

ADME NTP Study S0196 Dimethyloldihydroxyethyleneurea

The contractor used the synonym 1,3-Dimethylol-4,5-dihydroxy-2-imidazolidinone and abbreviated the test article as DMDHEU.

Sex/Species: adult male F344 rats.

Vehicle: intravenous, [¹⁴C] DMDHEU reaction solution; oral gavage, [¹⁴C]DMDHEU reaction solution; dermal, not specified.

CASRN 1854-26-8

Radiolabeled with carbon-14 in the urea carbon; [¹⁴C]Dimethyloldihydroxyethyleneurea

Studies Performed:

- Single 50 mg/kg intravenous dose to rats with sacrifice 0.5, 2, or 72 hours postdose (n=4).
- Single 502, 979, or 1970 mg/kg oral gavage dose to rats with sacrifice 72 hours postdose (n=4 per dose).
- Single 4.2 mg/cm² dermal dose over a partially occlusive 10 cm² covered dose site with sacrifice 144 hours postdose. (Total dose is 42 mg averaging 133 ± 22 mg/kg for 3 rats.)
- Single 0.29, 3.5, or 13 mg/cm² dermal dose over a non-occlusive 2 cm² covered dose site with sacrifice 144 hours postdose. (Average dose of 2.0 ± 0.2, 22 ± 7, or 105 ± 10 mg/kg, respectively, for n equals 2, 2, or 4 rats, respectively.)

[¹⁴C]DMDHEU was prepared by the addition of two equivalents of formaldehyde to a slightly basic solution (pH circa 8.0) of the crystalline intermediate [¹⁴C]4,5-dihydroxy-2-imidazolidinone (DHEU). The reaction mixture was stirred at room temperature until the reaction was complete. The DHEU had been formed with [¹⁴C]urea and glyoxal (under slight modifications to the method from H. Petersen. 1969. Liebigs Ann. Chem., 726:89).

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Table 1

Recovery of Total Radioactivity After Administration of [^{14}C]DMDHEU to Male Fischer 344 Rats (% Dose)

Time (h)	Route	Dose (mg/kg)	Dose not ^a absorbed	Urine	Breath	Feces	Selected Tissues	Dose site Skin	Total
0.5	IV	51	N/A ^b	N/A	N/A	N/A	76.2 \pm 20.6 ^c	N/A	-
2.0	IV	58	N/A	N/A	N/A	N/A	18.0 \pm 1.31 ^c	N/A	-
72	IV	48	N/A	96.4 \pm 3.8 ^d	0.19 \pm 0.07 ^d	2.41 \pm 0.95 ^d	0.44 \pm 0.13 ^c	N/A	98.8 \pm 2.9
72	Oral	502	N/A	16.5 \pm 5.6 ^d	N/A	71.8 \pm 1.6 ^d	0.07 \pm 0.02 ^c	N/A	88.4 \pm 4.2
72	Oral	979	N/A	27.2 \pm 4.6 ^d	N/A	60.1 \pm 4.8 ^d	0.13 \pm 0.08 ^c	N/A	90.5 \pm 4.5
72	Oral	1970	N/A	36.5 \pm 6.7 ^d	0.56 \pm 0.19 ^d	39.0 \pm 3.3 ^d	0.44 \pm 0.29 ^d	N/A	76.5 \pm 6.5
144	Dermal ^e	133	67.0 \pm 2.1 ^c	17.1 \pm 8.3 ^c	0.03 \pm 0.02 ^c	3.0 \pm 3.8 ^c	0.24 \pm 0.2 ^c	2.8 \pm 1.1 ^c	90.1 \pm 7.2
144	Dermal ^f	24	88.5 \pm 4.7 ^g	4.91 \pm 0.81 ^g	0.03 \pm 0.04 ^g	0.97 \pm 0.85 ^g	0.18 \pm 0.04 ^g	2.9 \pm 1.7 ^g	96.4 \pm 4.4 ^g
144	Dermal ^h	2.0	88.1 \pm 1.3 ^g	1.23 \pm 0.11 ^g	N/A	2.17 \pm 2.0 ^g	0.46 \pm 0.06 ^g	9.70 \pm 2.8 ^g	98.6 \pm 0.6 ^g
144	Dermal ⁱ	109	72.9 \pm 4.9 ^{d,j}	4.68 \pm 4.80 ^d	N/A	2.09 \pm 1.6 ^d	0.21 \pm 0.06 ^d	j	79.9 \pm 3.3

