

## ADME NTP Study S0365 2-Chloronitrobenzene

The contract laboratory abbreviation for the test article is 2-CNB.

Sex/Species: geriatric male F344 rats (approximately 19 months old weighing 406-483 g at arrival).

Vehicle: oral, corn oil;

CASRN 88-73-3

Radiolabeled with carbon-14 at the ring position; 2-Chloronitrobenzene, [Ring-<sup>14</sup>C]-

Study Performed:

11-day repeat 65 mg/kg oral gavage administration to rats with sacrifice 72 hours after last administered radioactive dose on Day 9. (n=4)

2-Chloronitrobenzene was administered to 4 geriatric rats daily for 11 days. On Days 1, 5, and 9, <sup>14</sup>C-labeled compound was administered. On days 2-4, 6-8, and 10-11 unlabeled compound was administered. Rats were sacrificed on Day 12.

Urine and feces were collected to 96 hours following administration of 1<sup>st</sup> and 2<sup>nd</sup> radiolabeled doses and to 72 hours after the 3<sup>rd</sup> radiolabeled dose which corresponds to 24 hours after the last unlabeled dose.

This study is part of a series of NTP studies conducted in the same laboratory on the disposition and metabolism of 2-chloronitrobenzene in male Fisher 344 rats:

- S0104 – repeat oral administration of 65 mg/kg 2-CNB for 11 days to 9-week old rats (186-203 g at randomization)
- S0191 – single 0.65, 6.5, or 65 mg/kg 2-CNB dermal doses administered to 10-12 week old rats (200-225 g at randomization)
- S0364 – single oral dosing of 2.0, 20, or 200 mg/kg 2-CNB administered to 11-week old rats (198-231g at the time of randomization).

Metabolite profiles in pooled urine were determined using HPLC with 22 metabolites assigned the labels I-XXII.

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TABLE 1

Urinary excretion of <sup>14</sup>C-radioactivity by geriatric male Fischer-344 rats (19 months old) at intervals during treatment with 2-CNB at 65 mg/kg p.o. daily for 11 days.

Time (hr) <sup>a</sup>	Day <sup>14</sup> C-2-CNB administered		
	1	5	9
	Mean ± SD Dose Excreted (%) <sup>b</sup>		
0-4	12.3 ± 5.4	5.7 ± 7.0	6.6 ± 5.0
4-8	8.8 ± 3.6	10.3 ± 12.0	20.1 ± 9.0
8-24	42.4 ± 5.6	45.2 ± 11.0	25.6 ± 7.9
24-48	15.2 ± 1.6	9.0 ± 1.8	12.2 ± 5.4
48-72	4.9 ± 1.4	3.2 ± 1.1	6.4 ± 4.7
72-96	1.6 ± 0.6	1.7 ± 0.7	

Mean ± SD Dose Excreted (Cumulative %)

0-4	12.3 ± 5.4	5.7 ± 7.0	6.6 ± 5.0
0-8	21.1 ± 6.0	16.0 ± 14.8	26.6 ± 6.5
0-24	63.5 ± 3.2	61.3 ± 5.5	52.2 ± 9.2
0-48	78.7 ± 2.2	70.3 ± 4.7	64.4 ± 5.7
0-72	83.5 ± 1.5	73.5 ± 4.9	70.8 ± 5.5
0-96	85.1 ± 1.1	75.1 ± 4.4	

a Time after each <sup>14</sup>C-labeled dose.

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

**TABLE 2**

Fecal excretion of  $^{14}\text{C}$ -radioactivity by geriatric male Fischer 344 rats (19 months old) at intervals during treatment with 2-CNB at 65 mg/kg p.o. daily for 11 days.

