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DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity Study - Rabbits (§83-3B)

TEST MATERIAL: MAT 7484

SYNONYMS: Phostebupirim

PC Code: 129086
MRID No.: 420054-55

STUDY NUMBERS: T4024648
T2030621 (addendum)
18296 (Bayer report number)
18296A (Bayer report addendum number)
99812 (Report number)

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer AG, Federal Republic of Germany

TITLE OF REPORT: MAT 7484, Study of Embryotoxic Effects on Rabbits after Oral Administration

AUTHOR: M. Renhof

REPORT ISSUED: Study completion date: August 22, 1989

CONCLUSIONS:

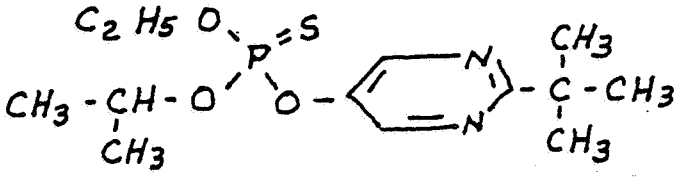
MAT 7484 was administered by oral intubation to pregnant rabbits on days 6 through 18 of gestation at doses of 0, 0.03, 0.1 and 0.3 mg/kg. The lowest two doses did not affect any parameter examined. The 0.3 mg/kg dose had a suggested effect on pregnant rabbits as evidenced by possible lower uterine weights, decreased number of live fetuses/litter and the higher number of resorptions/group as well as the number of litters with at least one resorption. There was also one rabbit that aborted her fetuses. Erythrocyte cholinesterase inhibition was also observed. No developmental effects were reported.

Maternal No Observed Effect Level (NOEL) = 0.1 mg/kg
Maternal Lowest Observed Effect Level (LOEL) = 0.3 mg/kg - suggested effect on resorptions and number of fetuses; inhibition of erythrocyte cholinesterase

I. TEST ARTICLE

Name: MAT 7484; O-[2-(1,1-dimethylethyl)-5-pyrimidinyl] O-ethyl O-(1-methylethyl) phosphorothioate; Phostebupirim

Formula:



Purity: 91.4%
Physical Properties: liquid
Lot Number: Eg. 15.10.86
Storage: refrigerated at approximately 8°C
Vehicle: deionized water with 0.5% Cremophor
Stability: 7 days

II. MATERIALS, METHODS AND RESULTS

A. Test Article and Dosing Solutions

The test article was administered by gavage at levels of 0 (control, vehicle), 0.03, 0.1 and 0.3 mg/kg. The rabbits received 5 ml/kg/day on gestation days 6 through 18. Analytical data are presented in Table 1. The formulation was stable for 7 days. **NOTE:** No statement was made as to the frequency of the preparation of fresh dosing solutions.

Table 1

ANALYSIS DATA OF SOLUTIONS OF MAT 7484 - DEVELOPMENTAL TOXICITY STUDY IN RABBITS

Nominal	% of Nominal - Storage Days			
mg/ml	Day 0	Day 3	Day 0	Day 7
0.002	98	99	91	91
0.600	102	103	95	92

mg/5 ml	% of Nominal	
	2/11/87	3/11/87
0.03	88	90
0.10	86	89
0.30	97	89

Data extracted from Report pages 108-111.

F. Body Weights

These were reported for days 0, 6-18 and 29.

Table 2

GROUP MEAN BODY WEIGHTS AND BODY WEIGHT GAINS OF PREGNANT RABBITS ADMINISTERED MAT 7484 DURING GESTATION DAYS 6 THROUGH 18

Dose mg/kg	No. Dams	Body Weights-g (gestation day) 0	6	10	14	18	29	Body Wt. gains-g (days) 0-6	6-18	18-29	0-29
0.0	13	2553	2556	2519	2533	2566	2723	3	10	157	170
0.03	13	2629	2625	2625	2631	2680	2801	-4	55	121	172
0.1	17	2632	2613	2616	2632	2672	2834	-19	59	162	202
0.3	16	2561	2563	2529	2547	2568	2700	2	5	132	139

Data extracted or calculated from Report pages 21-24.

There was no apparent effect of test article administration on body weights or weight gains during either the dosing period (days 6-18) or during the entire period of gestation (days 0-29). [No individual dam body weights were included in the report.] The difference between the control weight gain of 170 g during days 0-29 and the 0.3 mg/kg gain of 139 g is not considered to be a "real"/biological difference. Although no individual dam body weights were provided, the 31 g group mean difference (170 - 139 = 31) is well within expected biological variation and within the Registrant provided historical range (Report page 100) of 125.4-330.4 g.

