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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

007054

FEB 27 1989

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metiram (Polyram)<sup>®</sup> - EPA ID No. 014601

Caswell No.: 41A  
MRID No.: 407114-00  
409310-01

FROM: George Z. Ghali, Ph.D.  
Science Analysis and Coordination Branch  
Health Effects Division (TS-769C)

*G. Ghali 2-10-89*

TO: Geraldine Werdig, PM 50  
Data Call-In Branch  
Registration Division (TS-767C)

THRU: John Quest, Ph.D. *J.A. Quest 2/21/89*  
Science Analysis and Coordination Branch  
Health Effects Division (TS-769C)

and

Reto Engler, Ph.D., Chief  
Science Analysis and Coordination Branch  
Health Effects Division (TS-769C)

Registrant: BASF Corporation  
Parsippany, NJ 07054

Action Requested

Review and evaluation of a developmental toxicity study in rabbits submitted to the Agency in response to the Data Call-In (DCI) Notice of April 1, 1987 for EBDCs.

Conclusion and Recommendations

This study was submitted by the registrant in response to the DCI Notice for EBDCs. The study was evaluated by Dynarac Corporation under EPA Contract No. 68D80056, Task No. 112-E, Dynarac Report dated January 19, 1989.

*105/16*

According to Dynamac's report, maternal toxicity was observed at 40 and 120 mg/kg. A maternal NOEL of 10 mg/kg, the lowest dose tested, was identified. A definitive assessment of the developmental toxic potential of metiram was precluded by the inadequate examination of intracranial structures in fetuses from all groups.

"The HDI produced excessive maternal toxicity and maternal abortions. Only six litters with live fetuses were available for examination at this dose level. The intracranial structures of fetuses in all dose groups were not systematically examined; only fetuses showing gross external malformations were examined intracranially. This deficiency precluded the assessment of development toxicity at all dose levels."

The study was classified as Core-Supplementary.

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CONFIDENTIAL INFORMATION  
CONFIDENTIAL INFORMATION (NO 12045)

EPA: 68D80056  
DYNAMAC No.: 112-2  
January 18, 1969

DATA EVALUATION RECORD

METIRAM

Developmental Toxicity Study in ~~Rats~~ Rabbits

STUDY IDENTIFICATION: Hellwig, J. Report on the study of the prenatal toxicity of metiram-premix 95% in rabbits after oral (gavage) administration. (Unpublished study No. 68/0154 by BASF Corporation, Parsippany, NJ; dated May 1968.) Accession No. 467114-01.

APPROVED BY:

Robert J. Weir, Ph.D.  
Program Manager  
Dynamac Corporation

Signature: William L. McLaughlin

Date: Jan 18 1969

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1. CHEMICAL: Metiram: tris[amine]ethylenebis(dithio-carbamato)]zinc[2] [tetrahydro-1,2,4,7-dithiadiazocine-3,5-dithione] polymer.
2. TEST MATERIAL: Metiram-premix 95%, technical grade, was 97.9% pure and described as a light yellow solid.
3. STUDY/ACTION TYPE: Developmental toxicity study in rabbits.
4. STUDY IDENTIFICATION: Hellwig, J. Report on the study of the prenatal toxicity of metiram-premix 95% in rabbits after oral (gavage) administration. (Unpublished study No. 88/0154 by BASF Corporation, Farsippany, NJ; dated May 1988.) Accession No. 407114-01.

5. REVIEWED BY:

Guillermo Millicovsky, Ph.D.  
Principal Reviewer  
Dynamac Corporation

Signature: Patricia TurckDate: January 18 1989

Patricia A. Turck, M.S.  
Independent Reviewer  
Dynamac Corporation

Signature: Patricia TurckDate: January 18 19896. APPROVED BY:

I. Cecil Felkner, Ph.D.  
Developmental and Reproductive  
Toxicology Studies  
Technical Quality Control  
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Signature: I. Cecil FelknerDate: 1-18-89

George Ghali, Ph.D.  
EPA Reviewer

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Reto Engler, Ph.D.  
EPA Branch Chief  
Toxicology Branch I

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity  
Guideline §83-3.

