

ADME NTP Study S0073 2-Hydroxy-4-methoxybenzophenone

The contractor abbreviated the test article as HMB.

Sex/Species: male F344 rats.

Vehicle: intravenous, ethanol:Emulphor:water (5:2:3, v/v); oral, corn oil; dermal, ethanol or lotion.

CASRN 131-57-7

Radiolabeled with carbon-14 in the rings; 2-Hydroxy-4-methoxybenzophenone, [ring-UL-¹⁴C]

Studies Performed:

- Single 3, 30, or 300 mg/kg oral gavage dose to rats with sacrifice 72 hours postdose. (actual concentrations: 3.01, 28.1, or 293 mg/kg, respectively; n=3 per dose; Experiment A).
- Single 4.63 mg/kg intravenous dose to rats with sacrifice 5, 15, 30, and 60 minutes and 2, 4, 8, 24, and 72 hours postdose (Experiment B).
- Single 3000 mg/kg oral gavage dose to rats with sacrifice 72 hours postdose (actual dose 2560 mg/kg; n=4; Experiment C).
- Single 4.46 mg/kg intravenous dose to rats with sacrifice 4 hours postdose (bile excretion; n=4; Experiment E).
- Single 0.0516, 2.04, or 0.800 mg/rat dermal dose in ethanol vehicle with covered dose site and sacrifice at 0, 4, 24, or 72 hours postdose (0.00360, 0.0135, and 0.0127 mCi, respectively; 0.25, 1, or 4 % HMB, respectively; n=3; Experiment F).
- Single 0.05, 0.2, or 0.8 mg/rat dermal dose in lotion vehicle with covered dose site and sacrifice at 2, 6, 24, or 72 hours postdose (see Table 6 for actual nCi in dose; 0.25, 1, or 4 % HMB, respectively; n=3; Experiment G).

The suntan lotion vehicle was formulated as follows: Part A (5.0 g lanolin, 2.5 g white petroleum, 4.0 g stearic acid, and 0.05 g propylparaben) and Part B (5.0 mL propylene glycol, 0.1 g methylparaben, 1.0 mL triethanolamine, 0.05 sodium edetate; and 74.3 mL water) were heated, mixed, and allowed to cool to room temperature. After cooling 8 mL of water was added and the preparation was mixed thoroughly. For dosing, the lotion was drawn into one syringe, non-radiolabeled HMB and radiolabeled HMB were drawn together into a second syringe. The two syringes were connected by a stopcock valve and the dose administered, mixed, by alternating pushing of the plungers. The medium- and high-dose doses were not homogeneous by this dosing method so the results were expressed as % dose.

Toxicokinetics:

Pharmacokinetic half-lives were estimated with modified forms of the NONLIN (Metzler CM, Elfring GL, and McEwen AJ. A package of computer programs for pharmacokinetic modeling. Biometrics 30:562-563, 1974) and CSTRIP (Sedman AJ, and Wagner TG CSTRIP, a Fortran IV computer program for obtaining initial polyexponential parameter estimates. J. Pharm. Sci. 65:1006-1010, 1976) programs. The data were fitted to three-compartment open models. Statistical weights were determined from the measured concentrations.

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Table 1 (Experiments A and D)
Disposition of Radioactivity from [¹⁴C] HMB in
Rats Dosed Orally

