

ADME NTP Study S0105 4-Chloronitrobenzene

The contract laboratory abbreviation is 4-CNB.

Sex/Species: young adult male F344 rats (11 weeks old, weighing between 205-246 g at randomization).

Vehicle: oral, corn oil.

CASRN 100-00-5

Radiolabeled with carbon-14 in the ring; 4-Chloronitrobenzene, [Ring-¹⁴C]-

Studies performed:

Study S0105 – Single oral administration (gastric intubation) of 2, 20, and 200 mg/kg [¹⁴C]4-CNB to 11-week old rats with sacrifice 24 or 72 hours postdose. **This is the second study** of a four-part study on 4-chloronitrobenzene (4-CNB).

Companion studies:

The first study (S0077) examined the effect of single dermal administrations of 0.65, 6.5, or 65 mg/kg [¹⁴C]4-CNB (dose site covered) to 10-12 week old male Fischer 344 rats with sacrifice 72 hours postdose.

The third study (S0779) investigated the effect of 11-day repeat 65 mg/kg 4-CNB daily dosing by oral administration (gastric intubation) on young adult male rats (9 weeks old). Rats were sacrificed on Day 12.

A fourth study (S0363) investigated the effect of 11-day repeat 65 mg/kg 4-CNB daily dosing by oral administration (gastric intubation) on geriatric male rats (approximately 19 months old). The same dosing and sampling regime as for S0779 was used.

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TABLE 1

Urinary excretion of ^{14}C -radioactivity by male Fischer-344 rats after oral administration of ^{14}C -4-chloronitrobenzene

Time (hr)	Dose (mg/kg)		
	2	20	200
	Mean \pm SD Dose Excreted (%) ^a		
0-4	6.2 \pm 4.6	0.6 \pm 0.2	1.2 \pm 0.9
4-8	4.2 \pm 4.0	8.5 \pm 2.8	2.5 \pm 1.4
8-24	42.6 \pm 6.4	32.2 \pm 3.9	21.8 \pm 1.4
24-48	16.3 \pm 2.7	20.3 \pm 3.4	30.5 \pm 7.8
48-72	4.7 \pm 1.6	6.7 \pm 1.2	12.0 \pm 1.0
	Mean \pm SD Dose Excreted (Cumulative %) ^a		
0-4	6.2 \pm 4.6	0.6 \pm 0.2	1.2 \pm 0.9
0-8	10.3 \pm 6.4	9.1 \pm 2.9	3.7 \pm 0.6
0-24	52.9 \pm 5.3	41.2 \pm 4.3	25.5 \pm 1.1
0-48	69.2 \pm 2.7	61.5 \pm 5.3	56.0 \pm 7.5
0-72	73.9 \pm 1.5	68.2 \pm 4.5	68.0 \pm 6.5

^a Mean of data from 4 rats.

TABLE 2

Fecal excretion of ¹⁴C-radioactivity by male Fischer-344 rats after oral administration of ¹⁴C-4-chloronitrobenzene

<u>Time (hr)</u>	<u>Dose (mg/kg)</u>		
	<u>2</u>	<u>20</u>	<u>200</u>
	<u>Mean ± SD Dose Excreted (%)^a</u>		
0-4	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
4-8	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
8-24	6.5 ± 1.2	2.1 ± 1.0	0.2 ± 0.4
24-48	4.1 ± 0.4	6.4 ± 1.0	7.3 ± 1.0
48-72	1.2 ± 0.1	1.8 ± 0.4	4.8 ± 0.6
	<u>Mean ± SD Dose Excreted (Cumulative %)^a</u>		
0-4	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
0-8	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
0-24	6.6 ± 1.2	2.1 ± 1.0	0.2 ± 0.4
0-48	10.7 ± 1.0	8.5 ± 0.3	7.5 ± 1.3
0-72	11.8 ± 1.0	10.3 ± 0.4	12.3 ± 1.1

^a Mean of data from 4 rats.

