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NC-129 Developmental Toxicity (§81-3b)

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DATA EVALUATION RECORD

STUDY TYPE: Teratology - Developmental Toxicity/Rabbit (§83-3b)

DP BARCODE: D220275

P. C. CODE: 129105

MRID No: 436804-16

SUBMISSION No.: S495345

TEST MATERIAL: Pyridaben

SYNONYMS: NC-129

CAS NO.: 96489-71-3

STUDY REPORT NUMBERS: Project No.: 44R0021/92080
BASF REG. Doc. No.: 95/10404

SPONSOR: BASF Corporation Agricultural Products, RTP, NC

TESTING FACILITY: BASF Aktiengesellschaft Crop Protection, Rhein, Germany

TITLE OF REPORT: Toxicology Study Report. Study of the Prenatal Toxicology of NC-129 in Rabbits After Dermal Application

AUTHOR: J. Hellwig

REPORT ISSUED: March 30, 1995

EXECUTIVE SUMMARY:

A developmental toxicity study (MRID# 436804-16) on NC-129 (99.7% a.i.) was performed in Himalayan rabbits in which the test compound was administered to groups of female pregnant rabbits (14-15/group) by dermal application at dose levels of 0, 70, 170, or 450 mg/kg/day from gestational days 6-19, inclusive.

Maternal toxicity, observed at 70 mg/kg/day, was manifested by moderate to severe skin reactions. At ≥170 mg/kg/day, there was body weight loss (≥14.2 g) and food consumption (≥24%) and moderate to severe skin reactions in 50% of the animals. In addition, the severity of skin reactions increased in a time- and dose-dependent manner. The maternal systemic NOEL was 70 mg/kg/day.

Developmental toxicity observed at 450 mg/kg/day (HDT) consisted of increase in the incidence of fetuses with incompletely ossified skull. The developmental NOEL was 170 mg/kg/day.

Maternal NOEL for dermal toxicity = not established
Maternal LOEL for dermal toxicity = 70 mg/kg/day, based on skin reactions.

Maternal NOEL for systemic toxicity = 70 mg/kg/day
Maternal LOEL for systemic toxicity = 170 mg/kg/day, body weight loss and decreased food consumption.

Developmental toxicity NOEL = 170 mg/kg/day
Developmental toxicity LOEL = 450 mg/kg/day, based on retarded growth of fetuses

The maternal findings were in general, similar to those seen in a range-finding study conducted by the performing laboratory; Study # 24R0751/90133; Title: Results of a range-finding prenatal toxicity study with NC-129 in Himalayan rabbits after dermal application; 1993.

This study is classified as <u>Acceptable</u> and <u>satisfies</u> the guideline requirement for a developmental toxicity study (§83-3b) in rabbits.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: NC-129
   Description: White, crystalline powder
   Test Substance No.: 92/21
   Batch number: 900304
   Purity: 99.7%
   Stability: At least 4 hours at room temperature
   Storage Conditions: Refrigerator, dry

2. Vehicle Control: 0.5% w/v aqueous carboxymethylcellulose supplied by HOECHST AG, Frankfurt, FRG.

3. Test Animals: Species: Rabbit
   Strain: Himalayan, Outbred (Chbb:HM)
   Age and Weight at initiation: 21 to 26 weeks and mean weight of 2,585 g.
   Source: Karl Thomae, Biberach an der Riss, FRG
   Housing: Individually in cages
   Diet - Pelleted Kliba maintenance diet type 23-341-4 (Klingentalmuhle AG, Kaiseraugst, Switzerland) and tap water *ad libitum*
   Environmental Conditions: Temperature: 20-24^{0}C
   Relative Humidity: 30-70%
   Air changes: Not reported
   Photoperiod: 12 hours light/dark.
   Acclimation period: Five days

B. PROCEDURES AND STUDY DESIGN:

This study was designed to assess the effects of NC-129 on embryonic and fetal developmental in pregnant Himalayan rabbits following daily dermal application on gestation days 6 through 19, inclusive.

1. Mating: Does were fertilized by artificial insemination. A synthetic hormone, Receptal®, was given intramuscularly (0.2 ml) to does 1 hour before insemination. The pooled ejaculates were used for the artificial insemination. Male donors were kept under same environmental conditions as the females in this study. The day of insemination was designated as day 0 of gestation.

2. Animal Assignment and dose selection are presented in table 1. Animals were allocated to four groups by randomization based on their body weights as shown below.