		Dose															
		3.01 mg/kg (Expt. A)				28.1 mg/kg (Expt. A)				293 mg/kg (Expt. A)				2570 mg/kg (Expt. D)			
		% of Dose		nCi/g or ml		% of Dose		nCi/g or ml		% of Dose		nCi/g or ml		% of Dose		nCi/g or ml ^a	
Urine	(0-24 hr)	55.9	+ 11.8	1660	+ 290 ^b	58.0	+ 4.9	1890	+ 320 ^b	56.9	+ 6.5	1820	+ 270 ^b	31.2	+ 5.2	3860	+ 340 ^b
	(24-48 hr)	6.50	+ 3.2	1840	+ 660 ^b	5.03	+ 1.32	1740	+ 360 ^b	6.27	+ 1.26	2020	+ 85 ^b	35.2	+ 1.7	2280	+ 400 ^b
	(48-72 hr)	1.57	+ 0.56	56.5	+ 22.7 ^b	0.890	+ 0.214	28.7	+ 2.4 ^b	1.31	+ 0.18	45.7	+ 9.9 ^b	6.54	+ 4.8	861	+ 386 ^b
Total		63.9	+ 8.2	- ^c	-	63.9	+ 5.8	-	-	64.5	+ 7.4	-	-	72.9	+ 7.1	-	-
Feces	(0-24 hr)	25.8	+ 5.7	1710	+ 260	20.8	+ 8.2	1630	+ 230	17.4	+ 7.0	1250	+ 310	1.08	+ 0.66	1180	+ 510
	(24-48 hr)	13.9	+ 6.8	679	+ 392	13.7	+ 4.8	661	+ 207	12.0	+ 3.2	596	+ 155	13.9	+ 5.8	10800	+ 1300
	(48-72 hr)	1.92	+ 2.0	97.4	+ 97.8	0.944	+ 0.421	46.2	+ 19.4	1.37	+ 0.64	64.0	+ 28.1	4.31	+ 0.80	1770	+ 370
Total		41.7	+ 4.8	-	-	35.4	+ 5.8	-	-	30.8	+ 4.6	-	-	19.3	+ 6.0	-	-
Stomach contents		0.020	+ 0.018	2.13	+ 2.34	0.005	+ 0.008	0.605	+ 0.974	0.018	+ 0.028	1.85	+ 2.61	0.029	+ 0.047	16.9	+ 27.0
Sm. intestine contents		0.091	+ 0.078	4.18	+ 4.36	0.052	+ 0.020	2.00	+ 0.60	0.043	+ 0.013	1.64	+ 0.54	0.053	+ 0.025	18.5	+ 9.7
Lg. intestine contents		0.285	+ 0.315	7.39	+ 7.80	0.126	+ 0.052	3.08	+ 0.89	0.127	+ 0.062	3.15	+ 1.11	0.269	+ 0.096	50.6	+ 25.0
Stomach		0.002	+ 0.002	0.331	+ 0.301	0.001	+ 0.001	0.131	+ 0.146	0.002	+ 0.002	0.291	+ 0.319	0.003	+ 0.004	3.99	+ 5.29
Small intestine		0.039	+ 0.034	2.53	+ 2.19	0.019	+ 0.005	1.49	+ 0.39	0.016	+ 0.005	1.18	+ 0.25	0.018	+ 0.010	11.1	+ 5.7
Large intestine		0.013	+ 0.013	1.84	+ 2.05	0.008	+ 0.001	1.11	+ 0.12	0.009	+ 0.003	1.10	+ 0.31	0.011	+ 0.004	16.5	+ 5.9
Liver		-	-	-	-	-	-	-	-	-	-	-	-	0.071	+ 0.007	9.96	+ 0.60
Lungs		-	-	-	-	-	-	-	-	-	-	-	-	0.002	+ 0.000	3.34	+ 0.19
Kidneys		-	-	-	-	-	-	-	-	-	-	-	-	0.009	+ 0.003	8.16	+ 2.37
Brain		-	-	-	-	-	-	-	-	-	-	-	-	< 0.001	-	0.113	+ 0.005
Muscle ^d		-	-	-	-	-	-	-	-	-	-	-	-	0.022	+ 0.005	0.376	+ 0.098
Spleen		-	-	-	-	-	-	-	-	-	-	-	-	< 0.001	-	0.499	+ 0.039
Fat ^e		-	-	-	-	-	-	-	-	-	-	-	-	0.021	+ 0.006	2.64	+ 0.84
Skin ^f		-	-	-	-	-	-	-	-	-	-	-	-	0.037	+ 0.003	2.02	+ 0.20
Plasma ^g		0.008	+ 0.004	0.130	+ 0.069	0.005	+ 0.001	0.097	+ 0.010	0.005	+ 0.001	0.086	+ 0.013	0.014	+ 0.003	2.46	+ 0.54
Whole blood ^h		0.011	+ 0.004	0.104	+ 0.042	0.008	+ 0.001	0.077	+ 0.013	0.008	+ 0.001	0.079	+ 0.010	0.020	+ 0.014	1.96	+ 0.33
Total recovery		106	+ 5	-	-	99.6	+ 6.7	-	-	95.4	+ 4.0	-	-	92.8	+ 2.0	-	-

