ADME NTP Study S0149  Divinylbenzene

The contract laboratory actually used purified m-Divinylbenzene (CASRN 108-57-6) with the abbreviation mDVB for this ADME study. The other National Toxicology Program (NTP) short-term and long-term carcinogenicity and genetic toxicology studies were performed using highly purified divinylbenzene (CASRN 1321-74-0). This ADME study is referenced using CASRN 1321-74-0 in the NTP databases.

Sex/Species: adult male F344 rats.
Vehicles: intravenous, 5% Emulphor in phosphate buffered saline (PBS pH 7.2); oral, corn oil.

CASRN 1321-74-0

Radiolabled with carbon-14 uniformly in the benzene ring; meta-Divinyl[U-$^{14}$C]benzene

Studies performed:

- Single 40, 400, or 1200 mg/kg oral gavage dose in rats with sacrifice 72 hours postdose. (N=4 for each group)

- Repeat 11-day 400 mg/kg/day oral gavage dose in rats with sacrifice 72 hours following the last dose. (N=4)

- Single 40 mg/kg intravenous dose in rats with sacrifice 72 hours postdose. (N=4)

- Single 400 mg/kg oral or 40 mg/kg intravenous administration of mDVB to rats with sacrifice 6 hours postdose (bile collection study; N=2 originally with N=1 surviving, for both groups).

For the repeat dose study, rats were dosed for 11 consecutive days. Doses given on days 3, 7, and 11 also contained radiolabel. Excreta was collected up to 96 hours postdose on days 3 and 7 and 72 hours postdose on day 11.

Only two animals receiving oral or intravenous administration of mDVB in the biliary study survived the extended period of anesthesia sufficiently long for analysis.

Oral pilot studies demonstrated that, regardless of the dose of 40 or 2000 mg/kg, only a minor amount of the dose was being eliminated in the breath ($CO_2$ 0.01-0.02%; volatile breath 0.97-1.52% of the dose; N=2 each dose group). Therefore, expired gases were not collected in any other oral dose studies performed.

To determine the amount of radioactivity associated with the gut tissue as opposed to that associated with the gut contents, a small (5 cm) section of the small and large intestine was removed from the rest and rinsed repeatedly with water. This section of the gut was then analyzed for radioactivity separately. These samples represent the

radioactivity actually in the tissue and are labeled, for example, small intestine, section in Tables 2, 3, 4, 5, and 7. The rest of the gut was analyzed along with its contents. The difference between the two samples represents radioactivity in the gut contents.

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Table 1

Comparison of Disposition of [$^{14}$C] 72 h after Single Dose Oral, Multi-Dose Oral and Intravenous Administration of 40, 400 or 1200 mg mDVB/kg to Male F344 Rats (% of dose, Mean ± SD, N=4)

| Study Code | Route | Dose | | Recovery of [$^{14}$C] (% of Dose) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | μCi | mg/kg | Breath | Urine | Feces | Total Excretion | Tissues |
| A | Oral | 30.8 ± 0.9 | 41.4 ± 0.9 | NS[a] | 71.8 ± 3.5 | 19.9 ± 3.1 | 94.5 ± 0.9[b] | 2.9 ± 0.4 |
| B | Oral | 26.7 ± 0.4 | 398.5 ± 2.1 | NS[a] | 75.5 ± 2.8 | 18.9 ± 1.9 | 96.7 ± 1.4[b] | 1.9 ± 0.2 |
| C | Oral | 27.7 ± 0.9 | 1239. ± 30. | NS[a] | 89.3 ± 4.8 | 5.4 ± 1.0 | 97.7 ± 2.9[b] | 1.7 ± 0.2 |
| E[c] | Oral | 31.5 ± 1.2 | 398.1 ± 14. | NS[a] | 88.2 ± 6.6 | 7.5 ± 3.4 | 95.8 ± 3.2[b] | |
| | | 30.7 ± 1.2 | 397.0 ± 2.7 | NS[a] | 83.9 ± 1.4 | 9.7 ± 1.3 | 94.1 ± 1.6[b] | |
| | | 31.2 ± 1.3 | 396.8 ± 16. | NS[a] | 85.8 ± 1.7 | 9.7 ± 1.6 | 95.5 ± 0.5[b] | 0.3 ± 0.0 |
| F | IV | 4.55 ± 0.1 | 40.7 ± 0.6 | 1.1 ± 0.2 | 81.6 ± 1.8 | 10.3 ± 0.4 | 93.6 ± 2.1[b] | 2.0 ± 0.4 |

[a] NS = No samples collected.
[b] Total excretion includes [$^{14}$C] recovered in cage rinse.
[c] Dose E = Multi-Dose Study.