^aDose recovered from cleansing of dermal dose site.^bNot applicable or samples not obtained.^cAverage \pm SD for three rats.^dAverage \pm SD for four rats.^eDose was 4.2 mg/cm² applied over a 10 cm² area and protected with a partially-occlusive fabric covering.^fDose was 3.5 mg/cm² applied over a 2 cm² area and protected with a non-occlusive screen.^gAverage \pm range for two rats.^hDose was 0.29 mg/cm² applied over a 2 cm² area and protected with a non-occlusive screen.ⁱDose was 13 mg/cm² applied over a 2 cm² area and protected with a non-occlusive screen.^j¹⁴C in dose site skin and that in the skin wash combined in this study.

Table 2
 Cumulative Excretion of Total ^{14}C After Intravenous Administration
 of [^{14}C]DMDHEU to Male Fischer 344 Rats (% Dose)

Dose (mg/kg)	48 ^a			
Excreta ^a	Urine	Breath	Feces	Total
Time (h)				
0-0.5				
0-2.0				
0-6	85.1 ± 4.9	0.005 ± 0.004	b	
6-12	92.6 ± 4.6	0.05 ± 0.02	b	
12-24	94.7 ± 3.4	0.13 ± 0.04	2.21 ± 0.88	97.0 ± 2.7
24-32	95.4 ± 3.2	0.16 ± 0.05	b	
32-48	95.8 ± 3.3	0.18 ± 0.06	2.65 ± 0.97	98.6 ± 2.4
48-72	96.0 ± 3.1		2.74 ± 1.01	98.9 ± 2.3

^aMean ± SD for four animals.

^bFeces were collected at 0-24, 24-48 and 48-72 h.

Table 3
Cumulative Excretion of Total ¹⁴C After Oral Administration of [¹⁴C]DMDHEU to Male Fischer 344 Rats (% Dose)^a

Dose (mg/kg)	502			979			1970			
	Urine	Feces	Total	Urine	Feces	Total	Breath	Urine	Feces	Total
Time (h)										
0-6	10.2 ± 3.6	b		15.9 ± 4.5	b		0.02 ± 0.00	17.9 ± 3.1	b	
6-12	14.0 ± 4.2	34.4 ± 7.0	48.4 ± 5.2	23.5 ± 2.0	22.7 ± 8.8	46.2 ± 8.5	0.08 ± 0.01	28.2 ± 2.2	3.38 ± 2.3	31.7 ± 1.4
12-24	16.0 ± 4.4	59.9 ± 9.0	75.8 ± 6.8	25.8 ± 3.4	48.0 ± 7.8	73.9 ± 5.7	0.24 ± 0.03	34.3 ± 5.5	18.1 ± 8.8	52.6 ± 4.5
24-30	16.6 ± 4.4	b		26.4 ± 3.7	b		c	35.1 ± 6.1	b	
30-48	16.6 ± 4.6	69.6 ± 3.4	86.1 ± 4.1	26.9 ± 3.7	59.5 ± 3.9	86.4 ± 1.8	0.46 ± 0.16	36.1 ± 6.6	35.6 ± 5.2	72.1 ± 4.2
48-54	16.6 ± 4.6	b		27.0 ± 3.8	b		c	36.2 ± 6.7	b	
54-72	16.7 ± 4.6	70.4 ± 3.1	87.1 ± 4.1	27.2 ± 3.8	60.2 ± 3.9	87.3 ± 1.9	0.56 ± 0.19	36.5 ± 6.7	39.0 ± 3.3	76.0 ± 6.5

^aValues are mean ± SD for four animals.

^bFeces samples were collected at 0-12, 12-24, 24-48, 48-72 h.

^cBreath (CO₂) samples were collected at 0-6, 6-12, 12-24, 24-48, 48-72 h.

