ADME NTP Study K10260 2-Hydroxy-4-methoxybenzophenone Toxicokinetics

The contractor used the abbreviation HMB for the test article.
Sex/Species: male and female Harlan Sprague Dawley rats.
Vehicle: intravenous, water:ethanol:alkamuls (3:5:2 v:v:v); oral, corn oil.

CASRN 131-57-7

Radiolabeled with carbon-14 uniformly on the unsubstituted phenyl ring; 2-Hydroxy-4-methoxybenzophenone, [benzene-^{14}C(U)]-

Studies Performed:

- Single 10 mg/kg intravenous dose to male rats with blood sampling at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose. (n=5, Group M)

- Single 10 mg/kg intravenous dose to female rats with blood sampling at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose. (n=5, Group N)

- Single 10 mg/kg oral gavage dose to male rats with blood sampling at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose. (n=5, Group K)

- Single 10 mg/kg oral gavage dose to female rats with blood sampling at 0 (predose), 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose. (n=3, Group L)

Toxicokinetics:

Parent plasma concentration versus time data was analyzed by noncompartmental (model independent) methods using validated WinNonlin v. 5.1 (Pharsight, Cary, NC). Mean absorption time (MAT) was calculated as MAT = $MRT_{oral\ gavage} - MRT_{iv}$ (where MRT is mean residence time). Bioavailability (F) was estimated for the extravascular routes of administration relative to the intravenous as a reference route according to the following equation: $f = (AUC_{other} \bullet Dose_{iv})/(AUC_{iv} \bullet Dose_{other})$.

Noncompartmental analysis was also conducted with the exclusion of the 24 hour time point (not shown) to compare TK parameters with minimal impact observed for AUC, implying that the majority of HMB was cleared prior to the 12-hour time point. Following intravenous administration to male and female rats, plasma concentration of HMB declined rapidly in a biexponential manner with sex-related clearance differences. All estimated oral administration toxicokinetic parameters showed statistically significant differences between male and female rats except for T_{max}.

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Table 1

Plasma Concentrations Following IV and Oral Gavage Administration of 10 mg/kg [^{14}C]HMB to Male and Female Harlan Sprague Dawley Rats

Individual and Mean ± SD Plasma Concentrations

Study K (Oral Gavage, Male Rat,10 mg/kg)

Time (hr)	HMB Plasma Concentration (ng/mL)							
	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ± SD		
0.083	0.42	1.45	0.06	2.57	0.58	1.02	±	1.01
0.25	0.66	2.65	1.04	2.70	1.71	1.75	±	0.92
0.5	1.69	3.20	0.38	2.23	3.01	2.10	±	1.14
1	3.42	5.83	1.29	2.68	3.38	3.32	±	1.65
2	4.50	7.47	1.16	3.16	5.08	4.27	±	2.34
4	12.00	4.12	1.09	4.37	3.96	5.11	±	4.07
6	7.12	4.59	0.94	3.05	2.55	3.65	±	2.34
8	4.08	8.01	0.74	1.52	1.65	3.20	±	2.96
10	3.40	4.09	1.86	1.39	1.70	2.49	±	1.19
12	3.10	3.57	13.24	1.90	1.41	4.64	±	4.88
24	0.73	0.77	0.33	0.56	0.29	0.53	±	0.22

Study L (Oral Gavage, Female Rat,10 mg/kg)

	HMB Plasma Concentration (ng/mL)							
Time (hr)	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ± SD		
0.083	1.19	0.51	0.64	0.71	-	0.76	±	0.30
0.25	0.97	1.01	0.93	1.13	-	1.01	±	0.08
0.5	1.93	1.67	1.89	3.88	-	2.34	±	1.03
1	1.98	2.26	2.12	2.78	-	2.29	±	0.35
2	2.11	2.16	3.00	2.94	-	2.55	±	0.48
4	1.86	2.19	2.06	4.42	-	2.63	±	1.20
6	1.94	2.04	2.15	3.01	-	2.28	±	0.49
8	1.25	1.25	1.65	1.73	-	1.47	±	0.26
10	0.90	0.94	1.21	1.74	-	1.20	±	0.39
12	0.88	0.64	0.95	1.06	-	0.89	±	0.18
24	0.63	0.66	0.57	0.95	-	0.71	±	0.17