TABLE 1. Animal Assignment[a]

Test Group	Dose Level (mg/kg/day)	#Animals per group
Control	0	15
1	70	15
2	170	15
4	450	15

[a]Due to technical difficulties, the study was carried out in 3 sections with a treatment interval of 7 days.

3. Dose Selection Rationale: The dose levels were selected based on the results of range-finding study (Study # 24R0751/90133) conducted in Himalayan rabbits (5/dose group) by the sponsor. In this study, dermal application of NC-129 at 100, 400, or 1000 mg/kg/day to the intact shaven skin of pregnant does caused decrease in food consumption and body weight gain, marginal indications of anemia possibly associated with reduced nutritional status (at ≥400 mg/kg/day) and slight eschar formation at application sites (≥100 mg/kg/day). The control group received distilled water with approx. 5 mg Cremophor® EL/100 ml as an emulsifier. Based on these results 70 mg/kg/day was chosen as the probable no-effect-level and 450 mg/kg/day as the highest dose level for the main study.

4. Dosing: All doses were in a volume of 3 ml/kg of body weight/day prepared fresh daily, as suspensions in 0.5% aqueous carboxymethyl-cellulose, during the dosing period. Control animals received vehicle alone. Dosing volumes were calculated according to individual body weights on GD 6 (post-insemination). The suspensions were stirred using a magnetic stirrer during dosing. NC-129 was suspended with vehicle using a high speed sonicator. The purity and homogeneity of the test substance were determined prior to the beginning of the study and at before the termination of the study. The stability of the test substance over a three year period was proven in an earlier study. The stability of the aqueous test suspensions over 5 and 24 hours was verified analytically by Nissan Chemical Industries (study No. NIS-87-044, 1987). Samples of the test substance suspensions were taken twice during the study for verification of concentrations and homogeneity by HPLC.

The dorsal skin of the trunk was shaven at least 18 hours before the first treatment. The test suspensions (0.3 ml/kg of body weight) were applied to the intact shaven dorsal skin under semiocclusive dressing for 6 hours/day during gestation day 6 through 19, inclusive. Following treatment, the application sites were washed off with warm water and dried.

C. OBSERVATIONS:

1. Maternal Observation and Evaluations - The animals were checked at least once daily for signs of toxicity and mortality (twice during working days). The site of application was examined twice daily and skin reactions were scored. Body weights were recorded on gestation days (GDs) 0, 2, 4, 6, 7, 9, 11, 14, 16, 19, 21, 23, 25 and 29. Food consumption was measured daily during the entire study period. Does were sacrificed by intravenous injection of pentobarbital on day 29 of gestation. Examinations at sacrifice consisted of:

- Gross pathology observations were made and gravid uterine and placental weights were determined.
- Number of corpora lutea
- Number of implantation sites; the uteri from apparently nonpregnant animals were stained using the Salewski (1964) technique to detect the implantation sites
- Numbers of resorptions (early and late) and live and dead fetuses
- Number and distribution of fetuses in each uterine horn

2. Fetal Evaluations - The fetuses were examined in the following manner:

- Individual fetal weight and sex
- External anomalies
- Visceral anomalies by dissecting the thoracic cavity and abdomen of all the fetuses following asphyxiation by CO_2; fetal heart and kidney sectioned and examined to assess the internal structure.
- Head anomalies (by cross sections of all fetal heads) using the technique of Wilson (1965) and fixation in Bouin's solution
- Skeletal anomalies for the remaining fetuses using the method of Dawson (1926) and stained skeletons (method of staining not specified) were placed on illuminated plate and examined

3. Historical control - Data were provided to allow comparison with concurrent controls.

D. STATISTICAL ANALYSIS: The following methods were used.

- Maternal body weight and body weight change, corrected body weight gain, food consumption, gravid uterine weights, number of corpora lutea, implantations, and live fetuses, proportion of pre- and post-

implantation loss, resorptions and live fetuses/litter, mean fetal body weight/litter and mean placental weight/litter--Dunnett's test

- Maternal mortality, incidence of pregnancy and number of litters with fetal findings--Fisher's Exact test

- Fetal findings (malformations, variations, retardations and/or unclassified observations)--Wilcoxon test

E. COMPLIANCE:

- A signed Statement of No Data Confidentiality Claim, dated May 19, 1995, was provided

- A signed Statement of Compliance with OECD and FRG GLPs, dated April May 19, 1995, was provided

- A signed Quality Assurance Statement, dated March 31, 1995 was provided

- A Flagging statement, dated April May 23, 1995, was provided.

