DATA EVALUATION REPORT

ZIRAM

Study Type: DEVELOPMENTAL ▩ RAT (83-3)

20

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

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Task Order No. 94-43I

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DATA EVALUATION REPORT

STUDY TYPE: Developmental ☒ Rat (83-3)

TOX. CHEM. NO: 931

P.C. CODE: 034805

MRID NO: 41908701

TEST MATERIAL: Ziram

SYNONYMS: zinc dimethyldithiocarbamate

STUDY NUMBER(S): ZIR 15/24/891371

SPONSOR: Ziram Task Force, Consortium No. 62405, c/o UCB Chemicals Corporation, 5505-A Robin Hood Road, Norfolk, Virginia 23513

TESTING FACILITY: Huntingdon Research Centre, Ltd., P.O. Box 2, Huntingdon, Cambridgeshire, PE18 6ES England

TITLE OF REPORT: A Study of the Effect of Ziram on Pregnancy of the Rat

AUTHORS: Janet A. Smith, Andrew M. Bryson, David M. John, and Alan Anderson

REPORT ISSUED: June 11, 1990 (final report date)

EXECUTIVE SUMMARY: Presumed pregnant Crl:CD® (SD) BR VAF/Plus rats, randomly assigned to one control and four treatment groups of 25 animals each, were administered Ziram by gavage at doses of 0, 1, 4, 16, or 64 mg/kg on gestation days (GD) 6-15 inclusive. Cesarean section examinations were performed on all surviving dams on GD 20, followed by external examination of all fetuses. Approximately one-half of each litter was examined for visceral anomalies and the remainder was fixed and stained for skeletal examinations. There were at least 22 pregnant animals per group.

All animals survived to terminal sacrifice on GD 20. Post-dosing salivation, generally during the last few days of dosing, was associated with treatment at 16 mg/kg in 2 of 25 animals and at 64 mg/kg in 9 of 25 animals. Generalized hair loss occurred in 2/25 control and 6/25 high- dose animals. No

clinical signs were associated with treatment with 1 or 4 mg/kg/day. Significantly ($p \leq 0.05$) reduced body weights (approximately 92% of control) occurred in the 64 mg/kg/day group as compared to controls during the treatment interval and continuing until sacrifice. The 16 mg/kg group also had significantly ($p \leq 0.05$) reduced mean body weight (94%) as compared to the control group during the treatment period; however, recovery occurred after treatment ended. Mean food consumption was significantly ($p \leq 0.01$) decreased in the 16 and 64 mg/kg groups as compared to controls beginning with GD 6-7 during the treatment interval and continuing to GD 16-17 for the high dose-group. In contrast, water consumption was significantly ($p \leq 0.01$) increased in the 16 and 64 mg/kg groups during the treatment period as compared to the control group. Water intake continued to be greater ($p \leq 0.05$) than controls for these two groups after the treatment interval but returned to the control level on the last day of the study. **Therefore, the maternal toxicity LOAEL is 16 mg/kg/day based on decreased body weights, reduced food consumption, salivation, and increased water intake during the treatment interval and the maternal toxicity NOAEL is 4 mg/kg/day.**

Mean fetal body weights of the high-dose litters were significantly ($p \leq 0.01$) lower than controls (89%). There were no differences between treated and control groups for number of fetuses per litter, implantations per dam, number of resorptions per dam, or fetal sex ratios, and there were no dams with whole litter resorption. Overall, there was no significant difference or dose-related trend in the number of treated litters affected as compared to control when the incidences of external, visceral, and skeletal malformations/ variations were combined. The number of litters affected in the control, 1, 4, 16, and 64 mg/kg groups was 13 of 23, 9 of 24, 8 of 22, 19 of 23, and 11 of 24, respectively. No treatment-related external or skeletal malformations/variations were seen in any fetuses from any group. However, there was a dose-related increase in the incidence of diaphragmatic lesions. The incidence of thinning of the diaphragm with protrusion of the liver occurred in 0/23, 0/24, 1/22, 4/23, and 6/24 ($p \leq 0.05$) litters in the 0, 1, 4, 16, and 64 mg/kg groups, respectively. **Therefore, the developmental toxicity LOAEL is 16 mg/kg/day based on diaphragmatic thinning, and the developmental toxicity NOAEL is 4 mg/kg/day.**

Classification: Acceptable/Guideline

This study satisfies the guideline requirement for a developmental toxicity study (83-3) in rats.