Study M (IV, Male Rat,10 mg/kg)

	HMB Plasma Concentration (ng/mL)							
Time (hr)	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ± SD		
0.083	15248	15248	17003	13117	15248	15173	±	1378
0.25	6348	5583	5382	5269	5683	5653	±	421
0.5	3104	2590	1951	1349	2001	2199	±	670
1	993	800	764	706	706	794	±	118
2	468	405	298	305	422	380	±	75
4	209	188	236	207	237	216	±	21
6	107	126	170	167	148	144	±	27
8	73.1	93.1	92.5	81.0	118.2	91.6	±	17.1
10	28.4	60.5	58.3	81.8	51.1	56.0	±	19.2
12	43.0	33.5	46.3	70.7	25.0	43.7	±	17.3
24	15.0	13.0	13.0	30.0	14.0	17.0	±	7.3

Study N (IV, Female Rat,10 mg/kg)

	HMB Plasma Concentration (ng/mL)							
Time (hr)	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5	Mean ± SD		
0.083	37430	34423	34954	30886	32478	34034	±	2493
0.25	15023	10561	12348	10119	11446	11899	±	1944
0.5	6078	4105	2991	3857	3981	4202	±	1136
1	4168	3655	3159	3849	3389	3644	±	393
2	2521	1047	1626	2293	1000	1697	±	698
4	545	384	600	699	409	527	±	132
6	589	204	379	448	228	369	±	160
8	442	129	156	200	200	225	±	125
10	217	18	82	283	283	177	±	121
12	67.1	36.6	52.3	192.9	26.5	75.1	±	67.7
24	11.0	10.0	9.0	11.0	6.0	9.4	±	2.1

Table 2

Plasma TK Parameters[a] Following IV and Oral Gavage Administration of 10 mg/kg [^{14}C]HMB to Male and Female Harlan Sprague Dawley Rats

Gender	Plasma TK Parameters[a]			
	Male		Female	
Route	IV	Oral	IV	Oral
$»_z$ (h^{-1})	0.11 ± 0.02[b]	0.1 ± 0.04[b]	0.19 ± 0.03	0.04 ± 0.01
$t_{1/2}$ (h)	6.6 ± 1.3[b]	6.4 ± 2.4[b]	3.6 ± 0.6	18.5 ± 4.9
$C_{max\ or\ C0}$ (ng/mL)	15200 ± 1400[b]	8.5 ± 4.0[b]	34000 ± 2500	2.9 ± 1.1
T_{max} (h)	—	6 ± 4	—	2.3 ± 1.3
AUC_{inf} ($ng^b h/mL$)	7695 ± 375[b]	80 ± 28[b]	19223 ± 2945	51 ± 13
Cl_{sys} (mL/min/kg)	21.7 ± 1.1[b]	—	8.82 ± 1.26	—
Vss (L/kg)	3.6 ± 1.5[b]	—	0.9 ± 0.2	—
MRT_{inf} (h)	2.7 ± 1.0[b]	10.5 ± 1.8[b]	1.8 ± 0.4	24.5 ± 6.1
F (%)	—	0.9 ± 0.4[b]	—	0.3 ± 0.1
MAT (h)	—	4.4 ± 1.7[b]	—	14.3 ± 6.2

[a]Definitions of TK parameters are as follows:
$»_z$ = terminal elimination rate constant, $t_{1/2}$ = half-life, C_{max} = maximum concentration, T_{max} = time of maximum concentration, AUC_{inf} = area under the curve through infinity, Cl_{sys} = systemic clearance, Vss = volume of distribution at steady state, MRT = mean resonance time, F = bioavailability, and MAT = mean absorption time

[b]Significantly different than corresponding parameter measured in females using Student's T test: $p < 0.05$