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4-23-90

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

APR 23 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 7969-53. DER for The Full Report of a Dermal Developmental Toxicity Study of Vinclozolin in the rat/34R0375/88074 (MRID No. 414130-01).

Tox. Chem. No.: 323C.
Project No.: 0-0913.
Record No.: 261329.

To: S Lewis/J Stone, PM 21
Registration Division (H7505C)

From: David G Anderson, PhD. David G Anderson 4/17/90
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Marion Copley, DVM Marion Copley 4/18/90
Section Head, Section 2
Toxicology Branch I (IRS)
Health Effects Division (H7509C).

CONCLUSIONS:

It can be conluded that Vinclozolin admisteration dermally to rats results in decreased anal-genital distance in males. ~~at 60 mg/kg/day the NOEL.~~

This is a full report on a dermal developmental toxicity study and confirms the result previously reported for preliminary report of these effects.

Doses Administered: 0, 60, 180, and 360 mg/kg/day, applied dermally to 25 Wistar rats/group.

Developmental Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Possible increased incidence of dilated renal pelvis, and hydroureter in fetuses occurred at 360 mg/kg/day and higher, but not in litters.

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Maternal Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for increases in absolute adrenal weights and at 360 mg/kg/day increases in absolute liver weights.

Core classification: Supplementary; stability data needs to be submitted. The study may upgradeable if this data submitted is adequate.

Requested Action:
The Registration Division requested that the Toxicology Branch 1 (IRS) review data on a dermal developmental toxicity study with Vinclozolin.

C. COMMENTS:
In this dermal study, the effect level for decreased anal-genital distance in males is 180 mg/kg/day and the NOEL is 60 mg/kg/day. The effect level for these same effects is 50 mg/kg/day and the NOEL is 15 mg/kg/day in an oral gavage study. Preliminary results from a percutaneous penetration study indicates that 26% of the dose applied is absorbed. Thus, a dermal dose with a NOEL of 60 mg/kg/day is calculated to be equivalent to an oral dose of 15.6 mg/kg/day [(60 mg/kg/day) X (0.26) = 15.6 mg/kg/day], and a corresponding dermal LEL of 180 mg/kg/day is calculated to be equivalent to an oral dose of 46.8 mg/kg/day [(180 mg/kg/day) X (0.26) = 46.8 mg/kg/day]. These results indicate that the dose levels from the oral developmental toxicity studies are supported by the dose levels from the dermal developmental toxicity study. In addition, the NOEL and LEL for adrenal weight increase in this dermal developmental toxicity study is identical with the NOEL and LEL for the pseudohermaphrodism, respectively.

D. Additional Needed Information:
The stability of Vinclozolin in 0.5% CMC was reported to be 80% in 24 hours at room temperature with only a summary statement about a metabolite being increased in proportion. With this degree of instability, the possibility of CMC aiding in the degedation of Vinclozolin and the variability of the analytical data from analyses of the dosing suspensions, it is necessary to verify the data on the stability of the dosing suspensions. Please submit summary data on the stability of Vinclozolin in 0.5% CMC. In addition, please submit information on the stability of Vinclozolin in 0.5% CMC at 40 degrees C, and on the degree of possible absorption of Vinclozolin by CMC.

Cover memo on a preliminary data on dermal developmental toxicity/Rat/B:\VINCLV13.23C\ MDERMDEV.PRE/D Anderson/3/13/90.

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Primary reviewer: David G Anderson, PhD. 4/11/90
Section 2, Tox. Branch 1 (H7509C).
Secondary reviewer: Marion Copley, DVM. 4/18
Section 2, Tox. Branch 1 (H7509C).

DATA EVALUATION REPORT

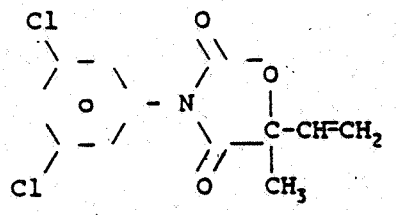
STUDY TYPE: Dermal Developmental Toxicity Study/83-3/Rat/34R0375/88074.

TOX. CHEM. No.: 323C

MRID No.: 414130-01.

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan.

SPONSOR: BASF Corp. Chemicals Div., Ag. Chem., PO Box 13528 Research Triangle Park, NC 27709-3528.

TESTING FACILITY: BASF Aktiengesellshaft, Dept. Toxicology, 6700 Ludwigshafen, Federal Republic of Germany.

STUDY NO.: 34R0375/88074. Reg. Doc. No. BASF 90/0025.

REPORT TITLE: Study of Prenatal Toxicity of Reg. No. 83 258 in Rats After Dermal Application.