Table 2

Concentration of Total Radioactivity in Selected Tissues
72 h after 40, 400 or 1200 mg mDVB/kg po (Mean ± SD)

| Tissue Name | N | 40 mg/kg μg eq/g | 400 mg/kg μg eq/g | 1200 mg/kg μg eq/g |
|---|---|---|---|---|
| Adipose | 4 | 0.550 ± 0.143 | 6.57 ± 1.00 | 17.2 ± 1.88 |
| Adrenal gland | 4 | 0.196 ± 0.032 | 2.50 ± 0.65 | 9.76 ± 3.95 |
| Blood | 4 | 0.141 ± 0.036 | 2.61 ± 0.87 | 29.4 ± 7.27 |
| Brain | 4 | 0.042 ± 0.008 | 0.503 ± 0.05 | 4.36 ± 0.66 |
| Heart | 4 | 0.094 ± 0.029 | 1.23 ± 0.32 | 8.40 ± 1.69 |
| Intestine, large | 4 | 6.63 ± 4.27 | 40.8 ± 12.9 | 172 ± 131 |
| Intestine, lg, sect[a] | 4 | 1.67 ± 0.310 | 9.43 ± 1.74 | 18.1 ± 12.9 |
| Intestine, sm, sect[a] | 4 | 2.23 ± 1.44 | 7.13 ± 4.17 | 12.6 ± 6.01 |
| Intestine, small | 4 | 12.4 ± 2.98 | 67.7 ± 18.8 | 28.5 ± 10.2 |
| Kidney | 4 | 0.456 ± 0.101 | 3.39 ± 0.54 | 13.9 ± 2.16 |
| Liver | 4 | 0.598 ± 0.091 | 3.67 ± 0.21 | 14.9 ± 2.62 |
| Lung | 4 | 0.129 ± 0.034 | 1.29 ± 0.57 | 11.6 ± 4.29 |
| Muscle | 4 | 0.116 ± 0.064 | 0.747 ± 0.37 | 3.65 ± 0.72 |
| Skin | 4 | 0.170 ± 0.031 | 2.11 ± 0.36 | 13.0 ± 2.76 |
| Spleen | 4 | 0.134 ± 0.032 | 1.60 ± 0.05 | 13.5 ± 3.36 |
| Stomach | 4 | 0.437 ± 0.207 | 3.06 ± 1.19 | 9.05 ± 3.36 |
| Stomach contents | 4 | 0.364 ± 0.245 | 3.82 ± 2.57 | 5.65 ± 6.24 |
| Testis | 4 | 0.054 ± 0.006 | 0.422 ± 0.10 | 2.55 ± 0.50 |

[a] Sections (10 cm) of the large and small intestines were cut away from the rest of gut and rinsed thoroughly. These figures represent radioactivity associated with the cellular matrix of the tissue.

Table 3

Tissue to Blood Ratios in Selected Tissues of Rats 72 h after Single Oral Doses of 40, 400 or 1200 mg mDVB/kg po (Mean ± SD)

