

## ADME NTP Study S0779 4-Chloronitrobenzene

The contract laboratory abbreviation is 4-CNB.

Sex/Species: Young adult male F344 rats (approximately 9 weeks old, weighing between 186-203 g at randomization).

Vehicle: oral, corn oil.

CASRN 100-00-5

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

Studies performed:

Study S0779 – 11-day repeat 65 mg/kg 4-CNB daily dose by oral administration (gastric intubation) in young adult F344 rats (9 weeks old). Radiolabeled [<sup>14</sup>C]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 is the third study** of a four-part study on 4-Chloronitrobenzene.

Companion studies:

The first study (S0077) examined the effect of single dermal administrations of 0.65, 6.5, or 65 mg/kg [<sup>14</sup>C]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 the single oral administration (gastric intubation) of 2, 20, or 200 mg/kg [<sup>14</sup>C]4-chloronitrobenzene in 11-week old male F344 rats. Rats were sacrificed at 24 and 72 hours postdose.

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 rats (male F344 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 <sup>14</sup>C-radioactivity by male Fischer-344 rats  
at intervals during treatment with 4-chloronitrobenzene  
at 65 mg/kg p.o. daily for 11 days.

| Time (hr) <sup>a</sup> | Day <sup>14</sup> C-4-Chloronitrobenzene Administered |            |            |
|------------------------|---|------------|------------|
|                        | 1   | 5          | 9          |
|                        | Mean ± SD Dose Excreted (%) <sup>b,c</sup>            |            |            |
| 0-4                    | 2.5 ± 3.2   | 0.3 ± 0.5  | 1.9 ± 2.4  |
| 4-8                    | 2.0 ± 2.8   | 8.1 ± 7.9  | 12.1 ± 8.3 |
| 8-24                   | 38.0 ± 6.6  | 44.5 ± 5.9 | 47.4 ± 4.1 |
| 24-48                  | 19.5 ± 1.9  | 19.9 ± 1.7 | 15.2 ± 2.1 |
| 48-72                  | 8.8 ± 0.9   | 6.1 ± 1.0  | 3.7 ± 1.4  |
| 72-96                  | 3.1 ± 0.5   | 1.9 ± 0.5  |            |
|                        | Mean ± SD Dose Excreted (Cumulative %) <sup>b,c</sup> |            |            |
| 0-4                    | 2.5 ± 3.2   | 0.3 ± 0.5  | 1.9 ± 2.4  |
| 0-8                    | 4.6 ± 3.9   | 8.4 ± 8.3  | 14.0 ± 9.1 |
| 0-24                   | 42.6 ± 3.7  | 52.8 ± 2.5 | 61.4 ± 5.0 |
| 0-48                   | 62.1 ± 2.0  | 72.7 ± 1.0 | 76.7 ± 3.0 |
| 0-72                   | 70.9 ± 1.2  | 78.8 ± 0.8 | 80.3 ± 1.8 |
| 0-96                   | 73.9 ± 1.0  | 80.7 ± 0.8 |            |

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

<sup>b</sup> Mean of data from 4 rats, except after day 5 dose, where mean is of data from 3 rats.

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

TABLE 2

Fecal excretion of <sup>14</sup>C-radioactivity by male Fischer-344 rats  
at intervals during treatment with 4-chloronitrobenzene  
at 65 mg/kg p.o. daily for 11 days.

| Time (hr) <sup>a</sup> | Day <sup>14</sup> C-4-Chloronitrobenzene Administered |            |            |
|------------------------|---|------------|------------|
|                        | 1   | 5          | 9          |
|                        | Mean ± SD Dose Excreted (%) <sup>b,c</sup>            |            |            |
| 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                   | 4.1 ± 1.6   | 4.5 ± 1.4  | 7.1 ± 1.5  |
| 24-48                  | 5.4 ± 1.3   | 7.2 ± 0.2  | 6.5 ± 0.8  |
| 48-72                  | 3.4 ± 0.6   | 2.1 ± 1.0  | 1.3 ± 0.4  |
| 72-96                  | 0.7 ± 0.1   | 0.4 ± 0.1  |            |
|                        | Mean ± SD Dose Excreted (Cumulative %) <sup>b,c</sup> |            |            |
| 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                   | 4.1 ± 1.6   | 4.5 ± 1.4  | 7.1 ± 1.5  |
| 0-48                   | 9.5 ± 0.9   | 11.7 ± 1.2 | 13.7 ± 1.1 |
| 0-72                   | 12.9 ± 0.8  | 13.8 ± 0.2 | 14.9 ± 0.7 |
| 0-96                   | 13.5 ± 0.9  | 14.2 ± 0.2 |            |

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

<sup>b</sup> Mean of data from 4 rats, except after day 5 dose, where mean is of data from 3 rats.

