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

Toxicokinetics Data Summary
Compound: Di-n-butyl Phthalate/ **Analyte:** Mono-n-butyl Phthalate
CAS Number: 84-74-2

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

Male

Treatment Group (mg/kg)

	20 IV Plasma[a]	**20 IV Plasma[b,e]**
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

Experiment Number: S0545 | **Toxicokinetics Data Summary** | **Request Date:** 7/11/2023

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Species/Strain: Rats/Sprague-Dawley | **CAS Number:** 84-74-2 | **Lab:** RTI

Male

	Treatment Group (mg/kg)		
	50 Gavage Plasma[c,f]	**100 Gavage Plasma[b,g]**	**200 Gavage Plasma[b,h]**
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

Experiment Number: S0545
Route: IV, Dosed Feed, Gavage
Species/Strain: Hamster/Syrian-Golden

Toxicokinetics Data Summary
Compound: Di-n-butyl Phthalate/ **Analyte:** Mono-n-butyl Phthalate
CAS Number: 84-74-2

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

Male

Treatment Group (ppm)	
1000 Dosed Feed Plasma[d]	**20000 Dosed Feed Plasma[d]**

Parameters Not Available

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)

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

[c] Models 200 and 201, PCNONLIN software, SCI Software, Lexington, KY, Noncompartmental analysis

[d] Analyzed using compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (PCNONLIN software, SCI Software, Lexington, KY). Simulations of plasma concentrations after dietary exposure were made using the method of superposition (Yuan, 1993) using a program written by R. D. Austin of RTI and food consumption data provided by NTP (hamster calculations used rat consumption data).

Yuan, J. (1993) Modeling Blood/Plasma Concentrations in Dosed Feed and Dosed Drinking Water Toxicology Studies. Toxicol. Appl. Pharmacol., 119,131-141.

EXCEPTIONS

[e] 16 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf) is less than 0.90.

[f] 40 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf) is less than 0.90

[g] 80 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.

[h] 160 mg MBP eq per kg.

ANALYTE

Mono-n-butyl Phthalate

TK PARAMETERS

Cmax_obs = Observed or Predicted Maximum plasma (or tissue) concentration
Tmax_obs = Time at which Cmax 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, ka
k10 = Elimination rate constant from the central compartment also ke or kelim
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 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

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_INTRAVENOUS 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.

TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

1000 ppm, 20000 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 intravenouse 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.