

ADME NTP Study S0363 4-Chloronitrobenzene

The contract laboratory abbreviation is 4-CNB.

Sex/Species: Geriatric male F344 rats (approximately 19 months old weighing between 325-492 g)

Vehicle: oral, corn oil

CASRN 100-00-5

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

Studies performed:

Study S0363 – 11-day repeat 65 mg/kg 4-CNB daily dosing by oral administration (gastric intubation) to geriatric male rats (approximately 19 months old). Radiolabeled [¹⁴C]4-CNB was given on study Days 1, 5, and 9. Unlabeled 4-CNB was given on days 2-4, 6-8, and 10-11. Rats were sacrificed on Day 12, 72 hours after the radioactive dose was administered on Day 9.

This study is the fourth 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 F344 rats with sacrifice 72 hours postdose.

The second study (S0105) examined the effect of a single oral administration (gastric intubation) of 2, 20, or 200 mg/kg [¹⁴C]4-chloronitrobenzene in 11-week old male F344 rats. Rats were sacrificed at 24 and 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 F344 rats (9 weeks old). The same dosing and sampling regime as for S0363 was used.

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Table 1: Urinary excretion of ¹⁴C radioactivity by geriatric male Fischer 344 rats (19 mo old) at intervals during treatment with 4-CNB at 65 mg/kg p.o. daily for 11 days

Time (hr) ^a	Day [¹⁴ C]4-CNB administered		
	1	5	9
	Mean ± SD dose excreted (%)^b		
0-4	1.2 ± 1.4	1.5 ± 1.2	7.0 ± 3.8
4-8	3.2 ± 3.0	7.3 ± 4.6	5.8 ± 3.4
8-24	28.3 ± 7.0	24.8 ± 10.7	21.3 ± 9.0
24-48	20.0 ± 3.2	20.3 ± 3.3	18.2 ± 1.8
48-72	10.4 ± 1.1	12.3 ± 2.9	12.8 ± 4.9
72-96	8.5 ± 3.4	7.7 ± 3.4	
	Mean ± SD dose excreted (cumulative %)		
0-4	1.2 ± 1.4	1.5 ± 1.2	7.0 ± 3.8
0-8	4.4 ± 4.2	8.8 ± 4.6	12.8 ± 4.3
0-24	32.7 ± 10.8	33.5 ± 14.7	34.1 ± 13.1
0-48	52.7 ± 13.9	53.8 ± 15.1	52.3 ± 14.5
0-72	63.1 ± 13.3	66.1 ± 13.1	65.2 ± 10.1
0-96	71.6 ± 10.2	73.7 ± 10.0	

^aTime after each ¹⁴C-labeled dose. N = 4.

^bData expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.

Table 2: Fecal excretion of ¹⁴C radioactivity by geriatric male Fischer 344 rats (19 mo old) at intervals during treatment with 4-CNB at 65 mg/kg p.o. daily for 11 days

Time (hr) ^a	Day [¹⁴ C]4-CNB administered		
	1	5	9
	Mean ± SD dose excreted (%)^b		
0-4	0.0 ± 0.0	0.5 ± 0.5	0.3 ± 0.3
4-8	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
8-24	0.7 ± 0.8	2.4 ± 2.9	1.7 ± 1.1
24-48	2.3 ± 2.1	1.9 ± 1.3	6.3 ± 1.9
48-72	1.7 ± 1.4	3.9 ± 1.8	2.4 ± 0.8
72-96	2.2 ± 2.6	3.5 ± 2.0	
	Mean ± SD dose excreted (cumulative %)		
0-4	0.0 ± 0.0	0.5 ± 0.5	0.3 ± 0.3
0-8	0.0 ± 0.0	0.5 ± 0.5	0.3 ± 0.3
0-24	0.7 ± 0.8	2.9 ± 2.6	1.9 ± 0.8
0-48	3.0 ± 2.9	4.8 ± 3.3	8.2 ± 2.6
0-72	4.7 ± 4.0	8.7 ± 4.4	10.6 ± 2.2
0-96	6.9 ± 2.4	12.2 ± 5.1	

^aTime after each ¹⁴C-labeled dose. N = 4.

^bData expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.

Table 3: Concentration of ^{14}C 4-CNB equivalents in tissues of geriatric male Fischer 344 rats (19 mo) at ca. 72 hr after administration of ^{14}C 4-CNB at 65 mg/kg p.o. on Day 9

Tissue	Concentration (% Day 9 dose/g $\times 10^2$)^a
Plasma	1.0 \pm 0.7
Blood cells	11.0 \pm 3.0
Liver	3.9 \pm 2.5
Kidney	4.7 \pm 2.3
Heart	1.5 \pm 1.1
Lung	3.9 \pm 3.2
Brain	0.8 \pm 0.7
Adipose tissue	30.0 \pm 28.0
Skeletal muscle	2.2 \pm 3.4
Spleen	8.0 \pm 2.0
Thymus	2.0 \pm 1.8
Testes	9.0 \pm 7.0

^aMean of data from four rats.

