EPA Reviewer: John E. Whalan _____ Date: _____
Review Section I, Toxicology Branch (7509C)
EPA Section Head: Roger L. Gardner _____ Date: _____
Review Section I, Toxicology Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity - Rat (83-3a)

TOX. CHEM. NO.: 923

P.C. CODE: 088002

MRID No.: 42827904 (Main study); 42827908 (Range-finding study)

TEST MATERIAL: Zinc Omadine® 48% Aqueous Dispersion

SYNONYMS: Zinc pyrithione

STUDY NUMBER(S): 397-055 (Main study); 397-053 (Range-finding study)

SPONSOR: Olin Chemicals, the Olin Corporation, Stamford, Connecticut

TESTING FACILITY: International Research and Development Corporation, 500 North Main Street, Mattawan, Michigan 49071

TITLE OF REPORT: Developmental Toxicity Study in Rats with Zinc Omadine®

AUTHOR: James L. Schardein

REPORT ISSUED: May 27, 1993 (Study completion date)

EXECUTIVE SUMMARY - In a developmental study (MRID 42827904), thirty pregnant Sprague-Dawley rats per group were administered Zinc Omadine by oral gavage on days 6-15 of gestation at doses of 0, 0.75, 3, or 15 mg/kg/day. One dam in the 15 mg/kg/day dose group died on gestation day 16 of unspecified causes. No maternal or developmental toxicity was observed at 0.75 mg/kg/day.

The most sensitive indicator of maternal toxicity was increased salivation immediately after dosing which was observed in the 3 and 15 mg/kg/day groups (27% and 97% of dams, respectively). Other dose-related signs seen at 15 mg/kg/day included biologically significant decreases in body weight gains (67%; $p \leq 0.01$; absolutes of 4-12%) and food consumption (24% during dosing, 16% throughout gestation; $p \leq 0.01$), and dilated pupils (57%). **The maternal toxicity NOEL is 0.75 mg/kg/day, and the maternal toxicity LOEL is 3.0**

mg/kg/day, based upon excessive salivation during the dosing period.

Developmental toxicity was characterized by a dose related increase in postimplantation loss at the mid and high doses with the 15 mg/kg/day group being significantly different than controls ($p \leq 0.01$). This correlated with an increase in early resorptions (3.6%/dam) with whole litter resorption occurring in 3 high dose dams. There was also a significant reduction ($p \leq 0.05$) in the number of live fetuses per litter (12.5/litter compared to 14.5/litter in the controls), mean fetal weights (16%), and gravid uterine weights (16%; $p \leq 0.01$) in the 15 mg/kg/day group as compared to controls.

A significantly greater number of litters in the 15 mg/kg/day group contained fetuses with external, visceral, or skeletal malformations/variations. The most common were digit anomalies (5 of 24 treated litters vs. 0 of 27 control litters; $p \leq 0.05$), dilated renal pelvis (7 of 24 treated litters vs. 1 of 27 control litters; $p \leq 0.05$) which is considered indicative of hydronephrosis, and a vertebral/rib anomaly (24 of 24 treated litters vs. 0 of 27 control litters; $p \leq 0.01$). Others included sternal, rib, and limb (radius or ulna absent) malformations. Dose-related fused ribs were observed in the mid and high-dose groups (3 fetuses/2 litters, and 5 fetuses/4 litters, respectively). Although pairwise comparisons, on the basis of litters, were not statistically significant ($p=0.226$ and $p=0.060$ for the mid and high-dose groups, respectively), a statistically significant linear trend was evident (Cochran-Armitage test; $p=0.009$), and historical control values were exceeded. **The developmental toxicity NOEL is 0.75 mg/kg/day, and the developmental toxicity LOEL is 3.0 mg/kg/day, based upon increased incidences of fused ribs.**

This study is classified **Acceptable** and satisfies the guideline requirement for a developmental study (83-3a) in rats.