G. Insemination, Fertilization and Caesarean Section

Eighteen females/group were mated and copulation observed. At Caesarean Section on gestation day 29, the following parameters were examined: uterine weights; corpora lutea; implantation sites; number and sex of fetuses; live and dead fetuses; resorptions; placental and fetal weight; and fetal crown-rump lengths.

One 0.3 mg/kg dam aborted on gestation day 20 (9 "fetuses"). Table 3 indicates a group mean uterine weight at the 0.3 mg/kg dose to be lower than the control value (284 versus 345). As noted in Tables 3 and 5, the number of live fetuses/litter appears to be lower in the 0.3 mg/kg dams than in the control or other treated groups. The group mean number of implantations in controls was 6.0 compared

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Table 5

THE NUMBER OF FETUSES AND RESORPTIONS PER DAM IN A DEVELOPMENTAL TOXICITY STUDY IN RABBITS WITH MAT 7484

Dose mg/kg	No. Females with Litters	Number/Dam
0	13	fetuses = 8,8,8,8,8,7,6,6,5,5,5,3,1 resorptions = 0,0,0,0,0,1,0,1,1,1,0,0,1
0.03	13 (14)	fetuses = 9,8,8,7,7,6,6,5,4,3,2,2,2,(0) resorptions = 0,3,0,0,0,2,1,0,0,0,0,5,2,(2)
0.1	17 (18)	fetuses = 9,8,8,8,8,8,8,7,7,7,6,6,5,5,5,4,1,(0) resorptions = 0,0,2,1,1,1,0,2,0,0,2,0,1,2,0,1,1,(5)
0.3	16 (18)	fetuses = 8,7,6,6,6,6,6,5,5,5,4,3,2,1,1,1,(0),(0) resorptions = 0,0,1,1,1,2,0,0,1,0,2,0,0,3,1,0,(7),(9)

(#) = Number of pregnancies; includes total resorptions and/or abortion

Data extracted from Report Tables 1-4, pages 95-98.

H. Fetal Examinations

Note: There was no indication in the Report of the number of fetuses that were: examined by Wilson's Technique (cranium), eviscerated for abdominal and thoracic evaluation or stained with Alizarin Red S for skeletal evaluation. Report page 12 states, "The examinations were performed in accordance with standardized methods (3, 4), which are described for rats and were appropriately applied to rabbits."

Fetuses were examined for external, cranial, visceral and skeletal changes.

There were no external, visceral or skeletal variations/ malformations described in this Report which were considered attributable to test article administration.

I. Cholinesterase Measurements

NOTE: An Addendum (Bayer Report No. 18296A, Study No. T2030621) to the main developmental toxicity study (Bayer Report No. 18296, Study No. T4024648) was titled, "MAT 7484, Study of the Maternal Toxicity Following Oral Administration to Rabbits."

No effects were noted on plasma or erythrocyte cholinesterase levels on day 7, prior to the second dose. On Day 14, prior to the 9th dose, there was an 18% ($p<0.05$) inhibition of plasma and a 56% ($p<0.0005$) inhibition of erythrocyte cholinesterase at 0.3 mg/kg only. On day 19 (24 hours after the last dose), cholinesterase values at the 0.3 mg/kg dose were slightly lower than control for plasma (16%, not statistically significant) and 73% ($p<0.0005$) lower than control for erythrocyte. Treated group brain levels were not lower than control values.

The only comments by this Reviewer regarding the Methods and Materials section, concern the absence of "UNITS" of measurement for the cholinesterase values in the ADDENDUM and an indication of when the dosing solutions were prepared (daily?, every other day?, etc.) as 3 and 7 day stability was reported.

Detailed statistical analyses were described in the report.

A Good Laboratory Practice Compliance Statement, Quality Assurance Statement and a list of Quality Assurance inspections were included in the Report.

The Registrant stated that the criteria of 40 CFR 158-34 for flagging studies for potential adverse effects were applied to the results of this study and that the study neither meets nor exceeds any of the applicable criteria. This Reviewer agrees.

III. DISCUSSION

Analytical data regarding test article purity and stability were acceptable.

There was no mortality and no clinical signs which were considered to be the result of MAT 7484 administration. No definitive effects of the test article were noted on body weights/gains either during dosing (gestation days 6 through 18) or during the entire period of gestation (Caesarean section on gestation day 29).

The following Caesarean section parameters may have been affected by 0.3 mg/kg of the test article: uterine weights, number of live fetuses/litter and the number of total resorptions/group as well as the number of litters with at least one resorption. In addition, one 0.3 mg/kg dam aborted her litter of 9 on gestation day 20. Therefore, there is the suggestion that this dose of the test article may have had a maternal effect. These pregnant rabbits may not have been able to retain their litters for the entire period of gestation.

No external, visceral or skeletal effects of test article administration on fetuses were reported.