AUTHOR(S): Gelbke, H. P.

REPORT ISSUED: February 1, 1990.

CONCLUSIONS:
Doses Administered: 0, 60, 180, and 360 mg/kg/day, applied dermally to 25 Wistar [Chbb:THOM (SPF)] rats/group.

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Dermal Developmental Toxicity Study/83-3/Rat/34R0375/ 88074.

Developmental Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Possible increased incidence of dilated renal pelvis, and hydroureter in fetuses occurred at 360 mg/kg/day and higher, but not in litters.

Maternal Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for increases in absolute adrenal weights and at 360 mg/kg/day increases in absolute liver weights.

Core classification: Supplementary because stability data must be submitted (See section E. Additional Needed information at the end of this DER.)

A. MATERIALS:

1. Test compound: Vinclozolin, Description: Solid white powder. Batch No. N 183. Purity: 99.2%.

2. Test animals: Species: Rats, Strain: Wistar [Chbb:THOM (SPF)]. Supplied by Karl Thomae, Biberach an der Riss, FRG. Acclimatization: about 2 weeks. Initial female body weights: about 241 g. Age: about 11-12 weeks at gestational day (gd) 0.

3. Environmental: Caging was stainless steel wire mesh with floor area of about 900 cm^2. Caging room disinfected with formaldehyde and ammonia. Temperature 20 - 24 degrees C. Humidity 30 - 70%. Light:dark = 12:12.

4. Food and Water: Food was ground Klida 343 feed supplied by Klingentalmuhle AG, CH-4303 Kaiseraugst, Switzerland. The water was tap water. Both were supplied ad libitum. Each batch of food was analyzed by the supplier and water was analyzed by BASF and the municipal water authority.

5. Mating: The breeding ratio was 4 females: 1 male. Gestaional day (gd) 0 was considered to be the day sperm was detected in vaginal smears or the day a vaginal plug was seen.

B. STUDY DESIGN: This study is a dermal developmental toxicity study conducted in rats. Vinclozolin was applied to the clipped backs of 25 female rats/group at 0, 60, 180 and 300 mg/kg/day from gestational day (gd) 6 through 19 for 6 hours/day.[1]

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[1] The dosing from gd 6 to 19 is a deviation from Guideline 83-3 which recommends dosing from gd 6 to 15. However, the effect on the anal-genital distance can not be demonstrated when dosing is terminated at day 15.

standard dose volume of 5 ml/kg was used based body weight at gd 6. The vehicle was distilled water and 0.5% carboxymethylcellulose. The application site was covered by a 4x4 cm gauze patch (4 layers), a rubberize linen patch and fixed in place by a stretchable bandage. The application site was inspected twice daily and observed at the time of application and after 6 hours. The application site was wiped with water and dried after 6 hours.

1. Stability and Dose analyses - Over 24 hours at room temperature the test material decreased in concentration to 80% and a metabolite increased to the same proportion.[2] The CMC vehicle may have contributed to this degree of instability. Approximate calculations of the degree of stability at the elevated body temperatures for the 6 hour dose application indicated that the concentration would be approximately 79% to 85% of nominal or an average of 85% to 92% of nominal.[3] This instability should not change the NOEL for this study. Doses were prepared daily and used immediately after preparation. One high dose was 87% of nominal but the remaining doses were reported to be acceptable. The analyses were reported in the Supplement, page 298 of the report. However the stability data was not submitted. The data on the stability of the dosing suspensions must be submitted.

Food consumption and body weight were determined on gd 0, 1, 3, 6, 8, 10, 13, 15, 17, 19 and 20. At gd 20 in dams, blood was drawn and the animals were sacrificed. Gross necropsy was conducted on the dams, and livers, adrenals and carcasses were weighed. Fetuses were weighed, the soft tissue and skeletons examined, and anal-genital distance determined relative to body weight (anal-genital index).

Test group	Dose mg/kg/day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	5	0.0	25
2. Low (LDT)	60	5	1200	25
3. Mid (MDT)	180	5	3600	25
4. High(HDT)	360	5	7200	25

[2] This was assumed to mean that the metabolite increased to about 20%.

[3] Linear kinetics and doubling of the rate of degradation for every 10 degree rise in temperature was assumed for these approximate calculations.

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Dermal Developmental Toxicity Study/83-3/Rat/34R0375/ 88074.