Special Review Criteria (40 CFR 154.7) None

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Zinc Omadine®
   Description: off-white liquid
   Lot/Batch #: 33-22902781
   Purity: 48% solids-in-water dispersion; 52.2% a.i.
   Stability of compound: not available
   CAS No.: 13463-41-7
   Structure: not available; molecular formula: $C_{10}H_8N_2O_2S_2Zn$

2. Vehicle and/or positive control

Deionized water was used as the diluent for the treatment solutions and for dosing all control animals. No positive control was used in the study.

3. Test animals

Species: Rat
Strain: Sprague-Dawley Crl:CD® VAF/Plus®
Age and weight at study initiation: 87 days; 213 - 295 g
Source: Charles River Laboratories, Portage, Michigan
Housing: Individually housed in suspended stainless steel cages
Diet: Purina Certified Rodent Chow® #5002 and tap water were available *ad libitum*.
Environmental conditions:
Temperature: 68-71°F
Humidity: 54-76%
Air changes: not listed
Photoperiod: 12 hour light/dark
Acclimation period: 10 days

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity potential of Zinc Omadine when administered by gavage to pregnant rats on gestation days (GD) 6 through 15, inclusive. Prior to use for the study, all females were weighed and subjected to a detailed physical examination.

1. Mating

Stock males of the same source and strain were used for breeding. One female and one male were placed together for mating. Copulation was determined by daily observation for a copulatory plug. Day 0 of gestation was defined by the presence of a copulatory plug.

2. Animal assignment and doses are presented in Table 1. Animals were assigned consecutively in a block design to one control or one of three treatment groups. The order in which the mated females were assigned corresponded to the day on which the vaginal plug was observed and the order in which the animal appeared on the breeding record.

TABLE 1: ANIMAL ASSIGNMENT

Dose Group	Dose (mg/kg/day)	Number Assigned
Control	0	30
Low	0.75	30
Mid	3	30
High	15	30

3. Dose selection rationale

Dose levels were selected by the sponsor based on the results of a range-finding study (MRID No. 428279-08) conducted by the testing facility. In this study, maternal toxicity was observed as statistically significant reduced body weight gains during the dosing interval at ≥5 mg/kg/day. A summary of the range-finding study is attached as Appendix A.

4. Dosing

All doses were given in a volume of 1 ml/kg of body weight/day. Dosing was based on the most recent individual body weight recorded on GD 0, 6, 9, 12, or 16.

5. Dose solution preparation and analysis

Test material was added to the appropriate amount of deionized water and the suspension shaken by hand then stirred with a magnetic stir bar and stir plate. Concentrations were adjusted to 100% purity based on 52.2% active ingredient. The test material was received from the sponsor as a 48% solids-in-water dispersion which was analyzed by the testing facility to determine the amount of active ingredient. The dosing solutions were analyzed for concentration at weeks 1 and 2 and for stability at week 1. Fresh dosing solutions were prepared weekly. The results of the concentration and stability analyses are given in Tables B-1 and B-2 in Appendix B. All measured values were within 5% of the expected concentration.

C. OBSERVATIONS

1. Maternal observations and evaluations

Dams were checked for mortality or changes in behavior and appearance twice daily. The presence and duration of clinical signs of toxicity were recorded once daily on GD 6 - 20. Body weights and feed consumption were measured on GD 0, 6, 9, 12, 16, and 20. Dams were sacrificed on GD 20 by CO_2 inhalation. Examinations at sacrifice consisted of gravid uterine weight, location of viable and nonviable fetuses, early and late resorptions, the number of total implantations and corpora lutea, and gross examination of the abdominal and thoracic cavities. Uteri from females that appeared nongravid were opened and stained in 10% ammonium sulfide for detection of implantation sites.

2. Fetal evaluations

Individual fetuses were weighed, sexed, and examined for external malformations and variations. One-half of the fetuses were placed in Bouin's solution for visceral examinations and the remainder fixed in alcohol for skeletal staining and examina-tions.

