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DICLORAN TECHNICAL **Two Year Chronic Toxicity (§83-1[b])**

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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: Two Year Chronic Toxicity - dog
OPPTS Number: 870.4100
OPP Guideline Number: §83-1b

DP BARCODE: D241078
PC CODE 031301
MRID NO: 00029056, 00082718, 00026810
SUBMISSION NO.: S541375
TOX. CHEM. NO.: 311

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 Number 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 Unpublished.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. MRID No. 00082718. Unpublished.

Kakuk, T. J., Weddon, T. W., and Thomas, R. W. (1979). Reevaluation of Potential Hepatic Effects of Botran in Beagle Dogs Supplemental Report. Agricultural Research and Development Laboratories, The Upjohn Company, Kalamazoo, MI. Technical Report No. 001-9610-79-005, December 7, 1979. MRID No. 00026810. Unpublished.

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DICLORAN TECHNICAL **Two Year Chronic Toxicity (§83-1[b])**

SPONSOR: The Upjohn Company, Kalamazoo, MI.

EXECUTIVE SUMMARY: In this chronic (104-107 weeks) oral toxicity study (MRID 00029056, 00082718), dicloran technical grade (Lot # PS02451, 97.1%) was administered in the diet to beagle dogs (4/sex/group) for up to 104 weeks at nominal doses of 0, 20, 100, or 3000 ppm (equivalent to 0, 0.5, 2.5 or 75 mg/kg/day). Hematological, clinical chemistry and urinalysis measurements were performed on all dogs at 0, 4, 8, 13, 26, 41, 52, 65, 78, 91, and 104 weeks. During the 14 th week, 1 male and 1 female dog from each group was sacrificed and complete autopsies were performed. Selected organs were weighed and histopathologic examination was performed. At termination (104-107 weeks), all surviving dogs were sacrificed, necropsied and selected organs were weighed and histopathological examination was performed.

No mortality was observed in 104 weeks except one female dog from the high dose group died in comatose state during the 74th week. This dog and one dog from the control group experienced a body weight loss. Analysis of variance indicated that there was no difference in body weights between treated dogs and controls at 104 week. All dogs showed normal reflex reactions and appeared normal with the exception of one female dog in the high dose group that died. At the high dose, watery lacrimation was present for all dogs soon after the start of the study and persisted throughout the study. Mild yellowing of the sclera, mucous membranes, and abdominal skin was noted for three dogs in the high dose which may be due to deposits of the chemical and/or its metabolite or liver toxicity (jaundice).

Hemoglobin values were slightly lower for the high dose starting at week 4. Similar trends were observed for the hematocrit values. Hemoglobin and hematocrit values were similar through out the study for the control, 20 ppm and 100 ppm dose group. Hematocrit values for the high-dose fluctuated. The erythrocytic series showed immature cells and numerous polychromatophilic macrocytes. Actual thrombocyte (platelets) counts were not conducted after 13 week because no differences in size or number were seen at the later intervals.

Clinical chemistry consisting of BUN (blood urea nitrogen), methemoglobin, fasting blood sugar and creatinine remained within control values for all dogs. Statistical analysis of serum chemistry indicated that significant elevation in serum glutamic pyruvic transaminase (SGPT), and serum alkaline phosphatase (SAP) values occurred in the high dose group during specific intervals of the study. Increase in the values for these parameters were first noted at week 8. The SGOT, SGPT and SAP values were similar for the controls, 20 ppm and 100 ppm dose group dogs. Results of bromsulphthalein (BSP) indicated elevated levels for two dogs in the high dose group. The elevated levels were not sustained indicating that this was probably not related to liver dysfunction.

Urinalysis indicated highly pigmented urine in the high-dose group. No remarkable abnormalities in urinalysis were observed between the controls and treated groups.

Organ weight data indicated that the 20 and 100 ppm treatment group organ weights were comparable to those of the control. However, statistically significant increases ($p < 0.05$) of

kidney, spleen, and liver weights were evident in the high dose group.

