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-^{14}C]-

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; $t_{½ß}$, 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.

Note on Accessibility: Persons with disabilities or using assistive technology may find some documents are not fully accessible. For assistance, contact Central Data Management or use our contact form and identify the documents/pages for which access is required. We will assist you in accessing the content of the files. NIEHS has helpful information on accessibility.

Table [1]

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

Route		Inhalation	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]
Urine	6	[d]	9.5 ± 11.2	12.9±8.9
	12	[d]	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 (Volatile)	12	[d]	1.2 ± 0.1	0.6±0.1
	24	19.6 ± 3.2	1.8 ± 0.3	1.0±0.1
	48	20.8 ± 3.0	2.1 ± 0.4	[d]
	72	[d]	2.4 ± 0.4	[d]
Breath (CO_2)	12	[d]	0.6 ± 0.0	[d]
	24	[d]	0.9 ± 0.0	[d]
	48	[d]	1.0 ± 0.1	[d]
	72	[d]	1.3 ± 0.1	[d]
Breath (Diene)	12	[d]	0.03 ± 0.00	[d]
	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]

[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* ^{14}C.
[f] Value is 88.9 ± 4.5 percent of the *administered* ^{14}C.

Table 2

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

Dose	54 ng MMT/mL air - 6 h post exposure[b]			54 ng MMT/mL air - 72 h post exposure[b]		
Tissue Name	ng-eq MMT per g Tissue	Tissue Plasma Ratio	Percent of Recovered 14C in Total Tissue[c]	ng-eq MMT per g Tissue	Tissue Plasma Ratio	Percent of Recovered 14C in Total Tissue[c]
Adipose	2079 ± 251	2.5 ± 0.5	8.45 ± 0.92	454 ± 23	2.6 ± 0.5	1.42 ± 0.08
Bladder	14679 ± 9283	17.6 ± 11.2	0.80 ± 0.28	370 ± 190	2.1 ± 1.2	0.01 ± 0.01
Brain	182 ± 39	0.2 ± 0.0	0.07 ± 0.01	26 ± 5	2.1 ± 1.2	0.01 ± 0.00
Carcass	380 ± 26	0.5 ± 0.1	63.46 ± 1.31	85 ± 18	0.5 ± 0.0	11.67 ± 2.18
Heart	492 ± 140	0.6 ± 0.2	0.10 ± 0.03	150 ± 54	0.8 ± 0.2	0.02 ± 0.01
Kidney	15112 ± 2121	18.1 ± 0.8	7.70 ± 0.55	1133 ± 325	6.2 ± 1.2	0.44 ± 0.10
Liver	3736 ± 196	4.5 ± 0.6	9.35 ± 0.73	2682 ± 901	14.9 ± 5.6	4.73 ± 1.13
Lung	8682 ± 3009	10.3 ± 2.5	3.73 ± 0.93	2896 ± 500	16.8 ± 6.6	0.92 ± 0.15
Muscle	332 ± 229	0.4 ± 0.3	9.41 ± 6.81	58 ± 11	0.3 ± 0.0	1.24 ± 0.15
Nasopharyngeal	6863 ± 729	8.3 ± 1.2	2.52 ± 0.63	1080 ± 86	6.1 ± 1.5	0.32 ± 0.05
Plasma	834 ± 103	unity	1.31 ± 0.16	183 ± 42	unity	0.22 ± 0.04
Skin	1412 ± 357	1.7 ± 0.5	13.85 ± 2.80	246 ± 59	1.4 ± 0.3	1.86 ± 0.40
Spleen	461 ± 57	0.6 ± 0.1	0.05 ± 0.01	130 ± 40	0.7 ± 0.1	0.02 ± 0.00
Testis	253 ± 37	0.3 ± 0.0	0.16 ± 0.02	67 ± 12	0.4 ± 0.0	0.03 ± 0.00
Trachea	14035 ± 2054	16.8 ± 0.8	0.42 ± 0.15	1146 ± 803	6.7 ± 5.2	0.02 ± 0.01

a Values are mean ± SD for four rats.
b Timed from the start of the exposure.
c Percent of recovered ^{14}C 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.

Table 3

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

Dose	0.81 mg MMT/kg body weight			0.37 mg MMT/kg body weight		
Tissue Name	ng-eq MMT per g Tissue	Tissue Plasma Ratio	Percent of Recovered ^{14}C in Total Tissue[b]	ng-eq MMT per g Tissue	Tissue Plasma Ratio	Percent of Recovered ^{14}C in Total 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	0.17 ± 0.04	34 ± 5	unity	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] Values are mean ± SD for four rats.
[b] Percent of recovered ^{14}C 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.

Table 4

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

Route	Inhalation (nose-only)		Intravenous			
Dose	54 ng MMT/mL air		0.81 mg MMT/kg body weight		0.37 mg MMT/kg 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	[c]	[c]	210	87	149.7	29.8
3	593.6	121.6	[c]	[c]	[c]	[c]
4	[c]	[c]	240	47	135.7	13.0
6	879.6	241.8	260	5.9	121.3	17.1
6.5	819.5	142.4	[c]	[c]	[c]	[c]
7	770.9	127.7	[c]	[c]	[c]	[c]
8	754.9	130.8	[c]	[c]	[c]	[c]
10	735.7	121.3	[c]	[c]	[c]	[c]
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

[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.

Table 5

Concentration of MMT in Plasma of F-344 Male Rats During and Following Administration of MMT (ng/g Plasma)[a]

Route	Inhalation (nose-only)		Intravenous	
Dose	54 ng MMT / mL air		0.37 mg MMT / kg 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]	[c]
4	[c]	[c]	0.29	0.12
6	35.25	37.03	0.14	0.09
6.5	120.02	81.44	[c]	[c]
7	56.42	50.54	[c]	[c]
8	22.13	27.16	[c]	[c]
10	22.92	9.90	[c]	[c]
12	18.05	12.87	[c]	[c]
24	4.45	3.85	[c]	[c]
48	0.28	0.34	[c]	[c]
72	0.55	0.61	[c]	[c]

[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

Table 6

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

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}
$t_{1/2\beta}$	1.451 ± 0.616 h
Cl	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