Any deviations from protocol were appropriately recorded.

II. RESULTS

A. TEST MATERIAL ANALYSES

The purity of the test compound prior to the beginning of the study and shortly before the termination of the study was 99.7% and 99.5%, respectively. The concentration analysis for the samples taken during the study indicated values within 11% of the target (range: 89%-107.3% of the nominal concentration). The test compound was homogeneously distributed in the dosing suspension. The reviewers concluded that overall, the stability analyses (by Nissan Chemical Industries) of the low and high dose samples (5 and 100 mg/kg/day) in 1% carboxymethylcellulose revealed values ≥95% of the target and that the test compound was stable in the vehicle for up to 24 hours.

B. MATERNAL TOXICITY

1. Mortality - No mortalities occurred during the study.

2. Clinical observations - Compound-related dose- and time-dependent increase in the incidence and severity of skin reactions were noted at all dose levels during the dosing period. These are summarized in Table 2. Some of the above reactions also persisted during the post-dosing period. The skin reactions consisted of moderate/severe erythema to slight eschar formation and/or slight edema. Moderate to severe erythema was noted in

3/14 , 5/15 and 7/14 females at 70, 170 and 450 mg/kg/day, respectively. No treatment-related clinical signs of systemic toxicity were noted at any dose level.

3. Body weight - Body weight gain data are summarized in Table 3. Compound-related decreases in body weight gain were observed at ≥170 mg/kg/day. The body weight loss was significantly higher from GD 7-9 at 170 mg/kg/day (-15.4 g; p≤0.05) and from GD 7-11 at 450 mg/kg/day (up to -29.7 g; p≤0.01) compared to controls. During the treatment-period (GD 6-19), the does from the 170 and 450 mg/kg/day dose groups lost 23.1 and 14.2 g, respectively. Although this decrease was not dose-related, it correlated with the reduced food consumption by these animals. The corrected body weight gain was lower in all dose groups. At 70 mg/kg/day, the body weight gain was comparable with the controls during the treatment-period; the decrease in body weight gain during the post-treatment period was not considered to be biologically significant.

The body weights of treated and control groups were comparable throughout the treatment-period.

4. Food consumption - Food consumption data are summarized in Table 4. During the entire treatment-period (GD 6-19), compound-related significant decreases in food consumption were observed at 170 (24%) and 450 mg/kg/day (32%). A compensatory increase in food consumption was noted on GD 21-29 at 450 mg/kg/day.

5. Food Efficiency - Food efficiency was not calculated in this study. The approximate food efficiency data was calculated for the dosing period (GD 6-19) and are summarized in Table 5. The food efficiency in groups receiving 170 and 450 mg/kg/day was lower (64% and 44% of control, respectively) compared to the control group indicating compound-related anorexia in maternal animals.

6. Necropsy Findings - At necropsy both treated and control animals had lung edema (2, 1, 1, and 3 does at 0, 70, 170, and 450 mg/kg/day, respectively). This finding was attributed to the sacrifice of the animals rather than treatment.

8. Cesarean section Data - Data are summarized in Table 6. No compound-related effects were observed at any dose groups during the study. There were no treatment-related and/or statistically significant differences in conception rate, in the mean number of corpora lutea and implantations or incidences of pre- and post-implantation losses, the number of resorptions and viable fetuses. The sex distribution of the fetuses and mean fetal weights in all test groups were comparable with the controls. The uterine weights were comparable within the treatment and control groups.

TABLE 2. Incidences of Clinical Signs[a] - Phase I

Findings	Dose Level (mg/kg/day)			
	0	70	170	450
No. pregnant dams examined	15	15	15	15
Severe erythema to slight eschar formation	0	0	3	7
Moderate to severe erythema	0	2	2	0
Slight eschar formation	0	10	5	4
Slight edema	0	1	2	4

[a]Data were extracted from Study No. 95/10404, p. 64-65.
[b]More than one clinical sign may be found in one dam; data on nonpregnant animals were excluded from analyses.