TABLE 3

Concentration of ¹⁴C-4-chloronitrobenzene equivalents in Fischer-344 rats at around 24 and 72 hr after oral administration of ¹⁴C-4-chloronitrobenzene

Tissue	Time (hr)	Mean ± SD Concentration (nmol/g) ^a		
		Dose (mg/kg)		
		2	20	200
Plasma	24	1.02 ± 0.13	11.23 ± 0.89	154.35 ± 6.59
	72	0.11 ± 0.03	1.44 ± 0.41	28.67 ± 4.55
Blood cells	24	8.78 ± 0.77	105.25 ± 5.05	821.45 ± 137.37
	72	9.38 ± 1.03	103.08 ± 7.40	823.68 ± 76.12
Liver	24	2.39 ± 0.14	25.90 ± 1.05	349.28 ± 19.79
	72	0.66 ± 0.07	7.66 ± 1.51	91.37 ± 6.59
Kidney	24	4.76 ± 1.04	52.00 ± 4.13	636.80 ± 66.39
	72	0.91 ± 0.08	10.30 ± 2.77	146.21 ± 36.73
Heart	24	1.14 ± 0.07	13.52 ± 2.62	155.70 ± 11.95
	72	0.64 ± 0.15	6.11 ± 3.46	57.23 ± 15.81
Lung	24	1.45 ± 0.14	15.82 ± 2.28	192.12 ± 39.07
	72	0.92 ± 0.13	8.93 ± 1.33	82.64 ± 17.67

Footnotes are defined on the following page.

TABLE 3 (continued)

Tissue	Time (hr)	Mean \pm SD Concentration (nmol/g) ^a		
		Dose (mg/kg)		
		2	20	200
Brain	24	0.51 \pm 0.08	5.98 \pm 0.99	89.25 \pm 5.93
	72	0.13 \pm 0.04	1.39 \pm 0.25	21.59 \pm 2.33
Fat	24	20.08 \pm 2.45	234.72 \pm 8.44	4100.84 \pm 252.78
	72	1.06 \pm 0.46	18.66 \pm 7.25	513.78 \pm 80.23
Skeletal muscle	24	0.45 \pm 0.08	5.60 \pm 1.61	81.45 \pm 30.65
	72	0.08 \pm 0.04	0.86 \pm 0.12	12.68 \pm 1.23
Spleen	24	2.05 \pm 0.32	19.90 \pm 2.95	291.99 \pm 56.05
	72	1.49 \pm 0.26	17.16 \pm 2.18	292.15 \pm 30.55
Thymus	24	1.12 \pm 0.28	10.97 \pm 2.49	179.32 \pm 43.94
	72	0.28 \pm 0.06	3.31 \pm 0.78	37.72 \pm 8.57
Testes	24	0.46 \pm 0.05	4.83 \pm 0.99	81.48 \pm 11.53
	72	0.08 \pm 0.01	1.00 \pm 0.23	18.20 \pm 2.23
Bone Marrow	24	0.61 \pm 0.06	10.80 \pm 9.18	106.68 \pm 42.17
	72	0.08 \pm 0.09	1.94 \pm 1.31	22.78 \pm 30.02

^a Mean of data from 4 rats.

TABLE 4

Percentage of the dose of ^{14}C -radioactivity in tissues of male Fischer-344 rats at around 24 and 72 hr after oral administration of ^{14}C -4-chloronitrobenzene

Tissue	Time (hr)	Mean \pm SD Fraction of Dose(%) ^{a, b}		
		Dose (mg/kg)		
		2	20	200
Plasma	24	0.30 \pm 0.04	0.33 \pm 0.02	0.42 \pm 0.02
	72	0.03 \pm 0.01	0.04 \pm 0.01	0.08 \pm 0.02
Blood cells	24	2.60 \pm 0.23	3.12 \pm 0.13	2.22 \pm 0.38
	72	2.82 \pm 0.30	3.07 \pm 0.17	2.33 \pm 0.25
Liver	24	0.76 \pm 0.06	0.84 \pm 0.04	0.90 \pm 0.05
	72	0.22 \pm 0.03	0.25 \pm 0.04	0.30 \pm 0.04
Kidney	24	0.26 \pm 0.05	0.30 \pm 0.03	0.34 \pm 0.04
	72	0.05 \pm 0.00	0.06 \pm 0.02	0.09 \pm 0.02
Heart	24	0.03 \pm 0.00	0.04 \pm 0.01	0.04 \pm 0.00
	72	0.02 \pm 0.01	0.02 \pm 0.01	0.02 \pm 0.00
Lung	24	0.04 \pm 0.00	0.05 \pm 0.00	0.06 \pm 0.01
	72	0.03 \pm 0.00	0.03 \pm 0.00	0.03 \pm 0.01
Brain	24	0.03 \pm 0.01	0.04 \pm 0.01	0.05 \pm 0.01
	72	0.01 \pm 0.00	0.01 \pm 0.00	0.01 \pm 0.00

Footnotes are defined on the following page.

