ADME NTP Study S0243 Methylcyclopentadienyl manganese tricarbonyl

The contract laboratory abbreviation for the test article is MMT. Sex/Species: young adult male F344 rats. Vehicles: intravenous, Intralipid® (Kaba Vitrum) or ethanol, Emulphor EL-620® (GAF), and phosphate buffered saline; inhalation, conditioned room air.

CASRN 12108-13-3 Radiolabeled with carbon-14 at the methyl carbon; Methylcyclopentadienyl manganese tricarbonyl, [2-methyl-¹⁴C]-

Methylcyclopentadienyl manganese tricarbonyl Studies Performed:

- 54 ng MMT/mL air 6-hour nose-only inhalation exposure with sacrifice at 6 or 72 hours post exposure (timepoints referenced to the start of the 6 hour exposure)
- Single 0.37 mg/kg intravenous dose in rats with sacrifice at 72 hours postdose.
- Single 0.81 mg/kg intravenous dose in rats with sacrifice at 72 hours postdose.

Intravenous data was analyzed using compartmental modeling techiniques with established models or models written to simultaneously solve intravenous and oral data sets (PCNONLIN SCI Software, Lexington, KY). Data were weighted as C⁻¹. A two-compartment mammillary model best fit the plasma data of the intravenous bolus administration but it was not possible to model the plasma data following inhalation exposure.

Parameters estimated were K_{12} and K_{21} , the intercompartmental rate constants; K_{10} , the elimination rate constant from the central compartment; V, the volume of the central compartment; V_{ss} , the overall distributional space; t_{2B} , the terminal elimination half-life; AUC, the area under the plasma concentration versus time curve extrapolated to infinity; Cl, the clearance; and MRT, the mean residence time.

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Route	Route		Intravenous							
Dose		54 ng MMT/mL air	0.81 mg MMT/kg body weight	0.37 mg MMT/kg body weight						
Excreta	End of Collection Period (h) ^b	(% of Recovered Dose) ^C	(% of Recovered Dose) ^C	(% of Recovered Dose) ^C						
l laine	â	d		100100						
Urine	6	d	9.5 ± 11.2	12.9±8.9						
	12		26.6 ± 7.5	28.3±3.0						
	24	34.2 ± 3.0	38.5 ± 5.2	39.0±2.9						
	48	45.9 ± 2.3	51.8 ± 2.4	49.3±2.4						
	72 ^e	53.6 ± 3.4	59.2 ± 2.4	56.6±2.7						
Feces	24	0.9 ± 1.0	9.3 ± 3.7	9.4±2.9						
	48	2.3 ± 1.7	16.3 ± 4.9	16.0±3.3						
	72	7.2 ± 5.7	17.8 ± 4.7	19.7±3.7						
Breath	12	d	1.2 ± 0.1	0.6±0.1						
(Volatile)	24	19.6 ± 3.2	1.8 ± 0.3	1.0±0.1						
(Volatile)	48		2.1 ± 0.4	d						
	72	20.8 ± 3.0 d	2.4 ± 0.4	d						
D		d		d						
Breath	12	- d	0.6 ± 0.0	d						
(CO ₂)	24	d	0.9 ± 0.0	d						
	48	d	1.0 ± 0.1	d						
	72	u	1.3 ± 0.1							
Breath	12	d	0.03 ± 0.00	d						
(Diene)	24	d	0.07 ± 0.00	d						
(=)	48	d	0.10 ± 0.15	d						
	72	d	0.13 ± 0.15	d						
Total		81.6 ± 3.4	81.4 ± 6.4 ^e	77.3±5.6 ^f						

Cumulative Excretion of Total ¹⁴C by F344-M Rats 72 h after Administration of [¹⁴C]MMT by Intravenous or Inhalation Exposure^a

^a Values are mean ± SD for four rats.
^b Time points are referenced to time of iv dosing or to the start of the 6 h inhalation exposure.
^c Value includes urine collected during the exposure period.
^d Sample not collected.
^e Value is 67.6 ± 5.0 percent of the administered ¹⁴C.

^f Value is 88.9 ± 4.5 percent of the *administered* ¹⁴C.

