

Methods for Determining Dose - Exposure Linearity (Dose Proportionality)

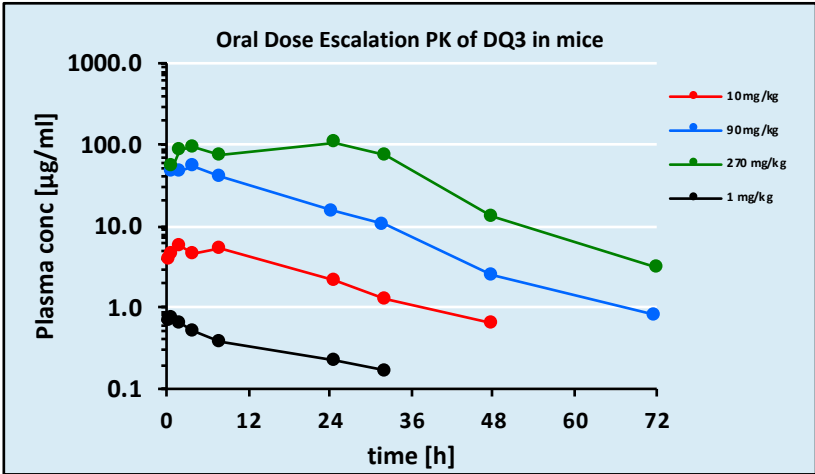
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To determine a dose range for a pharmacology study, a oral single ascending dose pharmacokinetic study was done in mice (table 1). The relationship between dose and AUC was explored to evaluate linearity of PK and dose proportionality using NCA, dose normalized plots, and AUC v Dose plots.

Table 1: Mean plasma concentration-time data of DQ3 in mice following single ascending oral doses

time [h]	Mean plasma conc. [µg/ml]			
	1 mg/kg	10 mg/kg	90 mg/kg	270 mg/kg
0.5	0.67	4.00	NE	NE
1	0.73	4.68	46.02	56.54
2	0.63	5.73	46.63	84.57
4	0.53	4.57	54.12	92.60
8	0.37	5.39	40.11	76.99
25	0.22	2.08	15.10	104.88
32	0.17	1.31	10.21	74.71
48	BLOQ	0.64	2.43	12.89
72	BLOQ	BLOQ	0.80	3.10

Graphical evaluation of PK curves



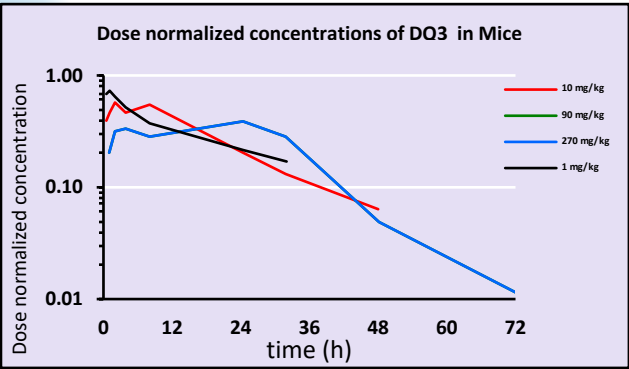
NCA PK Parameters estimated

Parameter	NCA PK Parameters			
Dose [mg/kg]	1.0	10.0	90	270
K _e [h ⁻¹]	0.036	0.054	0.063	0.077
t _{1/2} [h]	19.25	12.90	10.94	9.01
T _{max} [h]	1	2	4.5	24.3
C _{max} [µg/ml]	0.730	5.730	54.120	104.880
C _{max} /Dose	0.0007	0.0006	0.0006	0.0004
AUC _{INF_pred} [µg.h/ml]	15	135	1008	3547
AUC _{%Extrap_pred}	29.96	8.31	1.12	1.01
V/F [ml/kg]	1910	1381	1410	990
Cl/F [ml/h/kg]	69	74	89	76

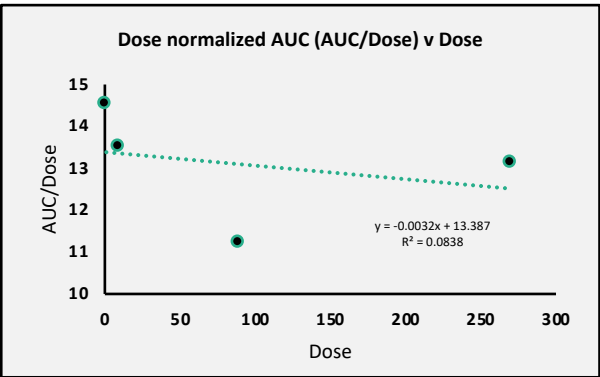
Dose proportionality estimation

Dose proportionality of AUC of DQ3 in mice								
Dose (mg/kg)	AUC _{inf} (µg.h/ml)	CL/F (ml/h/kg)	AUC/Dose	Model Predicted AUC	Log Dose	Log AUC	Predicted Log AUC	Model Predicted AUC
1	15	69	14.5	-29	0.000	1.163	1.156	14
10	135	74	13.5	89	1.000	2.129	2.125	133
90	1008	89	11.2	1140	1.954	3.003	3.051	1124
270	3547	76	13.1	3505	2.431	3.550	3.513	3261

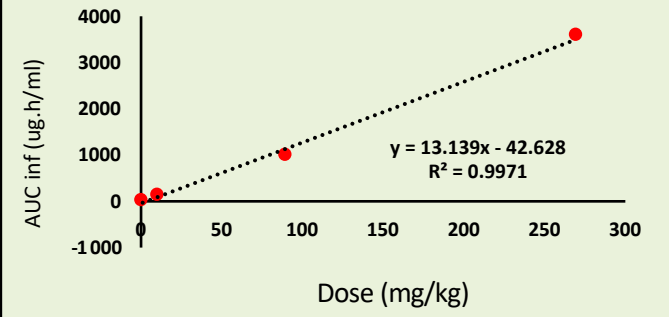
Dose normalized concentrations



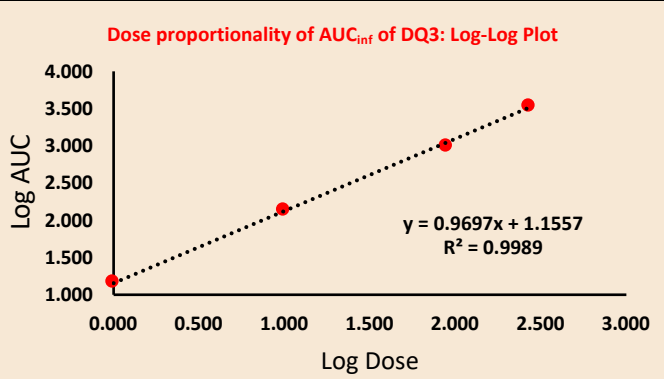
Plot of Dose normalized AUC v Dose



Dose Proportionality of AUC_{inf} of DQ3: Linear plot



Graphical estimation of linearity of AUC v Dose



Oral clearance (CL/F) was similar across doses. Dose normalized concentrations tended to superimpose. AUC/Dose ratios were similar across doses. AUC showed linear increase with dose with Log-Log plot showing a better fit than linear plot. No apparent trend between dose normalized AUC with dose

Conclusion: DQ3 demonstrated linear pharmacokinetics with dose proportional increase in AUC between 1 mg/kg and 270 mg/kg in mice