^aA larger amount of radioactivity was administered to these rats. For comparison with the dose of 293 mg/kg, the values should be divided by a factor of 8.7. Corresponding factors for 28.1 mg/kg and 3.01 mg/kg are 8.6 and 9.4, respectively.

^bExcluding cage rinses.

^c-, Not applicable or not determined.

^dConsidered to be 50% of body weight.

^eConsidered to be 7% of body weight.

^fConsidered to be 16% of body weight.

^gConsidered to be 5% of body weight. Not included in totals.

^hConsidered to be 9% of body weight.

Table 2 (Experiment B)
Disposition of Radioactivity at Various Times After Dosing
of Rats Intravenously with 4.63 mg/kg of [¹⁴C] HMB

	Time After dosing																	
	5 min (N=3)		15 min (N=3)		30 min (N=3)		60 min (N=3)		2 hr (N=5)		4 hr (N=6)		8 hr (N=5)		24 hr (N=5)		72 hr (N=3)	
	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml	% of Dose	µCi/g or ml
Total ^a	6.15 ± 1.01	-	5.20 ± 0.36	-	4.07 ± 0.79	-	2.14 ± 0.20	-	1.44 ± 1.13	-	2.30 ± 0.87	-	1.40 ± 1.04	-	1.29 ± 0.94	-	0.873 ± 0.740	-
Urine (8-24 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	57.1 ± 3.0	3560 ± 710 ^b	82.0 ± 5.0	3010 ± 650 ^b
Urine (24-48 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5.75 ± 0.30	376 ± 127 ^b
Urine (48-72 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.813 ± 0.230	40.0 ± 25.4 ^b
Total	-	-	-	-	-	-	-	-	-	-	-	-	-	-	57.1 ± 3.0	-	87.4 ± 5.0	-
Feces (24 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17.0 ± 3.1	1700 ± 360	13.3 ± 2.0	1770 ± 320
Feces (48 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.30 ± 1.02	500 ± 100
Feces (72 hr)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.00 ± 0.50	80.0 ± 25.0
Total	-	-	-	-	-	-	-	-	-	-	-	-	-	-	17.0 ± 3.1	-	21.3 ± 2.2	-
Org. contents	7.35 ± 1.70	-	15.1 ± 1.7	-	19.2 ± 2.2	-	27.4 ± 2.2	-	14.3 ± 1.4	-	11.0 ± 2.7	-	10.5 ± 1.0	-	0.90 ± 2.00	-	0.300 ± 0.100	-
Org. tissue	6.07 ± 0.47	284 ± 10	7.63 ± 0.85	400 ± 111	8.01 ± 0.70	401 ± 104	9.90 ± 1.57	496 ± 90	7.39 ± 1.30	420 ± 93	4.23 ± 0.41	250 ± 53	3.42 ± 0.30	217 ± 31	0.940 ± 0.209	47.5 ± 17.7	0.537 ± 0.014	2.27 ± 0.90
