Incoming

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

009896

DEC 16 1992

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: OFTANOL - Review developmental toxicity study (83-3(b)) to support reregistration

EPA IDENTIFICATION NUMBERS: P.C. Code: 109401
Caswell No.:
DP Barcode: D183258

FROM: Robert F. Kracke, Ph.D. Robert F. Kracke 4 Dec 92
Toxicology Branch II, Section IV
Health Effects Division (H7509C)

TO: Linda DeLuise
Product Manager (52)
Registration Division (H7505C)

THRU: Elizabeth Doyle, Ph.D. E.A. Doyle 12/8/92
Toxicology Branch II, Head Section IV
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and

Marcia van Gemert, Ph.D. Marcia van Gemert 12/9/92
Chief, Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Miles, Inc.
Agricultural Division
Kansas City, MO

Chemical: Isofenphos, Oftanol, technical

1-Methylethyl 2-[[ethoxy[(1-methyl-ethyl)-amino]phosphinothioyl]oxy] benzoate

Action Requested: The registrant, Miles, Inc., has submitted a developmental toxicity study (83-3(b)) to support reregistration of isofenphos.

1. A study entitled "A Developmental Toxicology Study in Rabbits with OFTANOL Technical" (MRID 423828-01) has been reviewed. The results of the study are as follows:

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The teratological effect of Oftanol was evaluated in rabbits treated at dosages of 0, 0.25, 1.25, and 7.5 mg/kg/day, throughout the organogenesis period (days 6 to 18). The maternal LOEL was based on the increased incidence of mortality, decreased body weight and body weight gain, and decreased food consumption. Significant (> 20%) inhibition of plasma, erythrocyte and brain cholinesterase activities was present at 1.25 and 7.5 mg/kg/day. No developmental toxicity was present at the highest dose tested (7.5 mg/kg/day).

	NOEL (mg/kg/day)	LOEL (mg/kg/day)
Maternal - Systemic	1.25 (MDT)	7.50 (HDT)
- Cholinesterase	0.25 (LDT)	1.25 (MDT)
Developmental	7.50 (HDT)	> 7.50

CLASSIFICATION: Core - Guideline

This study satisfies guideline requirements (83-3(b)) for Teratology - Developmental Toxicity in the rabbit.

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Reviewed by: Robert F. Fricke, Ph.D. Robert F. Fricke 4 Dec 92.
Section IV, Tox. Branch II (H7509C)
Secondary Reviewer: Elizabeth A. Doyle, Ph.D.
Section IV, Tox. Branch II (H7509C)

009896

DATA EVALUATION RECORD

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

P.C. CODE: 109401

MRID NO.: 423828-01

TEST MATERIAL: Isofenphos, Oftanol, technical

SYNONYMS: 1-Methylethyl 2-[[ethoxy[(1-methyl-ethyl)-amino]phosphinothioyl]oxy] benzoate

STUDY NUMBER: 102694

SPONSOR: Miles, Inc.
Agricultural Division
Kansas City, MO

TESTING FACILITY: Corporate Toxicology - Healthcare
Miles Inc.
Elkart, IN

TITLE OF REPORT: A Developmental Toxicology Study in Rabbits with OFTANOL Technical

AUTHOR: G.R. Clemens, D.S. Grosso, and R.E. Hartnagel, Jr.

REPORT ISSUED: 16 June 1992

CONCLUSIONS: The teratological effect of Oftanol was evaluated in rabbits treated at dosages of 0, 0.25, 1.25, and 7.5 mg/kg/day, throughout the organogenesis period (days 6 to 18). The maternal LOEL was based on the increased incidence of mortality, decreased body weight and body weight gain, and decreased food consumption. Significant (> 20%) inhibition of plasma, erythrocyte and brain cholinesterase activities was present at 1.25 and 7.5 mg/kg/day. No developmental toxicity was present at the highest dose tested (7.5 mg/kg/day).

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CLASSIFICATION: Core - Guideline

This study satisfies guideline requirements (83-3) for Teratology - Developmental Toxicity in the rabbit.

