ADME NTP Study S0814 Diethanolamine

The contract laboratory abbreviation for the test article is DEA.
Sex/Species: adult male F344 rats and B6C3F1 mice.
Vehicles: intravenous, phosphate buffered saline; oral, water; dermal, 95% ethanol.

CASRN 111-42-2
Radiolabeled with carbon-14, randomly labeled; Diethanolamine hydrochloride, [^{14}C(U)]-

Radiolabeled N,N-Dimethyl diethanolammonium (N,N-dimethyl[^{14}C]DEA) was synthesized by alkylation of [^{14}C]DEA with methyl iodide.

Diethanolamine Studies Performed:

1. Single 7.5 mg/kg intravenous administration in rats with sacrifice 48 hours postdose. (Tables 1 and 2)

2. Single 2.1, 7.6, or 27.5 mg/kg dermal exposures in rats with covered dose sites and sacrifice 48 hours postdose. (Tables 3 and 4)

3. Single 7.9 mg/kg single oral gavage administration in rats with sacrifice 48 hours postdose. (Tables 5 and 6)

4. 7.8 mg/kg oral gavage dose repeated daily for 5 days in rats with sacrifice 48 hours after last dose. (Table 7)

5. 7.8 mg/kg oral gavage dose repeated daily five days per week in rats for 2 weeks with tissue distribution 72 hours after last dose. (Table 8)

6. 7.8 mg/kg oral dose repeated daily five days per week in rats for 4 weeks with tissue distribution 72 hours after last dose. (Table 8)

7. 7.8 mg/kg oral gavage dose repeated daily five days per week in rats for 8 weeks, with tissue distribution 72 hours after last dose. (Table 8)

8. 7.8 mg/kg oral gavage dose repeated daily five days per week in rats for 4 weeks followed by a 4 week washout period to follow the depuration of DEA. DEA equivalents were determined in excreta on selected days during the washout period. After the 4 weeks of dosing, tissues were analyzed 4 weeks plus 72 hours after the last dose. (Tables 10 and 11)

9. Single 8 mg/kg intravenous administration in rats with serial sacrifice at 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hours postdose. (N=1 rat per time point, Table 9)

10. Single 0.7 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose. (Table 12)

11. 0.7 mg/kg oral gavage dose repeated daily five days per week for 1 week in rats with sacrifice 72 hours after the last dose. (Tables 13 and 14)

12. 0.7 mg/kg oral gavage dose repeated daily five days per week for 2 weeks in rats with sacrifice 72 hours after the last dose. (Tables 13 and 15)

13. 0.7 mg/kg oral gavage dose repeated daily five days per week for 4 weeks in rats with sacrifice 72 hours after the last dose. (Tables 13 and 16)

14. Single 200 mg/kg oral gavage dose in rats with cumulative sacrifice 72 hours postdose. (Table 17)

15. 200 mg/kg oral gavage dose repeated daily five days per week for 1 week in rats with sacrifice 72 hours following the last dose. (Tables 18 and 19)

16. 200 mg/kg oral gavage dose repeated daily five days per week for 2 weeks in rats with cumulative excretion (during 2nd week of dosing) and sacrifice 72 hours following the last dose. (Tables 18 and 19)

17. 200 mg/kg oral gavage dose repeated daily five days per week for 2 weeks in rats with cumulative excretion (during last week of dosing) and sacrifice 72 hours following the last dose. (Tables 18 and 19)

18. Single 14.9 mg/kg intravenous administration in mice with sacrifice 48 hours postdose. (Tables 20 and 21)

19. Single 8, 23, or 81.1 mg/kg dermal administration in mice with covered dose sites and sacrifice 48 hours postdose. (Tables 22 and 23)

20. Single 7 mg/kg oral gavage dose of N,N-dimethyldiethanolammonium (DMDEA) in rat with sacrifice 48 hours postdose. (Table 24)

The intravenous and dermal doses for both species were single administration doses. For dermal studies, all dose sites were covered.

The tissue residue data shown for the 7.8 mg/kg oral 4-week dose followed by 4 week washout (Table 11, Study 10) were compared with that obtained in the 4-week repeat oral dosing experiments (Table 8, Study 8) to calculate an estimated percent elimination of DEA equivalents over the 4-week washout phase.

