014663

**DICLORAN TECHNICAL** **Subchronic Oral Toxicity (§82-1[a])**

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Registration Action Branch 1/HED (7509C)

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DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 002624 for Original DER

**NOTE:**
This study was previously reviewed and classified as Core Minimum data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Subchronic Oral Toxicity feeding - rats
OPPTS Number: 870.3100 OPP Guideline Number: §82-1a

DP BARCODE: D241078 SUBMISSION NO.: S541375
PC CODE 031301 TOX. CHEM. NO.: 311
MRID NO: 00029056

TEST MATERIAL (PURITY): Dicloran Technical (97.1%)

COMPOSITION/SYNONYM(S): 2,6-dichloro-4-nitroaniline; DCNA; Botran™

CITATION: Woodward, G., Cronin, M. T. I. (1962). U- 2069: 13- Week Interim Report. Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks. Woodward Research Corporation, Herndon, Virginia. Original Report Date: May 4, 1962, Title page and Table of Compilation Date: December 7, 1979. MRID No. 00029056. Unpublished.

Woodward, G., Cockrell, K. O., Woodward, G. (1964). U-2069: Safety Evaluation by Oral Administration to Rats and Dogs for 104 Weeks. Final Report, Prepared by Woodward Research Corporation, Herndon, Virginia. The Upjohn Company, Kalamazoo, MI. MRID No. 00082718. Unpublished.

SPONSOR: The Upjohn Company, Kalamazoo, MI.

EXECUTIVE SUMMARY: In a 90-day toxicity study (MRID 00029056), dicloran technical (Lot # PS02451, 97.1%) was administered in the diet to albino rats (35/sex/group) for up to 104 weeks at nominal doses of 0, 20, 100, or 3000 ppm (equivalent to 0, 1, 5 and 150 mg/kg/day). This is an interim report (13 Weeks) of a 104 week study. For the first four weeks, the feeding levels were one half the desired dosage in an attempt to maintain the drug intake per kilogram of



(1)

body weight at a constant level. Hematological measurements were performed on five males and five females of the control and high dose level rats at 4 and 8 weeks and in addition, on five female rats on the 100 ppm level at 8 weeks. Hematological measurements were also performed on five males and five females from each dose group at 13 week prior to sacrifice of these rats. At 13 weeks, 5 males and 5 females from each group were sacrificed, selected organs weighed and histopathologic examination was performed.

No mortality (except one female in 100 ppm group) was observed in 13 weeks. Body weights, body weight gain and food consumption of male and female rats in 20 ppm and 100 ppm dose group were comparable to control rats. Body weight gain and food consumption was slightly depressed in the high dose rats. Decreased in body weight gain of the male rats in high dose were 93.2%, 89.6%, and 89.0% of the control values at 4 week, 8 week and 14 week, respectively. Decreased in body weight gain of the female rats in high dose were 83.8%, 77.8%, and 76.1% of the control values at 4 week, 8 week and 14 week, respectively. No treatment related effects were observed on the hematological parameters measured.

Increase in liver and kidney weights were observed in the high dose rats. Histopathological examination of the tissues from the 13-week autopsy revealed all within normal limits or comparable to controls with the exception of the livers and adrenals of the high dose rats. Mild hepatic cell changes were observed in some of the livers and slight adrenal cortical atrophy of the high dose rats.

**The LOAEL is 3000 ppm (equivalent to 150 mg/kg/day) based on reduced body weight gain, increased liver and kidney weights, and histopathological changes in the liver and adrenals. The NOAEL is 100 (equivalent to 5 mg/kg/day).**

The submitted study is classified as **acceptable/guideline (§82-2[a])** and does satisfy the requirements for a subchronic toxicity study in rats.

**Note:** This study does not conform to the current guideline requirements. Homogeneity and stability of the diet was not measured. The actual concentration of dicloran in the prepared diet was not determined. Clinical chemistry, urinalysis and ophthalmoscopic examination was not performed. Achieved mean doses were not calculated. Only, five rats /sex/group were evaluated at the 13 week treatment duration. No statistical analysis was performed

COMPLIANCE: No Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Table 1. Body Weights[A]

