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DICLORAN TECHNICAL

EPA Primary Reviewer: P. V. Shah, Ph.D.
Registration Action Branch 1/HED (7509C)

Subchronic Oral Toxicity (§82-1(a))

P.V. Shah, Date 4/17/01

EPA Secondary Reviewer: Guruva Reddy, D.V.M., Ph.D.
Registration Action Branch 1/HED (7509C)

Guruva Reddy, Date 4/18/01

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR NO. 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 Unpublished.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 Unpublished.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

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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.

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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

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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 extracted from the Study Report, Page 20, Mean value of 5 rats.

N/A= Not measured

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Table 3. Selected Organ Weights at 13 week Sacrifice^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 extracted 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..