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Table [1]

Cumulative Excretion of Radioactivity 48 h after Intravenous Administration of [^{14}C]DEA (7.5 mg/kg) to Male F-344 Rats (N=3)

End of Collection Period (h)	% of Dose Appearing in: Urine	Feces
24	16.5 ± 1.9	0.35 ± 0.02
48	28.3 ± 2.5	0.60 ± 0.03

Table 2

Tissue Distribution of Radioactivity 48 h after Intravenous Administration of [^{14}C]DEA (7.5 mg/kg) to Male F-344 Rats (N=3)

Tissue	ng-eg DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	1117 ± 130	4.28 ± 0.43	1.05 ± 0.11
Blood	261 ± 16	Unity	0.18 ± 0.00
Brain	2572 ± 192	9.85 ± 0.17	0.30 ± 0.02
Heart	4663 ± 225	17.87 ± 0.60	0.19 ± 0.01
Kidney	38820 ± 4584	148.4 ± 11.08	3.95 ± 0.53
Liver	43170 ± 2603	166.0 ± 17.27	27.09 ± 1.50
Lung	10110 ± 3735	38.69 ± 14.58	0.76 ± 0.11
Muscle	2380 ± 258	9.10 ± 0.47	15.31 ± 1.00
Skin	1988 ± 161	7.61 ± 0.19	4.54 ± 0.13
Spleen	9557 ± 1038	36.79 ± 5.60	0.31 ± 0.04
Total			53.70 ± 1.77

Table 3

Disposition of Radioactivity 48 h after Dermal Application of [^{14}C]DEA to Male F-344 Rats

	% of Dose		
	2.1 mg/kg (N=5)	7.6 mg/kg (N=5)	27.5 mg/kg (N=4)
Absorbed			
Tissues	1.1 ± 0.8	4.3 ± 2.0	7.3 ± 4.1
Urine	0.6 ± 0.4	1.7 ± 0.6	4.2 ± 2.9
Feces	0.03 ± 0.02	0.2 ± 0.1	0.2 ± 0.2
Dose site	1.2 ± 0.3	4.3 ± 0.9	4.5 ± 0.9
Total	2.9 ± 1.3	10.5 ± 2.6	16.2 ± 7.7
Unabsorbed			
Appliance	0.71 ± 0.19	1.2 ± 0.1[a]	0.9 ± 0.9
Skin wash	84.1 ± 4.4	72.0 ± 10.1[a]	8.9 ± 8.3
Gauze	6.6 ± 2.7	9.8 ± 5.5[a]	60.4 ± 14.4
Total	91.4 ± 2.0	82.9 ± 6.5[a]	70.2 ± 8.2
Total Recovery	94.3 ± 1.3	92.9 ± 4.2[a]	86.4 ± 2.4

[a] N=3

Table 4

Tissue Distribution of Radioactivity 48 h after Dermal Application of [^{14}C]DEA to Male F-344 Rats

Tissue	ng-eq DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
	2.1 mg/kg (N=5)		
Adipose	7 ± 6	1.66 ± 0.73	0.02 ± 0.02
Blood	4 ± 1	Unity	0.01 ± 0.00
Brain	11 ± 9	2.60 ± 1.11	0.00 ± 0.00
Heart	29 ± 19	6.76 ± 2.42	0.00 ± 0.00
Kidney	213 ± 180	47.33 ± 22.86	0.08 ± 0.06
Liver	246 ± 193	55.95 ± 24.23	0.53 ± 0.37
Lung	44 ± 28	10.09 ± 3.88	0.01 ± 0.01
Muscle	12 ± 10	2.80 ± 1.27	0.28 ± 0.22
Skin	13 ± 11	2.85 ± 1.38	0.10 ± 0.09
	7.6 mg/kg (N=5)		
Adipose	116 ± 51	4.54 ± 0.72	0.11 ± 0.5
Blood	25 ± 8	Unity	0.02 ± 0.01
Brain	141 ± 79	5.36 ± 1.30	0.02 ± 0.01
Heart	395 ± 168	15.49 ± 2.04	0.02 ± 0.01
Kidney	3158 ± 1527	123.3 ± 25.41	0.34 ± 0.16
Liver	3477 ± 1565	135.1 ± 18.23	2.17 ± 0.97
Lung	891 ± 597	34.19 ± 14.11	0.06 ± 0.03
Muscle	179 ± 82	6.95 ± 1.03	1.14 ± 0.53
Skin	165 ± 88	6.34 ± 1.40	0.37 ± 0.20
	27.5 mg/kg (N=4)		
Adipose	972 ± 615	7.22 ± 1.64	0.25 ± 0.16
Blood	133 ± 88	Unity	0.03 ± 0.02
Brain	715 ± 316	6.12 ± 1.74	0.03 ± 0.01
Heart	2199 ± 1153	17.82 ± 2.99	0.03 ± 0.02
Kidney	18830 ± 10310	152.9 ± 25.87	0.70 ± 0.40
Liver	17260 ± 9276	140.4 ± 24.60	3.90 ± 2.12
Lung	5333 ± 3262	44.73 ± 13.91	0.09 ± 0.04
Muscle	951 ± 592	7.29 ± 1.18	1.67 ± 1.06
Skin	949 ± 513	7.70 ± 1.61	0.59 ± 0.33

