range is 10-120 minutes, V1 is V beta, F prime is 0.0170 which 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 10-360 minutes, V1 is V beta, F prime is 0.0182 which 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 10-480 minutes, V1 is V beta, F prime is 0.0259 which 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.

FEMALE

[l]Beta range is 30-180 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.

[m]Beta range is 10-300 minutes, V1 is V beta, F prime is 0.0304 which 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.

[n]Beta range is 10-360 minutes, V1 is V beta, F prime is 0.0208 which 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.

[o]Beta range is 45-480 minutes, V1 is V beta, F prime is 0.0225 which 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.

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

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Blood was collected for 9-11 time points using 3 mice/dose/sex or 5 mice/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

50 mg/kg Male and Female

Single intravenous doses of d,l-Camphor were administered to the tail vein. For dermal studies, mice were administered a single dermal dose of 2 mL/kg body weight of the dosing solution within an approximately 1/2 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

200 mg/kg, 500 mg/kg, 1000 mg/kg Male and Female

Single intravenous doses of d,l-Camphor were administered to the tail vein. For dermal studies, mice were administered a single dermal dose of 2 mL/kg body weight of the dosing solution within an approximately 1/2 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.