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

D. STATISTICAL ANALYSIS

Mean maternal body weights, body weight changes and food consumption, mean numbers of corpora lutea, total implantations, live fetuses and mean fetal body weights were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variance and the appropriate t-test using Dunnett's multiple comparison tables or pairwise comparisons with a Bonferroni correction to determine the significance of differences. Male and female sex ratios and the proportions of litters with malformations and developmental variations were compared using the Chi-square test for homogeneity of R×C contingency tables and/or Fisher's exact test. The proportion of resorbed and dead fetuses and postimplantation losses were compared using the Kruskal-Wallis test. The levels of significance were set at $p \leq 0.05$ and $p \leq 0.01$.

E. COMPLIANCE

Signed and dated GLP and Quality Assurance statements were provided.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality

One dam in the 15 mg/kg/day dose group died on GD 16. All other animals survived until scheduled sacrifice on GD 20.

2. Clinical Observations

A significantly ($p \leq 0.01$) greater number of animals in the 3 and 15 mg/kg/day groups had increased salivation that occurred immediately after dosing with 8 of 30 (27%) and 29 of 30 (97%) affected, respectively compared to 0 of 30 controls affected. Dilated pupils were observed in 17 (57%) of the high dose animals both before and after dosing, and persisted beyond the end of the treatment period in 8 animals. Clinical signs observed

in the one high-dose animal that died on day 16 included excess salivation, hair loss, and yellow staining on the ventral thorax and abdomen.

3. Body Weight

There were significant ($p \leq 0.01$), reductions in body weight gain of 22% and 67% during the treatment period for the 3 and 15 mg/kg/day groups, respectively, as compared to controls. Considering that absolute body weights for these groups deviated from control values by 0-2% and 4-12% during the treatment period, only the high-dose weight changes can be considered biologically significant.

The high dose animals continued to have significantly lower weight gains ($p \leq 0.05$) for the remainder of the study with overall body weight gain for the entire gestation period decreased 30% compared to the control group. The corrected weight change (final body weight gain minus gravid uterine weight) for the entire gestational period was also reduced ($p \leq 0.01$) in the 15 mg/kg/day group (37%). These data are presented in Table 2. Overall mean body weights were significantly ($p \leq 0.01$) decreased for the high dose animals as compared to controls beginning on GD 12 (Table B - 3, Appendix B).

TABLE 2: BODY WEIGHT GAINS (g)

Group (mg/kg/d)	GD 0-6	GD 6-16	GD 16-20	GD 0-20	Corrected Body Weight Gains[a] (GD 0-20)
0	35 ± 6.9	51 ± 9.8	63 ± 7.0	148 ± 14.9	67 ± 12.8
0.75	36 ± 7.0	46 ± 11.3	66 ± 12.5	148 ± 25.4	66 ± 12.6
3.0	37 ± 7.4	40 ± 13.0**	62 ± 12.3	138 ± 25.0	65 ± 16.5
15.0	36 ± 7.7	17 ± 14.6**	51 ± 19.4*	103 ± 27.6**	42 ± 17.7**

Data taken from Table 5, p. 37, MRID No. 428279-04.
[a] Corrected body weight gain = body weight gain minus gravid uterine weight.
* Significantly different from control, $p \leq 0.05$.
** Significantly different from control, $p \leq 0.01$.

4. Food consumption

Food consumption data are summarized in Table 3. Food consumption was significantly ($p \leq 0.01$) reduced in the 15 mg/kg/day animals during the treatment period (24%) and throughout gestation (16%) as compared to controls.

TABLE 3: FOOD CONSUMPTION (g/animal/day)

Group (mg/kg/d)	GD 0-6	GD 6-16	GD 16-20	GD 0-20
0	23.3 ± 3.51	24.0 ± 2.17	27.2 ± 2.46	24.4 ± 2.20
0.75	22.3 ± 2.35	23.4 ± 2.17	26.7 ± 2.68	23.7 ± 2.13
3.0	22.3 ± 2.23	23.2 ± 1.80	26.6 ± 2.14	23.6 ± 1.55
15.0	21.8 ± 2.55	18.2 ± 2.01*	24.8 ± 3.91	20.6 ± 1.76*

Data taken from Table 6, p. 39, MRID No. 428279-04.
*Significantly different from control, $p \leq 0.01$.