Table 4
 Cumulative Excretion of Total ^{14}C After Dermal Administration
 of [^{14}C] DMDHEU to Male Fischer 344 Rats (% Dose)

Dose (mg/cm ²) Excreta	4.2 ^a				3.5 ^b			
	Breath ^c	Urine	Feces	Tc	Breath	Urine	Feces	Total
Time (h)								
0-12	0.004 ± 0.004	1.00 ± 1.35	d		0.011 ± 0.014	0.526 ± 0.45	d	
12-24	0.009 ± 0.007	5.52 ± 3.56	0.06 ± 0.04	5.58 ± 3.59	0.018 ± 0.023	0.861 ± 0.70	0.17 ± 0.22	1.04 ± 0.94
24-32	0.016 ± 0.009	9.16 ± 5.71	d		0.023 ± 0.029	1.00 ± 0.88	d	
32-48	0.028 ± 0.009	13.0 ± 7.4	0.22 ± 0.10	13.2 ± 7.5	0.031 ± 0.038	1.56 ± 1.17	0.31 ± 0.40	1.90 ± 1.61
48-72	g	15.0 ± 8.5	0.32 ± 0.15	15.3 ± 8.6	g	1.98 ± 1.22	0.42 ± 0.46	2.39 ± 1.68
72-96		15.8 ± 8.8	d			2.61 ± 0.63	d	
96-120		16.4 ± 8.8	d			3.70 ± 0.20	d	
120-144		17.1 ± 8.3	2.98 ± 3.80	20.1 ± 4.5		4.91 ± 0.81	0.97 ± 0.85	5.87 ± 0.04

Time (h)								
0-12		0.66 ± 0.26	e		0.54 ± 0.65	f		
12-24		0.80 ± 0.06	e		1.07 ± 1.2	0.118 ± 0.064	1.18 ± 1.2	
24-32			e			f		
32-48		1.05 ± 0.16	0.057 ± 0.013	1.11 ± 0.16	2.01 ± 2.1	0.223 ± 0.079	2.23 ± 2.0	
48-72		1.13 ± 0.15	0.127 ± 0.086	1.25 ± 0.064	2.76 ± 2.7	0.334 ± 0.11	3.09 ± 2.6	
72-96		1.18 ± 0.13	1.92 ± 2.07	3.09 ± 2.21	3.36 ± 3.5	0.500 ± 0.24	3.86 ± 3.3	
96-120		1.20 ± 0.12	2.11 ± 1.99	3.31 ± 2.12	4.01 ± 4.1	1.07 ± 0.68	5.08 ± 3.6	
120-144		1.23 ± 0.11	2.17 ± 1.98	3.39 ± 2.07	4.68 ± 4.8	2.09 ± 1.6	6.77 ± 3.8	

^a Dose applied as a solution over a 10 cm² rectangular area and protected with a partially-occlusive fabric. Values are mean ± SD for three animals.

^b Dose applied as a solution over a 2 cm² circular area and protected with a non-occlusive stainless steel wire mesh appliance. Values are mean ± range for two animals.

^c See b above. Values are mean ± SD for four animals.

^d Feces samples were collected at 0-24, 24-48, 48-72 and 72-144 h.

^e The first feces sample was 0-48 h.

^f Feces samples were collected at 24 h intervals.

^g Breath collection was discontinued at 48 h.

Table 5

Amount of ^{14}C in Tissues Following IV Administration of [^{14}C] DMDHEU

Tissue

Study #	DMDHEU-10	DMDHEU-11	DMDHEU-1
Target Dose (mg/kg)	50	50	50
Actual Dose (mg/kg) ^a	51	58	48
Length of Study (h)	0.5	2.0	72
Number of Animals	3	3	3