TABLE 3. Mean Body Weight Gain (g ± S.D.)[a]

Dose Group in mg/kg/day	Dosing Period (GD 6-19)	Post-Dosing Periods (GD 19-29)	Dosing and Post-dosing Periods (GD 0-29)	Corrected body Wt. Change[b]
0	47 ± 48.6	182 ± 52.4	270 ± 77.0	-150 ± 64.7
70	65 ± 44.6	155 ± 71.8	265 ± 98.5	-137 ± 81.1
170	-23 ± 133.8	146 ± 86.4	130 ± 164.7**	-205 ± 132.7
450	-14 ± 76.8	176 ± 54.4	178 ± 94.8	-187 ± 113.6

[a]Data were extracted from Study No. 95/10404, Tables 9 and 10, p. 62 and 63.

TABLE 4. Mean Food Consumption (g/animal/day ± S.D.)[a]

Dose Group in mg/kg/day	Dosing Period (GD 6-19)	Post-Dosing Period (GD 19-29)	Dosing and Post-dosing Periods (GD 0-29)
0	93 ± 5.3	104 ± 5.0	99 ± 7.7
70	95 ± 4.6	103 ± 5.1	100 ± 6.7
170	71 ± 6.7	91 ± 12.3	84 ± 15.2
450	63 ± 8.2	104 ± 21.4	84 ± 24.1

[a]Data were extracted from Study No. 95/10404, Table 4, p. 57.

TABLE 5. Mean Food Efficiency (g body wt.gain/100 g food)[a,b]

Study Period in Days	Dose Groups (mg/kg/day)			
	0	70	170	450
6-19	51.0	68.4	-32.4	-22.2
% Control	- -	134.1	64.0	44.0

[a]Data were extracted and calculated by the Reviewer from Study No. 95/10404, Tables 4 and 9, p. 57 and 62, respectively.
[b]Food efficiency is expressed as body weight gain (g) over a given time period divided by food consumption (g) over the same period multiplied by 100.

TABLE 6. Cesarean Section Observations for Phase I Study[a]

Parameter	Dose Level (mg/kg/day)			
	0	30	100	300
No. animals assigned	15	15	15	15
No. animals mated	15	15	15	15
No. animals pregnant	15	14	15	14
Pregnancy rate (%)	100	93	100	93
Gravid Uterine Wt.	381.0 ± 49.7[b]	356.0 ± 95.9	328.0 ± 93.3	349.2± 82.1
Total corpora lutea	117 (15)[c]	112 (14)	118 (15)	116 (14)
Corpora lutea/dam	8.0 ± 1.3	8.0 ± 2.2	8.0 ± 1.1	8.3 ± 1.7
Total implantations	111	97	105	100
Implantations/dam	7.4 ± 1.3	7.0 ± 2.5	7.0 ± 1.4	7.1 ± 2.1
Total live fetuses	103	90	93	92
Live fetuses/dam	7.0 ± 1.3	6.4 ± 2.1	6.2 ± 1.9	7.0 ± 1.9
Total resorptions	8	7	12	8
Early	6	4	9	6
Late	2	3	3	2
Resorptions/dam	0.5 ± 0.5	0.5 ± 0.7	0.8 ± 0.9	0.6 ± 0.8
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Fetal weight/litter (g)	41.0 ± 2.4	41.4 ± 3.1	39.0 ± 6.1	40.0 ± 4.8
Preimplantation loss (%)	5.0	14.0	11.0	15.0
Postimplantation loss(%)	7.2	6.1	12.7	7.2
Sex ratio (% male)	44	42	46	50

[a]Data were extracted from Study No. 95/10404, Tables 14-17, pages 67-70.
[b]Mean ± S.D.
[c]Number of does included in the analyses

C. DEVELOPMENTAL TOXICITY

A summary of all classified fetal external, soft tissue, and skeletal observations is provided in Table 7 and the incidences of selected external, visceral, and skeletal fetal findings are presented in Tables 8, 9 and 10, respectively. These included malformations, variations, retardations and unclassified observations which were defined by the study author as follows:

- Malformations (applies to external, soft tissue and skeletal observations): rare and/probably lethal findings;
- Variations (applies to external, soft tissue, and skeletal observations): alternate structures occurring normally in control population and have generally no adverse effect on survival;
- Retardations (applied to skeletal observations only): delays in development compared to normal at the time of skeletal examination; and,
- Unclassified observations (applies to external and soft observations only): observations that could be classified as malformations or variations.