5. Gross pathology

No gross pathologic findings correlated with treatment. A consolidated mass in the intestinal mesentery was observed in one control, one 3 mg/kg/day, and two 15 mg/kg/day rats. Another high-dose rat had black, pinpoint foci on the liver.

6. Cesarean section data

Cesarean section observations are summarized in Table 4. There was a dose related increase in postimplantation loss at the mid and high dose with the 15 mg/kg/day group significantly ($p \leq 0.01$) different than controls. This was due to an increase in early resorptions with whole litter resorption occurring in 3 high dose animals. The number of live fetuses per litter was significantly ($p \leq 0.05$) reduced at the 15 mg/kg/day dose level (12.5 live fetuses per litter, as compared to 14.5 for the controls).

Mean fetal weights and gravid uterine weights were both reduced 16% in the high dose animals as compared to control ($p \leq 0.01$). Although not statistically significant, gravid uterine weights were also reduced by 10% at the 3.0 mg/kg/day dose level, compared to controls.

TABLE 4: CESAREAN SECTION OBSERVATIONS

Observation	0 mg/kg/day	0.75 mg/kg/day	3.0 mg/kg/day	15 mg/kg/day
# Animals on Study	30	30	30	30
# Pregnant	27	30	25	28
Pregnancy Rate (%)	90	100	83.3	93.3
Maternal Mortality (N)	0	0	0	1
Aborted (N)	0	0	0	0
Corpora Lutea/Dam	17.2 ± 2.3	17.5 ± 3.53	17.1 ± 2.82	17.7 ± 2.39
Implantation Sites/Dam	15.3 ± 2.34	16.0 ± 3.33	15.2 ± 3.47	16.0 ± 1.74
Preimplantation Loss (%)	10.8	8.6	11.0	9.4
Postimplantation Loss (#/dam)	0.8 ± 0.96	0.8 ± 0.76	1.4 ± 1.66	3.7 ± 4.88**
Postimplantation Loss (%)	5.3	5.0	9.4	22.9
Gravid Uterine Weight (g)	80.9 ± 12.0	81.9 ± 18.13	73.2 ± 18.23	67.8 ± 10.57**
Total Live Fetuses	392	457	345	350
Live Fetuses/Litter	14.5 ± 2.14	15.2 ± 3.36	13.8 ± 3.62	12.5 ± 4.80*
Mean Fetal Weight (g)	3.6 ± 0.50	3.4 ± 0.23	3.4 ± 0.34	3.0 ± 0.29**
Sex Ratio (% male)[a]	55.6	53.6	53.6	52.7
Total Dead Fetuses (N)	0	0	0	0
Dams with all resorptions (N)	0	0	0	3
Total Resorptions	22	24	36	99
Resorptions/Dam	0.8 ± 0.96	0.8 ± 0.76	1.4 ± 1.66	3.7 ± 4.88**
Early Resorptions/Dam	0.8 ± 0.96	0.8 ± 0.76	1.4 ± 1.66	3.6 ± 4.88**
Late Resorptions/Dam	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.19

Data taken from Table 7 pp. 40-42, MRID No. 428279-04.
[a] Calculated by reviewer.
N number of animals.
* Significantly different from control, $p \leq 0.05$.
** Significantly different from control, $p \leq 0.01$.

B. DEVELOPMENTAL TOXICITY

A summary of all observed malformations and variations is given in Appendix B (Tables B-4 and B-5 taken from the study report). The most commonly observed malformations/variations in this study are described below and listed in Tables 5a, 5b, and 5c.

1. External examination

External examination data are listed in Table 5a. Note that digit findings would be observed skeletally and externally. The most common malformations observed externally consisted of ectrodactyly (by far the most prevalent), syndactyly, polydactyly, and adactyly. A significantly ($p \leq 0.05$) greater incidence of ectrodactyly was observed in litters from the high-dose group (5 of 24) as compared to control litters (0 of 27). Historical control data did not list any incidence of any of the above listed findings associated with the digits. The incidences of these malformations are clearly associated with administration of the test material at the 15 mg/kg/day dose level.