A) ng-eq of DMDHEU per gram Tissue

Adipose	4473 ± 433	1742 ± 1064	116 ± 17
Adrenal gland	35986 ± 5755		485 ± 111
Bladder	1211776 ± 754225		881 ± 414
Blood	48403 ± 2749	13947 ± 1795	60 ± 12
Brain	2533 ± 738		50 ± 11
Cecum	13979 ± 1798		286 ± 71
Esophagus	37545 ± 21574		183 ± 33
Eye	16523 ± 3081		167 ± 23
Heart	16268 ± 460		77 ± 12
Intestine, large	19902 ± 4534		217 ± 82
Intestine, small	32054 ± 6851		55 ± 10
Kidney	357345 ± 98165	36285 ± 7739	92 ± 13
Liver	54665 ± 4068	8548 ± 1389	54 ± 10
Lung	41606 ± 5363		124 ± 3
Muscle	12669 ± 2181	3918 ± 247	289 ± 40
Plasma	61513 ± 5027	7622 ± 1263	9 ± 1
Prostate	164643 ± 137713	150224 ± 40402	525 ± 95
Seminal vesicle	20410 ± 4403	65391 ± 39330	490 ± 10
Skin	44611 ± 5595	7547 ± 1407	255 ± 145
Spleen	22920 ± 2822		85 ± 23
Stomach	23066 ± 1911		63 ± 16
Testis	15068 ± 1382		91 ± 16
Trachea	44364 ± 13381		145 ± 35
Contents, bladder	3759878 ± 2528510	1675843 ± 623213	
Contents, stomch	4914 ± 3102		
Contents, cecum	4503 ± 1809		
Contents, small intestine	35731 ± 8121		
Contents, large intestine	9558 ± 4133		

Table 5 (continued)

Tissue			
Study #	DMDHEU-10	DMDHEU-11	DMDHEU-1
B) Percent Dose in Total Tissue			
Adipose	.8733 ± .0586	.2990 ± .1664	.022 ± .002
Adrenal gland	.01347 ± .00098		.00021 ± .00002
Bladder	.50529 ± .39596		.00061 ± .00030
Blood	5.9533 ± .4994	1.5100 ± .1735	.008 ± .002
Brain	.02811 ± .00695		.00062 ± .00010
Cecum	.07899 ± .02149		.00175 ± .00074
Esophagus	.03231 ± .00565		.00028 ± .00010
Eye	.03087 ± .00707		.00032 ± .00009
Heart	.07581 ± .00352		.00053 ± .00006
Intestine, large	.14280 ± .04544		.00193 ± .00085
Intestine, small	.66583 ± .10294		.00150 ± .00027
Kidney	4.88074 ± 1.04776	.47398 ± .11055	.00145 ± .00020
Liver	5.50951 ± 2.63757	.50880 ± .06078	.00424 ± .00107
Lung	.38318 ± .12957		.00084 ± .00002
Muscle	12.4067 ± 2.511	3.38 ± .1510	.30 ± .07
Plasma	3.9467 ± .4236	.430 ± .0693	.0009 ± .0002
Prostate	.26223 ± .27023	.32902 ± .19239	.00081 ± .00018
Seminal vesicle	.12017 ± .05940	.42442 ± .28617	.00231 ± .00070
Skin	13.09 ± 1.99	1.95 ± .3345	.090 ± .087
Spleen	.09396 ± .01796		.00038 ± .00014
Stomach	.16370 ± .01318		.00050 ± .00006
Testis	.26226 ± .03094		.00180 ± .00012
Trachea	.02333 ± .01035		.00020 ± .00001
Contents, bladder	25.51484 ± 14.74407	8.66630 ± 1.50915	
Contents, stomach	.05710 ± .03022		
Contents, cecum	.12536 ± .04348		
Contents, small intestine	.85157 ± .13367		
Contents, large intestine	.03196 ± .02588		

Table 5 (continued)

Tissue			
Study #	DMDHEU-10	DMDHEU-11	DMDHEU-1
C) Tissue-Blood Ratio			
Adipose	.093 ± .0123	.120 ± .057	2.017 ± .574
Adrenal gland	.742 ± .090		8.623 ± 3.869
Bladder	24.786 ± 15.421		16.095 ± 10.023
Blood	1.000 ± 0.000	1.000 ± 0.000	1.000 ± 0.000
Brain	.052 ± .016		.883 ± .396
Cecum	.289 ± .035		4.774 ± .317
Esophagus	.780 ± .461		3.095 ± .457
Eye	.340 ± .044		2.832 ± .232
Heart	.336 ± .010		1.308 ± .097
Intestine, large	.409 ± .071		3.858 ± 2.137
Intestine, small	.659 ± .109		.951 ± .247
Kidney	7.329 ± 1.670	2.614 ± .578	1.609 ± .539
Liver	1.129 ± .028	.611 ± .020	.939 ± .323
Lung	.857 ± .065		2.135 ± .464
Muscle	.261 ± .030	.283 ± .020	4.932 ± .865
Plasma	1.272 ± .106	.545 ± .020	.159 ± .056
Prostate	3.306 ± 2.644	10.873 ± 3.359	9.222 ± 3.245
Seminal vesicle	.419 ± .071	4.512 ± 2.146	8.467 ± 1.933
Skin	.919 ± .062	.539 ± .033	4.170 ± 1.728
Spleen	.472 ± .032		1.532 ± .753
Stomach	.476 ± .019		1.122 ± .520
Testis	.311 ± .013		1.548 ± .308
Trachea	.922 ± .297		2.486 ± .627
Contents, bladder	76.787 ± 51.728	122.626 ± 54.572	
Contents, stomach	.102 ± .066		
Contents, cecum	.092 ± .031		
Contents, small intestine	.734 ± .129		
Contents, large intestine	.195 ± .075		

