014663

DICLORAN TECHNICAL **Chronic/Oncogenicity (§83-5)**

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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: Combined chronic toxicity/carcinogenicity
OPPTS Number: 870.4300 OPP Guideline Number: §83-5

DP BARCODE: D241078 SUBMISSION NO.: S541375
PC CODE 031301 TOX. CHEM. NO.: 311
MRID NO: 00029056, 00082718, 00086902

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 Unpublished.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. Prepared for The Upjohn Company, Kalamazoo, MI. MRID No. 00082718. Unpublished.

Musser, E. A. (1964). Analysis of data from "Two Year Chronic Toxicity Study of Rat and Dog by Woodward Research Corporation". Significance of Hemoglobin, Hematocrit and Liver Weight Changes in Dogs and Rats Treated for 2 Years with 100 ppm U-2069. The Upjohn Company, Kalamazoo, MI. April 10, 1964. MRID No. 00086902. Unpublished.

SPONSOR: The Upjohn Company, Kalamazoo, MI.

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EXECUTIVE SUMMARY: In a combined chronic/oncogenicity study (MRID 00029056, 00082718), 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). 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 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, 8, 13, 26, 40, 53, 66, 78, 92 and 104 weeks and in addition, on five female rats on the 100 ppm level at 8, 40, 53, 66, 78, 92 weeks. Hematological measurements were also performed on five males and five females from each dose group at 13, 26 and 104 weeks, 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. All surviving rats were sacrificed between 104-107 weeks, selected organs weighed and histopathologic examination was performed.

The results of 13 week study (interim report) are previously summarized in details in MRID 00029056 DER. There were no trends in mortality. Most deaths occurred after 71 weeks on study and were attributed to the age of the rats. The body weight gain at the high dose was depressed by approximately 29% for the male rats and 35% for the female rats. Food consumption was also reduced at the high dose more noticeable for the females.

No significant changes were observed on hematological parameters measured except slightly reduced hemoglobin and hematocrit values. It was noted for the high dose males at the 66 week interval. A reduction in hemoglobin was noted for one or two of the 100 and 20 ppm level males at termination. Slightly reduced hemoglobin and hematocrit values were noted only at the high dose females, with the exception of two 100 ppm females at termination. From the 66 week interval until termination the hemoglobin and hematocrit values remained slightly lower than controls. The hemoglobin and hematocrit values of 100 ppm dose group was statistically analysed (MRID 00086902), which suggest that these values were not statistically different from controls except the hematocrit value of males rats which was different at 5% level. It is not clear whether these slightly reduced values for hemoglobin and hematocrit were statistically different from the controls or not, since no statistical analysis was presented in the study report.

Gross necropsy observations made at termination showed similar findings and comparable incidence for both treated and control rats. Absolute and adjusted liver and kidney weights at 13 week and at terminal sacrifice were slightly increased for high dose males compared to the controls. An increased in relative kidney weight for the high dose males at terminal sacrifice was due to three individual rats. Histopathological examination of the tissues from the 13-week and terminal sacrifice 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 at 13 week sacrifice. At terminal sacrifice, high dose rats liver changes were characterized by hepatic cell enlargement, marked glycogen depletion, increased basophilia of the cytoplasm, and the presence of some necrobiotic hepatic cells. Similar changes but less marked were noted infrequently at the 100 ppm level. Slight hypertrophy noted at 20 and 100 ppm levels was not considered

significant change based on the histopathological examination.

Pituitary adenomas was the type of tumor most observed with 13 appearing in each of the control, 100 and 20 ppm groups and 15 for the 3000 ppm level. Mammary tumors were next in frequency. Tumors were also noted for other sites such as abdomen, liver, skin, rectum, and pancreas with no relation to dose level or group.

The administration of dicloran to rats up to 3000 ppm (150 mg/kg/day) in the diet provided inconclusive result in an overall treatment-related increase in incidence of tumor formation due to inadequate histopathology.

Under the conditions of this study, dosing is considered adequate to assess the carcinogenic potential of dicloran based upon the increased liver and kidney weights, and histopathological changes in the liver and adrenals noted at 3000 ppm.

