014663

DICLORAN

Developmental Study (§83-3[a])

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DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 003765 for Original DER

NOTE:
This study was previously reviewed and classified as Core Guideline. 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: Developmental Toxicity in Rats
OPPTS Number: 870.3700

OPP Guideline Number: §83-3a

DP BARCODE: D241078
PC CODE 031301
MRID NO: 00127890

SUBMISSION NO.: S541375
TOX. CHEM. NO.: 311

TEST MATERIAL (PURITY): Dicloran (93.7 % ai)

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

CITATION: Marks, T.A., Pope, S. M., Moerdyk, D. L., Stuckhardt, J. L., Morris, D. F. and Greenberg, J. H. (1982). U-2069; Segment II Teratology Study in the Rat Upjohn Company, Kalamazoo, MI. Technical Report No. 9610/82/7263/005, Report Issue Date July 26, 1982. MRID Number 00127890 Unpublished.

SPONSOR: The Upjohn Company, Kalamazoo, MI.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00127890), dicloran (93.7% a.i., Lot#: 713395) in a vehicle (0.5 mL 0.25% methylcellulose, 0.005 gm Tween 20 and 0.495 mL sterile water) was administered to pregnant Upj:TUC(SD)spf (24/dose) at dose levels of 0, 100, 200, or 400 mg/kg/day by gavage on gestation days (GDs) 6 through 15. Cesarean section was performed on all dams on GD 20. No premature deaths occurred during the study.

Treatment-related toxicity was characterized by clinical signs (CNS depression) at 200 and 400 mg/kg/day dose level. Data on clinical signs of toxicity were not reported in the report.

(1)

Decreased body weight gain was statistically significant in treated mothers at all dose levels compared to controls (71.2, 91.1, and 90.9 gm at 400, 200, 100 mg/kg/day, respectively vs 107.8 gm controls). Percent decreased in body weight gain compared to controls was 15.7, 15.5 and 34.0 at 100, 200 and 400 mg/kg/day, respectively. Maternal food consumption data were not provided in the study report. No abnormalities were observed at the necropsy.

Embryotoxicity was apparent in the 200 and 400 mg/kg/day test groups and included statistically significant decreases in mean fetal weights 4.1 and 3.5 grams at 200 and 400 mg/kg/day versus 4.4 grams control) and reductions in the number of fetuses per litters (many of these litterless dams were found to contain early implant sites). However, statistically significant differences in the mean number of resorption sites of the dams in each group which had fetuses were not detected. The mean number of implants per litter and the mean number of live fetuses per litter were comparable in all groups and there were no dead fetuses in the study.

No statistically or biologically significant increases in gross, visceral or skeletal malformations were detected. The statistically significant increasing dose-response trends observed for some variations were considered minor and consistent with the effects on fetal weight.

The maternal Lowest Observed Adverse Effect Level (LOAEL) is 100 mg/kg/day, based on decreased in body weight gain. The maternal No Observed Adverse Effect Level (NOAEL) was not established.

The developmental LOAEL is 200 mg/kg/day, based on significant decreases in mean fetal weights. The developmental NOAEL is 100 mg/kg/day.

Because no individual maternal observations (clinical signs, food consumption) nor fetal data were provided in the study report, this developmental toxicity study is classified **unacceptable/guideline (§83-3[a])**, and does not satisfy the guideline requirements for a developmental toxicity study in the rat. This study may be **upgraded** to acceptable pending submission of required observations.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Quality Assurance and Flagging statements were provided.

Attachment 1. Body Weight Gain of Dams[a]

Observations	Dosage mg/kg/day			
	0	100	200	400
No. of Animals	20	19	14	10
Body Weight at Day 0 (gm)	232.5	241.8	236.9	233.8
Body Weight at Necropsy (gm)	427.0	413.5	409.9	380.4
Gravid Uterine Weight (gm)	086.9	085.3	080.4	075.2
Absolute Body Weight Gain(gm)	107.8± 14.2	090.9± 12.75*	091.1± 21.89*	071.2± 20.59*
Absolute Body Weight Gain (% of the control)[b]		84.32	84.50	66.04

a Data extracted from the study report, Tables 5 a-d, pages 53-56, and Table 2, Page 102.
b Calculated by the reviewer
* Significantly different from controls at $p \leq 0.01$.

Attachment 2. Cesarean section observations [1]

Observation	Dose (mg/kg/day)			
	0	100	200	400
# Animals Assigned (Mated)	24	24	24	24
# Animals Pregnant Pregnancy Rate (%) [b]	21 (87.5)	24 (100)	24 (100)	20 (83.5)
# Nonpregnant	3	0	0	4
# Total Dams Died # Died Pregnant # Died Nonpregnant	0 0 0	0 0 0	0 0 0	0 0 0
Mean Maternal Absolute Body Weight Gain[a]	107.8	90.9[b]	91.1[b]	71.2[b]
No. Dams with Early Implants Only[c]	1	5	9[d]	10 [b]
Total # Live Fetuses (No. Litters)	239 (20)	226 (19)	164 (14)	123 (10)
Mean No. Live Fetuses/Litter	12.0	11.9	11.7	12.3
Total # Dead Fetuses	0	0	0	0
Mean No. Dead Fetuses/Litter	0.0	0.0	0.0	0.0
Total No. Resorptions	15	8	12	6
Mean No. Resorptions/Litter	0.8	0.4	0.9	0.6
No. Dams with Resorptions and/or Dead Fetuses	11	7	9	4
Total No. Implants	254	234	176	129
Mean No. Implants/Litter	12.7	12.3	12.6	12.9
Mean Body Weight Live Fetuses (g)[a]	4.4	4.3	4.1[d]	3.5[b]
Sex Ratio Live Fetuses (M:F)	1.0:0.9	1.0:0.8	1.0:1.1	1.0:1.1

[1] Data extracted from the study report, Tables 1, pages 46 of the study report.

a Treatment group differences were statistically significant (p 0.01)

b Two-sided p <0.01 versus vehicle controls.

c Significant increasing dose-response trend as the dose increased (p 0.01)

d Two-sided p<0.05 versus vehicle controls.

THE FOLLOWING ATTACHMENT 3, 4 and 5 ARE NOT AVAILABLE ELECTRONICALLY

These attachments were adopted from Table 2, 3 and 4, Pages 47-49 of the study report.

RIN-0985-06

DER/Memo. for MRID No.00127890

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