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I. Materials and Methods

A. Test compound: Oftanol, technical Description: clear, colorless liquid Batch #: 0-00-5281 Purity: 91.4% Contaminants: not given

B. Dose Preparation: Test article was suspended in 0.5% carboxymethylcellulose (Lot No. 58374, Aqualon Company, Wilmington, DE) and 0.04% Tween 80 NF (Lot No. 23546, ICN Biomedicals Inc., Cleveland, OH) in distilled water (Batch No. 3/19/91, Miles Corporate Toxicology - Healthcare Still No. L07054). Samples from the top, middle and bottom of all the dosing solutions were analyzed and found to be homogeneous (relative standard deviations ≤ 4.19%) and within 98.8 and 106.5% of the nominal concentration. Dosing suspensions were stable for 28 days when refrigerated (6.34°C).

C. Test Animal: Species: Rabbit, Strain: New Zealand White Source: Hazelton Research Animals, Kalamazoo, MI Age: > 10 months (males), > 37 weeks (females) Weight: 3.34 - 4.82 kg (males), 3.25 - 4.83 kg (females).

D. Study Design: This study was designed to assess the developmental toxicity potential of Oftanol when administered by oral gavage to rabbits on gestation days 6 through 18.

1. Mating: Females were artificially inseminated using semen collected from proven bucks. Semen, evaluated for motility and sperm counts, was diluted with normal saline and administered intravaginally to randomly selected does. Females were injected with human chorionic gonadotropin before (50 I.U.) and after (100 I.U.) insemination.

2. Group Arrangement: Females were randomly assigned to the following test groups:

Table 1: Animal Assignment to Study Groups

Test Group	Dosage* (mg/kg/day)	Number Assigned
Control (CON)	0	20
Low (LDT)	0.25	20
Middle (MDT)	1.25	20
High (HDT)	7.50	20

*. Weight of test article corrected tc yield 100% of active ingredient

4. Observations

a. Maternal Observations and Evaluations: Animals were checked twice daily for signs of toxicity, mortality and moribundity. Does were sacrificed on gestation day 29 and examined for gross abnormalities of the thoracic, abdominal and pelvic viscera. Animals which died or were sacrificed moribund during the study were also examined.

b. Fetal Evaluations: Live fetuses were dissected from the uterus, weighed and examined for morphological abnormalities. Following external examination, each fetus was euthanized with an intracranial injection of sodium pentobarbital, and examined for visceral and skeletal abnormalities.

E. Historical Control Data: Historical control data were provided to allow comparison with concurrent controls.

F. Statistical Analysis: Doe and fetal body weights, placental weights, food consumption and clinical pathology data were analyzed using Dunnett's Test to determine significant differences between the control and treatment groups. Developmental indices and parameters were evaluated using Fisher's Exact test, Chi-square test, Kruskal-Wallis and Dunn's test. Statistical evaluation of fetal skeletal data was performed using the Fisher's Exact and Chi-square tests.

G. Compliance: Signed and dated GLP and Quality Assurance statements were provided.

H. Flagging Statement: The sponsor applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of this study. This study neither meets nor exceeds any of the applicable criteria.

II. Results

A. Maternal Toxicity

1. Mortality: Three animals in the 7.5 mg/kg/day group died during the study, one on day 18 and two on day 19. A fourth animal died on day 12 of an apparent dosing trauma.

2. Clinical Observations: The only adverse clinical findings were soft stool, diminished stool output and perianal soiling noted in two of the three animals which died while on the study.

3. Body Weight: Significant changes in mean maternal body weights occurred after Day 18. During most of the study, the high-dose animals had mean body weights which were lower than the controls; the differences were not significant, however. From Day 19 through 29, the mean maternal body weight for the high-dose group was significantly lower than controls (Table 2). During the dosing period (Day 6-19), animals in the high-dose group showed significantly lower mean body weight gain than control animals (Table 2).