2. Visceral examination

Visceral examination data are listed in Table 5b. The incidence of distended ureters and undeveloped renal papilla (apparent hydronephrosis) was significantly ($p \leq 0.05$) greater in litters from dams treated with 15 mg/kg/day as compared to litters from control animals. In addition, two litters at the 15 mg/kg/day dose level each had one dimorphic fetus. A description of the two fetuses was not included in the test report, but likely this was observed externally. Diaphragmatic hernia was noted in one fetus in each of two litters at 3.0 mg/kg/day. Since this malformation was not seen at 15 mg/kg/day, it cannot be considered a compound-related effect.

3. Skeletal Examination

The incidence of skeletal malformations/variations is summarized in Table 5c. Skeletal malformations and variations were numerous at the high dose level in this study. There was a significant ($p \leq 0.01$) increase in the total number of affected litters in the 15 mg/kg/day group as compared to controls: 24 of 24 high-dose litters were affected compared to 9 of 27 control litters.

The most common fetal malformation, which was found exclusively in the 15 mg/kg/day fetuses, was a vertebral malformation seen with or without an associated rib malformation in all 24 litters (94% of fetuses). The test report lacked a clear and detailed description of this malformation.

Also prevalent were sternal malformations including fusion (18% of fetuses), malformation (20% of fetuses), reduced ossification (13% of fetuses), and misalignment of the sternebrae (38% of fetuses); less than 13 pairs of ribs (71% of fetuses);, and 24 or 25 presacral vertebrae (24% and 47%, respectively). Fused ribs occurred in 2 mid-dose and 4 high-dose litters (3 and 5 fetuses, respectively).

TABLE 5a: SELECTED EXTERNAL FETAL MALFORMATIONS/VARIATIONS

Observation	0 mg/kg/day	0.75 mg/kg/day	3.0 mg/kg/day	15 mg/kg/day[1]
Fetuses (litters) examined	392 (27)	457 (30)	345 (25)	334 (24)
Microphthalmia		1 (1)	1 (1)	
Anophthalmia			1 (1)	
Encephalocele		1 (1)		
Short tail			1 (1)	
Carpal flexure				1 (1)
Ectrodactyly				9 (5)*
Adactyly				1 (1)
Polydactyly				1 (1)
Syndactyly				1 (1)

Data taken from Appendix B, pp. 82-102, MRID No. 428279-04.

[1] There were only a total of 5 litters affected for any of these high dose effects.

* Litter incidence significantly different from control, $p \leq 0.05$; calculated by reviewer.

TABLE 5b: SELECTED VISCERAL FETAL MALFORMATIONS/VARIATIONS

Observation	0 mg/kg/day	0.75 mg/kg/day	3.0 mg/kg/day	15 mg/kg/day
Fetuses (litters) examined	194 (27)	229 (30)	173 (25)	163 (24)
Fetuses (litters) affected	8 (6)	4 (4)	4 (4)	19 (12)*
Folded retina	1 (1)	2 (2)	1 (1)	
Malformed brain				1 (1)
Dimorphism				2 (2)
Renal hypoplasia				1 (1)
Distended ureters	7 (5)	2 (2)		16 (10)*
Renal papillae not developed	1 (1)	2 (2)		12 (7)*
Diaphragmatic hernia			2 (2)	
Anal Atresia			1 (1)	

Data taken from Appendix B, pp. 82-102, MRID No. 428279-04.
*Litter incidence significantly different from control, $p \leq 0.05$; calculated by reviewer.

