

ADME NTP Study S0915 (+)-Kawain Toxicokinetics

The contractor used (+) Kawain for the test article.

Sex/Species: male F344 rats.

Vehicle: intravenous, plasma:Alkamuls 80:20, (v/v); oral, Alkumuls;

CASRN 1635-33-2

Radiolabeled with carbon-14 randomly in the phenyl ring; DL Kawain, [Phenyl-¹⁴C]. The [¹⁴C](+)-Kawain enantiomer was isolated by HPLC and used in the study.

Studies Performed:

(+) Kawain

- Single 7 mg/kg intravenous dose with blood sampling at 0, 2, 5, 10, 15, 30, 60, 90, 120, 240, 360, and 480 minutes postdose (n=4).
- Single 100 mg/kg gavage dose with blood sampling at 0, 2, 5, 10, 15, 30, 60, 90, 120, 240, 360, and 480 minutes postdose (n=4).

(+) Kawain with Kava (normalized to 100 mg kavalactones/kg)

- Single gavage dose of 100 mg kawain/kg co-administered with kava extract with blood sampling at 0, 2, 5, 10, 15, 30, 60, 90, 120, 240, 360, and 480 minutes postdose (actual average dose of total kavalactones 178 ± 3 mg/kg, n=4).
- Repeat (7 days) gavage dose of kava (normalized to 100 mg kavalactones/kg) followed by a single 100 mg [¹⁴C]kawain/kg gavage dose with blood sampling at 0, 5, 15, 30, 60, 180, 300, 600, 900, 1440 minutes post radiolabeled dose (n=5).

The co-administrated dose consisted of an oral dose of kava supplemented with [¹⁴C]kawain for a final oral dose of 100 mg kawain/kg. For the repeat oral kawain administration, kava extract was given for 7 days followed by a single dose of [¹⁴C](+)-kawain. The average daily dose contribution of kawain was 21.6 ± 0.2 mg/kg and of kavalactones, 102 ± 0.1 mg/kg, for the 7 days of kava extract administration.

Toxicokinetics:

Pharmacokinetic parameters for plasma levels were generated using noncompartmental pharmacokinetic methods with Excel (Microsoft ® Excel 2000). Plasma levels were displayed in figures (not shown) and are shown in a separate individual animal data file.

Bioavailability (F) of kawain following an oral dose was 52% with V_d (volume of distribution) and CL_s (systemic clearance) values of 15 mL/kg and 91mL/min/kg, respectively. The average bioavailability of kawain in the repeated dose study was calculated to be 40%.

Note on Accessibility: Persons with disabilities or using assistive technology may find some documents are not fully accessible. For assistance, contact [Central Data Management](#) or use our [contact form](#) and identify the documents/pages for which access is required. We will assist you in accessing the content of the files. NIEHS has helpful information on accessibility.