Histological examination revealed liver changes at the high dose characterized by irregular hepatic cell size, hepatic cell hypertrophy, increased pigmentation of hepatic cells and of liver macrophages. Changes in gall bladder were observed for the two dogs in the high dose group and one dog in the 20 ppm group.

The LOAEL is 3000 ppm (equivalent to 75 mg/kg/day) based on reduced body weight gain, increased liver, spleen and kidney weights, hematological and clinical biochemistry, and histopathological changes in the liver. The NOAEL is 100 (equivalent to 2.5 mg/kg/day).

The submitted study is classified as **acceptable/guideline (§83-1[b])** and does satisfy the requirements for a chronic toxicity study in dogs.

Note: This study does not conform to current guideline requirements. Homogeneity and stability of the diet was not measured. The actual concentration of dicloran in the prepared diet was not determined. Achieved mean doses were not calculated. No statistical analysis was performed. Means were not separated by sex.

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

MRID No. 00026810 is the report containing original study data of MRID No.00029056, and MRID No. 00082718, which were analyzed for statistical significance.

Table 1. Selected mean body weights (adjusted for week 1 body weights) and overall body weight gains (kg) in dogs treated with dicloran for 104 weeks.[a]

Duration	Dose Group (ppm)			
	0	20	100	3000
Male				
1	10.75	10.23	10.50	10.58
13	11.90	11.88	11.45	9.78
15	11.8	11.70	11.97	10.97
39	12.23	13.06	12.53	11.8
52	12.73	13.47	13.17	12.4
78	12.23	13.9	12.97	12.97
104	11.73	14.33	14.17	13.67
Body Wt. Gain	0.98	4.10 (418.36)	3.67 (374.49)	3.09 (315.31)
Female				
1	9.13	9.50	9.35	9.50
13	10.33	10.05	9.58	9.13
15	10.57	10.20	10.05	8.97
39	11.33	11.60	11.67	9.13
52	11.63	12.00	12.20	9.23
78	11.93	12.97	12.23	9.80
104	12.16	13.90	13.23	9.95
Body Wt. Gain	3.03	4.40 (145.21)	3.88 (128.05)	0.45 (14.85)

a Data obtained from the study report (MRID 00029056), pages 37-40; n=4 for week 1 and 13. For weeks 15 through 104, data obtained from the study report (MRID 00082718), pages 137-144; n=4 up to 13 week, then n=3. Value in parenthesis represents % of the control. Mean and Overall body weight gains were calculated by the reviewers.

Note: The body weight data were analyzed by using analysis of variance method (MRID 00026810). Male and female body weight values were combined. The result of this analysis indicate that there was no difference between body weight of dose group and control at 104 week.

Table 2. Analysis of Variance and Mean of Selected Hematological Parameters[A]

Study Week	Hematological Parameters and Dose Group							
	Hemoglobin (grams)				Hematocrit (%)			
	Control	20 ppm	100 ppm	3000 ppm	Control	20 ppm	100 ppm	3000 ppm
0	13.30	14.78	14.61	13.70	44.50	48.00	47.75	45.50
4	14.10^{b}	13.60^{ab}	14.58^{b}	11.80^{a}	46.62^{b}	45.62^{b}	48.50^{b}	40.88^{a}
8	15.61^{b}	14.66^{b}	15.06^{b}	12.82^{a}	50.75	48.62	49.62	47.?5
13	14.88^{b}	14.49^{b}	15.20^{b}	11.56^{a}	48.38^{b}	48.00^{b}	49.75^{b}	40.50^{a}
26	14.42^{ab}	15.28^{b}	15.25^{b}	13.30^{a}	47.92	50.50	50.33	46.00
41	14.70^{b}	14.43^{b}	14.30^{b}	12.45^{a}	48.17	47.33	47.83	44.00
52	16.28^{b}	16.08^{b}	15.02^{ab}	13.78^{b}	49.17	48.67	49.33	46.50
65	14.73	15.37	15.13	13.72	48.00	48.00	48.17	46.83
78	15.98^{b}	15.93^{b}	16.18^{b}	13.32^{a}	49.67	49.67	51.00	44.33
91	15.57^{b}	16.02^{b}	15.72^{b}	13.01^{a}	49.83^{b}	50.67^{b}	50.33^{b}	44.17^{a}
104	14.00^{ab}	16.15^{c}	15.60^{bc}	12.86^{a}	47.17^{ab}	51.83^{b}	51.33^{b}	43.92^{a}