Table 2: Mean Maternal Body Weight (kg) and Body Weight Gains (kg) (Data taken from Table II of study)

Day	CON	LDT	MDT	HDT
Mean Body Weight				
19	4.19	4.15	4.13	3.93*
21	4.20	4.16	4.11	3.90*
29	4.33	4.26	4.24	4.07*
Mean (%) Body Weight Gain				
6-19	0.19 (4.67%)	0.16 (3.91%)	0.17 (4.25%)	0.02** (0.51%)

* $p \leq 0.05$, ** $p \leq 0.01$

4. Food Consumption: Food consumption was measured on Day 1, 6, 7, 12, 15, 19, 23, and 29. At these times, animals were given exactly 130 g of diet (Purina Certified Rabbit Chow #5322); results are summarized in Table 3, below.

Table 3: Mean Food Consumption (g) (Data taken from Table III of study)

Day	CON	LDT	MDT	HDT
7	128.3	128.8	129.2	129.9*
19	121.2	128.4	115.1	82.3*

* $p \leq 0.05$

5. Gross Pathology: Necropsies were performed on Day 29 on all surviving maternal animals and animals which died during the study. The thoracic, abdominal and pelvic viscera were examined and the pregnancy status confirmed. Incidental findings, limited to the high-dose group, included stomach erosions in two that died during the study and another at scheduled sacrifice.

6. Cholinesterase Data: Plasma and erythrocyte cholinesterase activities were measured before treatment and on Days 19 and 29 of treatment; brain cholinesterase activity was measured on Day 29, at terminal sacrifice. Significant findings are presented in Table 4, below. Cholinesterase activities of plasma and erythrocytes, compared to pretreatment activities, and brain, compared to control values, were significantly decreased in the mid- and high-dose groups. Cholinesterase activities recovered during the post-treatment period; both plasma and erythrocyte activities were higher on Day 29 compared to Day 19 values.

Table 4: Cholinesterase Activities Measured before Treatment (PreRx) and on Days 19 and 29 (Data taken from Table IV of study)

	Day	CON	LDT	MDT	HDT
Plasma, U/ml	PreRx	0.50	0.49	0.50	0.47
	19	0.36 (73)[a]	0.34 (71)	0.25 (50•)	0.11 (23•)
	29	0.23 (47)	0.22 (47)	0.23 (47)	0.25 (53)
Erythrocyte, U/ml	PreRx	1.86	1.82	1.91	1.87
	19	1.89 (102)	1.72 (97)	0.85 (45•)	0.22 (13•)
	29	1.86 (101)	1.79 (99)	1.39 (74•)	0.96 (53•)
Brain, mU/g	29	2127	2158	1897•	1653•

a. Values in parentheses represent % of PreRx activity
• $p \leq 0.05$, •• $p \leq 0.01$

7. Cesarean Section Data: The cesarean section data are presented in Table 4, below. There were no statistically significant treatment-related effects on any of the parameters evaluated.

B. Developmental Toxicity: The incidence of external, visceral and skeletal abnormalities is summarized in Table 6, below. No statistically significant changes in the incidence of malformation were found. The malformations present were of low frequency and comparable between the study groups. There was no significant increase in the

incidence of external or visceral variations. Skeletal variations were limited to increased incidence of abnormal hyoid body or arch in the high-dose fetuses; the litter incidence was not altered by treatment. Other variations were noted, but were either of low frequency or were not dose-related.

III. Discussion/Conclusions

A. Maternal Toxicity: Systemic toxicity, observed only in the 7.5 mg/kg/day group, consisted of increased mortality, decreased body weight and body weight gain, and decreased food consumption. No significant, treatment-related changes were noted in the cesarean section data; each parameter measured was comparable across all the treatment groups.

Plasma, erythrocyte and brain cholinesterase activities were significantly decreased in animals in the mid- and high-dose groups. While plasma cholinesterase activities showed recovery on Day 29, erythrocyte and brain activities were still significantly decreased.

B. Developmental Toxicity: The only significant finding observed was an increased incidence of abnormal hyoid body or arch in the high-dose fetuses; the litter incidence was not altered by treatment. With the absence of any significant differences between control and treatment groups in the incidence of any malformations, the test compound is not developmentally toxic.

