

ADME NTP Study S0104 2-Chloronitrobenzene

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

Sex/Species: young adult male F344 rats (approximately 9 weeks old weighing 186-203 g at arrival).

Vehicles: oral, corn oil.

CASRN 88-73-3

Radiolabeled with carbon-14 in the ring; 2-Chloronitrobenzene, [Ring-¹⁴C]

Study Performed:

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

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

Urine and feces were collected to 96 hours following administration of 1st and 2nd radiolabeled doses and to 72 hours after the 3rd 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 F344 rats:

- 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).
- S0365 – repeat oral administration of 65 mg/kg 2-CNB for 11 days to geriatric rats (approximately 19 months old and 406-483 g at randomization)

Metabolite profiles in pooled urine were determined using HPLC with 24 metabolites assigned the labels I-XXIII and XIIA. Metabolite summary data is shown here with disposition data

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TABLE 1

Urinary excretion of ¹⁴C-radioactivity by male Fischer-344 rats
at intervals during treatment with 2-chloronitrobenzene
at 65 mg/kg p.o. daily for 11 days.

Time (hr) ^a	Day ¹⁴ C-2-Chloronitrobenzene Administered		
	1	5	9
	Mean ± SD Dose Excreted (%) ^{b,c}		
0-4	14.8 ± 9.9	9.6 ± 8.6	14.8 ± 11.5
4-8	11.4 ± 5.9	37.8 ± 6.9	36.3 ± 11.8
8-24	34.4 ± 6.3	23.4 ± 7.7	18.5 ± 3.0
24-48	7.7 ± 1.7	2.1 ± 0.6	2.7 ± 0.7
48-72	1.8 ± 0.6	0.9 ± 0.3	1.2 ± 0.1
72-96	0.9 ± 0.3	0.7 ± 0.5	
	Mean ± SD Dose Excreted (Cumulative %) ^{b,c}		
0-4	14.8 ± 9.9	9.6 ± 8.6	14.8 ± 11.5
0-8	26.2 ± 7.5	47.4 ± 7.1	51.1 ± 4.7
0-24	60.6 ± 2.2	70.8 ± 1.0	69.6 ± 3.2
0-48	68.2 ± 2.0	72.8 ± 1.5	72.3 ± 3.2
0-72	70.1 ± 2.4	73.7 ± 1.5	73.5 ± 3.2
0-96	70.9 ± 2.4	74.4 ± 1.9	

^a Time after each ¹⁴C-labeled dose.

^b Mean of data from 4 rats, except after day 5 dose, where mean is of data from 3 rats.

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

TABLE 2

Fecal excretion of ^{14}C -radioactivity by male Fischer-344 rats at intervals during treatment with 2-chloronitrobenzene at 65 mg/kg p.o. daily for 11 days.

Time (hr) ^a	Day ^{14}C -2-Chloronitrobenzene Administered		
	1	5	9
	Mean \pm SD Dose Excreted (%) ^{b,c}		
0-4	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
4-8	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
8-24	5.4 \pm 2.9	18.1 \pm 1.9	21.4 \pm 4.5
24-48	10.4 \pm 7.4	3.4 \pm 0.8	4.2 \pm 0.5
48-72	1.1 \pm 0.8	1.0 \pm 0.1	1.0 \pm 0.1
72-96	3.2 \pm 5.1	0.5 \pm 0.1	
	Mean \pm SD Dose Excreted (Cumulative %) ^{b,c}		
0-4	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
0-8	0.0 \pm 0.0	0.0 \pm 0.0	0.0 \pm 0.0
0-24	5.4 \pm 2.9	18.1 \pm 1.9	21.4 \pm 4.5
0-48	15.7 \pm 5.9	21.5 \pm 2.0	25.6 \pm 4.8
0-72	16.8 \pm 6.6	22.5 \pm 2.1	26.6 \pm 4.8
0-96	19.9 \pm 3.0	23.0 \pm 2.2	

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

^b Mean of data from 4 rats, except after day 5 dose, where mean is of data from 3 rats.

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

TABLE 3

Concentration of ^{14}C -2-chloronitrobenzene-equivalents in tissues of male Fischer-344 rats at around 72 hr after administration of ^{14}C -2-chloronitrobenzene at 65 mg/kg p.o. on day 9.

<u>Tissue</u>	<u>Concentration (% dose/g x 10⁻²)^a</u>
Plasma	0.33 ± 0.03
Blood Cells	1.2 ± 0.1
Liver	27 ± 2
Kidney	33 ± 5
Heart	0.67 ± 0.23
Lung	1.1 ± 0.1
Brain	0.20 ± 0.02
Fat	1.7 ± 0.4
Skeletal Muscle	0.28 ± 0.01
Spleen	1.7 ± 0.2
Thymus	0.55 ± 0.05
Testes	0.54 ± 0.28

^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 72 hr after administration of ^{14}C -2-chloronitrobenzene at 65 mg/kg p.o. on Day 9

<u>Tissue</u>	<u>Mean \pm SD Fraction of Dose (%)^{a, b}</u>
Plasma	0.02 \pm 0.01
Blood Cells	0.10 \pm 0.01
Liver	3.42 \pm 0.31
Kidney	0.52 \pm 0.10
Heart	0.01 \pm 0.01
Lung	0.01 \pm 0.00
Brain	<0.01
Fat	0.29 \pm 0.10
Skeletal Muscle	0.28 \pm 0.02
Spleen	0.02 \pm 0.00
Thymus	<0.01
Testes	0.02 \pm 0.01
Total	4.67 \pm 0.36

^a 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.

