

ADME NTP Study S0148 Methyl ethyl ketoxime

The contract laboratory abbreviation for the test article is MEKO.

Sex/Species: adult male F344 rats.

Vehicles: intravenous, isotonic saline; oral, water; dermal, acetone.

CASRN 96-29-7

Radiolabeled with carbon-14 in the 2-position; 2-Butanone oxime, [2-¹⁴C]

Studies Performed:

- Single 2.7, 27, or 270 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose.
- Single 2.7 or 270 mg/kg dermal dose in rats with covered dose site and sacrifice 72 hours postdose.
- Single 27 mg/kg intravenous dose in rats with sacrifice 72 hours postdose.

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Table 1
 Distribution of Radioactivity into the
 Excreta of Rats Administered
 Oral Doses of [¹⁴C]MEKO

End of Collection Period (h)	% of Dose Appearing in:				
	Urine	Volatiles	CO ₂	Feces	Total
<u>2.7 mg/kg Oral</u>					
2		1.3 ± 0.1	37.4 ± 3.3		38.6 ± 3.3
4		1.8 ± 0.1	55.2 ± 2.3		57.1 ± 2.2
8	9.9 ± 1.0	2.6 ± 0.2	64.2 ± 2.5	0.2 ± 0.1	76.8 ± 1.9
12		3.2 ± 0.2	66.6 ± 2.5		69.8 ± 2.3
24	12.1 ± 0.6	4.4 ± 0.3	68.5 ± 2.5	0.8 ± 0.2	85.7 ± 1.8
48	12.5 ± 0.7	5.0 ± 0.4	70.4 ± 2.4	1.1 ± 0.2	89.0 ± 1.4
72	12.7 ± 0.7	5.2 ± 0.4	71.3 ± 2.3	1.4 ± 0.2	90.7 ± 1.4
<u>27 mg/kg Oral</u>					
2		2.7 ± 0.2	13.2 ± 6.6		15.9 ± 6.7
4		4.1 ± 0.6	37.1 ± 5.6		41.1 ± 4.9
8	14.3 ± 2.2	4.7 ± 0.6	53.4 ± 4.0	0.2 ± 0.1	72.6 ± 1.7
12		5.2 ± 0.6	56.5 ± 3.5		61.8 ± 3.0
24	17.7 ± 2.6	6.0 ± 0.5	58.7 ± 3.6	0.8 ± 0.1	83.2 ± 1.6
48	18.5 ± 2.6	6.5 ± 0.5	60.2 ± 3.7	1.3 ± 0.2	86.5 ± 1.7
72	18.9 ± 2.7	6.6 ± 0.5	60.9 ± 3.9	1.6 ± 0.3	88.0 ± 1.9
<u>270 mg/kg Oral</u>					
2		2.3 ± 0.3	2.3 ± 0.5		4.6 ± 0.6
4		6.4 ± 1.0	7.7 ± 1.2		14.1 ± 1.4
8	8.8 ± 2.2	13.1 ± 3.3	19.2 ± 1.7	0.1 ± 0.1	41.1 ± 5.3
12		16.3 ± 3.9	30.8 ± 2.4		47.0 ± 4.2
24	24.8 ± 2.5	17.4 ± 3.7	46.1 ± 3.7	0.4 ± 0.1	88.7 ± 1.9
48	25.7 ± 2.5	17.8 ± 3.6	48.3 ± 3.9	0.8 ± 0.2	92.5 ± 1.4
72	25.9 ± 2.5	17.9 ± 3.6	49.1 ± 3.9	1.0 ± 0.2	93.9 ± 1.3

Table 2

Tissue Distribution of Radioactivity 72 h After
Oral Administration of [¹⁴C]MEKO
to Male F-344 Rats