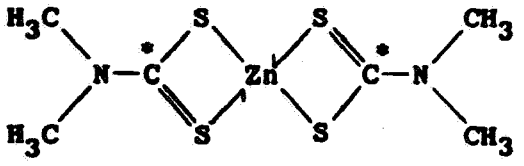
Special Review Criteria: (40 CFR 154.7) None

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Ziram

Description: white powder
Lot/Batch No.: 8331 AA
Purity: 98.9% a.i.
Stability of compound: known by sponsor to be stable for the duration of the study
CAS No.: 137-30-4
Structure:



2. Vehicle and/or positive control

A 1% aqueous solution of methylcellulose was used as the dosing vehicle and negative control. No positive control was used.

3. Test animals

Species: rat
Strain: Sprague-Dawley (Crl:CD® BR VAF/Plus)
Age and weight at study initiation: 8-10 weeks; 161-218 g on day 2 of pregnancy
Source: Charles River, Portage, Michigan
Housing: Rats were housed 5/cage in suspended galvanized metal cages.
Diet: Animals were given Labsure Laboratory Animal Diet No. 1 and tap water *ad libitum*.
Environmental conditions:
Temperature: 21 ± 2°C
Humidity: 55 ± 4%
Air changes: not given
Photoperiod: 12 hour light/dark
Acclimation period: none

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of Ziram when administered by gavage to rats on gestation days 6 through 15, inclusive.

1. Mating

Animals were mated to males of the same strain while at the supplier. The day sperm were present in the vaginal smear or the presence of a vaginal plug was observed, was designated as gestation day (GD) 0.

2. Animal assignment and dose selection is presented in Table 1. Animals were assigned to treatment groups by computerized stratified randomization of body weights on GD 2.

TABLE 1. Animal Assignmnet

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control	0	25
Low Dose	1	25
Mid-1 Dose	4	25
Mid-2 Dose	16	25
High Dose	64	25

Data taken from page 16, MRID No. 419087-01.

3. Dose selection rationale

Doses were based on a preliminary study (data included with MRID No. 419087-01) in which doses of 0, 5, 20 or 80 mg Ziram/kg were administered by gavage to rats on GD 6-15, inclusive. At 20 and 80 mg/kg/day, dams had post-dosing salivation (80 mg/kg only), hair loss, increased water and decreased food consumption, reduced body weight gain, increased postimplantation loss, and ▒small foetuses▒ with reduced fetal body weights. Increased water consumption, slight reduced feed intake, and slightly reduced body weight gain occurred at 5 mg/kg. No gross structural abnormalities were observed in any fetuses from any group. Therefore, based on maternal toxicity, doses for the main study were chosen at 1, 4, 16, and 64 mg/kg/day. See Appendix A for additional details on the range-finding study.

4. Dosing

All doses were in a volume of 0.1 mL/100 g of body weight/day prepared daily during the dosing period. Dosing was based on individual body weight on gestation days 6, 8, 10, 12 and 14.

5. Dose solution preparation and analysis

The high-dose concentration was prepared by suspension of a weighed amount of test article in 1% aqueous methylcellulose. Lower concentrations were prepared by serial dilution. The dosing solutions were analyzed for concentration on day 2 of dosing and the analysis showed all dosing solutions to be within 9% of nominal. Absence of test article was confirmed in the vehicle. Concentrations of 1 and 80 mg/mL were tested for physical (homogeneity) and chemical stability. The data show that homogeneity could be maintained by magnetic stirring and that the formulations could be successfully resuspended after 4 hours at room temperature or 24 hours at 4°C; all values from the top, middle, or bottom were within 6% of nominal. The chemical was stable in 1% methylcellulose during storage at room temperature in the dark for 4 hours or at 4°C for 24 hours with all measured values within 4% of nominal.

C. OBSERVATIONS

1. Maternal observations and evaluations

The animals were checked for mortality or clinical signs once daily. All animals were weighed on GD 2, 3, 6, 8, 10, 12, 14, 16, 18, and 20. Water consumption was measured daily on GD 2-20 and food consumption was measured on each day body weights were taken. Dams were sacrificed by CO_2 asphyxiation on GD 20 and examined grossly. Any abnormal tissues were preserved for histological examination. Ovaries and uteri were examined to determine the number of corpora lutea and number and distribution of live and dead fetuses. Uteri that appeared not pregnant were stained in 10% ammonium sulfide to visualize implantation sites.