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

TABLE 3

Concentration of  $^{14}\text{C}$ -4-chloronitrobenzene-equivalents in tissues of male Fischer-344 rats at around 72 hr after administration of  $^{14}\text{C}$ -4-chloronitrobenzene at 65 mg/kg p.o. on day 9.

| <u>Tissue</u>   | <u>Mean <math>\pm</math> SD Concentration (% dose/g <math>\times 10^{-2}</math>)<sup>a</sup></u> |
|-----------------|--|
| Plasma          | 0.34 $\pm$ 0.08  |
| Blood Cells     | 12 $\pm$ 0   |
| Liver           | 1.9 $\pm$ 0.1  |
| Kidney          | 2.8 $\pm$ 0.3  |
| Heart           | 1.2 $\pm$ 0.1  |
| Lung            | 1.8 $\pm$ 0.3  |
| Brain           | 0.26 $\pm$ 0.03  |
| Fat             | 3.0 $\pm$ 1.7  |
| Skeletal Muscle | 0.19 $\pm$ 0.04  |
| Spleen          | 7.9 $\pm$ 0.3  |
| Thymus          | 0.44 $\pm$ 0.11  |
| Testes          | 0.22 $\pm$ 0.03  |

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

TABLE 4

Percentage of the dose of  $^{14}\text{C}$ -radioactivity in tissues of male Fischer-344 rats at around 72 hr after administration of  $^{14}\text{C}$ -4-chloronitrobenzene at 65 mg/kg p.o. on Day 9.

| Tissue          | Mean $\pm$ SD Fraction of Dose (%) <sup>a, b</sup> |
|-----------------|--|
| Plasma          | 0.03 $\pm$ 0.01                                    |
| Blood Cells     | 0.95 $\pm$ 0.04                                    |
| Liver           | 0.18 $\pm$ 0.01                                    |
| Kidney          | 0.05 $\pm$ 0.01                                    |
| Heart           | 0.01 $\pm$ 0.01                                    |
| Lung            | 0.02 $\pm$ 0.00                                    |
| Brain           | 0.00 $\pm$ 0.01                                    |
| Fat             | 0.59 $\pm$ 0.33                                    |
| Skeletal Muscle | 0.19 $\pm$ 0.03                                    |
| Spleen          | 0.15 $\pm$ 0.01                                    |
| Thymus          | <0.01  |
| Testes          | 0.01 $\pm$ 0.00                                    |
| Total           | 2.17 $\pm$ 0.33                                    |

<sup>a</sup> 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.

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

TABLE 5

Recovery of <sup>14</sup>C-radioactivity at intervals during the treatment of male Fischer 344 rats with 4-chloro-nitrobenzene at 65 mg/kg p.o. daily for 11 days.

| Sample <sup>a</sup> | Day <sup>14</sup> C-4-Chloronitrobenzene Administered |            |            |
|---------------------|---|------------|------------|
|                     | 1   | 5          | 9          |
|                     | Mean ± SD Dose Recovered (%) <sup>b,c</sup>           |            |            |
| Urine               | 73.9 ± 1.0  | 80.7 ± 0.8 | 80.3 ± 1.8 |
| Feces               | 13.5 ± 0.9  | 14.2 ± 0.2 | 14.9 ± 0.7 |
| Cage Rinse          | 3.7 ± 0.8   | 2.1 ± 0.1  | 2.1 ± 1.0  |
| Tissues             |   |            | 2.2 ± 0.3  |
| Total               | 91.1 ± 0.9  | 97.1 ± 0.7 | 99.5 ± 0.8 |

<sup>a</sup> Urine and feces were collected up to 96 hr after administration of <sup>14</sup>C-4-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.

<sup>b</sup> Mean of data from 4 rats, except after Day 5 dose, where mean is of data from 3 rats.

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