[A] Data extracted from the Report (MRID No. 00026810), Table 1, Pages 9-13. Average value of 8 dogs (4 dogs/sex/group) for the first 13 weeks, then average value of 6 dogs (3/sex/group).

abc- means in a row with no common superscripts differ at the 0.05 level.

Table 3. Analysis of Variance and Mean of Selected Clinical Parameters[A]

Dose Group	Parameters Measured and Duration											
	Alk. Phos	SGOT										
	13 Week	O Week	4 Week	8 Week	13 Week	26 Week	41 Week	52 Week	65 Week	78 Week	91 Week	104 Week
0 ppm	0.875[a]	24.88	20.62	12.75[a]	17.00	14.67	15.17	13.83	14.00	20.17	19.00[a]	14.00
20 ppm	0.825[a]	20.00	13.50	15.12[a]	14.75	16.67	16.50	11.67	14.33	12.67	13.17[b]	15.00
100 ppm	0.888[a]	25.00	15.38	15.75[a]	14.88	13.33	14.17	9.67	13.83	12.50	13.83[b]	12.17
3000 ppm	1.788[b]	23.88	14.75	143.37[b]	17.00	18.50	20.67	19.50	35.17	27.67	14.08[b]	15.58
		SGPT										
0 ppm		10.38	31.50	10.62[a]	17.88[(a)]	15.17	13.00	10.00	11.83	14.83[(a)]	12.50	11.00
20 ppm		11.88	11.75	12.62[a]	14.75[(a)]	16.33	16.17	10.17	13.33	13.00[(a)]	18.50	15.50
100 ppm		14.12	12.88	14.38[a]	15.88[(a)]	14.00	14.50	8.83	16.17	14.50[(a)]	15.17	24.17
3000 ppm		11.62	17.88	143.87[b]	31.62[(b)]	30.67	33.67	31.50	43.17	28.00[(b)]	25.67	32.00

[A] Data extracted from the Report (MRID No. 00026810), Table 4, Pages 20-24. Average value of 8 dogs (4 dogs/sex/group) for the first 13 weeks, then average value of 6 dogs (3/sex/group).

ab- means in a column with no common superscripts differ at the 0.05 level.

(ab)-Means with no common superscripts differ near the 0.05 level.

Alk. Phos .= alkaline phosphatase

SGOT = serum glutamic oxalacetic transaminase.

SGPT = serum glutamic pyruvic transaminase.

Table 4. Analysis of Variance and Means of Body Weight and Selected Organs at 13 Week[A]

Dose Group	Selected Organ Weight at 104 Weeks					
	Body Weight	Thyroid	Heart	Kidney	Spleen	Liver
Control	11.12	1.16	83.73	55.37	30.53[(a)]	292.17[(a)]
20 ppm	13.65	1.06	91.00	55.32	49.73[(ab)]	384.00[(ab)]
100 ppm	13.57	1.29	87.58	55.63	48.85[(ab)]	360.50[(a)]
3000 ppm	10.80	1.11	77.63	68.68	58.22[(b)]	478.00[(b)]

A Data exctracted from the study report (MRID 00026810), Table 7, page 29 and 31. Mean of six dogs.

(ab) Means with no common superscripts differ near the 0.05 level.