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 (mg/kg)	
	20 IV Plasma[a,d]	**20 IV Plasma[b]**
Cmax_obs (ug/mL)	35.0	
Beta Half-life (minute)	18.0	
k01 (minute^{-1})		0.0284 ± 0.0052
k10 (minute^{-1})		0.0718 ± 0.018
Cl (mL*min/kg)	20.3	
V1 (L/kg)		0.391 ± 0.10
MRT (minute)	18.0	
AUCinf_pred (ug/mL*min)	788	

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	Treatment Group (mg/kg)		
	67 Gavage Plasma[a,e]	**282 Gavage Plasma[a,f]**	**1333 Gavage Plasma[a,g]**
Cmax_obs (ug/mL)	39.6	167	364
Tmax_obs (minute)	20	40	60
Beta Half-life (minute)	40.4	31.9	358
Cl (mL*min/kg)	20.1	13.4	8.69
MRT (minute)	73.8	90.7	477
AUCinf_pred (ug/mL*min)	2635	16866	122686
F	1.01	1.52	2.34

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

Parameters Not Available

LEGEND

MODELING SOFTWARE

PCNONLIN

MODELING METHOD & BEST FIT MODEL

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

[b] compartmental modeling techniques with established models or models written to simultaneously solve iv and oral data sets (PCNONLIN), 1-compartmental model using equations derived from simultaneous fitting the iv and low oral dose data (Studies X and Y)

[c] 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. Using the 1-compartment equation derived from fitting the iv and low oral data from the toxicokinetic studies, plasma concentrations of mono-n-butyl phthalate (MBP) attained after 7-8 days of dosing with 1000 or 20,000 ppm di-n-butyl phthalate (DBP) in the feed were simulated. Simulated curves not shown.

EXCEPTIONS

[d] 16 mg MBP eq per kg. Concentrations at 2.5 minutes were not used in analysis (clinical signs of lethargy in animals for 3-4 minutes after dosing and anomalous nature of the data).

[e] 53 mg MBP eq per kg. For MRT parameter (Estimate(0-T)/Estimate(inf) is less than 0.90.

[f] 226 mg MBP eq per kg. Data a 600 minute could not be included in the calculation of the terminal half-life.

[g] 1066 mg MBP eq per kg. For MRT parameter and AUCinf pred (Estimate(0-T)/Estimate(inf) is less than 0.90.

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
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
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 PARAMETERS PROTOCOL (cont'd)

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

67 mg/kg, 282 mg/kg, 1333 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 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.