TABLE 5c: SELECTED SKELETAL FETAL MALFORMATIONS/VARIATIONS

Observation	0 mg/kg/day	0.75 mg/kg/day	3.0 mg/kg/day	15 mg/kg/day
Fetuses (litters) examined	198 (27)	228 (30)	172 (25)	171 (24)
Fetuses (litters) affected	12 (9)	9 (5)	6 (5)	162 (24)*
Skull (malformed, fused)		1 (1)	2 (1)	
Fused ribs			3 (2)	5 (4)
Rib malformation				3 (3)
< 13 pairs of ribs	8 (5)	2 (2)	1 (1)	122 (22)*
Fused sternebrae				30 (14)*
Sternal malformation				35 (13)*
Sternebrae unossified: 1,2, 3, and/or 4	1 (1)	2 (2)		23 (13)*
Misaligned sternebrae: 1, 2, 3, 4, and/or 5	4 (4)	4 (2)	2 (2)	66 (24)*
24 presacral vertebrae				41 (15)*
25 presacral vertebrae	1 (1)	2 (2)		81 (22)*
Vertebral malformation w/ or w/o an associated rib malformation				153 (24)*
Limb malformation				2 (2)
Alto-occipital defect				2 (1)
Tail malformation			1 (1)	

Data taken from Appendix B pp. 82-102, MRID No. 428279-04.

* Litter incidence significantly different from control, $p \leq 0.01$; calculated by reviewer.

III. DISCUSSION

A. MATERNAL TOXICITY

The mid and high doses of Zinc Omadine in this study were sufficient to cause maternal toxicity. The most sensitive indicator, salivation, was seen in the mid and high-dose dams. Other dose-related signs seen at the high-dose included biologically significant decreases in body weight gains and food consumption, and dilated pupils. The death of one high-dose dam was attributed to treatment but no necropsy data were included to verify the cause of death. Maternal toxicity at the 3 mg/kg/day dose level was generally considered mild.

B. DEVELOPMENTAL TOXICITY

1. Deaths/Resorptions

There was a dose related increase in postimplantation loss at the mid and high dose with the 15 mg/kg/day group significantly ($p \leq 0.01$) different from controls. This correlated with an increase in early resorptions with whole litter resorption occurring in 3 high dose animals. The number of live fetuses per litter was significantly ($p \leq 0.05$) lower in the 15 mg/kg/day group and slightly lower in the 3 mg/kg/day dose group as compared to controls.

2. Altered Growth

Mean fetal weights were significantly ($p \leq 0.01$) reduced in litters from the 15 mg/kg/day group dams as compared to controls. A slight decrease in the gravid uterine weight was noted at 3.0 mg/kg/day while the difference was statistically significant ($p \leq 0.01$) at the 15 mg/kg/day dose level (see Table 4 of this review). The incidence of "renal papillae not developed" was also increased at the 15 mg/kg/day dose level. It could not be determined if it was due to maternal toxicity rather than a direct compound related effect.

3. Malformations

Ectrodactyly was observed in a significantly ($p \leq 0.05$) greater number of litters from the 15 mg/kg/day dams as compared to control dams (5 of 24 vs. 0 of 27, respectively). The authors did not consider carpal flexure seen in one high-dose litter a malformation but instead classified it as a variation. No incidence of this type of limb defect was observed in the concurrent controls or was listed in the historical control data included with the study.

The finding of fused ribs in the mid and high-dose groups is a particular cause for

concern. Although the incidences are few (3 fetuses/2 litters, and 5 fetuses/4 litters, in the mid and high-dose groups, respectively), there is a dose-relationship, and historical incidences are exceeded. The historical control data show that rib malformations (not otherwise specified) were seen in only 2 of 33 studies, with only one fetuses being affected in each study. Pairwise comparisons of the mid and high-dose groups to the control group incidences of fused ribs (on the basis of litters) were not statistically significant ($p=0.226$ and $p=0.060$ for the mid and high-dose groups, respectively). A statistically significant linear trend was evident, however (Cochran-Armitage test; $p=0.009$).

The authors cite apparent hydronephrosis as a variation. This has been described in the published literature as rapid growth of the renal parenchyma accompanied by a slow increase in renal papillary length which may result in an apparent hydronephrosis. The differentiation between real and apparent hydronephrosis is usually clarified postnatally when it is determined whether the finding resolves due to continued growth or whether it persists. The significantly ($p < 0.05$) greater number of litters affected in the 15 mg/kg/day group coupled with the statistically significant increase in the incidence of distended ureters is probably indicative of true hydronephrosis and should be considered a malformation in the absence of additional data.