TOX CHEM. NO.:

ACCESSION NUMBER: 407114-01.

TEST MATERIAL: Metiram-premix 95%.

SYNONYMS: Tris[ammine[ethylenebis(dithiocarbamate)]zinc [2']  
[tetrahydro-1,2,4,7-dithiadiazocine-3,8-dithione] polymer.

STUDY NUMBER: 68/0154.

SPONSOR: BASF Corporation.

TESTING FACILITY: BASF Aktiengeschaft.

TITLE OF REPORT: Report on the study of the prenatal toxicity of  
metiram-premix 95% in rabbits after oral (gavage) administration.

AUTHOR(S): J. Hellwig.

REPORT ISSUED: May 1988.

CONCLUSIONS: Maternal toxicity was observed at 40 and 120 mg/kg;  
a maternal NOEL of 10 mg/kg, the lowest dose tested, was  
identified. A definitive assessment of the developmental toxic  
potential of metiram was precluded by the inadequate examination  
of intracranial structures in fetuses from all groups.

CLASSIFICATION: Core Supplementary.

A. MATERIALS

Test Compound: Purity: 97.9%  
 Description: Light yellow solid  
 Batch No.: 765  
 Contaminants: Not reported.

Vehicle(s): Double-distilled water with 0.5% carboxymethyl cellulose.

Test Animals: Species: Rabbit  
 Strain: Himalayan Chbb: HM  
 Source: Carl Thomae, FRG  
 Age: Between 34 and 44 Weeks old at gestation day (GD) 0.  
 Weight: Approximately 2700 g at GD 0.

B. STUDY DESIGN

This study was designed to assess the developmental toxicity potential of metiram-premix 95% when administered by gavage on GD 7 through 19, inclusive.

Mating: By artificial insemination. GD 0 was designated as the day of insemination.

Group Arrangement:

[Animals were randomly assigned to test groups.]

Test Group	Dose Level (mg/kg/day)	Number Assigned
Control (sham treated)	0	15
Low-dose treatment (LDT)	10	15
Mid-dose treatment (MDT)	40	15
High-dose treatment (HDT)	120	15

Dosing:

All dose suspensions were in a volume of 10 mL/kg of body weight and prepared daily during the dosing period. Results of a range-finding study were provided to support dose selection. Dosing was performed in the mornings. The dosing solutions were analyzed for concentration and stability. Dosing was based on body weight at GD 7.

Observations:

The animals were checked daily for mortality or abnormal condition throughout gestation. Food consumption was measured daily and body weights were measured every 2 or 3 days during the gestation period. Dams were sacrificed and fetuses were delivered by cesarean section on GD 29. Examinations at sacrifice consisted of:

- Gross necropsy of dams.
- Measurement of gravid uterine weight.
- Number of corpora lutea.
- Number and distribution of plantation sites.
- Numbers of early/late resorptions and dead fetuses.
- Number of live fetuses.

The fetuses were examined in the following manner:

- Fetal weights were measured.
- Fetal sex was determined.
- Fetal viability and external abnormalities were recorded.
- Condition of placental membranes/fluids was noted.
- Placental weight was measured.
- Contents of fetal thoracic and abdominal cavities were examined fresh.
- Heads of fetuses having severe external malformations were fixed in Bouin's solution and examined by Wilson's method.
- Skeletons were examined by Dawson's method.

Statistical Analysis:

The following statistical analyses were used:



- Dunnett test: food consumption, body weight/weight gain, corrected body weight gain, gravid uterine weight, placental weight, fetal weight, corpora lutea, implantations, implantation losses, resorptions, and live fetuses.
- Fisher exact test: conception rate, maternal mortality, and fetal findings.

Compliance:

- A signed Statement of Confidentiality Claim was provided.
- A signed Statement of Compliance with EPA's GLPs was provided.
- A signed Quality Assurance Statement was provided.

C. RESULTS

1. Maternal Toxicity:

Mortality: Only one female from the HDT group died during this study; this death occurred on GD 25 and was associated with apathy and abdominal distention.