The LOAEL for this combined chronic toxicity/ carcinogenicity rat feeding study 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 **Unacceptable (§83-5)** and does not satisfy the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in rats. This study cannot be upgraded.

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. A total of 35 rats/sex/dose were used at the start of the study. Only, five rats /sex/group were evaluated at the 13 week treatment duration. No statistical analysis was performed. Inadequate histopathology was performed. Several animals in the control and high dose were not examined and not all animals that died during the study were examined..

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

Table 1. Survival of Rats at 104 Week- Terminal Sacrifice[A]

Sex		DoseGroup			
		Control	20 ppm	100 ppm	3000 ppm
Male	Survived	16	13	15	20
	Dead	14	17	15	10
Female	Survived	21	17	20	24
	Dead	9	13	10	6

[A] Data extracted from the study report (MRID 00082718), Page 3. Each group had 35 rats/sex at the start. Five rats/sex/group were sacrificed at 13 Week.

Table 2. 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
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)**
15	479	470	495	436	277	266	268	231
39	617	596	622	545	323	312	318	258
52	630	612	633	553	335	323	329	269
78	693	688	694	584	381	367	375	294
104	693	662	706	521	447	434	466	322
Body Weight Gain (15-104)[C]	**214**	**192 (89.7)**	**211 (98.6)**	**85 (39.8)**	**170**	**168 (98.8)**	**198 (116.5)**	**91 (53.5)**
Body Weight Gain (O-104)[C]	**596**	**567 (95.1)**	**609 (102.2)**	**425 (71.3)**	**361**	**349 (96.7)**	**378 (104.7)**	**235 (65.1)**

A Data extracted from the study report (MRID 00029056), pages 11-18 and MRID 00082718, Page 3. No statistical analysis was provided in the study report.

B Mean value (Average of 35 rats/sex/dose at start; 5 rats/sex/dose sacrificed at 13 week)

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

Table 3 A. Hemoglobin Vales at Selected Intervals[A]

Dose Group	Parameters Measured (unit) and Study Duration								
	Hemoglobin (g %)								
	8 Weeks	13 Weeks	26 Weeks	40 Weeks	53 Weeks	66 Weeks	78 Weeks	92 Weeks	104 Weeks
Male									
Control	15.3	15.3	15.7	14.1	14.1	15.4	15.4	15.0	14.5
3000 ppm	15.4	15.4	14.2	13.8	13.8	12.2	13.0	13.5	13.0
100 ppm	N/A	15.5	14.9	14.3	13.6	14.9	15.1	13.8	13.8
20 ppm	N/A	15.5	15.4	N/A	N/A	N/A	N/A	N/A	13.2
Female									
Control	15.5	16.2	14.1	13.7	14.3	13.5	14.8	15.4	13.8
3000 ppm	14.7	15.1	14.2	12.2	14.5	12.7	13.3	12.1	13.0
100 ppm	15.8	15.5	14.2	14.0	14.4	13.8	16.7	14.7	14.2
20 ppm	N/A	15.5	14.2	N/A	N/A	N/A	N/A	N/A	13.9

[A] Data exctracted from the Study Report (MRID 00029056), Page 20 for 8 and 13 Weeks Observations and other intervals from Study Report (MRID 00082718), Pages 85-88. Mean value of 5 rats.

N/A= Not measured

Table 3 B. Hematocrit Vales at Selected Intervals[A]

Dose Group	Parameters Measured (unit) and Study Duration								
	Hematocrit (%)								
	8 Weeks	13 Weeks	26 Weeks	40 Weeks	53 Weeks	66 Weeks	78 Weeks	92 Weeks	104 Weeks
Male									
Control	51	50	51	49	47	49	52	50	50
3000 ppm	50	52	48	47	47	44	47	47	46
100 ppm	N/A	51	50	48	47	49	49	48	47*
20 ppm	N/A	51	51	N/A	N/A	N/A	N/A	N/A	47
Female									
Control	50	50	47	47	48	45	48	49	46
3000 ppm	52	48	47	45	46	47	40	42	44
100 ppm	N/A	53	48	47	49	46	51	49	47
20 ppm	N/A	49	49	N/A	N/A	N/A	N/A	N/A	49

[A] Data exctracted from the Study Report (MRID 00029056), Page 20 for 8 and 13 Weeks Observations and other intervals from Study Report (MRID 00082718), Pages 85-88. Mean value of 5 rats.