Tissue	ng-eq BOX per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
<u>2.7 mg/kg (N=4)</u>			
Adipose	187 ± 98	0.92 ± 0.46	0.47 ± 0.26
Blood	204 ± 19	Unity	0.37 ± 0.03
Kidney	546 ± 31	2.69 ± 0.23	0.13 ± 0.01
Liver	411 ± 38	2.01 ± 0.05	0.60 ± 0.08
Muscle	118 ± 14	0.58 ± 0.78	2.00 ± 0.33
Skin	463 ± 78	2.30 ± 0.53	2.78 ± 0.57
Testis	215 ± 21	1.05 ± 0.06	0.08 ± 0.01
<u>Total</u>			<u>6.4 ± 1.2</u>
<u>27 mg/kg (N=4)</u>			
Adipose	2470 ± 1470	1.45 ± 0.84	0.64 ± 0.39
Blood	1690 ± 440	Unity	0.32 ± 0.09
Kidney	4880 ± 890	2.95 ± 0.53	0.14 ± 0.02
Liver	3930 ± 660	2.39 ± 0.46	0.63 ± 0.12
Muscle	850 ± 250	0.51 ± 0.09	1.49 ± 0.45
Skin	3380 ± 460	2.10 ± 0.55	2.08 ± 0.29
Testis	1740 ± 80	1.07 ± 0.21	0.07 ± 0.00
<u>Total</u>			<u>5.4 ± 1.2</u>
<u>270 mg/kg (N=4)</u>			
Adipose	11500 ± 4500	0.95 ± 0.40	0.29 ± 0.12
Blood	12200 ± 1000	Unity	0.23 ± 0.02
Kidney	38700 ± 3700	3.18 ± 0.34	0.10 ± 0.02
Liver	27300 ± 3300	2.24 ± 0.20	0.46 ± 0.06
Muscle	8160 ± 2310	0.67 ± 0.15	1.40 ± 0.43
Skin	25200 ± 6600	2.06 ± 0.52	1.52 ± 0.41
Testis	15300 ± 1400	1.25 ± 0.07	0.06 ± 0.01
<u>Total</u>			<u>6.4 ± 1.2</u>

Table 3
Disposition of Radioactivity After
Intravenous Administration of [¹⁴C]MEKO
(2.7 mg/kg) to Male F-344 Rats

End of Collection Period (h)	% of Dose Appearing in:				
	Urine	Volatiles	CO ₂	Feces	Total
2		1.1 ± 0.1	22.7 ± 1.6		23.9 ± 1.7
4		2.6 ± 0.1	37.4 ± 1.4		40.0 ± 1.4
8	16.4 ± 1.2	4.8 ± 0.2	43.9 ± 1.2	0.2 ± 0.2	65.2 ± 2.1
12		6.5 ± 0.2	45.4 ± 1.1		51.9 ± 1.2
24	19.4 ± 0.9	9.1 ± 0.7	46.9 ± 1.0	0.8 ± 0.1	76.1 ± 1.8
48	20.5 ± 0.8	10.9 ± 0.8	48.1 ± 0.8	1.3 ± 0.1	80.8 ± 1.5
72	21.4 ± 0.8	11.4 ± 0.8	48.8 ± 0.7	1.8 ± 0.2	83.4 ± 1.2

Tissue	ng-eq DEA per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
Adipose	249 ± 82	0.98 ± 0.37	0.63 ± 0.21
Blood	261 ± 31	Unity	0.49 ± 0.08
Kidney	525 ± 38	2.046 ± 0.34	0.14 ± 0.00
Liver	579 ± 71	2.248 ± 0.41	0.85 ± 0.06
Muscle	127 ± 14	0.497 ± 0.10	2.19 ± 0.20
Skin	457 ± 97	1.79 ± 0.51	2.78 ± 0.53
Testis	201 ± 12	0.78 ± 0.86	0.08 ± 0.00

Table 4
 Distribution of Radioactivity into the
 Excreta of Rats Administered
 Dermal Doses of [¹⁴C]MEKO

