ADME NTP Study S0364 2-Chloronitrobenzene

The contract laboratory abbreviation for the test article is 2-CNB.
Sex/Species: young adult male F344 rats (approximately 11 weeks old weighing 198-231 g at time of randomization).
Vehicle: oral, corn oil.

CASRN 88-73-3

Radiolabeled with carbon-14 in the ring; 2-Chloronitrobenzene [Ring-^{14}C]-

Study Performed:

Single oral gavage dose of 2.0, 20, or 200 mg/kg 2-CNB administered to rats with at 24 and 72 hours postdose.

Each dose group had 8 rats, with a set of 4 animals for each of the sacrifice times (24 and 72 hours).

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:

- 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)

- 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 23 metabolites assigned the labels I-XXIII.

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TABLE 1

Urinary excretion of ^{14}C-radioactivity by male Fischer-344 rats after oral administration of ^{14}C-2-chloronitrobenzene

Time (hr)	Dose (mg/kg) 2	20	200
	Mean ± SD Dose Excreted (%)[a]		
0-4	8.1 ± 8.2	15.4 ± 5.9	5.7 ± 0.4
4-8	23.6 ± 7.0	9.2 ± 4.0	6.5 ± 1.2
8-24	24.8 ± 5.3	28.5 ± 4.9	27.0 ± 4.7
24-48	2.4 ± 0.2	3.7 ± 0.6	21.8 ± 1.9
48-72	0.8 ± 0.2	1.0 ± 0.2	12.5 ± 2.3
	Mean ± SD Dose Excreted (Cumulative %)[a]		
0-4	8.1 ± 8.2	15.4 ± 5.9	5.7 ± 0.4
0-8	31.7 ± 4.9	24.5 ± 2.5	12.2 ± 1.6
0-24	56.4 ± 3.0	53.0 ± 4.7	39.2 ± 6.1
0-48	58.8 ± 3.2	56.7 ± 4.4	61.0 ± 4.5
0-72	59.6 ± 3.1	57.7 ± 4.2	73.5 ± 2.2

[a] Mean of data from 4 rats, except at 200 mg/kg mean of data from 3 rats.

TABLE 2

Fecal excretion of ^{14}C-radioactivity by male Fischer-344 rats after oral administration of ^{14}C-2-chloronitrobenzene

Time (hr)	Dose (mg/kg) 2	20	200
	Mean ± SD Dose Excreted (%)[a]		
0-4	8.0 ± 8.0	0.0 ± 0.0	0.0 ± 0.0
4-8	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
8-24	21.9 ± 2.2	19.8 ± 3.4	0.0 ± 0.1
24-48	5.2 ± 0.7	5.0 ± 1.1	1.8 ± 3.1
48-72	1.1 ± 0.3	1.5 ± 0.6	5.1 ± 2.1
	Mean ± SD Dose Excreted (Cumulative %)[a]		
0-4	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
0-8	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.0
0-24	21.9 ± 2.2	19.8 ± 3.4	0.0 ± 0.1
0-48	27.1 ± 1.7	24.8 ± 2.5	1.8 ± 3.1
0-72	28.2 ± 1.5	26.3 ± 2.0	6.9 ± 1.6

[a] Mean of data from 4 rats, except at 200 mg/kg mean of data from 3 rats.

TABLE 3

Concentration of ^{14}C-2-chloronitrobenzene equivalents in tissues of male Fischer-344 rats at around 24 and 72 hr after oral administration of ^{14}C-2-chloronitrobenzene

Tissue	Time (hr)	Mean ± SD Concentration (nmol/g)[a] Dose (mg/kg) 2	20	200
Plasma	24	0.18 ± 0.01	2.42 ± 0.37	145.9 ± 18.9
	72	0.05 ± 0.01	0.46 ± 0.02	24.79 ± 3.21
Blood Cells	24	0.26 ± 0.01	3.74 ± 0.36	134.2 ± 40.6
	72	0.20 ± 0.01	2.60 ± 0.21	63.46 ± 1.27
Liver	24	11.86 ± 0.62	135.0 ± 22.5	788.4 ± 71.4
	72	6.73 ± 1.02	67.06 ± 6.17	373.1 ± 96.5
Kidney	24	3.61 ± 0.27	46.91 ± 2.08	1106.7 ± 89.3
	72	2.11 ± 0.46	23.01 ± 1.89	803.2 ± 25.6
Heart	24	0.12 ± 0.01	1.56 ± 0.17	97.5 ± 14.2
	72	0.07 ± 0.02	0.63 ± 0.08	19.69 ± 3.32
Lung	24	0.34 ± 0.03	3.87 ± 0.14	147.2 ± 13.5
	72	0.14 ± 0.01	1.50 ± 0.15	48.19 ± 2.52

Footnotes are defined on the following page.