Abortions: A total of 0, 0, 2, and 8 females aborted in the control, LDT, MDT, and HDT groups, respectively. The increased incidence of abortions was considered to be compound related.

Clinical Observations: A dose-related decrease in defecation that was directly associated with reduced food consumption (see below) was reported for the MDT and HDT groups. Other findings (conjunctivitis, skin lesions, and alopecia) were regarded as incidental since they occurred sporadically in all groups.

Body Weight: Significant ( $p \leq 0.01$ ) reductions in body weight were noted during the dosing and postdosing periods for the HDT group. Values for the MDT group were also reduced, but the differences were not statistically significant.

TABLE I: Body Weight Gains and Corrected Body Weight (g)<sup>a</sup>

Group	Prior to Dosing Period	Dosing Period	Post-Dosing Period	Entire Gestation Period	Corrected <sup>b</sup> Body Weight Entire Gestation Period
Control:	7.9 ± 37.4	32.4 ± 57.2	94.2 ± 53.3	134.6 ± 85.4	2584.8 ± 37.6
LDT	27.4 ± 60.8	17.1 ± 72.5	109.5 ± 75.2	153.9 ± 103.1	2542.0 ± 43.5
MDT	22.1 ± 71.1	-20.5 ± 114.5	136.1 ± 89.6	145.7 ± 191.9	2500.1 ± 207.6
HDT	18.6 ± 49.3	-161.3 ± 162.7**	157.5 ± 57.7	148.2 ± 212.0	2458.4 ± 118.0

<sup>a</sup>Data were extracted from CB: Tables 007 and 008.

<sup>b</sup>The corrected body weight gain for the entire gestation period was the body weight gain at term minus gravid uterine weight.

\*\*Significantly different from control value ( $p \leq 0.01$ ).

Prior to dosing, the maternal weight gain for controls was approximately one half that of the HDT. However, during the dosing period (statistically significant differences occurred only for the HDT group), a dose-related reduction in maternal body weight gain and a compensatory postdose increase in weight gain was noted when compared to the control group. No significant differences in corrected body weight were reported.

Food Consumption: Significant ( $p \leq 0.01$ ) reductions in food consumption were observed during the dosing and postdosing periods for the HDT group. In the LDT and MDT groups, significant ( $p \leq 0.01$ ) decreases were also noted during the dosing period. A significant ( $p \leq 0.01$ ) dose-related trend towards reduced food consumption was evident after analysis by the reviewers (Table II).

TABLE II: Food Consumption Data (g/animal/day)<sup>a</sup>

Gestation Days	Control	Group		
		LDT	MDT	HDT
0-6	109.34 ± 14.00	116.9 ± 29.17	117.5 ± 24.35	112.4 ± 23.98
7-19	89.9 ± 24.76 <sup>b**</sup>	75.7 ± 33.95 <sup>**</sup>	57.0 ± 38.79 <sup>**</sup>	34.9 ± 40.51 <sup>**</sup>
20-29	100.0 ± 25.58 <sup>b**</sup>	106.4 ± 31.08	90.8 ± 47.14	63.3 ± 64.46 <sup>**</sup>

<sup>a</sup>Data extracted from CB: Tables 001, 002, and 003. Values represent mean ± S.E.

<sup>\*\*</sup>Significantly different from controls by Kruskal-Wallis nonparametric analysis of variance ( $p \leq 0.01$ ).

<sup>b\*\*</sup>A significant negative trend with increasing dose denoted at the control by regression analysis ( $p \leq 0.01$ ).

Gross Pathological Observations: The investigators supplied the following data: several animals in the MDT and HDT groups exhibited distention of the large intestine, no feces in the rectum, and stomach filled with very hard dry food. These findings were related to reductions in food consumption and body weight. In addition, some females that aborted (and the female that died) had fatty liver degeneration. Other findings (liquid in abdominal cavity, blind-ending uterine horns, and uterine mucosal cysts) occurred sporadically among some females in all groups and, therefore, were not considered to be compound related.