TABLE 4 (continued)

Tissue	Time (hr)	Mean \pm SD Fraction of Dose(%) ^{a, b}		
		Dose (mg/kg)		
		2	20	200
Fat	24	15.05 \pm 1.82	17.56 \pm 0.70	28.14 \pm 2.13
	72	0.80 \pm 0.35	1.40 \pm 0.53	3.68 \pm 0.61
Skeletal muscle	24	1.68 \pm 0.30	2.09 \pm 0.56	2.80 \pm 1.08
	72	0.30 \pm 0.14	0.32 \pm 0.04	0.45 \pm 0.07
Spleen	24	0.04 \pm 0.01	0.04 \pm 0.01	0.06 \pm 0.01
	72	0.03 \pm 0.01	0.04 \pm 0.01	0.09 \pm 0.02
Thymus	24	0.01 \pm 0.00	0.01 \pm 0.00	0.02 \pm 0.01
	72	<0.01	<0.01	<0.01 \pm 0.00
Testes	24	0.05 \pm 0.01	0.05 \pm 0.01	0.07 \pm 0.01
	72	0.01 \pm 0.00	0.01 \pm 0.00	0.02 \pm 0.00
Bone Marrow	24	<0.01	<0.01	<0.01
	72	0.00 \pm 0.00	0.00 \pm 0.00	0.00 \pm 0.00
Total	24	20.84 \pm 2.00	24.45 \pm 0.52	35.10 \pm 3.09
	72	4.31 \pm 0.24	5.23 \pm 0.71	7.09 \pm 0.88

^a Mean of data from 4 rats.

^b Percentages were calculated from the organ weights and by assuming that plasma = 3.75%, blood cells = 3.75%, fat = 9.50% and skeletal muscle = 47.5% of body weight.

TABLE 5

Recovery of ¹⁴C-radioactivity at around 24 hr after oral administration of ¹⁴C-4-chloronitrobenzene to male Fischer-344 rats

Sample ^a	Mean ± SD Dose Recovered (%)		
	Dose (mg/kg)		
	2	20	200
Urine	46.6 ± 2.3	43.1 ± 5.8	23.5 ± 4.0
Feces	4.5 ± 1.4	5.0 ± 0.9	0.5 ± 0.5
Cage Rinse	4.6 ± 2.5	3.2 ± 1.1	4.1 ± 1.7
Tissues	20.8 ± 2.0	24.5 ± 0.5	35.1 ± 3.1
Total	76.5 ± 4.1	75.7 ± 5.6	63.2 ± 5.3

^a Urine and feces were collected up to the time of sacrifice, at around 24 hr. At sacrifice tissues and cage rinse were collected. N = 4 rats per group.

TABLE 6

Recovery of ^{14}C -radioactivity at around 72 hr after oral administration of ^{14}C -4-chloronitrobenzene to male Fischer-344 rats

Sample ^a	Mean \pm SD Dose Recovered (%)		
	Dose (mg/kg)		
	2	20	200
Urine	73.9 \pm 1.5	68.2 \pm 4.5	68.0 \pm 6.5
Feces	11.8 \pm 1.0	10.3 \pm 0.4	12.3 \pm 1.1
Cage Rinse	3.1 \pm 0.7	2.6 \pm 0.6	2.8 \pm 0.6
Tissues	4.3 \pm 0.3	5.3 \pm 0.7	7.1 \pm 0.9
Total	93.2 \pm 1.8	86.3 \pm 4.2	90.2 \pm 5.2

^a Urine and feces were collected up to the time of sacrifice at around 72 hr.

At sacrifice tissues and cage rinse were collected.

N = 4 rats per group.