Table 4: Percentage of dose of 4-CNB-derived radioactivity in tissues of geriatric male Fischer 344 rats (19 mo) at ca. 72 hr after administration of [¹⁴C]4-CNB at 65 mg/kg p.o. on Day 9

Tissue	Fraction of Day 9 Dose (%)^a Mean ± SD^b
Plasma	0.14 ± 0.10
Blood cells	1.50 ± 0.36
Liver	0.46 ± 0.26
Kidney	0.13 ± 0.07
Heart	0.02 ± 0.01
Lung	0.07 ± 0.07
Brain	0.02 ± 0.01
Adipose tissue	10.66 ± 9.72
Skeletal muscle	3.75 ± 5.63
Spleen	0.19 ± 0.05
Thymus	0.03 ± 0.02
Testes	0.07 ± 0.07
Total	17.03 ± 15.58

^aPercentages were calculated from the organ weights and by assuming that plasma = 3.75%, blood cells = 3.75%, fat = 9.5%, and skeletal muscle = 47.5% of body weight.

^bMean of data from four rats.

Table 5: Recovery of ^{14}C radioactivity at intervals during the treatment of geriatric male Fischer 344 rats with 4-CNB at 65 mg/kg p.o. daily for 11 days

Sample ^a	Day [^{14}C]4-CNB administered		
	1	5	9
	Mean \pm SD dose recovered (%) ^b		
Urine	71.6 \pm 10.2	73.7 \pm 10.0	65.2 \pm 10.1
Feces	6.9 \pm 2.4	12.2 \pm 5.1	10.6 \pm 2.2
Cage rinse			5.5 \pm 3.2
Tissues			17.1 \pm 15.6
Total	78.5 \pm 12.2	85.9 \pm 14.4	98.2 \pm 7.4

^a Urine and feces were collected up to 96 hr after administration of [^{14}C]4-CNB on Days 1 and 5, and up to the time of sacrifice (ca. 72 hr) after administration on Day 9. Cage rinse and tissues were collected at ca. 72 hr after the Day 9 dose. N = 4.

^bData expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.

Table 6: Comparison of the disposition and metabolism characteristics of [¹⁴C]4-CNB in young adult and geriatric male Fischer 344 rats at 65 mg/kg p.o. with those at 2, 20 and 200 mg/kg p.o.

Parameter	Mean fraction of dose (%) ^a				
	Dose (mg/kg)				
	2 ^b	20 ^b	65 ^c young adult	65 geriatric	200 ^b
Minimum extent absorption ^d	78	73	74	72	75
Excreted urine, 0-24 hr	52.9	41.2	42.6	32.7	25.5
0-72 hr	73.9	68.2	73.9	71.6	68.0
Excreted feces, 0-24 hr	6.6	2.1	4.1	0.7	0.2
0-72 hr	11.8	10.3	13.5	6.9	12.3
Total recovery, 0-72 hr	93.2	86.3	91.1	78.5	90.2
Excreted urine, 0-72 hr or 0-96 hr as:					
F	8.2	5.9	4.2	1.7	3.6
M	11.5	13.9	18.1	20.1	19.1
O	12.7	12.0	12.3	9.2	9.1
P	3.9	3.4	2.3	5.1	1.9
Q	8.2	8.7	16.1	12.3	11.1
W	13.7	10.2	11.1	9.4	12.8
Other metabolites ^e	19.2	16.1	14.2	15.5	9.5
Total metabolites	73.5	66.8	75.5	71.6	65.2

^aMean of data from 3-4 rats, or mean of duplicate analyses of pooled urine samples from 3-4 rats.

^bData from reference 1.

^cData from reference 2.

^dEqual to the dose excreted in urine in 0-72 hr or 0-96 hr, with or without the % of dose in tissues at 72 hr. Extent of absorption was probably higher, as there was evidence for biliary secretion.

^eTotal of 20 other metabolites, each of which represented less than 5% of the dose.

Table 7: Effect of pretreatment with 4-CNB on the disposition and metabolism of [¹⁴C]4-CNB in geriatric male Fischer 344 rats

Parameter	Mean ± SD fraction of dose (%) ^{a,b}		
	Duration of pretreatment with 4-CNB		
	0	4	8
Minimum extent absorption ^c	72	74	82
Excreted urine, 0-24 hr	32.7 ± 10.8	33.5 ± 14.7	34.1 ± 13.1
0-72 hr or 0-96 hr	71.6 ± 10.2	73.7 ± 10.0	65.2 ± 10.1
Excreted feces, 0-24 hr	0.7 ± 0.8	2.9 ± 2.6	1.9 ± 0.8
0-72 hr or 0-96 hr	6.9 ± 2.4	12.2 ± 5.1	10.6 ± 2.2
Tissues at, 72 hr			17.0 ± 15.6
Total recovery, 0-72 hr	78.5 ± 12.2	85.9 ± 14.4	98.2 ± 7.4
Excreted urine, 0-72 hr or 0-96 hr as:			
M	20.1	24.8	23.4
O	9.2	6.3	5.4
P	5.1	5.2	4.6
Q	12.3	11.0	8.5
W	9.4	8.3	6.7
Other metabolites ^d	16.5	18.3	16.5
Total metabolites	71.6	73.9	65.1

^aMean of data from four rats, or mean of duplicate analyses of pooled urine samples from 3-4 rats.

^bData expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.

^cEqual to the dose excreted in urine in 0-72 or 0-96 hr with or without the % of dose in tissues at 72 hr. Extent of absorption was probably higher, as there was evidence for biliary secretion

^dTotal of 20 other metabolites, each of which represented less than 5% of the dose and constituted a similar fraction of the Day 1, Day 5 and Day 9 radio-labeled doses.