Table 5

Cumulative Excretion of Radioactivity 48 h after Oral Administration of [^{14}C]DEA (7.9 mg/kg) to Male F-344 Rats (N=4)

End of Collection Period (h)	% of Dose Appearing in: Urine	Feces
24	9.03 ± 2.48	1.60 ± 0.20
48	22.00 ± 1.81	2.42 ± 0.33

Table 6

Tissue Distribution of Radioactivity 48 h after Oral Administration of [^{14}C]DEA (7.9 mg/kg) to Male F-344 Rats (N=4)

Tissue	ng-eq DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	1843 ± 368	6.70 ± 1.19	1.64 ± 0.33
Blood	274 ± 6	Unity	0.18 ± 0.01
Brain	2415 ± 70	8.80 ± 0.41	0.27 ± 0.02
Heart	4785 ± 206	17.45 ± 0.99	0.19 ± 0.01
Kidney	53890 ± 2784	196.5 ± 11.91	5.01 ± 1.04
Liver	42480 ± 1847	154.8 ± 7.09	27.34 ± 1.15
Lung	8048 ± 1343	29.36 ± 5.17	0.71 ± 0.02
Muscle	2670 ± 162	9.73 ± 0.62	16.29 ± 1.14
Skin	2358 ± 138	8.59 ± 0.44	5.10 ± 0.40
Spleen	10010 ± 329	36.49 ± 1.20	0.32 ± 0.01
Total			57.1 ± 2.71

Table 7

Tissue Distribution of Radioactivity 48 h after the Final Dose Administered in a Five-day Repeat Oral Dosing of [^{14}C]DEA (7.8 mg/kg/day) to Male F-344 Rats (N=4)

Tissue	ng-eg DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	6148 ± 870	5.81 ± 0.93	1.24 ± 0.16
Blood	1064 ± 106	Unity	0.16 ± 0.01
Brain	12440 ± 915	11.73 ± 0.83	0.31 ± 0.02
Heart	19050 ± 767	18.04 ± 1.92	0.18 ± 0.01
Kidney	196870 ± 34920	187.9 ± 44.97	4.56 ± 0.48
Liver	145820 ± 20840	138.7 ± 27.49	18.19 ± 1.02
Lung	37660 ± 7611	35.22 ± 4.62	0.62 ± 0.03
Muscle	9033 ± 1206	8.47 ± 0.34	12.44 ± 1.23
Skin	8480 ± 579	8.01 ± 0.75	4.18 ± 0.27
Spleen	35520 ± 4480	33.81 ± 6.42	0.25 ± 0.02
Total			42.1 ± 1.78

Table 8

Tissue Distribution of Radioactivity 72 h After the Final Dose Administered in Repeat Oral Dosings of [^{14}C]DEA (7-8 mg/kg/day)