End of Collection Period (h)	% of Dose Appearing in:				
	Urine	Volatiles	CO ₂	Feces	Total
	<u>2.7 mg/kg Dermal</u>				
2		11.6 ± 3.2	0.9 ± 0.1		12.5 ± 3.2
4		18.7 ± 6.9	2.4 ± 0.3		21.2 ± 7.2
8	3.5 ± 0.6	26.9 ± 5.1	4.1 ± 0.7	0.2 ± 0.1	34.6 ± 5.2
12		30.8 ± 5.0	5.3 ± 1.0		36.1 ± 5.2
24	4.4 ± 0.9	32.9 ± 5.2	5.9 ± 1.1	0.3 ± 0.2	43.4 ± 5.6
48	4.6 ± 0.9	34.2 ± 5.4	6.4 ± 1.3	0.3 ± 0.2	45.6 ± 5.9
72	4.8 ± 0.9	34.7 ± 5.5	6.6 ± 1.3	0.4 ± 0.2	46.5 ± 6.2
	<u>270 mg/kg Dermal</u>				
2		13.5 ± 0.9	0.5 ± 0.0		13.9 ± 0.8
4		29.5 ± 1.5	2.3 ± 0.4		31.8 ± 1.1
8	5.9 ± 0.9	44.0 ± 2.2	7.4 ± 1.3	0.2 ± 0.1	57.5 ± 1.5
12		50.2 ± 2.0	10.5 ± 1.7		60.7 ± 1.1
24	8.7 ± 0.6	54.0 ± 2.0	12.5 ± 1.6	0.5 ± 0.0	75.6 ± 0.6
48	9.3 ± 0.6	55.8 ± 1.9	13.5 ± 1.7	0.6 ± 0.1	79.2 ± 0.6
72	9.7 ± 0.7	56.4 ± 1.9	14.0 ± 1.7	0.7 ± 0.1	80.8 ± 0.7

Table 5

Distribution of Radioactivity 72 h After
 Dermal Administration of [¹⁴C]MEKO
 to Male F-344 Rats

Tissue	ng-eq MEKO per g Tissue	Tissue Blood Ratio	% Dose in Total Tissue
<u>2.7 mg/kg</u>			
Adipose	17 ± 3	0.29 ± 0.05	0.04 ± 0.01
Blood	58 ± 10	Unity	0.11 ± 0.03
Kidney	85 ± 22	1.50 ± 0.36	0.02 ± 0.00
Liver	94 ± 14	1.66 ± 0.31	0.11 ± 0.02
Muscle	16 ± 3	0.28 ± 0.06	0.27 ± 0.05
Skin	79 ± 16	1.37 ± 0.16	0.47 ± 0.10
Testis	31 ± 8	0.55 ± 0.11	0.02 ± 0.01
<u>270 mg/kg</u>			
Adipose	3030 ± 410	0.42 ± 0.05	0.07 ± 0.01
Blood	7300 ± 1330	Unity	0.13 ± 0.03
Kidney	13160 ± 1960	1.82 ± 0.17	0.03 ± 0.00
Liver	11700 ± 1200	1.63 ± 0.17	0.14 ± 0.00
Muscle	2230 ± 200	0.31 ± 0.04	0.37 ± 0.03
Skin	11100 ± 2320	1.53 ± 0.20	0.66 ± 0.15
Testis	5340 ± 640	0.74 ± 0.11	0.02 ± 0.00

Table 6

Disposition of Radioactivity 72 h After
 Dermal Application of [¹⁴C]MEKO to
 Male F-344 Rats (N=4)

	<u>270 mg/Kg</u>	<u>% of Dose</u>	<u>2.7 mg/Kg</u>
<u>Absorbed</u>			
Tissues	1.4 ± 0.2		1.0 ± 0.2
Dose site	0.1 ± 0.0		0.1 ± 0.0
Feces	0.7 ± 0.1		0.4 ± 0.2
Urine	9.7 ± 0.7		4.8 ± 0.9
CO ₂	14.0 ± 1.7		6.6 ± 1.3
Total	25.9 ± 2.7		13.0 ± 2.4
<u>Unabsorbed</u>			
Appliance	0.8 ± 0.0		2.5 ± 0.4
Skin wash	0.1 ± 0.0		0.2 ± 0.1
Gauze	N.D		0.1 ± 0.1
Total	0.9 ± 0.0		2.8 ± 0.5
Volatiles Traps	56.4 ± 1.9		34.7 ± 5.5
<u>Total Recovery</u>	83.2 ± 0.9		50.5 ± 6.6