2. Fetal evaluations

Live fetuses were weighed, tagged, and examined for external abnormalities. One half of each litter was preserved in Bouin's solution for subsequent visceral examination and the remainder fixed in 74 OP industrial methylated spirit for subsequent staining for skeletal examination. All fetuses were sexed by gonadal inspection following preservation.

3. Historical control data were not provided to allow comparison with concurrent controls.

D. STATISTICAL ANALYSIS

Analysis of variance, followed by Williams' test were used for assessing intergroup differences in absolute values for mean water and food consumption and body weight during gestation. Mean values of litter size, pre- and postimplantation losses, litter weight, mean pup weight, sex ratio, and the abnormality incidence rate were analyzed by the Kruskal-Wallis test. Intergroup comparisons were made by the non-parametric equivalent of the `t' test together with the Jonckheere test for an ordered series of treatments. Where 75% of the values for a given variable consisted of one value, a Fisher's exact test was used.

E. COMPLIANCE

Signed and dated GLP and quality assurance statements were present.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality

All animals survived to terminal sacrifice on GD 20.

2. Clinical observations

Post-dosing salivation, generally during the last few days of dosing, was associated with treatment at 64 mg/kg in 9 of 25 animals and at 16 mg/kg in 2 of 25 animals. Generalized hair loss occurred in 2/25 control and 6/25 high-dose animals. No clinical signs were associated with treatment at 1 or 4 mg/kg.

3. Body weight

Selected group mean maternal body weights are listed in Table 2. Significantly ($p \leq 0.05$) reduced body weights occurred in the 64 mg/kg group as compared to controls during the treatment interval and continuing until sacrifice. The 16 mg/kg group also had significantly ($p \leq 0.05$) reduced mean body weight as compared to the control group on GD 14 of the treatment period.

TABLE 2. Mean maternal body weights (grams)					
Day of Gestation	0 mg/kg	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
6	219.3 ± 10.1	220.8 ± 11.0	220.0 ± 11.3	219.1 ± 11.4	218.3 ± 10.1
10	242.7 ± 14.0	244.1 ± 13.7	243.9 ± 14.0	231.5 ± 12.0	224.9 ± 10.2*
14	269.0 ± 15.2	270.0 ± 16.4	267.0 ± 18.4	253.6 ± 13.3*	245.8 ± 12.5*
18	312.4 ± 17.5	313.2 ± 22.8	313.1 ± 22.8	299.4 ± 16.8	282.9 ± 15.2*
20	341.7 ± 21.9	340.4 ± 28.2	343.1 ± 28.2	328.7 ± 19.6	315.3 ± 18.1*

Data calculated by reviewer from individual body weights, Appendix 4, pages 54-58, MRID No. 419087-01.
*Significantly different from control, $p \leq 0.05$; calculated by reviewer using the ANOVA with Scheffe's test to separate means.

4. Food consumption

Food and water consumption data are summarized in Table 3. Mean food consumption was significantly ($p \leq 0.01$) decreased in the 16 and 64 mg/kg groups as compared to controls during the treatment interval and continuing to GD 16-17 for the high dose-group. Recovery was seen in both of these groups after treatment ended. In contrast, water consumption was significantly ($p \leq 0.01$) increased in the 16 and 64 mg/kg groups during the treatment period as compared to the control group. Water intake continued to be greater ($p \leq 0.05$) than controls for these two groups after the treatment interval until GD 16-17.

TABLE 3. Food and water consumption data (g/rat/day)					
Days of Gestation	0 mg/kg	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
	Food Consumption				
3-5	23.1	23.6	22.4	22.8	22.9
6-7	24.8	24.2	23.5	17.4**	14.1**
8-9	25.2	24.9	24.0	20.0**	17.3**
10-11	25.7	26.2	25.1	22.0**	18.8**
12-13	26.4	28.7	25.3	22.9**	19.6**
14-15	27.7	28.5	26.5	24.0**	20.7**
16-17	29.3	30.2	29.2	28.3	26.2**
18-19	29.6	29.3	28.6	28.6	28.1
	Water Consumption				
3-5	28.5	29.3	28.7	29.5	28.4
6-7	29.8	30.1	33.6	41.2**	43.5**
8-9	29.9	30.5	33.2	44.7**	49.2**
10-11	32.0	34.4	36.9	45.2**	47.7**
12-13	33.9	36.0	38.0	51.2**	43.2**
14-15	37.1	38.4	41.1	48.1**	47.6**
16-17	40.1	44.0	43.2	45.2*	43.8*
18-19	40.5	43.8	43.1	43.9	44.7