Tissue	ng-eq/g tissue	Tissue/Blood Ratio	Percent Dose in Tissue
	2-Week Repeat Dosing		
Blood	1790 ± 110	Unity	0.137 ± 0.010
Brain	18300 ± 1400	10.2 ± 0.7	0.191 ± 0.020
Liver	205000 ± 16000	114 ± 4	12.3 ± 1.2
Spleen	45900 ± 1700	26 ± 1	0.154 ± 0.013
	4-Week Repeat Dosing		
Blood	4110 ± 620	Unity	0.156 ± 0.020
Brain	28100 ± 2400	7.0 ± 1.2	0.131 ± 0.037
Liver	295000 ± 14000	73 ± 10	7.9 ± 0.4
Spleen	60400 ± 3500	15 ± 2	0.107 ± 0.010
	8-Week Repeat Dosing		
Blood	5750 ± 970	Unity	0.115 ± 0.021
Brain	31200 ± 2800	5.6 ± 1.2	0.080 ± 0.011
Liver	294000 ± 22000	53 ± 10	4.12 ± 0.12
Spleen	55300 ± 1100	9.9 ± 1.7	0.06 ± 0.00

Table 9

Tissue Distributions following a Single iv Dosing of [^{14}C]DEA (8.0 mg/kg) to Male F-344 Rats

Nanogram Equivalents DEA per g Tissue

Time (h)	0.25	0.5	1	2	3	4	6	8	12
Tissue									
Adipose	2150	2400	1190	1260	1830	1900	1470	1690	2970
Blood	1800	1060	750	510	376	414	414	470	319
Brain	1060	1190	1340	1550	1450	1720	1760	1850	1770
Heart	5930	6310	6700	6320	5890	6580	7620	6900	6730
Kidney	118000	137000	161000	157000	154000	180000	151000	156000	110000
Liver	47400	57000	59800	73900	74900	58900	92200	88200	75900
Lung	8850	12100	10800	16400	15000	14900	22900	16200	11400
Muscle	6830	6710	5680	4700	4020	4120	4180	3900	3700
Skin	4440	3990	3330	3090	3120	3280	7910	3000	2900
Spleen	12400	11600	12900	12600	12100	13600	14700	15200	12600

Percentage of Dose Appearing in Tissue

Time (h)	0.25	0.5	1	2	3	4	6	8	12
Tissue									
Adipose	1.81	2.02	0.962	1.04	1.49	1.55	1.13	1.30	2.58
Blood	1.12	0.665	0.453	0.314	0.226	0.251	0.236	0.268	0.206
Brain	0.115	0.128	0.141	0.151	0.141	0.166	0.162	0.180	0.194
Heart	0.265	0.246	0.246	0.254	0.257	0.247	0.257	0.234	0.236
Kidney	11.7	8.52	14.5	14.0	13.5	14.0	12.5	12.4	10.1
Liver	26.7	29.6	29.2	36.4	38.3	25.7	37.6	35.6	36.0
Lung	0.883	0.868	0.991	1.03	1.03	1.06	1.15	1.05	0.954
Muscle	39.4	38.9	31.6	26.8	22.3	23.1	22.1	20.6	22.1
Skin	9.04	8.20	6.56	6.20	6.16	6.51	14.8	5.57	6.11
Spleen	0.404	0.365	0.358	0.364	0.388	0.406	0.406	0.382	0.372

Tissue to Blood Ratios

Time (h)	0.25	0.5	1	2	3	4	6	8	12
Tissue									
Adipose	1.20	2.25	1.58	2.47	4.88	4.58	3.55	3.60	9.31
Brain	0.589	1.12	1.78	3.04	3.86	4.14	4.24	3.93	5.55
Heart	3.30	5.96	8.93	12.4	15.7	15.9	18.4	14.7	21.1
Kidney	65.7	130	215	307	410	434	364	332	343
Liver	26.4	53.8	79.8	145	199	142	223	188	237
Lung	4.93	11.5	14.4	32.2	39.9	36.0	55.3	34.6	35.6
Muscle	3.80	6.34	7.57	9.23	10.7	9.94	10.1	8.30	11.6
Skin	2.47	3.77	4.44	9.06	8.31	7.92	19.1	6.34	9.08
Spleen	6.92	10.9	17.3	24.6	32.2	32.7	35.59	32.3	39.4

[a] N=1 for each timepoint.

Table 10

Recovery of DEA Equivalents in Excreta During Selected Days Following a 4-Week Repeat Oral Dosing with [^{14}C]DEA (7-8 mg/kg/day)

Collection Interval	μCi Excreted[a]		
	Urine	Feces	Total
Day 35-36	0.43 ± 0.04	0.01 ± 0.00	0.44 ± 0.04
Day 42-43	0.20 ± 0.02	<0.005	0.20 ± 0.02
Day 49-50	0.10 ± 0.01	<0.005	0.10 ± 0.01
Day 56-57	0.04 ± 0.01	<0.005	0.04 ± 0.01

[a] Values are means ± SD for five rats.
[b] Includes cage rinse.