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Caesarean Section Observations:TABLE III: Caesarean Section Observations<sup>a</sup>

Observations	Group			
	Control	LDT	MDT	HDT
No. animals assigned	15	15	15	15
No. animals mated	15	15	15	15
Pregnancy rate (%)	93	100	93	100
Maternal wastage				
No. died	0	0	0	1
No. died/pregnant	0	0	0	1
No. nonpregnant	1	0	1	0
No. aborted	0	0	2	8
No. premature delivery	0	0	0	0
No. animals with live fetuses	14	15	12	6
Corpora lutea/dam	7.6±1.4 <sup>b</sup>	7.5±1.0	8.0±1.4	6.5±0.8
Implantations/dam	5.5±2.0	5.8±2.1	6.4±1.1	5.3±1.9
Total live fetuses	63	75	69	26
Live fetuses/dam	4.5±2.4	5.0±2.0	5.8±1.4	4.3±1.9
Total resorptions <sup>b</sup>	14	12	8	6
Early	10	10	6	5
Late	4	2	2	1
Resorptions/dam	1.0±1.0	0.8±1.4	0.7±0.7	1.0±0.9
Total dead fetuses	0	0	0	0
Dead fetuses/dam	0	0	0	0
Mean fetal weight (g)	44.0±3.6	43.7±5.0	41.0±7.3	38.5±6.6
Preimplantation loss (%)	28.5	23.4	19.3	18.8
Postimplantation loss (%)	21.1	11.3	11.1	17.9
Sex ratio (% male)	36.8	51.2	45.9	29.2

<sup>a</sup>Data was extracted from CBI Tables 013, 014, 015, and 016.<sup>b</sup>Mean ±S.D.

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## 2. Developmental Toxicity:

### External Examinations:

TABLE IV: External Fetal Examinations<sup>a</sup>

Observations	Groups			
	Control	LDT	MOT	HDT
No. litters evaluated	14	15	12	6
No. fetuses evaluated	63	75	69	26
Pseudopyelosis (forelimb)				
No. (%) fetuses	0	1(1.3)	0	1(3.8)
No. (%) litters	0	1(6.7)	0	1(17)

<sup>a</sup>Data extracted from CB: Table 019.

No compound-related effects on external findings were noted from the above data.

### Visceral Examinations:

TABLE V: Visceral Examinations<sup>a</sup>

Observations	Group			
	Control	LDT	MOT	HDT
No. litters evaluated	14	15	12	6
No. fetuses evaluated	63	75	69	26
Hypoplasia of spleen				
No. (%) fetuses	0	1(1.3)	0	0
No. (%) litters	0	1(6.7)	0	0
Agenesis of Gallbladder				
No. (%) fetuses	0	1(1.3)	0	1(3.8)
No. (%) litters	0	1(6.7)	0	1(17)
Separated origin of carotids				
No. (%) fetuses	37(59)	39(52)	25(36)*	12(46)
No. (%) litters	12(86)	14(93)	11(92)	3(50)
Focal necrosis of liver				
No. (%) fetuses	2(3.2)	0	0	0
No. (%) litters	2(14)	0	0	0

(continued)

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TABLE V: Visceral Examinations<sup>a</sup> (continued)

Observations	Group			
	Control	LOT	MDT	HDT
Blood coagulum around bladder				
No. (%) fetuses	0	1(1.3)	1(1.4)	0
No. (%) litters	0	1(6.7)	1(8.3)	0

<sup>a</sup>Data extracted from CBI Tables 022, 023, and 025.

\*Significantly different from control value ( $p \leq 0.05$ ).

A significant ( $p \leq 0.05$ ) decrease in fetal incidence of separated origin of the carotids was seen in the MDT group. This was not considered to be compound related because a similar increase was not observed at the HDT.