Data taken from Tables 2 and 3, pages 34 and 35, respectively, MRID No. 419087-01.
*Significantly different from control, $p \leq 0.05$.
**Significantly different from control, $p \leq 0.01$.

5. Gross pathology

No treatment-related gross abnormalities were seen at necropsy in any animal from any group.

6. Cesarean section data

Data for the observations made at cesarean section are listed in Table 4. There was a dose-related decrease in mean fetal body weights. Fetal weights of the high-dose litters were significantly ($p \leq 0.01$) lower than those of controls. However, there were no differences between treated and control groups for number of fetuses per litter, implantations per dam, number of resorptions per dam, or fetal sex ratios. There were no dams with whole litter resorption.

TABLE 4. Cesarean section observations					
Observation	0 mg/kg	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
No. Animals Assigned	25	25	25	25	25
No. Animals Pregnant	23	24	22	23	24
Pregnancy Rate (%)	92	96	88	92	96
Maternal Mortality	0	0	0	0	0
No. Aborted	0	0	0	0	0
No. Premature Delivery	0	0	0	0	0
Corpora Lutea/Dam	13.2	12.9	13.1	13.1	12.4
Implantation/Dam	11.9	11.4	11.9	12.2	11.8
Total Live Fetuses	261	255	253	266	272
Live Fetuses/Dam	11.3	10.6	11.5	11.6	11.3
Mean Fetal Weight (gm)	3.35	3.29	3.28	3.20	2.98**
Sex Ratio (% Male)	48.1	57.6	50.1	51.7	50.0
Dams with Whole Litter Resorption	0	0	0	0	0
Resorptions/Dam	0.5	0.8	0.4	0.6	0.5
Early	0.4	0.7	0.4	0.6	0.4
Late	0.1	0.1	0	0	0.1
Preimplantaion Loss (%)	9.6	11.5	9.0	6.5	4.9
Postimplantation Loss (%)	4.7	7.6	3.4	5.1	3.7

Data taken from Tables 1, 5, and 6, pages 33, 38, and 39, respectively, MRID No. 419087-01.
**Significantly different from control, $p \leq 0.01$.

B. DEVELOPMENTAL TOXICITY

There was no significant difference or dose-related trend apparent in the number of treated litters affected as compared to control when the incidences of external, visceral, and skeletal malformations/variations were combined. The number of litters affected in the control, 1, 4, 16, and 64 mg/kg groups was 13 of 23, 9 of 24, 8 of 22, 19 of 23, and 11 of 24, respectively. However, when visceral malformations/variations are examined separately, a significantly greater number of high-dose litters contained fetuses with thinning of the diaphragm: 6 of 24 vs. 0 of 23 controls.

1. External examination

No treatment-related external malformations/variations were seen in fetuses from any group. One fetus in one control litter had a subcutaneous hemorrhage of the left pinna. In the high-dose group, one fetus in each of two litters had a subcutaneous hemorrhage (nasal and dorsocervical regions, respectively) and another fetus in a third litter had an umbilical hernia. No other external anomalies were observed.

2. Visceral examination

Selected visceral malformations/variations are listed in Table 5a. A significantly ($p \leq 0.05$) greater number of litters in the 16 mg/kg group were affected as compared to controls: 16 of 23 versus 9 of 23, respectively. This was mainly due to the incidence rates of brain/eye hemorrhage and renal dilation, however, a dose-related trend was not apparent. There was a dose-related trend in the incidence of diaphragmatic lesions. The incidence of thinning of the diaphragm with protrusion of the liver occurred in 0/23, 0/24, 1/22, 4/23, and 6/24 ($p \leq 0.05$) litters in the 0, 1, 4, 16, and 64 mg/kg groups, respectively. The incidences at 16 and 64 mg/kg/day were outside the historical control range (1 fetus in 1 litter in a total of 7 studies). One fetus from a 1 mg/kg group litter had numerous malformations.