TABLE 3 (continued)

Tissue	Time (hr)	Mean ± SD Concentration (nmol/g)[a] Dose (mg/kg) 2	20	200
Brain	24	0.05 ± 0.00	0.81 ± 0.14	75.24 ± 7.28
	72	0.04 ± 0.01	0.29 ± 0.04	8.41 ± 0.73
Fat	24	0.81 ± 0.09	12.29 ± 3.33	1854.0 ± 442.0
	72	0.12 ± 0.01	1.26 ± 0.18	176.9 ± 15.3
Skeletal Muscle	24	0.08 ± 0.03	0.98 ± 0.32	119.3 ± 72.0
	72	0.03 ± 0.00	0.24 ± 0.03	11.29 ± 3.80
Spleen	24	0.18 ± 0.01	2.12 ± 0.21	104.1 ± 20.0
	72	0.33 ± 0.17	1.74 ± 0.45	67.08 ± 3.58
Thymus	24	0.15 ± 0.01	2.19 ± 0.12	152.1 ± 35.7
	72	0.07 ± 0.01	0.77 ± 0.05	29.90 ± 4.70
Testes	24	0.08 ± 0.01	1.04 ± 0.20	60.58 ± 9.23
	72	0.04 ± 0.01	0.31 ± 0.07	12.37 ± 0.35
Bone Marrow	24	0.31 ± 0.16	1.63 ± 1.90	72.23 ± 29.40
	72	0.08 ± 0.17	#[b]	88.9 ± 53.5

[a] Mean of data from 4 rats, except at 72 hr, 200 mg/kg mean of data from 3 rats.

[b] Mean ± SD not calculable because radioactivity in all samples was less than twice background for the system.

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-2-chloronitrobenzene

Tissue	Time (hr)	Mean ± SD Fraction of Dose (%)[a,b] Dose (mg/kg) 2	20	200
Plasma	24	0.05 ± 0.00	0.07 ± 0.01	0.39 ± 0.05
	72	0.01 ± 0.01	0.01 ± 0.00	0.07 ± 0.01
Blood Cells	24	0.07 ± 0.01	0.10 ± 0.01	0.31 ± 0.09
	72	0.05 ± 0.00	0.07 ± 0.01	0.14 ± 0.01
Liver	24	4.20 ± 0.22	4.36 ± 0.21	2.82 ± 0.24
	72	2.25 ± 0.32	2.34 ± 0.18	1.57 ± 0.45
Kidney	24	0.20 ± 0.01	0.25 ± 0.01	0.65 ± 0.08
	72	0.12 ± 0.02	0.14 ± 0.01	0.50 ± 0.02
Heart	24	<0.01	<0.01	0.02 ± 0.00
	72	<0.01	<0.01	0.00 ± 0.01
Lung	24	0.01 ± 0.00	0.01 ± 0.00	0.05 ± 0.01
	72	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01
Brain	24	<0.01	0.01 ± 0.01	0.04 ± 0.01
	72	<0.01	<0.01	0.01 ± 0.01

Footnotes are defined on the following page.

TABLE 4 (continued)

Tissue	Time (hr)	Mean ± SD Fraction of Dose (%)[a,b] Dose (mg/kg) 2	20	200
Fat	24	0.61 ± 0.07	0.92 ± 0.27	12.47 ± 2.66
	72	0.09 ± 0.01	0.10 ± 0.01	1.18 ± 0.10
Skeletal Muscle	24	0.28 ± 0.11	0.36 ± 0.12	4.03 ± 2.44
	72	0.10 ± 0.01	0.09 ± 0.01	0.38 ± 0.13
Spleen	24	<0.01	<0.01	0.02 ± 0.01
	72	0.01 ± 0.01	<0.01	0.02 ± 0.00
Thymus	24	<0.01	<0.01	0.01 ± 0.01
	72	<0.01	<0.0	<0.01
Testes	24	0.01 ± 0.00	0.01 ± 0.00	0.05 ± 0.01
	72	<0.01	<0.01	0.01 ± 0.00
Bone Marrow	24	<0.01	0.00 ± 0.00	<0.01
	72	0.00 ± 0.00	#[c]	<0.01
Total	24	5.42 ± 0.31	6.08 ± 0.35	20.85 ± 2.86
	72	2.64 ± 0.30	2.75 ± 0.17	3.90 ± 0.66

[a] Mean of data from 4 rats, except at 72 hr, 200 mg/kg mean of data from 3 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.