History - This study was conducted in response to a study from Japan under Japanese guidelines for BASF Japan [K Takehara, M Itabashi, T Inoue and M Tajima, "Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration", conducted by Nippon Institute for Biological Science, 2221-1 Shin-machi, Ohme-shi, Tokyo 198, December 1979 for BASF Japan]. This study from Japan differed from EPA guideline studies essentially in that the test material was administered in the diet, and from gd 0 through 21, 11 days longer than the OPP requirements of gd 6 through 15. This current study was also conducted for a longer dosing period, 6 through 19, but the dose was applied dermally. **This study demonstrated effects on the anal-genital distance in males, and verifies the study results from Japan and the gavage developmental toxicity study from Germany.**

C. METHODS AND RESULTS: Numbered tables were copied from the submitted report.

1. Clinical Signs - Were observed at least daily.

Results - No clinical signs occurred at any dose level.

2. Observation of the Application Site - The application site was observed twice daily.

Results - No remarkable observations were reported at any dose level.

3. Body Weight - They were weighed on gd 0, 1, 3, 6, 8, 10, 13, 15, 17, 19, and 20. The body weight gain was determined between successive weighings.

Results - Body weights and body weight gain did not appear to demonstrate a significant dose related decrement or elevation. However, a statistically significant body weight gain decrement occurred gd 13-15 at the 360 mg/kg/day dose level, but body weight gains (Table 004) occurred at all other gestational days and carcass weight (Table 006) was nominally increased over control values. This significant body weight gain decrement during gd 13-15 was not accompanied by an increase or decrease in food consumption which was nominally elevated at all dose levels (Table 001). Although there was a slight trend to increasing body weight, the effect was minimal and not significant. This nominally increased trend was also reflected by the relative efficiency and food consumption data below.

4. Food consumption - Food consumption was determined and mean daily intake was calculated. Efficiency was not specified.

Food consumption was determined gd 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10, 10 to 13, 13 to 15, 15 to 17, 17 to 19, and 19 to

20.

Results - Food consumption was nominally elevated in the 360 mg/kg/day dose group (Table 001). None of the values were significantly different from control values. The relative efficiency of food utilization from gd 6-19 was 3.63 in controls, 3.73 at 60 mg/kg/day, 3.70 at 180 mg/kg/day and 3.83 at 360 mg/kg/day. Although a trend of increasing efficiency is noted, with the variability of the data, this trend may be incidental. However, the trend is consistent with a trend for increasing body weight gain with increasing dose level.

5. Blood was collected - Blood was collected from the retroorbital venus plexus. Blood was collected on gd 20. When a percent change is reported below and in parentheses, it refers to percent of control values.

The CHECKED (X) parameters were examined.

a. Hematology -

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Reticulocytes (RETI)
Total plasma protein (TP)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc.(MCHC)
X Mean corpuscular volume (MCV)

Results - Platelets (93%) and MCHC (97%) were statistically significantly depressed at 360 mg/kg/day (Table 008). Reticulocytes were nominally elevated at all dose levels. The effects on the platelets, MCHC and reticulocytes were minimal and may not have been test material related.

6. Necropsy of Mothers and Fetal Examinations: Dams were sacrificed on gd 20. Pregnant uteri were weighed and subtracted from the weight of the dam. The corpora lutea, the number of viable fetuses, dead fetuses, resorptions, and implantation sites were counted. Fetal weights were determined and malformations and variations were determined. The ratio of the anal-genital distance to body weight was determined.

a. Gross pathology on Mothers - No dose related gross pathological effects were reported.

b. Results on Mothers - The carcass weight of dams, and the gravid uterus was not statistically significantly different from control values. Absolute liver weights (107% of control values) were statistically significantly increased at 360 mg/kg/day and absolute adrenal weights (109-111% of control values) were statistically significantly increased at 180 and 360 mg/kg/day (Table 012). The relative weights of these organs were only nominally elevated in the two highest dose groups. These increased adrenal weights may have implications on the body weight gains seen earlier.

Reproduction data and corpora luteal counts did not differ

from control values. However, pre- and post-implantation loss was nominally decreased in highest dose group (Table 015) and late resorption was statistically significantly decreased at the highest dose level (Table 016).

c. Results of the Fetal Examination - The fetal anal-genital distances are reported in Table 018. A statistically significant dose related decrease occurred in the ratio of the anal-genital distance to the body weight in male fetuses at 180 mg/kg/day and higher. (In other studies, MRID # 411322-01, the male fetuses in the 1000 mg/kg/day dose group looked like females, but on examination of the placement and appearance of the male gonads, they appeared to be superficially normal. On this basis the phenomenon was considered to be pseudohermaphroditism.)

Fetal weights did not differ from control values (Table 017). The number of live fetuses which was elevated in all dose groups probably has no biological significance (Table 017).