Table 11

Tissue Distribution of Radioactivity 4 Weeks After the Final Dose Administered in a 4-Week Repeat Oral Dosing of [^{14}C]DEA (7-8 mg/kg/day) to Male F-344 Rats

Tissue	ng-eq/g Tissue[a]	Percent Washout[b]	Tissue/Blood Ratio	Percent Dose in Tissues
Blood	2860 ± 840	31%	Unity	0.13 ± 0.04
Brain	2690 ± 270	90%	1.0 ± 0.3	0.02 ± 0.00
Liver	12800 ± 2900	96%	4.8 ± 2.0	0.38 ± 0.09
Spleen	4210 ± 560	93%	1.6 ± 0.5	0.01 ± 0.00

[a] Values are means ± SD for five rats.
[b] Calculated from the ng-eq values found after necropsy of the 4-week repeat dosing animals (see Table 9).

Table 12

Cumulative Excretion of Radioactivity Collected Following a Single Oral Dose of [^{14}C]DEA (0.7 mg/kg) to Male F-344 Rats

Time (h)	% Dose in Urine	% Dose in Feces	% Dose Recovered in Excreta
0-24	11.0 ± 1.1	1.39 ± 0.20	12.4 ± 1.1
24-48	19.1 ± 1.1	1.96 ± 0.40	21.1 ± 0.9
48-72	29.9 ± 3.5	2.53 ± 0.71	32.5 ± 3.3

Tissue Distribution of Radioactivity 72 h Following a Single Oral Dose of [^{14}C]DEA (0.7 mg/kg/day) to Male F-344 Rats (N=4)

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	25 ± 4	unity	0.193 ± 0.028
Brain	271 ± 11	10.9 ± 2.1	0.341 ± 0.041
Kidney	4080 ± 480	163 ± <1	4.79 ± 0.45
Liver	3810 ± 180	152 ± 3	23.9 ± 0.4
Spleen	969 ± 218	39.3 ± 3.0	0.378 ± 0.108

Table 13

Tissue Distribution of Radioactivity 72 h Following the Last Dose in a Repeat Oral Dosing of [^{14}C]DEA (0.7 mg/kg/day) to Male F-344 Rats (N=4)

One-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	73 ± 26	unity	0.110 ± 0.040
Brain	1280 ± 40	19.2 ± 7.0	0.333 ± 0.021
Kidney	15400 ± 2170	226 ± 6	3.44 ± 0.38
Liver	13400 ± 800	200 ± 7	16.3 ± 0.5
Spleen	2560 ± 170	38 ± 3	0.22 ± 0.01

Two-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	179 ± 47	unity	0.120 ± 0.056
Brain	2230 ± 60	13.0 ± 2.9	0.281 ± 0.012
Kidney	26800 ± 3700	158 ± 6	2.84 ± 0.25
Liver	21400 ± 900	125 ± 8	11.3 ± 0.7
Spleen	3450 ± 450	20 ± 4	0.13 ± 0.010

Four-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	258 ± 71	unity	0.099 ± 0.026
Brain	3270 ± 190	13.3 ± 2.9	0.184 ± 0.020
Kidney	29000 ± 3000	117 ± 2	1.60 ± 0.15
Liver	25700 ± 2400	104 ± >1	7.36 ± 0.38
Spleen	4400 ± 800	17.6 ± 3.9	0.090 ± 0.017

Table 14

Distribution of Radioactivity in Excreta Collected During a One-Week Repeat Oral Dosing of [^{14}C]DEA (0.7 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.11	0.25	0.033		0.279
24-48	4.22	0.57	0.133		0.698
48-72	6.33	1.12	0.180		1.30
72-96	8.44	1.61	0.324		1.94
96-120	10.6	2.14	0.451		2.59
120-144		2.83	0.477		3.31
144-168		3.08	0.901		3.98
Cage Wash				0.72	4.70

Table 15

Distribution of Radioactivity in Excreta Collected During Days 8-14 of a Two-Week Repeat Oral Dosing of [^{14}C]DEA (0.7 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)[a]	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.17	0.64	0.0647		0.701
24-48	4.33	1.46	0.135		1.60
48-72	6.50	2.42	0.196		2.62
72-96	8.66	3.47	0.280		3.75
96-120	10.8	4.35	0.393		4.75
120-144		5.17	0.553		5.72
144-168		6.01	0.599		6.61
Cage Wash				0.770	7.38

[a] Time 0 is at the beginning of Day 8.