Time (hr) <sup>a</sup>	Day $^{14}\text{C}$ -2-CNB administered		
	1	5	9
	Mean $\pm$ SD Dose Excreted (%) <sup>b</sup>		
0-4	0.0 $\pm$ 0.0	0.4 $\pm$ 0.4	0.1 $\pm$ 0.1
4-8	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
8-24	1.4 $\pm$ 2.1	6.5 $\pm$ 2.7	7.4 $\pm$ 5.3
24-48	16.3 $\pm$ 2.8	9.2 $\pm$ 6.8	7.2 $\pm$ 3.7
48-72	3.7 $\pm$ 1.2	4.9 $\pm$ 4.8	4.3 $\pm$ 5.1
72-96	1.0 $\pm$ 0.4	0.7 $\pm$ 0.5	
	Mean $\pm$ SD Dose Excreted (Cumulative %)		
0-4	0.0 $\pm$ 0.0	0.4 $\pm$ 0.4	0.1 $\pm$ 0.1
0-8	0.0 $\pm$ 0.0	0.4 $\pm$ 0.4	0.1 $\pm$ 0.1
0-24	1.4 $\pm$ 2.1	7.0 $\pm$ 2.5	7.5 $\pm$ 5.4
0-48	17.7 $\pm$ 4.6	16.2 $\pm$ 5.3	14.6 $\pm$ 7.1
0-72	21.4 $\pm$ 3.4	21.0 $\pm$ 1.3	18.9 $\pm$ 2.1
0-96	22.4 $\pm$ 3.2	21.7 $\pm$ 1.3	

a Time after each  $^{14}\text{C}$ -labeled dose.

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

TABLE 3

Concentration of  $^{14}\text{C}$ -2-CNB-equivalents in tissues of geriatric male Fischer-344 rats (19 months old) at around 72 hr after administration of  $^{14}\text{C}$ -2-CNB at 65 mg/kg p.o. on day 9.

Tissue	Concentration (% of the Day 9 dose/g x $10^2$ ) <sup>a</sup>
Plasma	0.44 ± 0.23
Blood Cells	1.30 ± 0.60
Liver	35.00 ± 18.00
Kidney	27.00 ± 3.00
Heart	0.55 ± 0.25
Lung	1.20 ± 0.40
Brain	0.19 ± 0.09
Adipose Tissue	1.50 ± 0.70
Skeletal Muscle	0.33 ± 0.18
Spleen	1.70 ± 0.50
Thymus	0.47 ± 0.20
Testes	1.10 ± 0.40

<sup>a</sup> Mean of data from 4 rats.

TABLE 4

Percentage of dose of 2-CNB-derived radioactivity in tissues of geriatric male Fischer-344 (19 months old) rats at around 72 hr after administration of  $^{14}\text{C}$ -2-CNB at 65 mg/kg p.o. on Day 9

Tissue	Fraction of Day 9 Dose (%) <sup>a</sup> Mean $\pm$ SD <sup>b</sup>
Plasma	0.06 $\pm$ 0.02
Blood Cells	0.17 $\pm$ 0.05
Liver	6.04 $\pm$ 1.63
Kidney	0.80 $\pm$ 0.07
Heart	0.01 $\pm$ 0.01
Lung	0.01 $\pm$ 0.01
Brain	0.00 $\pm$ 0.01
Adipose Tissue	0.52 $\pm$ 0.17
Skeletal Muscle	0.56 $\pm$ 0.22
Spleen	0.02 $\pm$ 0.00
Thymus	<0.01
Testes	0.02 $\pm$ 0.01
Total	8.21 $\pm$ 1.96

<sup>a</sup> Percentages 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.

<sup>b</sup> Mean of data from 4 rats.

TABLE 5

Recovery of  $^{14}\text{C}$ -radioactivity at intervals during the treatment of geriatric male Fischer 344 rats with 2-CNB at 65 mg/kg p.o. daily for 11 days.

<sup>a</sup> Sample	Day $^{14}\text{C}$ -2-CNB administered		
	1	5	9
	<sup>b</sup> Mean $\pm$ SD Dose Recovered (%)		
Urine	85.1 $\pm$ 1.1	75.1 $\pm$ 4.4	70.8 $\pm$ 5.5
Feces	22.4 $\pm$ 3.2	21.7 $\pm$ 1.3	18.9 $\pm$ 2.1
Cage Rinse			2.5 $\pm$ 0.9
Tissues			8.2 $\pm$ 2.0
Total	107.5 $\pm$ 2.5	96.9 $\pm$ 5.1	100.4 $\pm$ 5.4

<sup>a</sup> Urine and feces were collected up to 96 hr after administration of  $^{14}\text{C}$ -2-CNB on Days 1 and 5, and up to the time of sacrifice, at around 72 hr, after administration on Day 9. Cage rinse and tissues were collected at around 72 hr after the Day 9 dose.

<sup>b</sup> Data expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.