Liver	0.54 ± 0.704	227 ± 31	0.30 ± 0.30	102 ± 12	2.14 ± 0.472	103 ± 14.0	2.11 ± 0.20	87.5 ± 0.1	1.52 ± 0.50	52.0 ± 10.0	1.02 ± 0.14	31.0 ± 5.7	0.775 ± 0.111	30.4 ± 5.0	0.345 ± 0.027	10.0 ± 1.0	0.070 ± 0.010	2.51 ± 0.27
Lungs	0.027 ± 0.040	107 ± 13	0.060 ± 0.006	130 ± 14	0.127 ± 0.010	80.0 ± 3.0	0.150 ± 0.004	45.0 ± 13.1	0.009 ± 0.010	20.5 ± 5.0	0.053 ± 0.004	10.5 ± 1.2	0.010 ± 0.004	5.00 ± 1.01	0.002 ± 0.000	0.049 ± 0.110	< 0.001	0.150 ± 0.010
Kidneys	1.90 ± 0.10	510 ± 50	3.05 ± 0.10	511 ± 14	1.40 ± 0.17	265 ± 32	0.745 ± 0.103	142 ± 31	0.944 ± 0.343	110 ± 44	0.200 ± 0.043	55.1 ± 7.3	0.233 ± 0.093	44.0 ± 4.2	0.074 ± 0.013	14.0 ± 2.3	0.021 ± 0.005	3.00 ± 0.67
Muscle ^c	34.0 ± 4.1	92.1 ± 11.0	10.0 ± 1.0	50.0 ± 5.0	0.04 ± 0.54	24.0 ± 1.4	5.05 ± 0.33	15.0 ± 1.04	4.03 ± 0.80	11.1 ± 1.0	3.20 ± 0.71	0.27 ± 1.07	1.41 ± 0.17	4.50 ± 0.55	0.120 ± 0.047	0.003 ± 0.117	0.010 ± 0.000	0.043 ± 0.023
Fat ^d	3.13 ± 0.34	60.0 ± 6.6	4.73 ± 1.51	92.3 ± 27.0	4.01 ± 1.40	83.4 ± 27.5	2.71 ± 0.71	52.5 ± 14.0	2.43 ± 0.87	40.0 ± 13.4	3.72 ± 0.85	74.0 ± 15.0	1.70 ± 0.72	30.2 ± 13.0	0.493 ± 0.134	0.74 ± 0.71	0.025 ± 0.010	0.473 ± 0.305
Skin ^e	0.50 ± 0.060	71.8 ± 8.2	10.7 ± 1.0	81.0 ± 0.0	0.50 ± 0.41	73.0 ± 4.2	0.64 ± 0.30	57.3 ± 3.0	4.20 ± 0.42	37.2 ± 3.7	2.34 ± 0.97	20.3 ± 0.5	1.02 ± 0.10	0.04 ± 0.70	0.120 ± 0.022	1.11 ± 0.10	0.020 ± 0.010	0.343 ± 0.144
Plasma ^f	11.0 ± 1.4	31.0 ± 3.0	9.01 ± 0.00	289 ± 20	4.07 ± 0.44	122 ± 17	2.00 ± 0.30	31.0 ± 11.2	1.43 ± 0.31	39.4 ± 14.3	0.090 ± 0.004	10.4 ± 2.0	0.401 ± 0.074	12.7 ± 2.0	0.483 ± 0.030	2.30 ± 0.56	0.004 ± 0.001	0.110 ± 0.020
Whole blood ^g	12.5 ± 1.3	100 ± 10	10.4 ± 0.0	157 ± 10	5.95 ± 0.40	70.1 ± 10.2	2.70 ± 0.37	41.4 ± 0.1	1.50 ± 0.50	24.3 ± 0.2	0.712 ± 0.104	11.0 ± 1.5	0.490 ± 0.077	7.72 ± 1.16	0.103 ± 0.021	1.50 ± 0.44	0.000 ± 0.002	0.117 ± 0.025
Total Recovery	80.1 ± 0.0	-	79.7 ± 0.7	-	65.4 ± 2.7	-	50.7 ± 3.0	-	41.5 ± 0.5	-	20.0 ± 2.4	-	27.5 ± 1.0	-	87.0 ± 4.2	-	80.0 ± 7.2	-

^aValues for rats with more than 1.0% of the dose remaining in the tail were not included in the calculations.

^b-, not applicable.

^cConsidered to be 50% of body weight.