Table 16

Distribution of Radioactivity in Excreta Collected During Days 22-28 of a Four-Week Repeat Oral Dosing of [^{14}C]DEA (0.7 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)[a]	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.09	1.186	0.051		1.237
24-48	4.17	2.546	0.119		2.664
48-72	6.26	3.939	0.185		4.124
72-96	8.34	5.396	0.252		5.65
96-120	10.43	7.158	0.311		7.47
120-144		8.495	0.364		8.86
144-168		9.807	0.408	0.671	10.89

[a] Time 0 is at the beginning of Day 22.

Table 17

Cumulative Excretion of Radioactivity Following a Single Oral Dose of [^{14}C]DEA (200 mg/kg) to Male F-344 Rats

Time (h)	% Dose Appearing in Urine	% Dose Appearing in Feces	% Dose Recovered in Excreta
0-24	19.7 ± 2.2	2.61 ± 2.0	22.3 ± 3.5
24-48	28.9 ± 1.7	2.70 ± 2.1	31.6 ± 2.5
48-72	47.0 ±15.6	2.81 ± 2.2	46.7 ±15.6

Tissue Distribution of Radioactivity 72 h Following a Single Oral Dosing of [^{14}C]DEA (200 mg/kg) to Male F-344 Rats (N=4)

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	5960 ± 1560	unity	0.158 ± 0.041
Brain	77100 ± 2800	13.8 ± 4.5	0.345 ± 0.012
Kidney	704000 ± 8000	125 ± 6	2.92* ± 0.02
Liver	749000 ± 7000	134 ± 3	17.8 ± 0.7
Spleen	250000 ± 6000	44.3 ± 2.2	0.329 ± 0.029

Table 18

Tissue Distribution of Radioactivity 72 h Following the Last Dose in a Repeat Oral Dosing of [^{14}C]DEA (200 mg/kg/day) to Male F-344 Rats (N=4)

One-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	17900 ± 8800	unity	0.095 ± 0.047
Brain	338000 ± 9000	26.8 ± 2.5	0.313 ± 0.006
Kidney	1480000 ± 10000	122 ± 11.	1.23 ± 0.04
Liver	1950000 ± <10000	155 ± 29	9.56 ± 0.33
Spleen	543000 ± 8000	44.4 ± 0.1	0.150 ± 0.016

Two-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	38200 ± 2700	unity	0.102 ± 0.006
Brain	583000 ± 9000	15.3 ± 0.9	0.261 ± 0.011
Kidney	1830000 ± 60000	48.0 ± 5.2	0.733 ± 0.058
Liver	2870000 ± <10000	75.1 ± 3.0	6.20 ± 0.61
Spleen	68000 ± 5000	17.9 ± 2.2	0.087 ± 0.002

Four-week

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	62300 ± 3300	unity	0.09 ± 0.005
Brain	789000 ± 5000	12.7 ± 1.40	0.184 ± 0.029
Kidney	1840000 ± 70000	29.50 ± 1.30	0.427 ± 0.031
Liver	2450000 ± 50000	39.4 ± 2.10	3.080 ± 0.240
Spleen	66000 ± 6000	10.6 ± 0.8	0.055 ± 0.008

Table 19

Distribution of Radioactivity in Excreta Collected During a One-Week Repeat Oral Dosing of [^{14}C]DEA (200 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)[a]	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.02	0.37	0.094		0.460
24-48	4.04	1.02	0.230		1.25
48-72	6.06	1.78	0.429		2.21
72-96	8.08	2.62	0.647		3.26
96-120	10.1	3.40	0.866		4.26
120-144		3.98	0.905		4.89
144-168		4.37	1.25		5.61
Cage Wash				0.55	6.16

Distribution of Radioactivity in Excreta Collected During Days 8-14 of a Two-Week Repeat Oral Dosing of [^{14}C]DEA (200 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)[a]	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.14	0.79	0.090		0.88
24-48	4.27	1.91	0.179		2.09
48-72	6.41	3.13	0.321		3.45
72-96	8.54	4.31	0.626		4.93
96-120	10.7	5.34	0.760		6.10
120-144		6.01	0.960		6.97
144-168		6.67	1.33		8.00
Cage Wash				0.53	8.53

[a] Time 0 is at the beginning of Day 8.