Table 1

Individual and Mean Plasma Kawain Pharmacokinetic Parameters in Male Rats

Study	Route	Body Weight kg	Dose mg/kg	Animal ID	C _{max} mg/mL	T _{max} min	λ_z min ⁻¹	T _{1/2α} min	AUC ₀ [∞] min- μg/mL	V _{ss} /F L/kg	CL/F mL/min/ kg
IV	IV	0.180	7.36	PK5-R1	7.48	0	0.0278	24.9	83.7	1.77	87.9
		0.186	7.13	PK5-R2	8.25	0	0.0390	17.8	66.7	1.87	107
		0.186	7.15	PK5-R3	7.35	0	0.0225	30.8	83.5	1.71	85.6
		0.189	7.11	PK5-R4	5.61	0	0.00897	77.3	92.7	5.41	76.7
				Mean	7.17	2.00	0.0246	37.7	81.7	2.67	89.3
				SE	0.556	0.00	0.00624	13.5	5.41	0.907	6.34
Single Dose	Oral	0.201	96.2	PK4-R1	2.34	90	0.0131	53.0	755	27.5	127
		0.212	95.4	PK4-R2	3.26	30	0.00917	75.6	461	32.7	207
		0.211	96.5	PK4-R3	2.42	60	0.0100	69.2	415	28.6	232
		0.207	98.5	PK4-R4	2.51	30	0.00647	107	558	38.8	177
				Mean	2.63	52.5	0.00968	76.2	547	31.9	186
				SE	0.211	14.4	0.00136	11.3	75.2	2.55	22.5
Co-admin- istration of kava	Oral	0.203	98.3	PK6-R1	7.45	30	0.00241	288	2490	17.0	39
		0.204	98.7	PK6-R2	5.38	240	0.00766	90.5	1730	13.5	57
		0.200	102	PK6-R3	4.57	240	0.00396	175	2040	16.4	50
		0.205	98.3	PK6-R4	4.10	90	0.00379	183	1550	19.7	63
				Mean	5.38	150	0.00445	184	1950	16.6	52.5
				SE	0.738	53.4	0.00112	40.4	206	1.25	5.15
Repeated Dose	Oral	0.185	103	PK7-R1	2.86	5	0.00422	164	648	41.0	159
		0.195	97.4	PK7-R2	4.55	60	0.00944	73.5	602	18.7	162
		0.191	102	PK7-R3	9.02	5	0.00677	102	293	24.8	348
		0.184	107	PK7-R4	4.56	5	0.0186	37.3	295	17.3	362
		0.184	103	PK7-R5	2.30	30	0.00831	83.4	409	41.6	252
				Mean	4.66	21.0	0.00946	92.2	450	28.2	257
				SE	1.18	10.9	0.00244	20.9	75.0	5.31	43.6

Table 2
Pharmacokinetic Parameters in Male F-344 Rats After Intravenous Dose of 7 mg/kg Kawain

Animal ID	Body Wt (kg)	Dose (mg/kg)	C _{MAX} (μg/mL)	β (min ⁻¹)	T _{1/2β} (min)	AUC _{0-∞} (μg/min/mL)	V _d (L/kg)	CL _S (mL/min/kg)	α (min ⁻¹)	T _{1/2α} (min)
PK5-R1	0.180	7.36	5.82	0.0309	22.4	83	2.87	88.7	0.157	4.4
PK5-R2	0.186	7.13	4.88	0.0355	19.5	64	3.12	111	0.163	4.3
PK5-R3	0.186	7.15	5.59	0.0289	24.0	82	3.00	86.7	0.133	5.2
PK5-R4	0.189	7.11	3.99	0.0095	72.8	88	8.49	80.9	0.139	5.0
Average ^a	0.185	7.19	5.07	0.026	26.4	79	4.37	91.8	0.148	4.7
SD	0.004	0.12	0.82	0.011	-----	11	2.75	13.2	0.014	-----
CV%	2	2	16	44	-----	13	63	14	10	-----

^a T_{1/2β} and T_{1/2α} average results were calculated as the harmonic means.

Table 3
Pharmacokinetic Parameters in Male F-344 Rats After Oral Dose of 100 mg/kg Kawain

Animal ID	Body Wt. (kg)	Dose (mg/kg)	C _{MAX} (µg/mL)	T _{MAX} (min)	k _{el} (min ⁻¹)	T _{1/2kel} (min)	AUC _∞ (µg/min ² /mL)	V _d /F (L/kg)	CL _S /F (mL/min/kg)	K _a (min ⁻¹)	T _{1/2Ka} (min)
PK4-R1	0.201	96.2	2.34	90	0.0074	93.1	760	17.0	127	0.0126	55
PK4-R2	0.212	95.4	3.26	30	0.0067	104.9	465	31.1	205	0.1552	4.5
PK4-R3	0.211	96.5	2.42	60	0.0084	82.4	416	27.6	232	0.1261	5.5
PK4-R4	0.207	98.5	2.51	30	0.0043	161.3	574	39.9	172	0.0712	9.7
PK4-R5	0.208	99.0	15.9	10	0.0111	62.0	1145	7.74	86.5	1.6089	0.4
Average ^{a,b}	0.208	96.7	2.63	53	0.0067	103.6	554	28.9	184	0.0913	7.6
SD	0.005	1.3	0.42	29	0.0017	-----	153	9.5	45	0.0630	-----
CV%	2	1	16	55	26	-----	28	33	25	69	-----

^a Averages are reported for 4 rats only. Results from rat PK4-R5 were not included in the averages.

^b T_{1/2kel} and T_{1/2Ka} average results were calculated as the harmonic means.