[c] Mean ± SD not calculable because radioactivity in all samples was less than twice background for the system.

TABLE 5

Recovery of ^{14}C-radioactivity at around 24 hr after oral administration of ^{14}C-2-chloronitrobenzene to male Fischer-344 rats

Sample[b]	Mean ± SD Dose Recovered (%)[a]		
	Dose (mg/kg)		
	2	20	200
Urine	59.2 ± 1.6	59.3 ± 2.8	42.2 ± 3.4
Feces	23.3 ± 4.2	18.9 ± 9.4	1.3 ± 1.6
Cage Rinse	2.8 ± 0.9	2.2 ± 0.2	2.3 ± 1.0
Tissues	5.4 ± 0.3	6.1 ± 0.4	20.9 ± 2.9
Total	90.7 ± 3.2	86.4 ± 8.8	66.7 ± 4.9

[a] Mean of data from 4 rats.

[b] Urine and feces were each collected up to the time of sacrifice, at around 24 hr. At sacrifice tissues and cage rinse were collected.

TABLE 6

Recovery of ^{14}C-radioactivity at around 72 hr after oral administration of ^{14}C-2-chloronitrobenzene to male Fischer-344 rats

Sample[b]	Mean ± SD Dose Recovered (%)[a]		
	Dose (mg/kg)		
	2	20	200
Urine	59.6 ± 3.1	57.7 ± 4.2	73.5 ± 2.2
Feces	28.2 ± 1.5	26.3 ± 2.0	6.9 ± 1.6
Cage Rinse	0.8 ± 0.7	1.3 ± 0.7	1.5 ± 0.1
Tissues	2.6 ± 0.3	2.8 ± 0.2	3.9 ± 0.7
Total	91.2 ± 2.7	88.0 ± 5.2	85.9 ± 0.9

[a] Mean of data from 4 rats, except at 200 mg/kg mean of data from 3 rats.

[b] Urine and feces were collected up to the time of sacrifice, at around 72 hr. At sacrifice tissues and cage rinse were collected.

TABLE 7

Effect of dose on the disposition and metabolism of ^{14}C-2-chloronitrobenzene administered orally to male Fischer-344 rats

Parameter		Mean ± SD Fraction of Dose (%)[a] Dose (mg/kg) 2	20	200
Minimum Extent Absorption[b]		62	61	77
Excreted Urine	0-24 hr	56.4 ± 3.0	53.0 ± 4.7	39.2 ± 6.1
	0-72 hr	59.6 ± 3.1	57.7 ± 4.2	73.5 ± 2.2
Excreted Feces	0-24 hr	21.9 ± 2.2	19.8 ± 3.4	0.0 ± 0.1
	0-72 hr	28.2 ± 1.5	26.3 ± 2.0	6.9 ± 1.6
Tissues at	24 hr	5.4 ± 0.3	6.1 ± 0.4	20.9 ± 2.9
	72 hr	2.6 ± 0.3	2.8 ± 0.2	3.9 ± 0.7
Total Recovery	0-72 hr	91.2 ± 2.7	88.0 ± 5.2	85.9 ± 0.9
Excreted Urine	0-48 hr or 0-72 hr as			
X		2.9 ± 0.2	2.4 ± 0.7	0.2 ± 0.3
XI		2.9 ± 0.5	3.2 ± 0.3	21.1 ± 1.5
XV		0.4 ± 0.1	1.0 ± 0.6	5.9 ± 3.0
XIX		8.2 ± 0.9	8.4 ± 0.6	5.9 ± 1.8
XXI		27.3 ± 4.2	26.4 ± 1.6	23.2 ± 3.0
Other Metabolites[c]		16.5 ± 1.6	18.1 ± 2.6	17.5 ± 2.7
Total Metabolites		58.2	59.5	73.8

Footnotes are defined on the following page.

TABLE 7 (continued)

[a] Mean of data from 3-4 rats.

[b] Equal to the dose excreted in urine in 0-72 hr plus the dose in tissues at 72 hr. Extent of absorption was probably higher as there was evidence for biliary secretion.

[c] Total of 18 other metabolites, each of which represents less than 5% of the dose.