^a Average for animals whose tissues were analyzed.

Table 6

Amount of ^{14}C in Tissues 72 Hours Following Oral Administration of [^{14}C] DMDHEU

Tissue

Study #	DMDHEU-7	DMDHEU-8	DMDHEU-9
Target Dose (mg/kg)	500	1000	2000
Actual Dose (mg/kg) ^a	502	992	1970
Number of Animals	3	3	4

A) ng-eq of DMDHEU per gram Tissue

Adipose	473 ± 377	415 ± 101	1684 ± 1002
Adrenal gland			1689 ± 433
Bladder			6609 ± 2049
Blood	168 ± 113	230 ± 78	789 ± 350
Brain			634 ± 185
Cecum			112110 ± 134273
Esophagus			4816 ± 1555
Eye			960 ± 207
Heart			2148 ± 967
Intestine, large			18307 ± 8998
Intestine, small			8477 ± 7109
Kidney			3723 ± 2582
Liver	387 ± 129	465 ± 40	2282 ± 920
Lung			1456 ± 544
Muscle	476 ± 128	1387 ± 289	4347 ± 1669
Plasma	139 ± 42	440 ± 147	635
Prostate	877 ± 212	1860 ± 461	6502 ± 3280
Seminal vesicle	1070 ± 345	2800 ± 278	8409 ± 2572
Skin	453 ± 31	957 ± 646	3636 ± 817
Spleen			1567 ± 468
Stomach			2886 ± 698
Testis			1718 ± 665
Trachea			2938 ± 829
Contents, stomach			9285 ± 6885
Contents, cecum			248838 ± 251358
Contents, small intestine			133789 ± 232354
Contents, large intestine			196436 ± 146082

Table 6 (continued)

Tissue	DMDHEU-7	DMDHEU-8	DMDHEU-9
B) Percent Dose in Total Tissue			
Adipose	.0089 ± .0071	.0039 ± .0009	.0096 ± .0079
Adrenal gland			.00002 ± .00001
Bladder			.00008 ± .00003
Blood	.0020 ± .0013	.0014 ± .0004	.0023 ± .0011
Brain			.00021 ± .00006
Cecum			.02014 ± .02554
Esophagus			.00014 ± .00007
Eye			.00005 ± .00001
Heart			.00032 ± .00017
Intestine, large			.00323 ± .00151
Intestine, small			.00513 ± .00359
Kidney			.00142 ± .00091
Liver	.00269 ± .00094	.00175 ± .00006	.00416 ± .00194
Lung			.00026 ± .00007
Muscle	.046 ± .012	.066 ± .01	.1012 ± .0393
Plasma	.00087 ± .0003	.00093 ± .0004	.00046 ± .00055
Prostate	.00020 ± .00005	.00017 ± .00007	.00041 ± .00030
Seminal vesicle	.00059 ± .00033	.00085 ± .00025	.00078 ± .00029
Skin	.013 ± .001	.014 ± .0092	.0235 ± .0064
Spleen			.00016 ± .00003
Stomach			.00074 ± .00022
Testis			.00088 ± .00029
Trachea			.00012 ± .00009
Contents, stomach			.00192 ± .00157
Contents, cecum			.20132 ± .21360
Contents, small intestine			.03800 ± .06184
Contents, large intestine			.03155 ± .02177

Table 6 (continued)