TABLE 6

Comparison of the disposition and metabolism characteristics of <sup>14</sup>C-2-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 (%) <sup>a</sup>				
	2 <sup>b</sup>	Dose (mg/kg)			200 <sup>b</sup>
		20 <sup>b</sup>	65 adult <sup>c</sup>	geriatric	
Minimum Extent Absorption <sup>d</sup>	62	61	71	85	77
Excreted Urine 0-24 hr	56.4	53.0	60.6	63.5	39.2
0-72 hr	59.6	57.7	70.9	85.1	73.5
Excreted Feces 0-24 hr	21.9	19.8	5.4	1.4	0.0
0-72 hr	28.2	26.3	19.9	22.4	6.9
Total Recovery 0-72 hr	91.2	88.0	93.1	107.5	85.9
Excreted Urine 0-72 hr or 0-96 hr as:					
I	0.7	0.7	0.1	6.4	1.8
X	2.9	2.4	3.2	6.3	0.2
XI	2.9	3.2	12.7	5.6	21.1
XV	0.4	1.0	0.3	4.5	5.9
XIX	8.2	8.4	6.4	7.4	5.9
XXI	27.3	26.4	21.4	25.2	23.2
Other Metabolites	16.5	18.1	27.6	29.8	17.5
Total Metabolites <sup>e</sup>	58.2	59.5	71.9	85.2	73.8

TABLE 6 (continued)

- a Mean of data from 3-4 rats or mean of duplicate analyses of pooled urine samples from 3-4 rats.
- b Data from reference number 1 (NTP ADME Study S0364).
- c Data from reference number 2 (NTP ADME Study S0104).
- d Equal to the dose excreted in urine in 0-72 hr or 0-96 hr with and without the dose in tissues at 72 hr. Extent of absorption was probably higher as there was evidence for biliary secretion.
- e Total of 16-18 other metabolites.



TABLE 7

Effect of pretreatment with 2-CNB on the disposition and metabolism  
of  $^{14}\text{C}$ -2-CNB in geriatric male Fischer-344

Parameter	Mean $\pm$ SD Fraction of Dose (%) <sup>a,b</sup>		
	Pretreatment (days)		
	0	4	8
Minimum Extent Absorption <sup>c</sup>	85	75	79
Excreted Urine 0-24 hr	63.5 $\pm$ 3.2	61.3 $\pm$ 5.5	52.2 $\pm$ 9.2
0-72 hr or 0-96 hr	85.1 $\pm$ 1.1	75.1 $\pm$ 4.4	70.8 $\pm$ 5.5
Excreted Feces 0-24 hr	1.4 $\pm$ 2.1	7.0 $\pm$ 2.5	7.5 $\pm$ 5.4
0-72 hr or 0-96 hr	22.4 $\pm$ 3.3	21.7 $\pm$ 1.3	18.9 $\pm$ 2.1
Tissues at 72 hr			8.2 $\pm$ 2.0
Total Recovery 0-72 hr	107.5 $\pm$ 2.5	96.9 $\pm$ 5.1	100.4 $\pm$ 5.4
Excreted Urine 0-72 hr or 0-96 hr as:			
I	6.4	5.9	5.2
II	0.6	0.5	0.9
VI	3.4	5.9	5.1
VII	2.9	6.0	4.8
IX	3.6	4.7	4.2
X	6.3	1.1	0.1
XI	5.6	8.7	10.1
XIII	4.4	4.6	4.3
XVI	0.6	1.3	1.2
XVIII	1.1	0.9	1.1
XIX	7.4	3.6	2.6
XXI	25.2	13.1	10.6
Other Metabolites	17.7	18.8	20.7
Total Metabolites	85.2	75.1	70.8

Footnotes are defined on the following page.

TABLE 7 (continued)

- <sup>a</sup> Mean of data from 4 rats or mean of duplicate analyses of pooled urine samples from 3-4 rats.
- <sup>b</sup> Data expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.
- <sup>c</sup> Equal to the dose excreted in urine in 0-72 hr or 0-96 hr with and without the dose in tissues at 72 hr. Extent of absorption was probably higher as there was evidence for biliary secretion.
- <sup>d</sup> Total of 10 other metabolites, each of which represented less than 5% of the dose and constituted a similar fraction of the Day 1 and Day 9 radiolabeled doses.