

Experiment Number: K10262
Route: Intravenous, Gavage
Species/Strain: Mouse/B6C3F1

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

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Battelle Northwest Laboratory

Male

Treatment Group (mg/kg)

35 IV Plasma^{a,c}

35 Gavage Plasma^b

70 Gavage Plasma^b

140 Gavage Plasma^b

C ₀ min_pred (ug/mL)	17.1 ± 3.0			
C _{max} _obs (ug/mL)		1.13 ± 0.18	1.27 ± 0.13	1.91 ± 0.14
T _{max} _obs (min)		20	10	20
Alpha (min ⁻¹)	0.0872 ± 0.0068			
Alpha Half-life (min)	7.95 ± 0.62			
Beta (min ⁻¹)	0.00587 ± 0.00162			
Beta Half-life (min ⁻¹)	118 ± 33			
Cl (mLmin ⁻¹ kg ⁻¹)	148 ± 5			
Cl _I _F (mL*min* mLmin ⁻¹ *kg ⁻¹)		522 ± 24	595 ± 26	690 ± 50
V ₁ (L/kg)	25.2 ± 7.0			
AUC _{0-T} (ug mL ⁻¹ min)	197 ± 6	67.0 ± 3.1	118 ± 5	203 ± 15
AUC _{inf} _pred (ug mL ⁻¹ min)	208 ± 23			
F (percent)		34 ± 4		

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Female

Treatment Group (mg/kg)

35 IV Plasma^{a,c}

35 Gavage Plasma^b

70 Gavage Plasma^b

140 Gavage Plasma^b

C ₀ min _{pred} (ug/mL)	18.0 ± 2.5			
C _{max_obs} (ug/mL)		1.94 ± 0.17	2.54 ± 0.17	3.99 ± 2.10
T _{max_obs} (min)		10	20	5
Alpha (min ⁻¹)	0.0666 ± 0.0045			
Alpha Half-life (min)	10.4 ± 0.7			
Beta (min ⁻¹)	0.00679 ± 0.00131			
Beta Half-life (min ⁻¹)	102 ± 20			
Cl (mLmin ⁻¹ kg ⁻¹)		108 ± 2		
Cl _{1_F} (mL*min* mLmin ⁻¹ *kg ⁻¹)		348 ± 14	338 ± 18	350 ± 31
V ₁ (L/kg)	16.0 ± 3.1			
AUC _{0-T} (ug mL ⁻¹ min)	278 ± 3	101 ± 4	207 ± 11	400 ± 36
AUC _{inf_pred} (ug mL ⁻¹ min)	284 ± 25			
F (percent)		36 ± 3		

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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), α and β are the rate constants (min^{-1}) obtained from the fit, A_0 and B_0 are the intercepts on the ordinate (concentration) axis of the extrapolated initial and terminal phases, respectively. weighting factor of $[\text{mean plasma IEG concentration}]^{-2}$.

^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.

EXCEPTIONS

^cCl is total clearance, V2 represent Vapp

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 of the alpha phase
Beta = Hybrid rate constant of the beta phase
Beta Half-life = Half-life of the beta phase

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TK PARAMETERS (cont'd)

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

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

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_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 mice IEG concentrations were above the LOD and only 14 out of 83 measurements fell between the LOD and the ELOQ.

TK_INTRAVENTOUS PLASMA

35 mg/kg Male and Female

Animals were weighed the morning of dosing for calculation of the dosing volume. Non-fasted mice were given a single bolus intravenous injection through a Silastic catheter surgically implanted by the supplier followed by approximately 0.2 mL of heparinized saline solution (10 units/mL). Three mice/sex were bled at each time point with the exception of the last time point for males where only two animals were available for bleeding. Each mouse was bled only once and the maximum amount of blood was collected via a closed chest cardiac puncture. 14 time points. Animals were anesthetized with approximately 70 percent CO₂-30 percent O₂.

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TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

35 mg/kg, 70 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. Three mice/sex were bled at each time point with the exception of the last time point for males where only two animals were available for bleeding. Each mouse was bled only once and the maximum amount of blood was collected via a closed chest cardiac puncture. 14 time points. Animals were anesthetized with approximately 70 percent CO₂-30 percent O₂.