^dConsidered to be 1% of body weight.

^eConsidered to be 10% of body weight.

^fConsidered to be 5% of body weight; values are not included in calculation of the total recovery.

^gConsidered to be 8% of body weight.

^hExcluding cage rinse.

Table 3 (Experiment B)

Half-Life Values Derived for Elimination of Radioactivity from Plasma and Various Tissues of Rats Dosed Intravenously with 4.63 mg/kg of [¹⁴C] HMB

<u>Sample</u>	<u>Elimination Phase</u>		
	<u>Alpha</u>	<u>Beta</u>	<u>Gamma</u>
Gut tissue	7.86 ^a	99.4	637
Liver	11.4	240	1200
Lungs	12.1	98.3	726
Kidneys	20.5	311	2020
Muscle	8.12	85.5	514
Fat	5.16 ^a	15.3	519
Skin	35.7	113	624
Plasma	18.9	268	1030
Whole blood	17.6	208	1050

^a Absorption phase. An authentic value for the alpha phase was not derived.

Table 4 (Experiment E)

Biliary Excretion of Radioactivity by Rats
Dosed Intravenously with [¹⁴C] HMB (4.46 mg/kg)

Time after dosing (hr)	Biliary excretion	
	by Intervals	Cumulative
	(% of dose)	
0.25	9.52 ± 3.94	9.52 ± 3.94
0.5	7.74 ± 2.24	17.3 ± 6.1
0.75	5.32 ± 1.45	22.6 ± 5.8
1.0	3.97 ± 1.77	26.5 ± 5.6
1.5	4.06 ± 0.48	30.6 ± 6.0
2.0	2.24 ± 0.50	32.9 ± 6.4
2.5	1.40 ± 0.38	34.3 ± 6.5
3.0	0.937 ± 0.567	35.2 ± 6.6
3.5	0.742 ± 0.517	36.0 ± 6.8
4.0	0.630 ± 0.454	36.6 ± 6.9

Table 5 (Experiment F)

Disposition of Radioactivity in Rats Dosed Topically with [¹⁴C] HMB Dissolved in Ethanol