| Tissue Name | N | 40 mg/kg TBR | 400 mg/kg TBR | 1200 mg/kg TBR |
|---|---|---|---|---|
| Adipose | 4 | 3.98 ± 0.94 | 2.65 ± 0.67 | 0.60 ± 0.11 |
| Adrenal gland | 4 | 1.42 ± 0.21 | 1.05 ± 0.51 | 0.36 ± 0.20 |
| Blood | 4 | unity | unity | unity |
| Brain | 4 | 0.30 ± 0.04 | 0.20 ± 0.04 | 0.15 ± 0.03 |
| Heart | 4 | 0.66 ± 0.07 | 0.52 ± 0.25 | 0.29 ± 0.03 |
| Intestine, large | 4 | 52.6 ± 38.4 | 16.6 ± 6.90 | 6.18 ± 5.58 |
| Intestine, lg, sect[a] | 4 | 12.2 ± 2.36 | 3.78 ± 0.89 | 0.64 ± 0.46 |
| Intestine, sm, sect[a] | 4 | 18.3 ± 16.6 | 2.67 ± 0.98 | 0.43 ± 0.14 |
| Intestine, small | 4 | 91.6 ± 28.4 | 28.7 ± 13.1 | 1.02 ± 0.52 |
| Kidney | 4 | 3.27 ± 0.33 | 1.40 ± 0.53 | 0.49 ± 0.10 |
| Liver | 4 | 4.33 ± 0.53 | 1.50 ± 0.41 | 0.52 ± 0.06 |
| Lung | 4 | 0.93 ± 0.13 | 0.50 ± 0.21 | 0.39 ± 0.07 |
| Muscle | 4 | 0.88 ± 0.62 | 0.28 ± 0.04 | 0.13 ± 0.02 |
| Skin | 4 | 1.24 ± 0.25 | 0.84 ± 0.17 | 0.45 ± 0.04 |
| Spleen | 4 | 0.97 ± 0.23 | 0.66 ± 0.19 | 0.46 ± 0.08 |
| Stomach | 4 | 2.99 ± 1.24 | 1.34 ± 0.73 | 0.30 ± 0.04 |
| Stomach contents | 4 | 2.37 ± 1.46 | 1.78 ± 1.34 | 0.18 ± 0.17 |
| Testis | 4 | 0.39 ± 0.06 | 0.17 ± 0.05 | 0.09 ± 0.02 |

[a] Section of large and small intestine were 10 cm sections that were cut away from the main section of gut and rinsed thoroughly. These figures represent radioactivity associated with the cellular matrix of the tissue.

Table 4

Recovery of Radioactivity from Selected Tissues of Rats after Doses of 40, 400 or 1200 mg mDVB/kg po (Mean ± SD)

| Tissue Name | N | 40 mg/kg % Dose | 400 mg/kg % Dose | 1200 mg/kg % Dose |
|---|---|---|---|---|
| Adipose | 4 | 0.130 ± 0.032 | 0.156 ± 0.023 | 0.118 ± 0.011 |
| Adrenal gland | 4 | b | b | b |
| Blood | 4 | 0.021 ± 0.005 | 0.039 ± 0.012 | 0.126 ± 0.026 |
| Brain | 4 | 0.001 ± b | 0.001 ± b | 0.002 ± b |
| Heart | 4 | 0.001 ± b | 0.001 ± b | 0.002 ± b |
| Intestine, large | 4 | 0.534 ± 0.311 | 0.371 ± 0.113 | 0.309 ± 0.131 |
| Intestine, lg, sect[a] | 4 | 0.008 ± 0.004 | 0.006 ± 0.001 | 0.003 ± 0.002 |
| Intestine, sm, sect[a] | 4 | 0.010 ± 0.009 | 0.003 ± 0.002 | 0.001 ± 0.001 |
| Intestine, small | 4 | 0.975 ± 0.287 | 0.508 ± 0.099 | 0.047 ± 0.003 |
| Kidney | 4 | 0.008 ± 0.002 | 0.006 ± 0.001 | 0.008 ± 0.001 |
| Liver | 4 | 0.055 ± 0.006 | 0.036 ± 0.003 | 0.040 ± 0.004 |
| Lung | 4 | 0.002 ± 0.001 | 0.002 ± 0.002 | 0.005 ± 0.003 |
| Muscle | 4 | 0.138 ± 0.076 | 0.088 ± 0.041 | 0.125 ± 0.023 |
| Skin | 4 | 0.060 ± 0.010 | 0.075 ± 0.011 | 0.133 ± 0.023 |
| Spleen | 4 | 0.001 ± b | 0.001 ± b | 0.002 ± b |
| Stomach | 4 | 0.004 ± 0.002 | 0.003 ± 0.001 | 0.003 ± 0.001 |
| Stomach contents | 4 | 0.025 ± 0.020 | 0.011 ± 0.007 | 0.001 ± 0.001 |
| Testis | 4 | 0.001 ± b | 0.001 ± b | 0.002 ± b |

[a] Section of large and small intestine were 10 cm sections that were cut away from the main section of gut and rinsed thoroughly. These figures represent radioactivity associated with the cellular matrix of the tissue.
[b] Value is less than 0.0005.