| Study Duration (week) | Body Weight (grams)[B] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Male | | | | Female | | | |
| | 0 | 20 ppm | 100 ppm | 3000 ppm | 0 | 20 ppm | 100 ppm | 3000 ppm |
| 0 | 97 | 95 | 97 | 96 | 86 | 85 | 88 | 87 |
| 1 | 139 | 139 | 143 | 136 | 122 | 123 | 125 | 119 |
| 2 | 179 | 178 | 187 | 175 | 152 | 147 | 149 | 139 |
| 3 | 217 | 216 | 230 | 209 | 167 | 163 | 166 | 156 |
| 4 | 259 | 257 | 272 | 247 | 185 | 181 | 183 | 170 |
| **Body Weight Gain (0-4)[C]** | **162** | **162 (100)** | **175 (108.0)** | **151 (93.2)** | **99** | **96 (97.0)** | **95 (96.0)** | **83 (83.8)** |
| 5 | 292 | 291 | 306 | 268 | 200 | 193 | 199 | 178 |
| 6 | 327 | 327 | 338 | 299 | 215 | 207 | 214 | 188 |
| 7 | 353 | 357 | 366 | 325 | 230 | 222 | 227 | 200 |
| 8 | 377 | 377 | 386 | 347 | 239 | 229 | 234 | 206 |
| **Body Weight Gain (0-8)[C]** | **280** | **282 (100.7)** | **289 (103.2)** | **251 (89.6)** | **153** | **144 (94.1)** | **146 (95.4)** | **119 (77.8)** |
| 9 | 398 | 395 | 408 | 364 | 245 | 237 | 242 | 209 |
| 10 | 416 | 417 | 429 | 380 | 254 | 243 | 245 | 215 |
| 11 | 432 | 435 | 445 | 395 | 261 | 251 | 252 | 222 |
| 12 | 442 | 447 | 457 | 407 | 267 | 257 | 257 | 225 |
| 13 | 452 | 453 | 467 | 415 | 270 | 259 | 261 | 228 |
| 14 | 470 | 462 | 480 | 428 | 274 | 265 | 265 | 230 |
| **Body Weight Gain (0-14)[C]** | **373** | **367 (98.4)** | **383 (102.7)** | **332 (89.0)** | **188** | **180 (95.7)** | **177 (94.1)** | **143 (76.1)** |

[A] Data extracted from the study report, pages 12-19. No statistical analysis was provided in the study report.

[B] Mean value (Average of 35 rats).

[C] Body weight gain calculated by the reviewer. Value in parenthesis represents % of the control

Table 2. Selected Hematologic Value[A]

| Dose Group | Parameters Measured (unit) and Study Duration | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Hemoglobin (g %)** | | | **Hematocrit (%)** | | | **White Blood Cells (1000/cmm)** | | |
| | 4 Weeks | 8 Weeks | 13 Weeks | 4 Weeks | 8 Weeks | 13 Weeks | 4 Weeks | 8 Weeks | 13 Weeks |
| **Male** | | | | | | | | | |
| Control | 14.7 | 15.3 | 15.3 | 49 | 51 | 50 | 20.4 | 19.3 | 19.6 |
| 3000 ppm | 14.4 | 15.4 | 15.4 | 49 | 50 | 52 | 24.8 | 20.4 | 22.6 |
| 100 ppm | N/A | N/A | 15.5 | N/A | N/A | 51 | N/A | N/A | 18.8 |
| 20 ppm | N/A | N/A | 15.5 | N/A | N/A | 51 | N/A | N/A | 18.9 |
| **Female** | | | | | | | | | |
| Control | 15.4 | 15.5 | 16.2 | 50 | 50 | 52 | 18.5 | 20.8 | 21.3 |
| 3000 ppm | 15.2 | 14.7 | 15.1 | 52 | 48 | 49 | 24.2 | 15.4 | 20.6 |
| 100 ppm | N/A | 15.8 | 15.5 | N/A | 53 | 50 | N/A | 21.7 | 14.5 |
| 20 ppm | N/A | N/A | 15.5 | N/A | N/A | 49 | N/A | N/A | 17.5 |

[A] Data exctracted from the Study Report, Page 20, Mean value of 5 rats.
N/A= Not measured

Table 3. Selected Organ Weights at 13 week Sacifice[a]

| Organ | | Weight (grams)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Male | | | | Female | | | |
| | | 0 | 20 ppm | 100 ppm | 3000 ppm | 0 | 20 ppm | 100 ppm | 3000 ppm |
| Body Weight | | 415 | 488 | 447 | 404 | 270 | 264 | 266 | 238 |
| Liver | Absolute | 14.02 | 16.51 | 14.97 | 19.28 | 8.45 | 8.70 | 9.02 | 10.47 |
| | Adjusted** | 3.35 | 3.38 | 3.35 | 4.77 | 3.13 | 3.32 | 3.39 | 4.40 |
| Kidney | Absolute | 2.74 | 3.25 | 2.97 | 3.01 | 1.82 | 1.84 | 1.75 | 1.74 |
| | Adjusted** | 0.66 | 0.67 | 0.66 | 0.75 | 0.67 | 0.70 | 0.66 | 0.73 |
| Spleen | Absolute | 0.58 | 0.69 | 0.66 | 0.63 | 0.53 | 0.54 | 0.50 | 0.47 |
| | Adjusted** | 0.14 | 0.14 | 0.15 | 0.16 | 0.20 | 0.21 | 0.19 | 0.20 |
| Adrenal*** | Absolute | 50.6 | 50.2 | 47.8 | 45.8 | 61.9 | 61.5 | 64.0 | 53.8 |
| | Adjusted** | 12.1 | 10.3 | 10.8 | 11.3 | 23.0 | 23.4 | 24.0 | 22.6 |

a Data exctracted from the study report, pages 25 and 26.
* Mean (average of 5 animals)
** Adjusted to body weight (mean relative organ weight in grams per 100 grams of body weight.
*** Absolute weight in mgs..