3. Skeletal examination

Selected skeletal malformations/variations are listed in Table 5b. There were no significant differences between treated and control groups for any observation.

TABLE 5a. Selected visceral malformations/variations

Observations	0 mg/kg	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
No. Pups (litters) examined	130 (23)	127 (24)	124 (22)	134 (23)	138 (24)
No. Pups (liters) affected	10 (9)	8 (7)	8 (7)	21 (16)*	18 (11)
Cardiac/Arterial abnormality	3 (3)	1 (1)	2 (2)	3 (3)	2 (2)
Brain/Eye hemorrhage	2 (2)	0 (0)	1 (1)	7 (7)	5 (4)
Testes displacement	2 (2)	0 (0)	0 (0)	1 (1)	0 (0)
Dilation of renal pelvis	2 (2)	6 (5)	3 (3)	6 (6)	3 (3)
Microphthalmia	0 (0)	1 (1)	0 (0)	0 (0)	3 (3)
Diaphragmatic thinning with protrusion of liver	0 (0)	0 (0)	1 (1)	5 (4)	6 (6)*
Diaphragmatic hernia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)

Data taken from Appendix 8, pages 74-97, MRID No. 419087-01.
*Litter incidence significantly different from control, $p \leq 0.05$; calculated by reviewer using Fisher's Exact Test.

TABLE 5b. Selected skeletal malformations/variations

Observations	0 mg/kg	1 mg/kg	4 mg/kg	16 mg/kg	64 mg/kg
No. Pups (litters) examined	131 (23)	128 (24)	129 (22)	132 (23)	134 (24)
No. Pups (liters) affected	8 (7)	5 (4)	5 (5)	10 (8)	3 (2)
Skull - reduced ossification	3 (3)	4 (4)	3 (3)	6 (5)	2 (1)
Skull - fused	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Ribs - fused	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Sternebrae - fused/misshapen	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Vertebrae - misshapen	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)
Vertebrae - 1 or 2 less	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Pelvic girdle - not ossified or asymmetric	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)

Data taken from Appendix 8, pages 74-97, MRID No. 419087-01.

III. DISCUSSION

A. MATERNAL TOXICITY

Clinical signs such as post-dosing salivation generally during the last few days of dosing, were associated with treatment at 16 mg/kg in 2 of 25 animals and at 64 mg/kg in 9 of 25 animals. No clinical signs were associated with treatment with 1 or 4 mg/kg/day.

The study authors analyzed body weight data by analysis of covariance using GD 6 body weights as the covariate. By this method, statistical significance was reached in the 16 and 64 mg/kg groups from GD 8 until GD 20. The results presented by the reviewer, analyzed by the analysis of variance, differ in that significantly lower body weights occurred in the 16 mg/kg group only on GD 14 during the treatment interval. However, neither statistical method changes the conclusions or NOAEL/LOAEL of the study. Reduced body weights correlated with significantly ($p \leq 0.01$) decreased food consumption in the 16 and 64 mg/kg groups during the treatment interval and continuing to GD 16-17 for the high dose-group. In contrast, water consumption was significantly ($p \leq 0.01$) increased in the 16 and 64 mg/kg groups during the treatment period as compared to the control group. The increased water consumption may be due to the irritating properties of the chemical. In a chronic feeding/oncogenicity study with Ziram in rats (MRID No. 434042-01), a dose-related incidence of depressions, raised areas, thickening, and white discolorations of the forestomach were accompanied by epithelial hyperplasia, edema, and ulceration. Although no gross lesions of the stomach were reported in the current study, the shorter duration of exposure (10 days versus 104 weeks) may not have allowed enough time for obvious lesions to develop.

B. DEVELOPMENTAL TOXICITY

1. Deaths/resorptions

No dead fetuses were reported in any group. There were no differences between treated and control groups in the number of fetuses per dam or resorptions per dam.

2. Altered growth

Fetuses in the high-dose group had significantly ($p \leq 0.01$) lower mean body weights than controls. No other effects, such as general reductions in ossification, indicated delayed development of the fetuses. The reduction in fetal body weights could be a result of maternal toxicity.