Distribution of Radioactivity in Excreta Collected During Days 22-28 of a Four-Week Repeat Oral Dosing of [^{14}C]DEA (200 mg/kg/day) to Male F-344 Rats

Cumulative Values Table

Time (h)[a]	µCi Dosed	µCi in Urine	µCi in Feces	µCi in Cage Wash	µCi Recovered in Excreta
0-24	2.52	1.14	0.067		1.21
24-48	5.03	2.58	0.194		2.78
48-72	7.55	4.07	0.290		4.36
72-96	10.1	5.82	0.409		6.23
96-120	12.6	7.66	0.530		8.19
120-144		8.77	0.569		9.34
144-168		9.55	0.668	0.494	10.7

[a] Time 0 is at the beginning of Day 22.

Table 20

Cumulative Excretion of Radioactivity 48 h after Intravenous Administration of [^{14}C]DEA (14.9 mg/kg) to Male B6C3F1 Mice (N=4)

End of Collection Period (h)	% of Dose Appearing in: Urine	Feces
24	11.5 ± 7.0	1.57 ± 0.36
48	25.5 ± 5.0	2.98 ± 0.86

Table 21

Tissue Distribution of Radioactivity 48 h after Intravenous Administration of [^{14}C]DEA (14.9 mg/kg) to Male B6C3F1 Mice (N=4)

Tissue	ng-eg DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	8139 ± 3464	16.20 ± 5.87	5.28 ± 1.90
Blood	502 ± 84	Unity	0.26 ± 0.03
Brain	4080 ± 185	8.30 ± 1.44	0.54 ± 0.04
Heart	11300 ± 322	23.02 ± 4.23	0.37 ± 0.03
Kidney	52070 ± 7613	104.8 ± 14.07	6.04 ± 0.90
Liver	50560 ± 9652	101.9 ± 18.88	20.36 ± 3.14
Lung	24920 ± 1681	50.43 ± 6.90	1.10 ± 0.05
Muscle	5199 ± 296	10.56 ± 1.78	15.79 ± 0.75
Skin	4162 ± 664	8.34 ± 0.98	4.04 ± 0.35
Spleen	14910 ± 1317	30.02 ± 2.72	0.30 ± 0.04
Total			54.10 ± 2.06

Table 22

Disposition of Radioactivity 48 h after Dermal Application of [^{14}C]DEA to Male B6C3F1 Mice

	% of Dose in Mice		
	8 mg/kg (N=5)	23 mg/kg (N=5)	81 mg/kg (N=4)
Absorbed			
Tissues	13.2 ± 3.5	18.9 ± 4.5	37.0 ± 5.6
Urine	7.5 ± 2.4	10.4 ± 2.7	16.4 ± 4.8
Feces	2.1 ± 0.7	1.4 ± 0.6	2.6 ± 2.2
Dose Site	4.0 ± 0.7	3.1 ± 0.5	2.2 ± 0.6
Total	26.8 ± 6.6	33.8 ± 7.2	58.1 ± 4.9
Unabsorbed			
Appliance	4.4 ± 1.8	1.9 ± 0.5	1.1 ± 0.2
Skin wash	34.6 ± 10.3	24.1 ± 10.0	16.5 ± 8.0
Gauze	20.3 ± 6.8	23.4 ± 10.5	7.1 ± 4.4
Total	59.2 ± 5.5	49.4 ± 8.8	24.8 ± 3.5

[a] Values are means ± SD.