C. Conclusions: The teratological effect of Oftanol was evaluated in rabbits treated at dosages of 0, 0.25, 1.25, and 7.5 mg/kg/day, throughout the organogenesis period. The maternal LOEL was based on the increased incidence of mortality, decreased body weight and body weight gain, and decreased food consumption. Significant (> 20%) inhibition of plasma, erythrocyte and brain cholinesterase activities was present at 1.25 and 7.5 mg/kg/day. No developmental toxicity was present at the highest dose tested (7.5 mg/kg/day).

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Classification: core - Guideline

This study satisfies the guideline requirements (83-3) for Teratology-Developmental Toxicity in the rabbit.

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Table 5: Cesarean Section Data (Taken from Table VI, Table VII, Appendix D of study)

	CON	LDT	MDT	HDT
Total Assigned	20	20	20	20
No. Gravid	20	19	18	18
With Nonviable Fetuses Only	0	0	0	0
With Viable Fetuses	20	19	18	14
Maternal Wastage				
No. Died Gravid	0	0	0	4[a]
No. Died Nongravid	0	0	0	0
No. Nongravid	0	1	2	2
No. Aborted	0	0	0	0
Corpora Lutea/Doe	9.0	8.1	7.6	7.8
Implantation Sites/Litter	8.8	8.6	7.6	6.8
% Pre-implantation Loss	10.2	4.3	12.8	16.2
% Post-implantation Loss	2.6	7.5	6.0	8.7
No. Resorptions/Litter	0.3	0.5	0.3	0.6
% Does with Resorptions	20.0	36.8	22.2	42.9
Does with 1 Resorption	3	5	3	3
Does with 2 Resorptions	1	2	1	3
Total No. of Resorptions	5	9	5	9
No. Live Fetuses/Litter[b]	8.5	7.9	7.2	6.1
Sex Ratio (Male:Female)	50:50	50:50	62:38	44:56
Mean Fetal Body Weight (g)/Litter				
Male	46.1	44.9	47.9	49.2
Female	44.6	43.2	47.6	48.3
Combined	45.4	44.0	47.7	48.7
Median Placental Weight (g)	5.6	5.6	5.9	6.1

[a] Includes one animal which died of an apparent dosing accident
[b] Calculated from data presented in Table VI

Table 6: Fetal Examinations

	CON	LDT	MDT	HDT
No. Fetuses Examined	170	151	130	86
No. Litters Examined	20	19	18	14
External Abnormalities				
Variations				
Fetal Incidence, No (%)	0 (0)	0 (0)	0 (0)	0 (0)
Litter Incidence, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Malformations				
Fetal Incidence, No (%	0 (0)	0 (0)	0 (0)	1 (1.7)
Litter Incidence, No. (%)	0 (0)	0 (0)	0 (0)	0 (0)
Visceral Abnormalities				
Variations				
Fetal Incidence, No (%)	1 (0.6)	1 (0.7)	2 (1.5)	2 (2.3)
Litter Incidence, No. (%)	1 (5.0)	1 (5.3)	2 (11.1)	2 (14.3)
Malformations				
Fetal Incidence, No (%)	0 (0)	1 (0.7)	1 (0.8)	1 (1.2)
Litter Incidence, No. (%)	0 (0)	1 (5.3)	1 (5.6)	1 (7.1)
Skeletal Abnormalities				
Variations				
Fetal Incidence, No (%)				
Abnormal Hyoid Body or Arch	129 (75.9)	125 (82.8)	110 (84.6)	78 (90.7*
Litter Incidence, No. (%)				
Abnormal Hyoid Body or Arch	20 (100)	19 (100)	18 (100)	13 (92.9
Vertebrae: Thoracic-Centra Incomplete Ossification	4 (20)	3 (15.8)	9 (50)	1 (7.1)
Malformations				
Fetal Incidence, No (%)	8 (4.7)	6 (4.0)	7 (5.4)	5 (5.8)
Litter Incidence, No. (%)	7 (5.0)	3 (15.8)	5 (27.8)	4 (28.6)

* $p \leq 0.05$, ** $p \leq 0.01$