On soft tissue examination, the combined incidence of dilated renal pelvis and hydroureter in fetuses but not in litters was each statistically significantly elevated at 360 mg/kg/day (Table 026). The incidence in litters was nominally elevated at 360 mg/kg/day. Historical controls indicated that incidence of hydroureter and dilated renal pelvis was 40% for fetuses and 83% for litters. This increase may not be dose related, since it occurred only in fetuses and was a frequent variation in this laboratory.

On skeletal examination, the combined incidence of fetuses with total variations and retardations was statistically significantly increased, but not for litters at 60 and 180 mg/kg/day (Table 035). Reduced ossification of the sternebrae at the 180 mg/kg/day dose level were statistically significant in fetuses but not in litters. In addition, the nominal increase at 360 mg/kg/day in litters was identical with the increase at 180 mg/kg/day but less than the increase at 60 mg/kg/day. Thus, these increases in reduced ossification did not appear to be dose related. Historical control data indicated that retardations were 38% for fetuses and 84% for litters. In other studies (MRID # 41132-01) the incidence of 14th rib may have been elevated but this effect did not occur in this study. The statistically significant effects occurring at 60 and 180 mg/kg/day in retardations may not have been dose related since they did not exhibit a good dose relationship and they were not significant at 360 mg/kg/day.

D. DISCUSSION AND ABSTRACT:

Vinclozolin was administered dermally (vehicle water and 0.5% carboxymethylcellulose) to 25 rats/group at 0, 60, 180, and 360 mg/kg/day from gestational day (gd) 6 through 19. At gd 20 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Marginal maternal toxicity was demonstrated by the statistically significant increase in absolute adrenal weight at 180 and 360 mg/kg/day. In addition,

absolute liver weights were statistically significantly elevated at 360 mg/kg/day dose level. No dose related gross abnormalities were noted in the kidneys, however, no histology was conducted on the organs. A statistically significant increase occurred during gd 13-15 in the body weight gain. The carcass weight and the body weight gain were all nominally elevated at 360 mg/kg/day over control values at gd 20. The body weight gain may have been test material related, but the effect was not statistically significant.

Pre- and post-implantation losses were nominally decrease and the number of live fetuses were nominally increased which are consistent with the statistically significant decrease in late resorptions at the 360 mg/kg/day dose level.

A statistically significant increase occurred in pseudohermaphroditism among male fetuses. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. The anal-genital distance/body weight ratio in male fetuses was statistically significantly decreased at 180 mg/kg/day and higher. The response was dose related. These results are consistent with possible hormonal or anti-hormonal effects from the test material.

Soft tissue examination of fetuses indicated a statistically significant increased incidence in dilated renal pelvis and a nominal increase in hydroureter, but the effect was only nominally elevated in litters at 360 mg/kg/day and may not be dose related.

In summary, marginal effects occurred for increased soft tissue variations at 360 mg/kg/day(HDT) and statistically significant decreases occurred in the anal-genital distance in males at 180 mg/kg/day and above. The NOEL is 60 mg/kg/day. In the gavage study the effect level for these same effects is 50 mg/kg/day and the NOEL is 15 mg/kg/day. Preliminary results from a percutaneous penetration study indicates that 26% of the dose applied is absorbed. Thus, a dermal dose with a NOEL of 60 mg/kg/day is calculated to be equivalent to an oral dose of 15.6 mg/kg/day [(60 mg/kg/day) X (0.26) = 15.6 mg/kg/day], and a corresponding dermal LEL of 180 mg/kg/day is calculated to be equivalent to an oral dose of 46.8 mg/kg/day [(180 mg/kg/day) X (0.26) = 46.8 mg/kg/day]. These results indicate that the dose levels from the oral developmental toxicity studies are supported by the preliminary data from the percutaneous absorption study and the dose levels from the dermal developmental toxicity study. In addition, the NOEL and LEL for adrenal weight increase in this dermal developmental toxicity study is identical with the NOEL and LEL for the pseudohermaphrodism, respectively. Thus, adrenal steroidgenesis could be affected or the test material may have hormonal or anti-hormonal effects.

A

E. Additional Needed Information:

The reported stability of Vinclozolin in 0.5% CMC was reported to be 80% in 24 hours at room temperature with only a summary statement about a metabolite being increased in proportion. With this degree of instability, the possibility of CMC aiding in the degradation of Vinclozolin and the variability of the analytical data from analyses of the dosing suspensions, it is necessary to verify the data on the stability of the dosing suspensions. Please submit summary data on the stability of Vinclozolin in 0.5% CMC. In addition, please submit information on the stability of Vinclozolin at 40 degrees C in 0.5% CMC, and on the possible effects on the degree of absorption of Vinclozolin by CMC.