Table 23

Tissue Distribution of Radioactivity following 48 h Dermal Exposure of [^{14}C]DEA to Male B6C3F1 Mice (N=5)

8 mg/kg

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	480 ± 174	8.43 ± 1.89	0.598 ± 0.219
Blood	57 ± 15	1 ± 0	0.055 ± 0.014
Brain	346 ± 121	6.03 ± 0.95	0.086 ± 0.030
Heart	1350 ± 500	23.3 ± 4.9	0.099 ± 0.034
Kidney	5880 ± 1150	107 ± 9	1.29 ± 0.28
Liver	7610 ± 1660	138 ± 2	6.45 ± 1.66
Lung	2490 ± 820	43.3 ± 4.0	0.236 ± 0.079
Muscle	568 ± 205	9.97 ± 1.91	3.26 ± 1.22
Skin	571 ± 73	11.0 ± 4.3	1.05 ± 0.14
Spleen	1600 ± 560	27.6 ± 4.2	0.063 ± 0.022

23 mg/kg

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	2510 ± 1010	8.96 ± 4.52	0.608 ± 0.270
Blood	300 ± 100	1.00 ± 0.00	0.099 ± 0.035
Brain	2050 ± 550	6.87 ± 0.72	0.141 ± 0.042
Heart	7440 ± 1910	25.2 ± 4.9	0.145 ± 0.040
Kidney	37010 ± 1080	123 ± 6	2.66 ± 1.04
Liver	38090 ± 8190	129 ± 2	8.55 ± 2.03
Lung	15360 ± 3710	52.0 ± 6.3	0.356 ± 0.116
Muscle	2600 ± 600	8.88 ± 1.40	5.06 ± 1.30
Skin	1930 ± 290	6.72 ± 1.29	1.21 ± 0.25
Spleen	8290 ± 2890	27.1 ± 5.2	0.088 ± 0.032

81 mg/kg

Tissue	ng Equivalents DEA per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Adipose	19800 ± 11010	10.76 7.18	1.83 1.73
Blood	1916 ± 170	Unity	0.18 0.02
Brain	13380 ± 681	7.04 ± 0.90	0.30 ± 0.03
Heart	35840 ± 5604	18.72 ± 2.52	0.27 ± 0.03
Kidney	198600 ± 50030	103.9 ± 24.40	4.20 ± 0.62
Liver	224000 ± 23260	117.5 ± 14.70	16.74 ± 0.62
Lung	92140 ± 5175	48.41 ± 5.63	0.77 ± 0.02
Muscle	17080 ± 3198	8.87 ± 1.08	9.52 ± 2.03
Skin	16400 ± 1527	8.56 ± 0.38	2.94 ± 0.29
Spleen	55960 ± 7649	29.18 ± 2.68	0.20 ± 0.02

Table 24

Cumulative Excretion of Radioactivity 72 h Following Oral Administration of N,N-dimethyl[^{14}C]DEA (ca. 8mg/kg) to Male F-344 Rats[a]

Collection Interval	Percent of Dose Recovered in:		
	Urine	Feces	Total
0-24 h	72.9 ± 7.5	0.6 ± 0.4	73.6 ± 7.7
24-48 h	83.7 ± 5.5	2.9 ± 2.4	86.6 ± 3.7
48-72 h	90.8 ± 4.0	3.2 ± 2.4	93.9 ± 1.8

Tissue Distribution of Radioactivity 72 h after Oral Administration of N,N-dimethyl[^{14}C]DEA (ca. 8mg/kg) to Male F-344 Rats[a]

Tissue	ng-eq per g Tissue	Tissue/Blood Ratio	% Dose in Total Tissue
Blood	157 ± 30	unity	0.0917 ± 0.0124
Brain	113 ± 10	0.729 ± 0.92	0.0088 ± 0.0003
Kidney	1460 ± 230	9.41 ± 1.58	0.111 ± 0.013
Liver	2100 ± 430	13.4 ± 1.0	0.817 ± 0.112
Lung	405 ± 92	2.57 ± 0.24	0.026 ± 0.003
Spleen	381 ± 65	2.44 ± 0.31	0.009 ± 0.001

Distribution of Radioactivity in Selected Tissues 72 h Following Oral Administration of N,N-dimethyl[^{14}C]DEA (ca. 8mg/kg) to Male F-344 Rats[a]

Extraction Phase	Percentage of Liver Radioactivity	Percentage of Brain Radioactivity
Aqueous	66.5 ± 10.4	62.8 ± 1.9
Organic	27.0 ± 3.6	31.5 ± 4.9
Protein Pellet	7.88 ± 1.57	5.64 ± 3.11

[a] (N=3)