Table 5

Concentration, Tissue to Blood Ratios and Recovery of Total Radioactivity in Selected Tissues from Rats 72 h after 40 mg mDVB/kg iv (Mean ± SD) - Study F

| Tissue Name | N | µg eq/g | TBR | % Dose |
|---|---|---|---|---|
| Adipose | 4 | 0.789 ± 0.225 | 5.13 ± 1.37 | 0.140 ± 0.043 |
| Adrenal gland | 4 | 0.919 ± 0.174 | 5.92 ± 0.66 | [a] |
| Blood | 4 | 0.155 ± 0.018 | 1.00 ± 0.00 | 0.020 ± 0.003 |
| Brain | 4 | 0.070 ± 0.012 | 0.45 ± 0.04 | 0.001 ± 0.000 |
| Heart | 4 | 0.116 ± 0.017 | 0.76 ± 0.13 | 0.001 ± 0.000 |
| Intestine, large | 4 | 5.61 ± 1.58 | 35.9 ± 8.07 | 0.648 ± 0.225 |
| Intestine, lg, sect[b] | 4 | 1.41 ± 1.02 | 8.84 ± 5.87 | 0.010 ± 0.009 |
| Intestine, sm, sect[b] | 4 | 2.93 ± 1.48 | 18.7 ± 8.79 | 0.017 ± 0.010 |
| Intestine, small | 4 | 8.81 ± 1.72 | 57.0 ± 9.21 | 0.660 ± 0.121 |
| Kidney | 4 | 0.687 ± 0.150 | 4.44 ± 0.74 | 0.012 ± 0.003 |
| Liver | 4 | 0.860 ± 0.120 | 5.57 ± 0.44 | 0.088 ± 0.012 |
| Lung | 4 | 0.428 ± 0.232 | 2.79 ± 1.49 | 0.005 ± 0.002 |
| Muscle | 4 | 0.167 ± 0.094 | 1.06 ± 0.53 | 0.204 ± 0.120 |
| Plasma | 4 | 0.082 ± 0.010 | 0.53 ± 0.01 | 0.006 ± 0.001 |
| Skin | 4 | 0.166 ± 0.022 | 1.08 ± 0.16 | 0.072 ± 0.011 |
| Spleen | 4 | 1.56 ± 0.144 | 10.1 ± 1.07 | 0.009 ± 0.001 |
| Stomach | 4 | 0.407 ± 0.146 | 2.56 ± 0.68 | 0.004 ± 0.001 |
| Stomach Contents | 4 | 0.885 ± 0.560 | 5.55 ± 3.33 | 0.011 ± 0.005 |
| Tail | 4 | 0.144 ± 0.081 | 0.97 ± 0.63 | 0.117 ± 0.066 |
| Testis | 4 | 0.126 ± 0.047 | 0.84 ± 0.38 | 0.003 ± 0.001 |

[a] Value is less than 0.005.

[b] Sections (10 cm) of the large and small intestine were cut away from the rest of the gut and rinsed thoroughly. These figures represent radioactivity associated with the cellular matrix of the tissue.

Table 6

Cumulative Excretion of Radioactivity after Repeated Administration of mDVB at 400 mg/kg/d (% of Dose ± SD)[a]

| Sample Time | 3rd Dose | | | 7th Dose | | | 11th Dose | | |
|---|---|---|---|---|---|---|---|---|---|
| | Urine | Feces | Total Excretion | Urine | Feces | Total Excretion | Urine | Feces | Total Excretion |
| 6 h | 24.2 ± 5.4 | NS | 24.2 ± 5.4 | 12.5 ± 3.5 | NS | 12.5 ± 3.5 | 18.9 ± 2.2 | NS | 18.9 ± 2.2 |
| 12 h | 56.0 ± 7.9 | 0.0 | 56.0 ± 7.9 | 48.1 ± 3.2 | 0.1 ± 0.2 | 48.3 ± 3.3 | 58.7 ± 2.2 | 2.3 ± 0.8 | 61.0 ± 2.9 |
| 24 h | 81.0 ± 5.6 | 6.4 ± 3.8 | 87.3 ± 2.2 | 74.9 ± 2.7 | 7.9 ± 1.4 | 82.8 ± 3.1 | 77.2 ± 1.3 | 8.3 ± 1.7 | 85.4 ± 1.3 |
| 48 h | 86.2 ± 6.4 | 7.3 ± 3.4 | 93.5 ± 3.1 | 81.3 ± 1.6 | 9.4 ± 1.3 | 90.8 ± 1.6 | 82.3 ± 1.7 | 9.5 ± 1.6 | 91.7 ± 0.8 |
| 72 h | 87.1 ± 6.5 | 7.5 ± 3.4 | 94.5 ± 3.2 | 82.6 ± 1.4 | 9.6 ± 1.3 | 92.2 ± 1.2 | 83.8 ± 1.7 | 9.7 ± 1.6 | 95.5 ± 0.5 |
| 96 h | 87.5 ± 6.5 | 7.5 ± 3.4 | 95.7 ± 3.2[c] | 83.2 ± 1.4 | 9.7 ± 1.2 | 93.5 ± 0.9[c] | NS[b] | NS[b] | NS[b] |