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TABLE 001

PROJECT NO. 34R0375/88074. PRENATAL TOXICITY STUDY IN RATS
DERMAL ADMINISTRATION
MEAN MATERNAL FOOD CONSUMPTION DURING GESTATION - GRAMS/ANIMAL/DAY

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
DAYS 0 TO 1	MEAN	19.9	19.5	19.6	19.8
	S.D.	2.39	2.44	2.73	2.09
	N	25	24	23	24
DAYS 1 TO 3	MEAN	22.6	22.9	23.1	23.0
	S.D.	2.64	2.31	2.84	2.50
	N	25	24	23	24
DAYS 3 TO 6	MEAN	23.5	23.6	23.7	24.1
	S.D.	2.15	2.33	2.27	[illegible]
	N	25	24	23	24
DAYS 6 TO 8	MEAN	22.4	23.4	23.5	[illegible]
	S.D.	2.20	1.68	2.90	[illegible]
	N	24	24	23	24
DAYS 8 TO 10	MEAN	24.9	24.3	26.2	[illegible]
	S.D.	2.91	2.65	2.74	[illegible]
	N	25	24	23	24
DAYS 10 TO 13	MEAN	26.9	26.9	27.6	[illegible]
	S.D.	2.15	2.45	2.28	[illegible]
	N	25	24	23	24
DAYS 13 TO 15	MEAN	28.7	28.6	29.9	30.0
	S.D.	2.57	2.49	2.49	[illegible]
	N	25	24	23	24
DAYS 15 TO 17	MEAN	30.2	30.2	30.8	30.6
	S.D.	[illegible]	2.43	2.38	[illegible]
	N	25	24	23	24
DAYS 17 TO 19	MEAN	30.9	30.9	31.1	[illegible]
	S.D.	2.53	2.44	2.40	[illegible]
	N	25	24	23	24
DAYS 19 TO 20	MEAN	28.7	28.6	27.9	28.8
	S.D.	3.31	3.51	2.60	[illegible]
	N	25	24	23	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01.

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PROJECT NO. 34R0375/88074: PRENATAL TOXICITY STUDY IN RATS
DERMAL ADMINISTRATION
MEAN MATERNAL BODY WEIGHT CHANGE DURING GESTATION -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
DAYS 0 TO 1	MEAN	6.3	5.3	5.9	6.1
	S.D.	4.10	3.59	4.31	3.81
	N	25	24	23	24
DAYS 1 TO 3	MEAN	11.8	13.9	13.2	12.2
	S.D.	4.21	3.83	3.83	4.25
	N	25	24	23	24
DAYS 3 TO 6	MEAN	12.4	12.2	12.1	13.4
	S.D.	4.23	4.52	4.13	3.74
	N	25	24	23	24
DAYS 6 TO 8	MEAN	2.8	4.7	5.1	5.7
	S.D.	3.20	4.12	4.63	5.28
	N	25	24	23	24
DAYS 8 TO 10	MEAN	10.0	9.7	10.2	[illegible]
	S.D.	5.47	3.52	4.22	[illegible]
	N	25	24	23	24
DAYS 10 TO 13	MEAN	19.1	18.9	19.1	[illegible]
	S.D.	4.83	4.31	5.18	[illegible]
	N	25	24	23	24
DAYS 13 TO 15	MEAN	13.8	14.4	16.5	16.8**
	S.D.	3.61	4.46	3.30	3.71
	N	25	24	23	24
DAYS 15 TO 17	MEAN	22.3	23.0	23.0	[illegible]
	S.D.	4.86	4.11	5.61	[illegible]
	N	25	24	23	24
DAYS 17 TO 19	MEAN	30.9	32.0	28.3	[illegible]
	S.D.	5.82	5.66	8.54	[illegible]
	N	25	24	23	24
DAYS 19 TO 20	MEAN	16.4	17.3	16.5	17.6
	S.D.	5.38	5.91	6.51	3.92
	N	24	24	23	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05, ** = P<0.01

PROJECT NO. 34R0375/88074 PRENATAL TOXICITY STUDY IN RATS
DERMAL ADMINISTRATION
MEAN GRAVID UTERINE WEIGHTS AND NET MATERNAL BODY WEIGHT CHANGE -- GRAMS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
GRAVID UTERUS	MEAN	77.5	82.8	79.0	84.4
	S.D.	15.88	10.70	19.13	12.44
	N	25	24	23	24
CARCASS	MEAN	306.9	309.1	315.8	314.8
	S.D.	21.97	20.49	21.54	19.82
	N	25	24	23	24
NET WEIGHT CHANGE FROM DAY 6	MEAN	38.1	37.1	40.0	41.[illegible]
	S.D.	9.82	9.92	9.00	8.50
	N	25	24	23	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

CARCASS WEIGHT = TERMINAL BODY WEIGHT MINUS UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 6 = CARCASS WEIGHT MINUS DAY 6 BODY WEIGHT

TABLE [illegible]

BASF TOXICOLOGY - DATATOX HC.2
PROJECT NUMBER 34R0375/88074

REG NO 83 258

PRINT DATE 25 OCT 89

HEMATOLOGICAL EXAMINATIONS

GROUP MEANS

Nominal days in study 20 D.C.