Table 4
Volume of Distribution Systemic Clearance Calculations for PK4 Animals (Oral 100 mg/kg)

Average Area Under the Curve for iv Dose		79					
Average iv Dose Delivered (mg/kg)		7.19					
Animal ID	Oral Dose (mg/kg)	Oral Dose AUC _{0-∞}	V _d /F (L/kg)	V _d (L/kg)	CL _s /F (mL/min/kg)	CL _s (mL/min/kg)	F (%)
PK4-R1	96.2	760	17.0	12.2	127	91.3	72
PK4-R2	95.4	465	31.1	13.8	205	90.9	44
PK4-R3	96.5	416	27.6	10.8	232	91.0	39
PK4-R4	98.5	574	39.9	21.2	172	91.2	53

Table 5
Pharmacokinetic Parameters in Male F-344 Rats After Oral dose of 100 mg/kg Kawain Coadministered With Kava

Animal ID	Body Wt. (kg)	Dose (mg/kg)	C _{MAx} (μg/mL)	T _{MAx} (min)	k _{el} (min ⁻¹)	T _{1/2kel} (min)	AUC _{0-∞} (μg/min ² /mL)	V _d /F (L/kg)	CL _S /F (mL/min/kg)	K _a (min ⁻¹)	T _{1/2Ka} (min)
PK6-R1	0.203	98.3	7.45	30	0.0024	287	1687	16.4	39.4	0.1287	5.38
PK6-R2	0.204	98.7	5.38	240	0.0047	146	1620	11.6	54.8	0.0330	21.03
PK6-R3	0.200	102.1	4.57	240	0.0025	277	1591	17.8	44.4	0.0100	69.04
PK6-R4	0.205	98.3	4.10	90	0.0038	184	1219	16.8	63.5	0.0484	14.31
PK6-R5	0.211	101.9	5.32	60	0.0060	115	1617	10.1	60.7	0.0136	51.15
Average ^{a,b}	0.203	99.4	5.38	150	0.0034	206	1529	15.7	51	0.0550	12.6
SD	0.002	1.8	1.48	107	0.0011	-----	211	2.8	11	0.0516	-----
CV%	1	2	28	71	33	-----	14	18	21	94	-----

^a Averages are reported for 4 rats only. Results from rat PK6-R5 were not included in the averages.

^b T_{1/2kel} and T_{1/2Ka} average results were calculated as the harmonic means.

Table 6
Volume of Distribution Systemic Clearance Calculations for PK6 Animals (Oral 100 mg/kg)
Kawain Coadministered with Kava

Average Area Under the Curve for iv Dose			79				
Average iv Dose Delivered (mg/kg)			7.19				
Animal ID	Oral Dose (mg/kg)	Oral Dose AUC _{0-∞}	V _d /F (L/kg)	V _d (L/kg)	CL _S /F (mL/min/kg)	CL _S (mL/min/kg)	F (%)
PK6-R1	98.3	2492	16.38	37.8	39.4	91	231
PK6-R2	98.7	1801	11.6	19.2	54.8	91	166
PK6-R3	102.1	2298	17.8	36.4	44.4	91	205
PK6-R4	98.3	1549	16.8	24.2	63.5	91	143

Table 7
Pharmacokinetic Parameters in Male F-344 Rats After 7-Day Repeat Oral dose of Kava
Followed by Single Oral Dose of 100 mg/kg Kawain

Animal ID	Body Wt. (kg)	Dose (mg/kg)	C _{MAX} (µg/mL)	T _{MAX} (min)	k _{el} (min ⁻¹)	T _{1/2kel} (min)	AUC _{0-∞} (µg/min ² /mL)	V _d /F (L/kg)	CL _s /F (mL/min/kg)
PK7-R1	0.185	102.7	2.86	5	0.0094	74	568	19.2	181
PK7-R2	0.195	97.4	4.55	60	0.0110	63	628	14.1	155
PK7-R3	0.191	102.4	9.02	5	0.0070	98	301	48.3	340
PK7-R4	0.184	107.0	4.56	5	0.0107	65	304	33.0	352
PK7-R5	0.184	102.6	2.30	30	0.0071	97	414	34.9	248
Average ^a	0.188	102.4	4.66	21	0.0090	77	443	29.9	255
SD	0.005	3.4	2.64	24	0.0019	-----	150	13.6	90
CV%	3	3	57	116	21	-----	34	45	35

^a The average result for T_{1/2kel} was calculated as a harmonic mean.