Skeletal Examinations:TABLE VI: Fetal Skeletal Examinations<sup>a</sup>

Observations	Group			
	Control	LDT	MDT	HDT
No litters evaluated	14	15	12	6
No fetuses evaluated	63	75	69	26
Sternebrae with various malformations				
No. (%) fetuses	0	1(1.3)	0	0
No. (%) litters	0	1(6.7)	0	0
Total skeletal malformations				
No. (%) fetuses	0	1(1.3)	0	0
No. (%) litters	0	1(6.7)	0	0
Bipartite sternebrae:				
No. (%) fetuses	0	1(1.3)	1(1.4)	0
No. (%) litters	0	1(6.7)	1(6.3)	0
Irregular shaped sternbrae(s)				
No. (%) fetuses	1(1.6)	2(2.7)	3(4.3)	4(15) <sup>*</sup>
No. (%) litters	1(7.1)	2(3)	3(25)	3(50)
Fused sternbrae				
No. (%) fetuses	1(1.6)	10(13) <sup>*</sup>	2(2.9)	2(7.7)
No. (%) litters	1(7.1)	7(47)	1(6.3)	1(17)
Accessory ribs(s)				
No. (%) fetuses	1(1.6)	2(2.7)	1(1.4)	2(7.7)
No. (%) litters	1(7.1)	2(13)	1(6.3)	2(33)
Total fetal skeletal variations				
No. (%) fetuses	3(4.8)	14(19) <sup>*</sup>	7(10)	6(23) <sup>*</sup>
No. (%) litters	2(14)	5(53)	5(42)	4(67)
Sternebrae, incompletely ossified or reduced in size				
No. (%) fetuses	11(17)	24(32)	23(33) <sup>**</sup>	3(12)
No. (%) litters	4(29)	10(67)	10(83)	3(50)
Sternebrae(s) not ossified				
No. (%) fetuses	13(21)	11(15)	22(32)	8(31)
No. (%) litters	5(43)	9(60)	9(75)	5(83)
Total skeletal retardations				
No. (%) fetuses	24(38)	35(47)	45(65) <sup>**</sup>	11(42)
No. (%) litters	8(57)	15(100) <sup>**</sup>	11(83)	6(100)

<sup>a</sup>Data entered from CBI Tables 027, 028, and 029.<sup>\*</sup>Significantly different from control value (p < 0.05).<sup>\*\*</sup>Significantly different from control value (p < 0.01).

No significant increases in the incidence of skeletal malformations were observed in the test groups when compared to controls. However, significant ( $p \leq 0.05$ ) increases in fetal and litter incidences of fused sternbrae at the LDI and of total skeletal variations at the HDT were noted. The fetal and litter incidences of incompletely ossified or small sternbrae were also significantly ( $p \leq 0.05$ ) increased at the MDT when compared to controls. However, since no apparent dose-related pattern was evident and incidences were within the range of historical control data, increases were not considered to be compound related.

**D. DISCUSSION/CONCLUSION:**

- a. Maternal Toxicity: The HDT was associated with an excessive incidence of abortions (8 out of 15 animals), severe reductions in body weight and food consumption, and related clinical signs and necropsy findings. Similar, but less severe, findings were noted at the MDT. No clear patterns of maternal toxicity were evident at the LDI.
  
- b. Developmental Toxicity: No developmental effects that could be attributed to the administration of metiraz-premix 95% were reported in this study.
  - i. Deaths/Resorptions: No compound-related effects were noted.
  
  - ii. Altered Growth: A slight, nonsignificant trend in fetal body weight reduction was noted; weights for the control, LDI, MDT, and HDT groups were 44.0, 43.7, 41.0, and 38.5, respectively. This was probably due to excessive maternal toxicity at the MDT and HDT.
  
  - iii. Developmental Anomalies: No compound-related effects were noted.
  
  - iv. Malformations: No compound-related effects were noted.



c. Study Deficiencies: 1. The HDT produced excessive maternal toxicity and maternal abortions. Only six litters with live fetuses were available for examination at this dose level. 2. The intracranial structures of fetuses in all dose groups were not systematically examined; only fetuses showing gross external malformations were examined intracranially. This deficiency precluded the assessment of developmental toxicity at all dose levels.

E. CLASSIFICATION: Supplementary data.

Maternal NOEL = 10 mg/kg (LDT).  
Maternal LOEL = 40 mg/kg (MDT).  
Developmental Toxicity NOEL = could not be established.  
Developmental Toxicity LOEL = could not be established.

F. RISK ASSESSMENT: Not applicable.

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