FEMALES		WBC GIGA/L	RBC TERA/L	HGB MMOL/L	HCT L/L	MCV FL	MCH FMOL	MCHC MMOL/L	PLT GIGA/L
GROUP 0	M	5.76	5.80	7.73	0.299	51.52	1.33	25.85	1161
0 MG/KG	SD	0.52	0.24	0.27	0.010	1.34	0.04	0.46	79
	N	26	25	25	25	25	25	25	25
GROUP 1	M	5.87	5.75	7.70	0.300	52.22	1.34	25.65	1128
60 MG/KG	SD	0.87	0.36	0.41	0.016	1.22	0.04	0.43	85
	N	24	24	24	24	24	24	24	24
GROUP 2	M	5.64	6.10*	8.01	0.314*	51.34	1.31	25.54	1129
180 MG/KG	SD	0.73	0.51	0.57	0.027	0.97	0.03	0.54	81
	N	23	23	23	23	23	23	23	23
GROUP 3	M	5.75	5.79	7.60	0.302	52.08	1.33	25.50*	1076**
360 MG/KG	SD	0.72	0.39	0.46	0.020	1.45	0.04	0.46	105
	N	24	24	24	24	24	24	24	24

Statistical Anova + Dunnette tests (two-sided) * P<0.05 ** P<0.01 (Statistical unit = Animal)

90/0025 0067

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Lab 012

BASF Department of Toxicology

Reg. Nr. 83288, PRAENATAL TOX. STUDY,
DERMAL APPLICATION IN RATS
ABSOLUTE WEIGHTS - MEAN VALUES

1
34R0375/00074
Oct/18/1989 KOPE
acupat system
psn:001

Sacrifice group			F1			
		Sex	F			
	Dose group		0	1	2	3
Body weight	g	M	376.524	385.387	387.665	392.470
		SD	33.014	26.147	29.257	27.776
		n	25.	24.	23.	24.
Liver	g	M	17.814	17.683	18.553	18.814*
		SD	1.682	1.727	2.131	1.74
		n	25.	24.	23.	24.
Adrenal glands	g	M	0.103	0.103	0.114**	0.112*
		SD	0.012	0.014	0.012	0.013
		n	25.	24.	23.	24.

Dunnett test
* P < 0.05 ** P < 0.01
two sided (statistical unit = animal)

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TABLE [illegible]

PROJECT NO 34R0375/88074. PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Females Mated	N	25	25	25	[illegible]
Pregnant	N	25	24	23	24
	%	100	96	92	96
Aborted	N	0	0	0	0
Premature Births	N	0	0	0	0
Dams with Viable Fetuses	N	25	24	23	24
Dams with all Resorptions	N	0	0	0	0
Female Mortality	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pregnant at C-section	N	25	24	23	24
	%	100	96	92	96
Corpora Lutea	MEAN	16.6	16.8	17.2	17.3
	S.D.	2.02	2.01	2.82	1.87
	TOTAL	415	402	395	414
Implantation Sites	MEAN	15.1	15.9	15.5	[illegible]
	S.D.	1.09	1.72	3.95	[illegible]
	TOTAL	377	382	356	[illegible]
Preimplantation Loss	MEAN%	9.6	4.7	11.1	[illegible]
	S.D.	14.26	6.22	19.29	[illegible]
Postimplantation Loss	MEAN%	8.5	6.7	6.6	[illegible]
	S.D.	8.19	6.11	5.68	[illegible]

SIGNIFICANTLY DIFFERENT FROM CONTROL a = P<0.05, b = P<0.01

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TABLE 016

PROJECT NO 34R0375/88074, PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Pregnant at C-section	N	25	24	23	24
Resorptions: Total	MEAN	1.4	1.0	1.1	1.0
	S.D.	1.23	0.95	0.55	1.08
	TOTAL	36	23	25	25
	MEAN%	9.5	6.2	6.6	6.5
	S.D.	8.19	6.33	5.68	6.71
Early	MEAN	1.2	0.9	1.0	1.0
	S.D.	1.25	0.99	0.98	1.08
	TOTAL	29	21	22	25
	MEAN%	7.5	5.7	5.8	6.5
	S.D.	7.64	6.55	5.91	6.71
Late	MEAN	0.3	0.1	0.1	0.0a
	S.D.	0.54	0.28	0.34	0.00
	TOTAL	7	2	3	0
	MEAN%	2.0	0.6	0.8	0.0a
	S.D.	1.98	1.90	2.06	0.00
Dead Fetuses	N	0	0	0	0

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01.