N/A= Not measured

* Significant at 5% level based on re-analysis of hematocrit, hemoglobin and liver wts values at terminal sacrifice of 100 ppm dose group only (MRID 00086902).

7

Table 4 A. 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	404	447	488	270	238	266	264
Liver	Absolute	14.02	19.28	14.97	16.51	8.45	10.47	9.02	8.70
	Adjusted**	3.35	4.77	3.35	3.38	3.13	4.40	3.39	3.32
Kidney	Absolute	2.74	3.01	2.97	3.25	1.82	1.74	1.75	1.84
	Adjusted**	0.66	0.75	0.66	0.67	0.67	0.73	0.66	0.70
Spleen	Absolute	0.58	0.63	0.66	0.69	0.53	0.47	0.50	0.54
	Adjusted**	0.14	0.16	0.15	0.14	0.20	0.20	0.19	0.21
Adrenal***	Absolute	50.6	45.8	47.8	50.2	61.9	53.8	64.0	61.5
	Adjusted**	12.1	11.3	10.8	10.3	23.0	22.6	24.0	23.4

a Data exctracted from the study report ((MRID 00029056) , 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.

Table 4 A. Selected Organ Weights at 104 week (Terminal) Sacifice[ab]

Organ		Weight (grams)*							
		Male				Female			
		0	20 ppm	100 ppm	3000 ppm	0	20 ppm	100 ppm	3000 ppm
Body Weight		678	628	675	521	440	428	471	318
Liver	Absolute	17.43	16.70	17.25	20.79	12.73	12.32	12.88	11.97
	Adjusted**	2.64	2.69	2.57	4.04	2.89	2.92	2.78	3.82
Kidney	Absolute	4.23	4.59	4.58	5.00	2.70	2.72	2.76	2.35
	Adjusted**	0.64	0.75	0.70	1.00	0.62	0.65	0.60	0.76
Spleen	Absolute	0.87	1.06	0.94	0.89	0.69	0.82	0.75	0.58
	Adjusted**	0.13	0.17	0.15	0.17	0.16	0.20	0.16	0.18
Adrenal***	Absolute	65.7	73.8	67.7	59.9	78.9	98.8	89.4	63.4
	Adjusted**	10.2	12.4	10.2	11.7	20.5	24.0	19.4	20.3

a Data exctracted from the study report (MRID 00082718), pages 108-109.
b Re-analysis of liver wts. of 100 ppm dose group is not significantly different from controls.
* Mean value (average of Surviving animals)
** Adjusted to body weight (mean relative organ weight in grams per 100 grams of body weight.
*** Absolute Weight in mgs.

Table 5. The Frequency of Major Liver Changes and Tumors in 146 Rats Sacrificed at the End of the Study[A]

Change	Dose Group (ppm)			
	Control	3000 ppm	100 ppm	20 ppm
No. of Rats per Group	37	44	35	30
Marked glycogen depletion, irregular hepatic cell size	5	22	7	7
Necrobiotic hepatic cells	0	11	5	1
Hepatic cell enlargement with basophilic cytoplasm	0	37	3	1
Pituitary adenomata	13	15	13	13
Mammary tumours	7	2	4	2
Other tumors	8	7	6	7

A Data extracted from the Study Report (MRID 00082718), Page 136.

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY

ATTACHMENT 1:

List of Tissues that were Weighed and Examined for Histopathology

Data extracted from the study report (MRID 00082718), Page 149

RIN-0985-06

DER/Memo. for MRID No.00029056, 00082718, 00086902

Page 13 is not included in this copy.

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