Table 8
Volume of Distribution Systemic Clearance Calculations for PK7 Animals (Oral 100 mg/kg)
7-Day Repeat Dose of Kava Followed by Single Dose of Kawain

Average Area Under the Curve for iv Dose 79
Average iv Dose Delivered (mg/kg): 7.19

Animal ID	Oral Dose (mg/kg)	Oral Dose AUC _{0-∞}	V _d /F (L/kg)	V _d (L/kg)	CL _s /F (mL/min/kg)	CL _s (mL/min/kg)	F (%)
PK7-R1	102.7	568	19.2	9.7	181	91.1	50
PK7-R2	97.4	628	14.1	8.3	155	91.0	59
PK7-R3	102.4	301	48.3	12.9	340	91.0	27
PK7-R4	107.0	304	33.0	8.5	352	91.0	26
PK7-R5	102.6	414	34.9	12.8	248	91.1	37

Table 9
Pharmacokinetic Parameters in Male F-344 Rats After Single Oral Dose of 100 mg/kg Kawain (PK4)
And After a Single Oral Dose of 100 mg/kg Kawain Following a 7-Day Repeat Oral Dose of Kava (PK7)

Summary of PK4 Pharmacokinetic Parameters

Animal ID	Body Wt (kg)	Dose (mg/kg)	C _{MAX} (µg/mL)	T _{MAX} (min)	k _{el} (min ⁻¹)	T _{1/2kel} (min)	AUC ₀ [∞] (µg/min/mL)	V _d (L/kg)	CL _S (mL/min/kg)	K _a (min ⁻¹)	T _{1/2Ka} (min)	F (%)
PK4-R1	0.201	96.2	2.34	90	0.0074	93	760	12.2	91.3	0.0126	55	71.9
PK4-R2	0.212	95.4	3.26	30	0.0067	105	465	13.8	90.9	0.1552	4.5	44.4
PK4-R3	0.211	96.5	2.42	60	0.0084	82	416	10.8	91.0	0.1261	5.5	39.2
PK4-R4	0.207	98.5	2.51	30	0.0043	161	574	21.2	91.2	0.0712	9.7	53.0
Average ^a	0.208	96.7	2.63	53	0.0067	104	554	14.5	91.1	0.0913	7.6	52.1
SD	0.005	1.3	0.42	29	0.0017	-----	153	4.6	0.2	0.0630	-----	14.4
CV%	2	1	16	55	26	-----	28	32	0	69	-----	28

Summary of PK7 Pharmacokinetic Parameters

Animal ID	Body Wt (kg)	Dose (mg/kg)	C _{MAX} (µg/mL)	T _{MAX} (min)	k _{el} (min ⁻¹)	T _{1/2kel} (min)	AUC ₀ [∞] (µg/min/mL)	V _d (L/kg)	CL _S (mL/min/kg)	K _a ^b (min ⁻¹)	T _{1/2Ka} ^b (min)	F (%)
PK7-R1	0.185	102.7	2.86	5	0.0094	74	568	9.7	91.1	-----	-----	50.3
PK7-R2	0.195	97.4	4.55	60	0.0110	63	628	8.3	91.0	-----	-----	58.7
PK7-R3	0.191	102.4	9.02	5	0.0070	98	301	12.9	91.0	-----	-----	26.8
PK7-R4	0.184	107.0	4.56	5	0.0107	65	304	8.5	91.0	-----	-----	25.9
PK7-R5	0.184	102.6	2.30	30	0.0071	97	414	12.8	91.1	-----	-----	36.7
Average ^a	0.188	102.4	4.66	21	0.0090	77	443	10.4	91.0	-----	-----	39.7
SD	0.005	3.4	2.64	24	0	-----	150	2.3	0.1	-----	-----	14.5
CV%	3	3	57	116	21	-----	34	22	0	-----	-----	37

^a T_{1/2kel} and T_{1/2Ka} average results were calculated as the harmonic means.

^b K_a and T_{1/2Ka} could not be accurately calculated for Study PK7. There was not a clear rise in Kawain concentration.