Concentration of ^{14}C in Tissues of F344-M Rats following Inhalation Exposure of $[^{14}\text{C}]\text{MMT}^a$

54 ng MMT/mL air - 6 h post exposure ^b				54 ng MMT/mL air - 72 h post exposure ^b													
			Tiss			Percent of Recovered 14C in Total Tissue ^c			ng-eq MMT per g Tissue		Tiss			Percent of Recovered 14C in Total Tissue ^c			
2079	±	251	2.5	±	0.5	8.45	±	0.92	454	±	23	2.6	±	0.5	1.42	±	0.08
14679	±	9283	17.6	±	11.2	0.80	±	0.28	370	±	190	2.1	±	1.2	0.01	±	0.01
182	±	39	0.2	±	0.0	0.07	±	0.01	26	±	5	2.1	±	1.2	0.01	±	0.00
380	±	26	0.5	±	0.1	63.46	±	1.31	85	±	18	0.5	±	0.0	11.67	±	2.18
492	±	140	0.6	±	0.2	0.10	±	0.03	150	±	54	0.8	±	0.2	0.02	±	0.01
15112	±	2121	18.1	±	0.8	7.70	±	0.55	1133	±	325	6.2	±	1.2	0.44	±	0.10
3736	±	196	4.5	±	0.6	9.35	±	0.73	2682	±	901	14.9	±	5.6	4.73	±	1.13
8682	±	3009	10.3	±	2.5	3.73	±	0.93	2896	±	500	[·] 16.8	±	6.6	0.92	±	0.15
332	±	229	0.4	±	0.3	9.41	±	6.81	58	±	11	0.3	±	0.0	1.24	±	0.15
6863	±	729	8.3	±	1.2	2.52	±	0.63	1080	±	86	6.1	±	1.5	0.32	±	0.05
834	±	103		unit	V	1.31	±	0.16	183	±	42		unit		0.22	±	0.04
1412	±	357	1.7	±	0.5	13.85	±	2.80	246	±	59	1.4	±	0.3	1.86	±	0.40
461	±	57	0.6	±	0.1	0.05	±	0.01	130	±	40	0.7	±	0.1	0.02	±	0.00
	±	37	0.3	±	0.0	0.16	±	0.02	67	±	12	0.4	±	0.0		_	0.00
14035	±	2054	16.8	±	0.8			0.15	1146	±	803	6.7	±	5.2	0.02	±	0.01
	9 2079 14679 182 380 492 15112 3736 8682 332 6863 834 1412 461 253	g Tiss 2079 ± 14679 ± 182 ± 380 ± 492 ± 15112 ± 3736 ± 8682 ± 332 ± 6863 ± 834 ± 1412 ± 461 ± 253 ±	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	g TissueRati 2079 ± 251 $2.5 \pm$ 14679 ± 9283 $17.6 \pm$ 182 ± 39 $0.2 \pm$ 380 ± 26 $0.5 \pm$ 492 ± 140 $0.6 \pm$ 15112 ± 2121 $18.1 \pm$ 3736 ± 196 $4.5 \pm$ 8682 ± 3009 $10.3 \pm$ 332 ± 229 $0.4 \pm$ 6863 ± 729 $8.3 \pm$ 834 ± 103 unity 1412 ± 357 $1.7 \pm$ 461 ± 57 $0.6 \pm$ 253 ± 37 $0.3 \pm$	g TissueRatio 2079 ± 251 2.5 ± 0.5 14679 ± 9283 17.6 ± 11.2 182 ± 39 0.2 ± 0.0 380 ± 26 0.5 ± 0.1 492 ± 140 0.6 ± 0.2 15112 ± 2121 18.1 ± 0.8 3736 ± 196 4.5 ± 0.6 8682 ± 3009 10.3 ± 2.5 332 ± 229 0.4 ± 0.3 6863 ± 729 8.3 ± 1.2 834 ± 103 unity 1412 ± 357 1.7 ± 0.5 461 ± 57 0.6 ± 0.1 253 ± 37 0.3 ± 0.0	g TissueRatio14C in 2079 ± 251 2.5 ± 0.5 8.45 14679 ± 9283 17.6 ± 11.2 0.80 182 ± 39 0.2 ± 0.0 0.07 380 ± 26 0.5 ± 0.1 63.46 492 ± 140 0.6 ± 0.2 0.10 15112 ± 2121 18.1 ± 0.8 7.70 3736 ± 196 4.5 ± 0.6 9.35 8682 ± 3009 10.3 ± 2.5 3.73 332 ± 229 0.4 ± 0.3 9.41 6863 ± 729 8.3 ± 1.2 2.52 834 ± 103 unity 1.31 1412 ± 357 1.7 ± 0.5 13.85 461 ± 57 0.6 ± 0.1 0.05 253 ± 37 0.3 ± 0.0 0.16	g TissueRatio14C in Tota 2079 ± 251 2.5 ± 0.5 $8.45 \pm$ 14679 ± 9283 17.6 ± 11.2 $0.80 \pm$ 182 ± 39 0.2 ± 0.0 $0.07 \pm$ 380 ± 26 0.5 ± 0.1 $63.46 \pm$ 492 ± 140 0.6 ± 0.2 $0.10 \pm$ 15112 ± 2121 18.1 ± 0.8 $7.70 \pm$ 3736 ± 196 4.5 ± 0.6 $9.35 \pm$ 8682 ± 3009 10.3 ± 2.5 $3.73 \pm$ 332 ± 229 0.4 ± 0.3 $9.41 \pm$ 6863 ± 729 8.3 ± 1.2 $2.52 \pm$ 834 ± 103 unity $1.31 \pm$ 1412 ± 357 1.7 ± 0.5 $13.85 \pm$ 461 ± 57 0.6 ± 0.1 $0.05 \pm$ 253 ± 37 0.3 ± 0.0 $0.16 \pm$	g TissueRatio14C in Total Tissue ^c 2079 \pm 2512.5 \pm 0.58.45 \pm 0.9214679 \pm 928317.6 \pm 11.20.80 \pm 0.28182 \pm 390.2 \pm 0.00.07 \pm 0.01380 \pm 260.5 \pm 0.163.46 \pm 1.31492 \pm 1400.6 \pm 0.20.10 \pm 0.0315112 \pm 212118.1 \pm 0.87.70 \pm 0.553736 \pm 1964.5 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103unity 1.31 ± 0.16 183 \pm 421412 \pm 357 1.7 ± 0.5 13.85 \pm 2.80246 \pm 59461 \pm 57 0.6 ± 0.1 0.05 ± 0.01 130 \pm 40253 \pm 37 0.3 ± 0.0 0.16 ± 0.02 67 ± 12	g TissueRatio14C in Total Tissuecg Tissue2079 \pm 2512.5 \pm 0.58.45 \pm 0.92454 \pm 232.614679 \pm 928317.6 \pm 11.20.80 \pm 0.28370 \pm 1902.1182 \pm 390.2 \pm 0.00.07 \pm 0.0126 \pm 52.1380 \pm 260.5 \pm 0.163.46 \pm 1.3185 \pm 180.5492 \pm 1400.6 \pm 0.20.10 \pm 0.03150 \pm 540.815112 \pm 212118.1 \pm 0.87.70 \pm 0.551133 \pm 3256.23736 \pm 1964.5 \pm 0.69.35 \pm 0.732682 \pm 90114.98682 \pm 300910.3 \pm 2.53.73 \pm 0.932896 \pm 50016.8332 \pm 2290.4 \pm 0.39.41 \pm 6.8158 \pm 110.36863 \pm 7298.3 \pm 1.22.52 \pm 0.631080 \pm 6.1834 \pm 103unity1.31 \pm 0.16183 \pm 421412 \pm 3571.7 \pm 0.513.85 \pm 2.80246 \pm 591.4<	g TissueRatio14C in Total Tissue ^c g TissueRatio2079 \pm 2512.5 \pm 0.58.45 \pm 0.92454 \pm 232.6 \pm 14679 \pm 928317.6 \pm 11.20.80 \pm 0.28370 \pm 1902.1 \pm 182 \pm 390.2 \pm 0.00.07 \pm 0.0126 \pm 52.1 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b