		Dose											
		0.0516 mg				0.204 mg				0.800 mg			
		% of Dose		nCi/g or ml ^a		% of Dose		nCi/g or ml		% of Dose		nCi/g or ml	
Urine	(0-24 hr) ^b	18.6	+ 6.9	116	+ 40 ^d	18.5	+ 5.4	573	+ 174 ^d	4.81	+ 1.49	152	+ 102 ^d
	(24-48 hr)	7.56	+ 3.18	98.6	+ 29.7 ^d	11.3	+ 2.2	539	+ 220 ^d	3.84	+ 0.61	224	+ 95 ^d
	(48-72 hr)	4.86	+ 1.67	56.1	+ 2.9 ^d	7.11	+ 1.04	354	+ 72 ^d	5.07	+ 1.81	200	+ 75 ^d
	Total	32.4	+ 12.2	-	-	39.2	+ 3.0	-	-	13.2	+ 2.5	-	-
Feces	(0-24 hr) ^b	6.09	+ 2.10	87.3	+ 30.1	6.30	+ 1.38	288	+ 71	1.59	+ 0.53	68.7	+ 25.8
	(24-48 hr)	6.87	+ 2.27	89.1	+ 31.5	8.23	+ 1.04	481	+ 65	3.05	+ 1.05	159	+ 42
	(48-72 hr)	3.71	+ 0.44	43.3	+ 11.4	6.67	+ 1.47	270	+ 54	4.44	+ 1.51	175	+ 58
	Total	16.9	+ 3.6	-	-	22.2	+ 1.7	-	-	9.15	+ 2.99	-	-
Gut contents	(4 hr)	3.76	+ 2.38	13.6	+ 5.2	2.02	+ 0.58	40.8	+ 19.1	0.357	+ 0.131	2.97	+ 2.33
	(24 hr)	6.42	+ 2.70	24.4	+ 10.2	4.73	+ 1.16	62.7	+ 7.1	2.55	+ 1.05	30.1	+ 9.0
	(72 hr)	1.83	+ 0.50	5.57	+ 1.87	2.85	+ 0.38	30.4	+ 3.6	2.96	+ 0.73	35.4	+ 6.3
Gut tissue	(4 hr)	0.962	+ 0.389	10.6	+ 5.4	0.736	+ 0.290	25.5	+ 10.7	0.124	+ 0.059	3.80	+ 1.47
	(24 hr)	0.771	+ 0.200	7.49	+ 1.79	0.958	+ 0.019	37.7	+ 4.4	0.334	+ 0.214	10.9	+ 6.1
	(72 hr)	0.398	+ 0.053	3.75	+ 0.55	0.541	+ 0.084	18.6	+ 2.9	0.596	+ 0.170	18.5	+ 4.8
Liver	(4 hr)	0.300	+ 0.139	2.15	+ 1.07	0.159	+ 0.056	3.95	+ 1.09	0.037	+ 0.015	0.725	+ 0.208
	(24 hr)	0.259	+ 0.097	1.54	+ 0.70	0.198	+ 0.036	5.04	+ 1.13	0.097	+ 0.030	2.19	+ 0.72
	(72 hr)	0.106	+ 0.007	0.559	+ 0.040	0.135	+ 0.008	2.73	+ 0.29	0.108	+ 0.027	2.26	+ 0.55
Lungs	(4 hr)	0.015	+ 0.009	0.828	+ 0.462	0.007	+ 0.002	1.35	+ 0.36	0.002	+ 0.001	0.296	+ 0.138
	(24 hr)	0.006	+ 0.002	0.291	+ 0.105	0.006	+ 0.000	1.15	+ 0.09	0.003	+ 0.001	0.551	+ 0.173
	(72 hr)	0.002	+ 0.000	0.114	+ 0.013	0.002	+ 0.000	0.402	+ 0.034	0.003	+ 0.001	0.433	+ 0.096
Kidneys	(4 hr)	0.153	+ 0.109	4.91	+ 3.61	0.062	+ 0.018	7.17	+ 1.97	0.016	+ 0.007	1.53	+ 0.58
	(24 hr)	0.108	+ 0.028	3.22	+ 0.76	0.120	+ 0.032	12.8	+ 3.3	0.065	+ 0.033	6.98	+ 4.17