NS - No sample collected
[a] Animals were administered 400 mg mDVB/kg/day for 11 consecutive days. Radiolabeled mDVB was administered on days 3, 7 and 11 only.
[b] Animals were sacrificed 72 h after dosing to facilitate comparison of tissue distribution to single dose study.
[c] Total excretion at 96 h includes [$^{14}$C] recovered in the cage rinse.

Table 7

Concentration, Tissue to Blood Ratios and Recovery of Total Radioactivity in Selected Tissues 72 h after Third Radiolabeled Dose - 400 mg mDVB/kg po (Mean ± SD) - Study E[a]

| Tissue Name | N | µg eq/g | TBR | % Dose |
|---|---|---|---|---|
| Adipose | 4 | 3.81 ± 0.535 | 2.15 ± 0.51 | 0.068 ± 0.011 |
| Blood | 4 | 1.81 ± 0.226 | unity | 0.024 ± 0.002 |
| Intestine, large | 4 | 3.54 ± 1.28 | 1.91 ± 0.48 | 0.042 ± 0.015 |
| Intestine, lg, sect[b] | 4 | 1.83 ± 0.309 | 1.04 ± 0.29 | 0.001 ± c |
| Intestine, sm, sect[b] | 4 | 1.45 ± 1.07 | 0.84 ± 0.69 | 0.001 ± c |
| Intestine, small | 4 | 3.74 ± 0.568 | 2.07 ± 0.25 | 0.036 ± 0.005 |
| Kidney | 4 | 2.91 ± 0.153 | 1.62 ± 0.15 | 0.005 ± c |
| Liver | 4 | 1.75 ± 0.108 | 0.98 ± 0.09 | 0.019 ± 0.001 |
| Lung | 4 | 1.11 ± 0.076 | 0.62 ± 0.04 | 0.001 ± c |
| Muscle | 4 | 0.177 ± 0.069 | 0.10 ± 0.05 | 0.022 ± 0.009 |
| Plasma | 4 | 0.272 ± 0.033 | 0.15 ± 0.01 | 0.002 ± c |
| Skin | 4 | 1.08 ± 0.144 | 0.60 ± 0.10 | 0.047 ± 0.006 |
| Stomach | 4 | 0.942 ± 0.126 | 0.52 ± 0.02 | 0.001 ± c |
| Stomach Contents | 4 | 0.815 ± 0.297 | 0.46 ± 0.20 | 0.002 ± 0.001 |

[a] Rats were given 400 mg mDVB/kg/day po for 11 consecutive days. Radiolabeled doses were given on the 3rd, 7th and 11th days. Animals were sacrificed 72 h after the third radiolabeled dose given on the 11th day.

[b] Sections (10 cm) of the large and small intestine were cut away from the rest of the gut and rinsed thoroughly prior to analysis. These figures represent radioactivity associated with the cellular matrix of the tissue.

[c] Value was less than 0.0005.

Table 8

Biliary Excretion of Radiolabel Following Oral and iv Administration of mDVB

| Time | Oral[a] % Dose | Oral[a] Cumulative % Dose | IV[b] % Dose | IV[b] Cumulative % Dose |
|---|---|---|---|---|
| 15 m | 0.1 | 0.1 | 2.3 | 2.3 |
| 30 m | 0.3 | 0.4 | 3.6 | 5.9 |
| 1 h | 0.9 | 1.3 | 7.2 | 13.1 |
| 2 h | 2.2 | 3.4 | 12.1 | 25.2 |
| 3 h | 2.6 | 6.0 | 6.1 | 31.3 |
| 4 h | 3.0 | 9.1 | 3.5 | 34.8 |
| 6 h | 5.1 | 14.1 | 2.7 | 37.5 |

[a] Rat G-M1 received 45.0 μCi and 313 mg/kg po.
[b] Rat G-M5 received 19.3 μCi and 42 mg/kg iv.