Values are mean ± SD for four rats. Timed from the start of the exposure. Percent of recovered ¹⁴C was based on the total radioactivity in the urine and feces plus the radioactivity present in tissues. Adipose assumed to be 7.0% of body weight; blood = 5.2%; С muscle = 48%; skin = 17%; plasma = 52% of blood.

Concentration of ¹⁴C in Tissues of F-344-Male Rats 72 h after Intravenous Administration of [¹⁴C]MMT^a

Dose	0.81 mg MMT/kg body weight				0.37 mg MMT/kg body weight													
Tissue Name	-	ų MN Tiss	/IT per sue	Tiss	ue P Rati	asma o	Percent ¹⁴ C in 1	of F Total	lecovered Tissue ^b			IMT per ssue	Tiss	sue F Rat	Plasma io			lecovered Tissue ^b
Adipose	150	±	44	2.5	±	0.8	1.10	±	0.30	76	±	4	2.3	±	0.5	1.38	±	0.20
Bladder	57	±	18	0.9	±	0.2	0.00	±	0.00	31	±	15	0.9	±	0.4	0.00	±	0.00
Brain	5.9	±	1	0.1	±	0.0	0.00	±	0.00	4	±	1	0.1	±	0.0	0.01	±	0.00
Carcass	25	±	2	0.4	±	0.1	7.4	±	0.64	11	±	2	0.3	±	0.1	7.83	±	0.79
Heart	47	±	8	0.8	±	0.3	0.02	±	0.00	53	±	58	1.5	±	1.6	0.04	±	0.05
Kidney	360	±	82	6.1	±	1.4	0.29	±	0.07	217	±	54	6.3	±	1.1	0.39	±	0.07
Liver	970	±	120	17	±	3.3	3.8	±	0.31	636	±	18	18.8	±	2.8	6.10	±	0.41
Lung	1200	±	81	21	±	3.3	0.69	±	0.08	1109	±	357	32.8	±	11.1	1.27	±	0.06
Muscle	16	±	1	0.3	±	0.0	0.79	±	0.04	12	±	5	0.3	±	0.1	1.42	±	0.61
Nasopharyngeal	46	±	4	0.8	±	0.1	0.02	±	0.00	29	±	6	0.8	±	0.1	0.04	±	0.00
Plasma	60	±	13		unity	1	0.17	±	0.04	34	±	5		uni	ty	0.24	±	0.02
Skin	39	±	6	0.7	±	0.1	0.69	±	0.09	22	±	5	0.6	±	0.1	0.96	±	0.11
Spleen	56	±	1	0.9	±	0.1	0.02	±	0.00	58	±	24	1.7	±	0.7	0.06	±	0.01
Tail	15	±	10	0.2	±	0.1	0.52	±	0.34	6	±	7	0.2	±	0.2	0.53	±	0.47
Testis	19	±	3	0.3	±	0.0	0.02		0.00	12	±	2	0.3	±	0.0	0.03	±	0.00
Trachea	65	±	8	1.1	±	0.2	0.00	±	0.00	46	±	9	1.3	±	0.2	0.01	±	0.00

a b

Values are mean ± SD for four rate. Percent of recovered ¹⁴C was based on the total radioactivity in the urine and feces plus the radioactivity present in tissues. Adipose assumed to be 7.0% of body weight; blood = 5.2%; muscle = 48%; skin = 17%; plasma = 52% of blood.

Route	Inhalation	(nose-only)		Intrav	enous	
Dose	54 ng M	MT/mL air	0.81 mg MMT/I	kg body weight	0.37 mg MMT/k	g body weight
Time (h) ^b	mean	SD	mean	SD	mean	SD
0.5	156.4	17.1	190	120	138.7	23.0
1	260.6	61.0	200	120	155.1	37.6
2	С	с	210	87	149.7	29.8
3	593.6	121.6	с	с	С	С
4	С	с	240	47	135.7	13.0
6	879.6	241.8	260	5.9	121.3	17.1
6.5	819.5	142.4	с	с	С	С
7	770.9	127.7	с	с	С	С
8	754.9	130.8	с	с	С	С
10	735.7	121.3	с	с	С	С
12	687.1	100.8	240	67	119.6	37.6
24	434.9	66.7	150	36	71.0	14.6
48	261.2	68.5	93	17	48.0	60.5
72	183.2	42.1	60	13	34.4	5.1

Concentration of ¹⁴C in Plasma of F-344 Male Rats During and following Administration of MMT (ng-eq/g Plasma)^a

a Mean ± SD for four rats.
b All time points referenced to time of administered iv dose or beginning of 6 h exposure.
c Sample not collected.

Concentration of MMT in Plasma of F-344 Male Rats During and Followin	ng
Administration of MMT (ng/g Plasma) ^a	

Route	Inhalation	(nose-only)	Intrave	nous
Dose	54 ng MM	/IT / mL air	0.37 mg MMT / k	g body weight
Time (h) ^b	mean	SD	mean	SD
0.5	15.23	8.66	5.17	1.74
1	38.31	27.15	1.46	0.37
2	c	c	0.67	0.37
3	45.42	35.04	c	с
4	С	C	0.29	0.12
6	35.25	37.03	0.14	0.09
6.5	120.02	81.44	c	С
7	56.42	50.54	с	С
8	22.13	27.16	с	с
10	22.92	9.90	c	с
12	18.05	12.87	c	С
24	4.45	3.85	c	с
48	0.28	0.34	c	с
72	0.55	0.61	c	С

a Mean ± SD for four rats.
b All time points referenced to time of administered iv dose or beginning of 6 h exposure.
c Sample not collected

Parameter	Estimate ± SE
K ₁₂	1.079 ± 0.824 h ⁻¹
K ₂₁	0.731 ± 0.338 h ⁻¹
K ₁₀	2.514 ± 1.729 h ⁻¹
t _{1/2β}	1.451 ± 0.616 h
CI	0.058 ± 0.023 ng/kg/h
V	0.023 ± 0.025 L/kg
V _{ss}	0.057 ± 0.046 L/kg
MRT	0.985 ± 0.466 h

Pharmacokinetic Parameter Estimates Derived to Describe the Disposition of Intravenously Administered MMT (0.37 mg/kg) in the Rat