4. Developmental Variations

Developmental variations were increased in this study especially at the high dose level. Variations consisted mainly of rib, vertebral, and sternebrae anomalies. Significant ($p \leq 0.01$) differences in the number of litters affected in the high dose group as compared to controls occurred for 24 and 25 presacral vertebrae, less than 13 pairs of ribs, and reduced ossification and misalignment of sternebrae (likely not a variation) and have been included as part of the malformation/variation analysis for this report.

C. STUDY DEFICIENCIES

Several findings which lack proper description by the study investigators include vertebral/rib malformations, dimorphism, sternal malformation and other findings. Although these anomalies should have been discussed, it was nevertheless possible to define a NOEL.

D. CORE CLASSIFICATION: Acceptable

1. Maternal NOEL = 0.75 mg/kg/day
2. Maternal LOEL = 3.0 mg/kg/day based on excessive salivation during dosing.

3. Developmental Toxicity NOEL = 0.75 mg/kg/day
4. Developmental Toxicity LOEL = 3.0 mg/kg/day based on increased incidence of fused ribs.
5. Increased incidences of vertebral/rib malformations, decreased live fetuses/dam, increased early resorptions, increased digit malformations, dilated renal pelvis, sternal, rib, limb (radius or ulna absent) and other malformations were observed at 15 mg/kg/day dose level.

APPENDIX A

Range-Finding Developmental Toxicity Study in Rats
with Zinc Omadine® (MRID No. 428279-08)

1. Methods

Pregnant Sprague-Dawley Crl:CD® VAF/Plus® rats (5 animals/group) were treated with Zinc Omadine by oral gavage at 0, 0.75, 2.0, 5.0, 10.0, or 15.0 mg/kg/day on gestation days 6-15 in a volume of 1 mL/kg. Dose levels were selected by the sponsor based on available data from previous studies. Animals were observed twice daily for mortality and clinical abnormalities and maternal body weights were recorded on days 0, 6, 9, 12, 16, and 20. On gestation day 20, dams were killed by CO_2 inhalation and the uterine contents examined for viable and nonviable fetuses, early and late resorptions, and the number of total implantations.

2. Results and Discussion

There was a treatment-responsive decrease in maternal weight gain beginning with the 5 mg/kg/day group. Significantly ($p \leq 0.05$) reduced weight gain occurred in the 5, 10, and 15 mg/kg/day group dams throughout the dosing period (GD 6-15) and the entire gestation period (GD 0-20) as compared to controls. Weight gains during the dosing interval were -26%, 2%, and 59% of controls for the 5, 10, and 15, mg/kg/day group dams, respectively. The excessive weight loss in the 5 mg/kg/day group is apparently due to 2 animals that lost either 35 or 41 grams during the dosing interval. Impaired hind limb function was observed in three dams at 5 mg/kg/day and in one dam at 15 mg/kg/day which the study author attributed to weight loss. Relative fetal body weight (mean gravid uterine weight divided by the mean number of viable fetuses) was reduced in the 5, 10, and 15 mg/kg/day groups as compared to control, but there were no statistically significant differences in the number of live fetuses per litter or mean uterine weights. Postimplantation loss at 15 mg/kg/day was increased slightly over historical control data. No treatment-related effects were seen on the number of viable fetuses, implantations, and corpora lutea.

Therefore, based on significant reductions in maternal body weight gains, the doses for the developmental study were chosen at 0, 0.75, 3, and 15 mg/kg/day.

3. Study Deficiencies

Dose solution concentrations were adjusted for percent purity based on a 48% solids-in-water dispersion. According to the main study, this differs from the percent active ingredient (52.2%) and the doses should have been based on the amount of active ingredient. This difference is slight, does not affect the data interpretation, and was addressed in the main study.

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APPENDIX B

Sign-off date: 08/29/96
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