^b Mean of data from 4 rats.

TABLE 5

Recovery of ¹⁴C-radioactivity at intervals during the treatment of male Fischer 344 rats with 2-chloro-nitrobenzene at 65 mg/kg p.o. daily for 11 days.

Sample ^a	Day ¹⁴ C-2-Chloronitrobenzene Administered		
	1	5	9
	Mean ± SD Dose Recovered (%) ^{b,c}		
Urine	70.9 ± 2.4	74.4 ± 1.9	73.5 ± 3.2
Feces	19.9 ± 3.0	23.0 ± 2.2	26.6 ± 4.8
Cage Rinse	2.2 ± 1.2	0.8 ± 0.6	0.7 ± 0.1
Tissues			4.7 ± 0.4
Total	93.1 ± 1.4	98.2 ± 1.0	105.3 ± 4.5

^a Urine and feces were collected up to 96 hr after administration of ¹⁴C-2-chloronitrobenzene on Days 1 and 5, and up to the time of sacrifice, at around 72 hr after administration on Day 9. Cage rinse was collected at 96 hr after the Day 1 and 5 doses and tissues and cage rinse were collected at around 72 hr after the Day 9 dose.

^b Mean of data from 4 rats, except after Day 5 dose, where mean is of data from 3 rats.

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

TABLE 6

¹⁴C-2-chloronitrobenzene in 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	200 ^b
Minimum Extent Absorption ^c	62	61	71	77
Excreted Urine 0-24 hr	56.4	53.0	60.6	39.2
0-72 hr	59.6	57.7	70.9	73.5
Excreted Feces 0-24 hr	21.9	19.8	5.4	0.0
0-72 hr	28.2	26.3	19.9	6.9
Total Recovery 0-72 hr	91.2	88.0	93.1	85.9
Excreted Urine 0-72 hr or 0-96 hr as:				
X	2.9	2.4	3.2	0.2
XI	2.9	3.2	12.7	21.1
XV	0.4	1.0	0.3	5.9
XIX	8.2	8.4	6.4	5.9
XXI	27.3	26.4	21.4	23.2
Other Metabolites	16.5	18.1	27.6	17.5
Total Metabolites	58.2	59.5	71.9	73.8

Footnotes are defined on the following page.

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.
- ^c 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.
- ^d Total of 16-19 other metabolites, each of which represented less than 5% of the dose.

TABLE 7

Effect of pretreatment with 2-chloronitrobenzene on the disposition and metabolism of ^{14}C -4-chloronitrobenzene in male Fischer-344 rats at intervals during treatment with 2-chloronitrobenzene at 65 mg/kg p.o.

Parameter	Mean \pm SD Fraction of Dose (%) ^{a,b}		
	Days of 2-Chloronitrobenzene Pretreatment		
	0	4	8
Minimum Extent Absorption ^c	71	74	78
Excreted Urine 0-24 hr	60.6 \pm 2.2	70.8 \pm 1.0	61.6 \pm 3.2
0-72 hr or 0-96 hr	70.9 \pm 2.4	74.4 \pm 1.9	73.5 \pm 3.2
Excreted Feces 0-24 hr	5.4 \pm 2.9	18.1 \pm 1.9	21.4 \pm 4.5
0-72 hr or 0-96 hr	19.9 \pm 3.0	23.0 \pm 2.2	26.6 \pm 4.8
Tissues at 72 hr			4.7 \pm 0.4
Total Recovery 0-72 hr	93.1 \pm 1.4	98.2 \pm 1.0	105.3 \pm 4.5
Excreted Urine 0-72 hr or 0-96 hr as:			
I	1.8	5.8	5.7
II	4.7	1.2	1.1
XI	12.7	10.7	8.0
XIII	0.7	0.3	4.2
XVI	0.8	0.9 ^d	5.7
XVIII	0.1	#	3.2
XIX	6.4	4.2	4.7
XXI	21.4	18.3 ^f	20.1
Other Metabolites ^e	23.0	32.9 ^f	20.7
Total Metabolites	71.9	74.5	73.5

Footnotes are defined on the following page.

TABLE 7 (continued)

- a Mean of data from 3-4 rats or mean of duplicate analyses of pooled urine samples from 3-4 rats.
- b Data expressed as a percentage of the radioactivity administered on Days 1, 5 or 9.
- c 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.
- d Not detectable.
- e Total of 16 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.
- f Increase in the fraction as other metabolites due to increase in each of metabolites VII, VIII and X to ca. 5% of the Day 5 dose.