3. Developmental malformations/variations

The dose-related incidence of diaphragmatic thinning/hernia is considered due to treatment with Ziram but the mechanism is unknown. It is possible that the two lesions are a continuum of the same malformation/variation. At the high dose, there is a discrepancy between the reviewer and the study summary table 8b (page 42) in the number of fetuses/litters affected with diaphragmatic thinning. For this Data Evaluation Record, the reviewer calculated all incidence rates from the individual animal data and found 6 fetuses in 6 litters. However, the study authors only report 5 fetuses in 5 litters. This reviewer could find no reason for the omission on the study summary table.

The highest overall litter incidence rate for external, visceral, and skeletal malformations/variations occurred in the 16 mg/kg group and cannot be explained. Since there is a lack of a dose-response, this is most likely an artifact or possibly caused by metabolic saturation at the highest dose.

C. STUDY DEFICIENCIES

Gravid uterine weights were not measured. Maternal body weight data were analyzed by the study authors using analysis of covariance based on GD 6 weight as the covariate. The reviewer was not comfortable with this type of analysis for body weights and reanalyzed the data using the analysis of variance.

The discrepancy in the number of fetuses and litters affected with thinning of the diaphragm is a mistake by the testing laboratory. Examination of the individual animal data by the reviewer and by the quality assurance person confirms that 6 fetuses in 6 high-dose litters were affected.

D. CORE CLASSIFICATION: Acceptable/Guideline

A developmental toxicity NOAEL has been assigned based on the available data.

1. Maternal NOAEL = 4 mg/kg/day
2. Maternal LOAEL = 16 mg/kg/day based on decreased body weights, reduced food consumption, and increased water intake during the treatment interval.
3. Developmental toxicity NOAEL = 4 mg/kg/day
4. Developmental toxicity LOAEL = 16 mg/kg/day based diaphragmatic thinning/hernia.

Appendix A

Dose range-finding study for Ziram administered by gavage to pregnant rats.

Experimental design

Doses of 0, 5, 20, and 80 mg Ziram/kg were administered by gavage to 10 pregnant rats/group on GD 6-15, inclusive. Dams were observed daily for signs of toxicity and food consumption and body weights measured on GD 4, 6, 8, 10, 12, 14, 16, 18, and 20. Water consumption was measured daily beginning on GD 8. On GD 20 animals were killed by CO_2 asphyxiation and examined grossly. Ovaries and uteri were examined for number of corpora lutea and number of live and dead fetuses. Uteri from animals that appeared not pregnant were stained with ammonium sulphide to reveal implantation sites. Fetuses were weighed and examined for external malformations/variations.

Results

Maternal

Note: Statistical analyses were not performed by the study authors on maternal toxicity parameters. Percentages have been calculated by the reviewer to determine the magnitude of difference between the treated groups and the control.

Post-dosing salivation was observed in 9/10 females in the high-dose group on days 13 and/or 14. Generalized hair loss affected 0, 1, 5, and 5 animals in the control, 5, 20, and 80 mg/kg groups, respectively from about day 14 until termination. Water consumption during the treatment interval was increased by 121-138% in the low-dose group, by 125-160% in the mid-dose group, and by 140-172% in the high-dose group as compared to the control group. Although still higher than controls, increases in water consumption were less pronounced from GD 16-20 in the treated groups. Food consumption was decreased in the mid- and high-dose groups during the treatment interval as compared to controls: 20 mg/kg, 78-87%; 80 mg/kg, 69-88%. Body weight gains were reduced during the treatment interval up to 86% in the low-dose group, 75% in the mid-dose group, and 70% in the high-dose group of the control amount. Slight recovery occurred in all treated groups following cessation of treatment.

Litter data

At the high dose, there was an increase ($p \leq 0.05$) in postimplantation loss mainly due to an increase in early resorptions as compared to controls. However, the high-dose group also had an increase ($p \leq 0.05$) in total implantations as compared to controls so that there was no difference between groups in the number of fetuses/litter. Mean body weights of fetuses from high-dose dams were significantly ($p \leq 0.01$) less than controls which correlated with the observation by the study authors of an increased number of ▒small foetuses▒ in this group. No external malformations/variations were observed in any fetus from any group.

Appendix B (Historical Control Data)

SignOff Date:8/2/00
DP Barcode:D172447
HED DOC Number:014277
Toxicology Branch: RAB2