Tissue	DMDHEU-7	DMDHEU-8	DMDHEU-9
C) Tissue-Blood Ratio			
Adipose	3.066 ± 3.058	1.861 ± .262	2.088 ± .758
Adrenal gland			2.661 ± 1.973
Bladder			9.833 ± 6.087
Blood	1.000 ± 0.000	1.000 ± 0.000	1.000 ± 0.000
Brain			.929 ± .472
Cecum			118.328 ± 100.386
Esophagus			7.320 ± 5.058
Eye			1.098 ± .367
Heart			2.286 ± .410
Intestine, large			29.653 ± 28.419
Intestine, small			9.668 ± 6.236
Kidney			4.591 ± 2.183
Liver	2.664 ± .986	2.183 ± .730	3.096 ± 1.041
Lung			2.042 ± .962
Muscle	3.530 ± 1.943	6.331 ± 1.470	6.041 ± 2.417
Plasma	1.141 ± 7.43	1.936 ± .251	.623
Prostate	6.362 ± 3.014	8.365 ± 1.380	8.615 ± 3.229
Seminal vesicle	7.263 ± 2.047	13.331 ± 5.222	11.632 ± 3.772
Skin	3.525 ± 1.839	4.022 ± 1.909	5.409 ± 3.116
Spleen			2.191 ± .791
Stomach			4.009 ± 1.203
Testis			2.367 ± .847
Trachea			4.177 ± 1.900

^a Average for animals whose tissues were analyzed.

Table 7

Amount of ^{14}C in Tissues 144 Hours Following Dermal Administration of [^{14}C] DMDHEU

Tissue

Study #	DMDHEU-2	DMDHEU-3	DMDHEU-4	DMDHEU-6
Dose (mg/cm^2) ₂	4.2	3.5	0.29	13
Dose Area (cm^2)	10	2	2	2
Occluded	partial	No	No	No
Number of Animals	3	2	2	4

A) ng-eq of DMDHEW per gram Tissue

Adipose	535 ± 506	34	35	363 ± 38
Adrenal gland			23	419 ± 109
Bladder			31	2024 ± 1885
Blood	373 ± 134	87	13	197 ± 75
Cecum			6	4179 ± 3600
Esophagus			5	483 ± 128
Eye			4	248 ± 90
Kidney	737 ± 577	188	3	311 ± 190
Liver	278 ± 130	48	2	179 ± 37
Muscle	195 ± 100	25	7	177 ± 59
Prostate			3	465 ± 267
Seminal vesicle			3	198 ± 121
Skin	853 ± 824	117	9	554 ± 400
Trachea			10	386 ± 173

B) Percent Dose in Total Tissue

Adipose	.042 ± .042	.02	.19	.034 ± .006
Adrenal gland			.00041	.00011 ± .00004
Bladder			.00029	.00104 ± .00103
Blood	.018 ± .004	.02	.041	.012 ± .004
Cecum			.00128	.01606 ± .01504
Esophagus			.00019	.00022 ± .00009
Eye			.00021	.00023 ± .00007
Kidney	.00369 ± .00312	.00551	.00129	.00255 ± .00202
Liver	.00733 ± .00495	.00775	.00408	.00658 ± .00223
Muscle	.070 ± .030	.06	.20	.084 ± .037
Prostate			.00022	.00107 ± .00073
Seminal vesicle			.00040	.00054 ± .00038
Skin	.099 ± .10	.06	.057	.073 ± .056
Trachea			.00030	.00024 ± .00017

Table 7 (continued)

Study #	DMDHEU-2	DMDHEU-3	DMDHEU-4	DMDHEU-6
C) Tissue-Blood Ratio				
Adipose	1.496 ± 1.493	.397	2.913	2.026 ± .678
Adrenal gland			2.291	2.508 ± 1.483
Bladder			3.753	12.308 ± 11.077
Blood	1.000 ± 0.000	1.000	1.000	1.000 ± 0.000
Cecum			.553	21.775 ± 16.969
Esophagus			.633	2.714 ± 1.270
Eye			.417	1.434 ± .686
Kidney	1.873 ± 1.572	2.349	.321	1.757 ± 1.125
Liver	.774 ± .376	.576	.233	1.015 ± .379
Muscle	.505 ± .16	.296	.720	1.012 ± .434
Prostate			.355	2.909 ± 2.162
Seminal vesicle			.357	1.114 ± .686
Skin	2.375 ± 2.433	1.512	.866	3.895 ± 4.431
Trachea			1.192	2.194 ± 1.014