

Experiment Number: K10262
Route: Intravenous, Gavage
Species/Strain: Rats/Fischer 344/N

Toxicokinetics Data Summary
Compound: Isoeugenol/ Analyte: Isoeugenol
CAS Number: 97-54-1

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

Male

Treatment Group (mg/kg)

17 IV Plasma^{a,c} 17 Gavage Plasma^b 35 Gavage Plasma^b 140 Gavage Plasma^b

C ₀ min _{pred} (ug/mL)	10.5 ± 1.2			
C _{max_obs} (ug/mL)		0.192 ± 0.022	1.02 ± 0.41	2.06 ± 0.73
T _{max_obs} (minute)		10	20	20
Alpha (min ⁻¹)	0.0869 ± 0.0064			
Alpha Half-life (min)	7.98 ± 0.59			
Beta (min ⁻¹)	0.0100 ± 0.0009			
Beta Half-life (min)	69.1 ± 6.2			
Cl (mL min ⁻¹ kg ⁻¹)	110 ± 2			
Cl _{1_F} (mL*min ⁻¹ *kg ⁻¹)		1062 ± 74	755 ± 65	499 ± 35
V ₁ (L/kg)	11.0 ± 1.0			
AUC _{0-T} (ug/mL*min)	131 ± 3	16.0 ± 1.1	92.7 ± 8.0	280 ± 19
AUC _{inf_pred} (ug mL ⁻¹ min)	146 ± 10			
F (percent)		17 ± 2		

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Female

Treatment Group (mg/kg)

17 IV Plasma^{a,c}

17 Gavage Plasma^b

35 Gavage Plasma^b

140 Gavage Plasma^b

C ₀ min _{pred} (ug/mL)	10.6 ± 0.9			
C _{max_obs} (ug/mL)		0.364 ± 0.103	1.82 ± 0.88	5.91 ± 2.28
T _{max_obs} (min)		10	2	5
Alpha (min ⁻¹)	0.0920 ± 0.0052			
Alpha Half-life (min)	7.54 ± 0.42			
Beta (min ⁻¹)	0.00872 ± 0.00044			
Beta Half-life (min)	79.5 ± 4.1			
Cl (mL min ⁻¹ kg ⁻¹)	105 ± 2			
Cl _{1_F} (mL*min ⁻¹ *kg ⁻¹)		564 ± 53	455 ± 29	339 ± 13
V ₁ (L/kg)	12.0 ± 0.7			
AUC _{0-T} (ug/mL*min)	139 ± 3	30.1 ± 2.8	154 ± 10	413 ± 16
AUC _{inf_pred} (ug mL ⁻¹ min)	156 ± 7			
F (percent)	11 ± 2			

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LEGEND

MODELING SOFTWARE
PROC NLIN

MODELING METHOD & BEST FIT MODEL

^aA nonlinear least-squares fitting program SAS PROC NLIN, SAS Institute, Inc., Cary, NC, Elimination of IEG was modeled for both species using a biphasic exponential equation $C(t) = A_0e^{-\alpha t} + B_0e^{-\beta t}$ () where C(t) is the plasma IEG concentration at any post-administration time (t), alpha and beta are the rate constants (min⁻¹) obtained from the fit, A₀ and B₀ are the intercepts on the ordinate (concentration) axis of the extrapolated initial and terminal phases, respectively. weighting factor of [mean plasma IEG concentration]⁻²

^bManual, Plasma MEG concentration-versus-time profiles for both species were characterized by an early absorption phase followed by at least one secondary peak which prevented estimation of elimination rates. No modeling was done on the oral gavage data. Parameters were calculated using observed values.

EXCEPTION

^cCl is total clearance, V₁ represents V_{app}

ANALYTE

Isoeugenol

TK PARAMETERS

C_{0min_pred} = Fitted plasma concentration at time zero (IV only)

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

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

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

Cl = Clearance, includes total clearance

Cl_{1_F} = Apparent clearance of the central compartment, also Cl_{1_F} for gavage groups in non-compartmental model

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TK_PARAMETERS (cont'd)

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
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
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

Plasma Isoeugenol (IEG) concentrations were measured using a validated gas chromatography-mass spectrometry (GC-MS) method. Plasma level of detection (LOD) is 0.0009 ug/mL, the limit of quantitation (LOQ) is 0.0031 ug/mL and the plasma experimental level of detection ELOQ is 0.015 ug/mL. All IV dosed rat IEG concentrations were above the LOD and only 3 out of 84 measurements fell between the LOD and the ELOQ. Toxicokinetic parameter estimates following intravenous administration were derived only from those plasma IEG measurements that were above the ELOQ.

TK_INTRAVENTOUS PLASMA

17 mg/kg Male and Female

Animals were weighed the morning of dosing for calculation of the dosing volume. Non-fasted rats were given a single bolus intravenous injection through a Silastic catheter surgically implanted by the supplier followed by approximately 0.5 mL of heparinized saline solution (10 units/mL). Animals were anesthetized with approximately 70 percent CO2-30 percent O2 and blood was collected from rats via the retroorbital sinus using heparinized micro-hematocrit capillary tubes. Rats were bled twice with three rats/sex/time point for 14 time points.

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TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

17 mg/kg, 35 mg/kg, 140 mg/kg Male and Female

Animals were weighed the day prior to dosing for calculation of the dosing volume and given a single gavage dose the next morning. Animals were anesthetized with approximately 70 percent CO₂-30 percent O₂ and blood was collected from rats via the retroorbital sinus using heparinized micro-hematocrit capillary tubes. Rats were bled twice with three rats/sex/time point for 14 time points.