	(72 hr)	0.040	+ 0.007	1.16	+ 0.24	0.048	+ 0.007	5.12	+ 0.75	0.040	+ 0.004	4.19	+ 0.45
Muscle ^e	(4 hr)	0.595	+ 0.240	0.295	+ 0.128	0.526	+ 0.272	0.924	+ 0.417	0.391	+ 0.059	0.621	+ 0.064
	(24 hr)	0.365	+ 0.094	0.170	+ 0.033	0.312	+ 0.033	0.545	+ 0.042	0.162	+ 0.078	0.259	+ 0.112
	(72 hr)	0.465	+ 0.179	0.203	+ 0.078	0.266	+ 0.085	0.431	+ 0.149	0.175	+ 0.036	0.317	+ 0.079
Fat ^f	(4 hr)	1.01	+ 0.69	3.54	+ 2.45	0.520	+ 0.274	6.91	+ 4.25	0.074	+ 0.032	0.824	+ 0.317
	(24 hr)	0.611	+ 0.169	2.10	+ 0.41	0.690	+ 0.255	8.85	+ 3.46	0.289	+ 0.123	3.39	+ 1.58
	(72 hr)	0.239	+ 0.092	0.751	+ 0.322	0.195	+ 0.020	2.24	+ 0.11	0.138	+ 0.009	1.55	+ 0.11
Skin (site of application)	(0 hr)	87.0	+ 4.0	-	-	93.1	+ 1.5	-	-	84.5	+ 5.9	-	-
	(4 hr)	73.1	+ 5.9	-	-	92.4	+ 0.4	-	-	85.4	+ 15.1	-	-
	(24 hr)	50.4	+ 9.8	-	-	65.4	+ 7.3	-	-	91.9	+ 9.2	-	-
	(72 hr)	27.3	+ 13.9	-	-	24.8	+ 3.8	-	-	57.9	+ 11.1	-	-
Skin ^g (other than site of application)	(4 hr)	0.624	+ 0.292	0.956	+ 0.463	0.181	+ 0.047	1.05	+ 0.36	0.077	+ 0.026	0.379	+ 0.101
	(24 hr)	0.520	+ 0.026	0.766	+ 0.033	0.337	+ 0.044	1.89	+ 0.30	0.182	+ 0.053	0.922	+ 0.287
	(72 hr)	0.161	+ 0.022	0.221	+ 0.037	0.135	+ 0.033	0.686	+ 0.193	0.165	+ 0.045	0.815	+ 0.241
Plasma ^h	(4 hr)	0.265	+ 0.143	1.30	+ 0.72	0.105	+ 0.029	1.90	+ 0.48	0.022	+ 0.011	0.343	+ 0.150
	(24 hr)	0.111	+ 0.051	0.859	+ 0.698	0.099	+ 0.007	1.77	+ 0.17	0.050	+ 0.017	0.818	+ 0.278
	(72 hr)	0.035	+ 0.002	0.153	+ 0.016	0.038	+ 0.005	0.615	+ 0.057	0.044	+ 0.007	0.697	+ 0.127
Whole blood ⁱ	(4 hr)	0.266	+ 0.130	0.728	+ 0.368	0.120	+ 0.032	1.20	+ 0.24	0.026	+ 0.014	0.223	+ 0.101
	(24 hr)	0.121	+ 0.049	0.317	+ 0.133	0.109	+ 0.009	1.08	+ 0.12	0.057	+ 0.021	0.510	+ 0.197
	(72 hr)	0.043	+ 0.005	0.104	+ 0.017	0.043	+ 0.004	0.386	+ 0.029	0.049	+ 0.009	0.428	+ 0.089
Total recovery	(0 hr)	87.0	+ 4.0	-	-	93.1	+ 1.5	-	-	84.5	+ 5.9	-	-
	(4 hr)	81.0	+ 2.2	-	-	96.7	+ 1.1	-	-	86.7	+ 14.6	-	-
	(24 hr)	82.7	+ 1.7	-	-	94.4	+ 1.9	-	-	103	+ 7	-	-
	(72 hr)	79.8	+ 5.5	-	-	90.3	+ 0.9	-	-	84.4	+ 6.1	-	-