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TABLE 017

PROJECT NO. 34R0375/88074: PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF REPRODUCTION DATA

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 160 MG/KG BW/DAY
Dams with Viable Fetuses	N	25	24	23	24
Live Fetuses	MEAN	13.6	15.0	14.4	15.3
	S.D.	3.01	2.10	3.63	2.44
	TOTAL	341	359	331	366
	MEAN%	90.5	93.8	93.4	93.5
	S.D.	8.19	6.43	6.68	6.71
Females	MEAN	6.8	7.5	6.3	7.5
	S.D.	2.15	2.21	2.16	2.04
	TOTAL	171	179	145	179
	MEAN%	45.7	46.7	43.9	46.0
	S.D.	11.74	11.59	16.99	12.31
Males	MEAN	6.8	7.5	8.1	7.8
	S.D.	2.57	2.38	3.00	2.30
	TOTAL	170	180	186	187
	MEAN%	44.8	47.1	49.6	47.5
	S.D.	14.07	13.61	14.58	11.31
PER CENT LIVE FEMALES		50.1	49.9	43.8	48.9
PER CENT LIVE MALES		49.9	50.1	56.2	51.1

SIGNIFICANTLY DIFFERENT FROM CONTROL. a = P<0.05, b = P<0.01.

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PROJECT NO. 34R0375/88074 PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
MEAN PLACENTAL WEIGHTS, MEAN AG DISTANCE AND AG INDEX

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 [illegible] MG/KG BW/DAY
PLACENTAL WEIGHTS UNITS, GRAMS					
of all Viable Fetuses	MEAN	0.44	0.42	0.43	0.43
	S.D.	0.036	0.034	0.057	0.037
	N	25	24	23	24
of Male Fetuses	MEAN	0.44	0.43	0.43	0.43
	S.D.	0.033	0.036	0.043	0.045
	N	25	24	22	24
of Female Fetuses	MEAN	0.43	0.42	0.42	0.42
	S.D.	0.043	0.033	0.059	0.036
	N	25	24	23	24
AG DISTANCE UNITS, MM					
of all Viable Fetuses	MEAN	1.7	1.7	1.6	1.6
	S.D.	0.22	0.29	0.17	0.18
	N	25	24	22	24
of Male Fetuses	MEAN	2.3	2.2	2.10	2.00
	S.D.	0.09	0.11	0.10	0.10
	N	25	24	22	24
of Female Fetuses	MEAN	1.0	1.0	1.0	1.0
	S.D.	0.08	0.06	0.09	0.08
	N	25	23	22	24
AG INDEX					
of all Viable Fetuses	MEAN	0.43	0.44	0.43	0.43
	S.D.	0.053	0.069	0.053	0.049
	N	25	24	22	24
of Male Fetuses	MEAN	0.58	0.59	0.54a	0.526
	S.D.	0.033	0.048	0.050	0.035
	N	25	24	22	24
of Female Fetuses	MEAN	0.27	0.28	0.28	0.28
	S.D.	0.024	0.029	0.032	0.028
	N	25	23	22	24

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05, b = P<0.01.

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PROJECT NO. 34R0375/88074: PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF FETAL SOFT TISSUE VARIATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Litters Evaluated	N	25	24	22	24
Fetuses Evaluated	N	166	176	159	175
Live	N	166	175	159	175
Dead	N	0	0	0	0
DILATED RENAL PELVIS					
Fetal Incidence	N	33	42	39	[illegible]
	%	19.9	24.0	24.5	[illegible]
Litter Incidence	N	16	21	15	[illegible]
	%	64.0	87.5	68.2	[illegible]
HYDROURETER					
Fetal Incidence	N	9	10	10	[illegible]
	%	5.4	5.7	6.3	[illegible]
Litter Incidence	N	6	7	6	[illegible]
	%	24.0	29.2	27.3	[illegible]
TOTAL FETAL SOFT TISSUE VARIATIONS					
Fetal Incidence	N	34	42	40	[illegible]
	%	20.5	24.0	25.2	[illegible]
Litter Incidence	N	16	21	15	[illegible]
	%	64.0	87.5	68.2	[illegible]

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05, ** = P<0.01.

