

Experiment Number: S0545

Toxicokinetics Data Summary

Request Date: 7/11/2023

Route: IV, Gavage

Compound: Di-n-butyl Phthalate/ Analyte: Mono-n-butyl Phthalate

Request Time: 10:03:16

Species/Strain: Rats/Sprague-Dawley

CAS Number: 84-74-2

Lab: RTI

Male

Treatment Group (mg/kg)

20 IV Plasma^{b,d}

20 IV Plasma^a

Cmax_obs (ug/mL)	44.8	
Alpha (minute ⁻¹)		0.0593 ± 0.012
Beta (minute ⁻¹)		0.000710 ± 0.0011
Beta Half-life (minute)	163	
k01 (minute ⁻¹)		0.0289 ± 0.0057
k10 (minute ⁻¹)		0.0246 ± 0.018
k12 (minute ⁻¹)		0.0337 ± 0.017
K21 (minute ⁻¹)		0.00171 ± 0.0017
Cl (mL*min/kg)	11.0	
V1 (L/kg)		0.407 ± 0.082
MRT (minute)	122	
AUCinf_pred (ug/mL*min)	1450	

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Treatment Group (mg/kg)

50 Gavage Plasma^{b,d}

100 Gavage Plasma^{b,e}

200 Gavage Plasma^{b,f}

	50 Gavage Plasma ^{b,d}	100 Gavage Plasma ^{b,e}	200 Gavage Plasma ^{b,f}
Cmax_obs (ug/mL)	21.0	42.0	123
Tmax_obs (minute)	20	30	60
Beta Half-life (minute)	379	290	279
Cl (mL*min/kg)	17.9	12.3	6.25
MRT (minute)	345	317	254
AUCinf_pred (ug/mL*min)	2230	6493	25583
F	0.62	0.90	1.76

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Species/Strain: Hamster/Syrian-Golden

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Male

Treatment Group (ppm)

1000 Dosed Feed Plasma^c

2000 Dosed Feed Plasma^c

Parameters Not Available

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LEGEND

MODELING METHOD
PCNONLIN

MODELING METHOD & BEST FIT MODEL

^a Compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (PCNONLIN), 2-compartmental model using equations derived from simultaneous fitting the iv and low oral dose data (Studies AB and AC)

^bModels 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Noncompartmental analysis. Secondary rise in plasma concentration indicate that additional factors such as enterohepatic recirculation should be considered in the analysis of the data.

^cModels 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Noncompartmental analysis

EXCEPTIONS

^d16 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf)) is less than 0.90.

^e40 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf)) is less than 0.90

^f80 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf)) is less than 0.90. Replicate 3 at 1440 minutes declared an outlier.

^g160 mg MBP eq per kg.

ANALYTE

Mono-n-butyl Phthalate

Experiment Number: S0545
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TK PARAMETERS

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

Beta = Hybrid rate constant of the beta phase

Beta Half-life = Half-life for the beta phase

k₀₁ = Absorption rate constant, k_a

k₁₀ = Elimination rate constant from the central compartment also k_e or k_{elim}

k₁₂ = Distribution rate constant from first to second compartment

k₂₁ = Distribution rate constant from second to first compartment

Cl = Clearance, includes total clearance

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

MRT = Mean residence time

AUC_{inf_pred} = Area under the plasma concentration versus time curve, AUC, extrapolated to time equals infinity

F = Bioavailability, absolute bioavailability

Experiment Number: S0545
Route: IV, Gavage
Species/Strain: Rats/Sprague-Dawley

Toxicokinetics Data Summary
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CAS Number: 84-74-2

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TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Di-n-butyl phthalate (DBP) and mono-n-butyl phthalate (MBP) were determined by a high performance liquid chromatography (HPLC) method in the plasma of mice, rats, and hamsters using UV detection (275 nm). Dipropyl phthalate was used as an internal standard. Sodium fluoride was added to the samples (present at approximately 0.01 g/mL blood) to inhibit non-specific esterase activity in the blood. Di-n-butyl phthalate (DBP) was found to be rapidly converted to Mono-n-butyl phthalate (MBP) in rodents. Toxicokinetic analyses were performed on MBP plasma concentrations.

TK_INTRA VENOUS PLASMA

20 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints. Blood was collected at selected post-dosing intervals by cardiac puncture under terminal anesthesia for mice and hamsters. Rats were sampled twice from alternating orbital plexus.

TK_GAVAGE PLASMA

50 mg/kg, 100 mg/kg, 200 mg/kg

Mice, Sprague Dawley rats, and Syrian (Golden) hamsters were administered a single intravenous or gavage dose. Blood was collected post-dosing from 3 animals/species/route/dose/timepoint for up to 13 timepoints. Blood was collected at selected post-dosing intervals by cardiac puncture under terminal anesthesia for mice and hamsters. Rats were sampled twice from alternating orbital plexus.

Experiment Number: S0545
Route: IV, Gavage
Species/Strain: Mouse/B6C3F1

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TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

1000 ppm, 2000 ppm

Date given as first exposure is date blood samples were first taken from that group. Mice, Wistar Furth rats, and Syrian hamsters were administered di-n-butyl phthalate (DBP) in certified NIH-07 feed (meal for dosed feed) for 7 days and into the 8th day. On the 7th day blood was taken from one animal per time point for 10-11 timepoints. Blood samples were collected beginning at 10 am on the 7th day and ending at 8 am on the 8th day (mice and rats). On the 7th day blood was taken from one hamster per time point for 10-11 timepoints beginning at 2 pm on day 7 and ending on 10 am (1000 ppm hamster) or noon (20,000 ppm hamster) on day 8. Animals had access to feed ad libitum. Mean dose received (mg DBP/kg body weight/day) excluding days 1-2 and 7-end were 167.13, 3440.91, 70.28, 1323.5, 60.63, and 1187.45 mg/DBP/kg/day for mouse 1000 ppm, mouse 20,000 ppm, rat 1000 ppm, rat 20,000 ppm, hamster 1000 ppm, and hamster 20,000 ppm doses, respectively. Because DBP was found to be rapidly converted to mono-n-butyl phthalate (MBP) in rodents, the kinetics of MBP was also examined following oral and intravenous administration of DBP. Toxicokinetic parameters are for MBP. Although no statement was made in final report, the protocol specified that animals administered DBP by dosed feed were between 11-15 weeks at time of first dose.