The fetal and litter incidences for external, soft-tissue, and other skeletal observations showed no statistically or biologically significant differences (Table 7). No compound-related external and soft-tissue malformations, variations, retardations, unclassified observations were observed in any dose group (Table 8, and 9). The only treatment-related fetal finding consisted of significant ($p \leq 0.5$) increase in the incidence of fetuses (litters) with skeletal retardation, an incompletely ossified skull, at 450 mg/kg/day (Table 10). The incidence of this finding on a litter basis (4.1%) exceeded the historical control value (0.1%; range: 0.0-0.9%). Therefore, this finding was considered to be treatment-related. Selected findings are discussed below.

1. External observations - At 450 mg/kg/day, one fetus had umbilical hernia (malformation). Two fetuses from two litters at 70 mg/kg/day and one fetus at 450 mg/kg/day had pseudoankylosis (variation). These findings are commonly seen in this strain of rabbit and were not considered to be treatment-related. No retardations and unclassified observations were seen.

2. Soft tissue Observations - Several soft tissue malformations were seen in single fetuses from all dose groups. These consisted of septal defect of the heart and/or dilatation of the aortic arch and the descending aorta (fetuses (litters): 2 (2), 2 (1) and 1 at 0, 70 and 450 mg/kg/day, respectively), agenesis of gall bladder (one fetus each at 0 and 70 mg/kg/day), hydrocephaly (one fetus each at 170 and 450 mg/kg/day),

TABLE 7. Summary of Fetal External, Soft Tissue, and Skeletal Observations[a]

Findings[b]	Dose Level (mg/kg/day) 0	70	170	450
No. fetuses (litters) examined	103 (15)	90 (14)	93 (15)	92 (14)
Total Malformations:				
No. fetuses (litters) with malformations	4 (4)	4 (3)	2 (2)	3 (3)
% affected fetuses/litter	4.0	5.4	3.0	3.0
Total Variations:				
No. fetuses (litters) with variations	26 (12)	18 (9)	22 (10)	16 (9)
% affected fetuses/litter	26.3	18.1	21.3	17.4
Total Retardations:				
No. fetuses (litters) with variations	32 (13)	42 (11)	39 (13)	28 (9)
% affected fetuses/litter	32.0	43.2	41.0	28.3

[a]Data were extracted from Study No. 95/10404, Table 38 and p. 91.
[b]More than one type of anomaly may be found in one fetus.

TABLE 8. Summary of Fetal External Observations[a]

Findings[b]	Dose Level (mg/kg/day) 0	70	170	450
No. fetuses (litters) examined	103 (15)	90 (14)	93 (15)	92 (14)
Malformations:				
No. fetuses (litters) with malformations	0	0	0	1
% affected fetuses/litter	0.0	0.0	0.0	1.2
Variations:				
No. fetuses (litters) with variations	0	2 (2)	0	1
% affected fetuses/litter	0.0	2.0	0.0	1.2

[a]Data were extracted from Study No. 95/10404, Table 18 and p. 71.
[b]More than one type of anomaly may be found in one fetus.

TABLE 9. Summary of Fetal Soft Tissue (Visceral) Observations[a]

Findings[b]	Dose Level (mg/kg/day) 0	70	170	450
No. fetuses (litters) examined	103 (15)	90 (14)	93 (15)	92 (14)
Malformations:				
No. fetuses (litters) with malformations	3 (3)	3 (2)	2 (2)	2 (2)
% affected fetuses/litter	3.0	4.0	3.0	2.0
Variations:				
No. fetuses (litters) with variations	17 (11)	7 (6)	13 (8)	9 (6)
% affected fetuses/litter	17.4	8.0	12.0	10.0

[a]Data were extracted from Study No. 95/10404, Table 22, p. 75.
[b]More than one type of anomaly may be found in one fetus.

TABLE 10. Summary of Fetal Skeletal Observations[a]

Findings[b]	Dose Level (mg/kg/day) 0	70	170	450
No. fetuses (litters) examined	103 (15)	90 (14)	93 (15)	92 (14)
Malformations:				
No. fetuses (litters) with malformations	1	1	0	0
% affected fetuses/litter	1.1	2.0	0.0	0.0
Variations:				
No. fetuses (litters) with variations	14 (9)	11 (7)	10 (6)	8 (5)
% affected fetuses/litter	14.2	12.0	11.0	9.0
Retardations:				
No. fetuses (litters) with variations	32 (13)	42 (11)	39 (13)	28 (9)
% affected fetuses/litter	32.0	43.2	41.0	28.3
Skull - Incompletely ossified[c]	0	1	0	4 (4)*
% affected fetuses/litter	0.0	0.9	0.0	4.1*

[a]Data were extracted from Study No. 95/10404, Table 29 to 36, p. 82 to 89.
[b]More than one type of anomaly may be found in one fetus
[c]Historical control data: No. fetuses (litters) with incompletely ossified skull = 44 (40); % affected fetuses/litter = 0.1. *p≤0.05

dilatation of left ventricle (one fetus at 450 mg/kg/day); and diaphragmatic hernia (one fetus at 170 mg/kg/day).