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PROJECT NO. 34R0375/88074: PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF ALL CLASSIFIED FETAL SKELETAL OBSERVATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Litters Evaluated	N	25	24	23	24
Fetuses Evaluated	N	175	184	172	191
Live	N	175	184	172	191
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	6	6	12	13
	%	3.4	3.3	7.0	6.8
Litter Incidence	N	5	5	10	10
	%	20.0	20.8	43.5	41.7
Affected Fetuses/Litter	MEAN%	3.3	3.1	6.6	6.9
	S.D.	7.73	6.69	8.32	9.86
TOTAL VARIATIONS					
Fetal Incidence	N	57	62	60	53
	%	32.6	33.7	34.9	27.7
Litter Incidence	N	21	23	21	21
	%	84.0	95.8	91.3	87.5
Affected Fetuses/Litter	MEAN%	33.4	34.1	37.3	28.5
	S.D.	21.61	21.56	22.51	19.91
TOTAL RETARDATIONS					
Fetal Incidence	N	55	80a	78b	66
	%	31.4	43.5	45.3	34.6
Litter Incidence	N	19	23	20	20
	%	76.0	95.8	87.0	83.3
Affected Fetuses/Litter	MEAN%	30.9	43.4	42.2	34.7
	S.D.	24.47	28.67	27.85	27.51

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01

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PROJECT NO. 34R0375/88074; PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF FETAL SKELETAL RETARDATIONS

		TEST GROUP 0 CONTROL CMC	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Litters Evaluated	N	25	24	23	24
Fetuses Evaluated	N	175	184	172	191
Live	N	175	184	172	191
Dead	N	0	0	0	0
STERNEBRA(E) INCOMPLETELY OSSIFIED OR REDUCED IN SIZE					
Fetal Incidence	N	28	38	41	23
	%	16.0	20.7	23.8	12.0
Litter Incidence	N	14	19	16	12
	%	56.0	79.2	69.6	50.0
STERNEBRA(E)-ONLY ONE OSSIFICATION CENTER					
Fetal Incidence	N	17	27	28	17
	%	9.7	14.7	16.3	8.9
Litter Incidence	N	11	17	18a	11
	%	44.0	70.8	78.3	45.8
METACARPAL BONES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	4.3	0.0
METATARSAL BONES INCOMPLETELY OSSIFIED					
Fetal Incidence	N	0	0	1	0
	%	0.0	0.0	0.6	0.0
Litter Incidence	N	0	0	1	0
	%	0.0	0.0	4.3	0.0
TOTAL FETAL SKELETAL RETARDATIONS					
Fetal Incidence	N	55	80a	78b	66
	%	31.4	43.5	45.3	34.6
Litter Incidence	N	19	23	20	20
	%	76.0	95.8	87.0	83.3

SIGNIFICANTLY DIFFERENT FROM CONTROL; a = P<0.05; b = P<0.01.

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TABLE 036

PROJECT NO. 34R0375/88074: PRENATAL TOXICITY STUDY IN RATS
DERMAL APPLICATION
SUMMARY OF ALL CLASSIFIED FETAL EXTERNAL, SOFT TISSUE, AND SKELETAL OBSERVATIONS

		TEST GROUP 0 CONTROL (MC)	TEST GROUP 1 60 MG/KG BW/DAY	TEST GROUP 2 180 MG/KG BW/DAY	TEST GROUP 3 360 MG/KG BW/DAY
Litters Evaluated	N	25	24	23	24
Fetuses Evaluated	N	341	359	331	366
Live	N	341	359	331	366
Dead	N	0	0	0	0
TOTAL MALFORMATIONS					
Fetal Incidence	N	6	7	12	11
	%	1.8	1.9	3.6	3.6
Litter Incidence	N	5	6	10	10
	%	20.0	25.0	43.5	41.7
Affected Fetuses/Litter	MEAN%	1.7	2.0	3.5	3.6
	S.D.	4.12	3.76	4.37	5.17
TOTAL VARIATIONS					
Fetal Incidence	N	91	104	100	106
	%	26.7	29.0	30.2	29.0
Litter Incidence	N	24	23	23	24
	%	96.0	95.8	100.0	100.0
Affected Fetuses/Litter	MEAN%	27.1	29.4	32.5	29.4
	S.D.	15.85	14.39	19.84	13.40
TOTAL RETARDATIONS					
Fetal Incidence	N	55	80a	78a	66
	%	16.1	22.3	23.6	18.0
Litter Incidence	N	19	23	20	20
	%	76.0	95.8	87.0	83.3
Affected Fetuses/Litter	MEAN%	15.9	22.2	21.8	18.7
	S.D.	12.74	14.76	14.35	14.55

SIGNIFICANTLY DIFFERENT FROM CONTROL: a = P<0.05; b = P<0.01.

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