^a A smaller amount of radioactivity was administered to these rats. For comparison with the medium dose, these values should be multiplied by a factor of 3.75 and, for comparison with the high dose, by a factor of 3.53.

^b These values were calculated for six rats per group. All the other values are for three rats per group.

^c -, not applicable or not determined.

^d Excluding cage rinses.

^e Considered to be 50% of body weight.

^f Considered to be 7% of body weight.

^g Considered to be 16% of body weight.

^h Considered to be 5% of body weight. Not included in totals.

ⁱ Considered to be 9% of body weight.

Table 6 (Experiment G)

Disposition of Radioactivity in Rats Dosed Topically
with [¹⁴C] HMB in a Lotion

		Intended Dose					
		0.05 mg ^a		0.2 mg		0.8 mg	
		(% of total recovered)					
Urine	(0-24 hr) ^b	18.3	+ 2.7	19.9	+ 3.4	10.4	+ 7.5
	(24-48 hr)	8.44	+ 1.48	9.11	+ 0.71	4.87	+ 2.21
	(48-72 hr)	6.17	+ 0.10	6.19	+ 1.02	5.02	+ 2.28
	Total	33.9	+ 5.1	34.6	+ 3.6	14.3	+ 5.3
Feces	(0-24 hr) ^b	6.26	+ 1.65	6.77	+ 0.93	3.39	+ 2.52
	(24-48 hr)	7.45	+ 1.12	7.75	+ 0.75	2.95	+ 0.90
	(48-72 hr)	4.91	+ 1.18	4.72	+ 0.60	3.02	+ 0.89
	Total	17.9	+ 2.2	19.2	+ 1.5	7.35	+ 2.12
Gut contents	(2 hr)	2.33	+ 2.47	0.367	+ 0.273	0.172	+ 0.032
	(6 hr)	3.55	+ 0.64	4.45	+ 1.19	1.85	+ 0.87
	(24 hr)	7.29	+ 1.68	7.00	+ 1.69	7.26	+ 3.21
	(72 hr)	2.57	+ 0.69	2.41	+ 0.37	2.29	+ 0.76
Liver	(2 hr)	0.212	+ 0.087	0.081	+ 0.056	0.034	+ 0.005
	(6 hr)	0.268	+ 0.069	0.362	+ 0.047	0.149	+ 0.062
	(24 hr)	0.290	+ 0.078	0.264	+ 0.041	0.342	+ 0.088
	(72 hr)	0.161	+ 0.012	0.141	+ 0.017	0.108	+ 0.023
Kidneys	(2 hr)	0.074	+ 0.033	0.031	+ 0.018	0.010	+ 0.003
	(6 hr)	0.108	+ 0.016	0.136	+ 0.017	0.054	+ 0.026
	(24 hr)	0.096	+ 0.020	0.109	+ 0.022	0.108	+ 0.020
	(72 hr)	0.056	+ 0.007	0.049	+ 0.004	0.040	+ 0.012
Fat ^c	(2 hr)	0.354	+ 0.180	0.106	+ 0.088	0.043	+ 0.012
	(6 hr)	0.556	+ 0.163	0.584	+ 0.213	0.371	+ 0.168
	(24 hr)	0.618	+ 0.006	0.655	+ 0.072	0.868	+ 0.266
	(72 hr)	0.268	+ 0.112	0.204	+ 0.038	0.240	+ 0.105
Site of application	(2 hr)	93.8	+ 4.8	99.5	+ 0.5	99.6	+ 0.1
	(6 hr)	95.1	+ 1.1	94.0	+ 1.4	96.9	+ 1.4
	(24 hr)	66.9	+ 4.4	64.5	+ 3.3	68.8	+ 10.6
	(72 hr)	45.3	+ 7.9	43.3	+ 3.6	76.8	+ 10.0
Plasma ^d	(2 hr)	0.162	+ 0.070	0.070	+ 0.040	0.032	+ 0.005
	(6 hr)	0.283	+ 0.040	0.306	+ 0.039	0.272	+ 0.156
	(24 hr)	0.233	+ 0.034	0.169	+ 0.036	0.401	+ 0.095
	(72 hr)	0.088	+ 0.022	0.058	+ 0.016	0.062	+ 0.012
Whole blood ^e	(2 hr)	0.361	+ 0.087	0.094	+ 0.052	0.147	+ 0.035
	(6 hr)	0.447	+ 0.038	0.395	+ 0.062	0.542	+ 0.375
	(24 hr)	0.246	+ 0.024	0.200	+ 0.030	0.652	+ 0.195
	(72 hr)	0.137	+ 0.054	0.095	+ 0.034	0.081	+ 0.017
		Intended Dose					
		0.05 mg ^a		0.2 mg		0.8 mg	
		(nCi)					
Total recovery	(2 hr)	1440,1450,1320		22800,19200,16300		6710,7180,4990	
	(6 hr)	1410,1380,1320		3160,3030,2560		6650,656,1050	
	(24 hr)	1490,1420,1560		3230,3180,3250		910,377,651	
	(72 hr)	3040 ^f ,1530,1580		3160,6190,8040		6860,4560,7900	

^aThe actual amount applied was 0.0588 mg.^bValues derived for 6 rats; all other values are for 3 rats.^cConsidered to be 7% of body weight.^dConsidered to be 5% of body weight. Not included in totals.^eConsidered to be 9% of body weight.^fThis rat may have been dosed twice.