Soft-tissue variations were seen in all dose groups and consisted of separated origins of carotids (fetuses (litters): 13 (10), 5 (4), 13 (8), and 5 (4) at 0, 70, 170, and 450 mg/kg/day, respectively), heart with traces of interventricular foramen/septum membranaceum (4 (4), 2 (2), 4 (4) at 0, 70, and 450 mg/kg/day, respectively) and dilated renal pelvis (1 fetus at 170 mg/kg/day).

The unclassified soft tissue observations were seen in one fetus each at 0, 70 and 170 mg/kg/day but not at 450 mg/kg/day. Focal liver necrosis was noted in a fetus at 170 mg/kg/day; while blood coagulum around urinary bladder was found in one fetus each at 0 and 70 mg/kg/day.

Because of the isolated incidences of the above soft tissue findings and their occurrence in historical controls, at a comparable or even higher incidences, they were considered to be unrelated to the treatment.

3. Skeletal Observations - The only skeletal malformation seen at 0, and 70 mg/kg/day was severely fused sternebrae (bony plate) in one fetus in each dose group.

The skeletal variations occurred without clear dose-response (fetuses (litters): 14 (9), 11 (7), 10 (6), and 8 (5) at 0, 70, 170, and 450 mg/kg/day, respectively) and consisted of skull (splitting of skull bone(s)), epactal bone between nasal and frontal bones, the ribs (shortened 12th, rudimentary cervical or accessory 13th rib (s) and the sternum (sternebra(e) of irregular shape, fused or accessory sternebra). These variations were found at a comparable frequency in the historical controls.

The skeletal retardations (incomplete or missing ossification of skull bones including hyoid bone, vertebral column, sternebra(e) and talus) were found in all dose groups. The only treatment-related finding consisted of incompletely ossified skull in 4 fetuses in 4 litters at 450 mg/kg/day. The incidence of this finding was higher than the concurrent control value (4 fetuses [4] litters versus 0). The percentage of affected fetuses per litter (4.1%) was also higher than the historical control value (0.1%; range: 0.0-0.9%). Therefore, this finding was considered to be treatment-related. The incidence of incompletely ossified thoracic vertebral body/bodies at 70 and 170 mg/kg/day was significantly increased compared to controls; however, because of absence of this finding at 450 mg/kg/day and lack of dose-response, it was not considered to be treatment-related.

III. DISCUSSION:

A. MATERNAL TOXICITY: Compound-related dermal toxicity was observed in maternal animals during the treatment period at 70 mg/kg/day. It was manifested as moderate to severe erythema and/or slight edema in 3/15 does. The severity of this finding was dose-and time-dependent. Addition findings noted at 170 and 450 mg/kg/day included significant weight loss associated with decrease in food consumption during the dosing period. Determination of food efficiency data for the dosing period indicated anorexia in animals receiving 170 and 450 mg/kg/day.

Based on these results, the maternal dermal toxicity LOEL was 70 mg/kg/day; the NOEL was not established. The maternal systemic LOEL was 170 mg/kg/day based on body weight loss and decreased food consumption during the treatment period; the NOEL was 70 mg/kg/day.

B. DEVELOPMENTAL TOXICITY:

1. Deaths/Resorptions: No treatment-related increases in fetal deaths or resorptions were observed.

2. Altered Growth: At 450 mg/kg/day, the incidence of fetuses/litters with incompletely ossified skull increased significantly compared to those for the concurrent and historical controls. Therefore, this finding was considered to be indicative of an altered (retarded) growth effect.

3. Developmental Anomalies: At 450 mg/kg/day, the percentage of fetuses per litter with incompletely ossified skull exceeded the historical control value. There was no compound-related increase in the number of fetuses and litters with malformations, variations, unclassified observations and other retardations.

Based on the altered growth of fetuses, the developmental NOEL and LOEL were 170 and 450 mg/kg/day, respectively.

C. CORE CLASSIFICATION: Acceptable