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Chemical:	**Fipronil**
PC Code:	**129121**
HED File Code	**13000 Tox Reviews**
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

011714

OCT 27 1995

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: M&B 46513 (Fipronil Metabolite) - Subchronic Rat Study

DP Barcode: D213239
PC Code: 129121
Case: 031271
Submission: S483208

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer Virginia A Dobozy 10/20/95
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Rick Keigwin/Ann Sibold, PM Team 10
Insecticide-Rodenticide Branch
Registration Division (7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head J M Ioannou 10/23/95
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Karl P. Baetcke, Ph.D., Acting Branch Chief
Toxicology Branch II
Health Effects Division (7509C) 10/25/95

Action Requested: Review subchronic rat study with M&B 46513, a fipronil metabolite.

Recommendation: The study has been reviewed and has been classified as acceptable. A comparison of the levels of toxicity in the acute and subchronic studies with the parent and this metabolite indicates that the metabolite is more toxic than the parent. (See Toxicity Comparisons - Parent vs. Metabolite.)

Study Summary

M&B 46513: 90-Day Toxicity Study in the Rat by Dietary Administration - MRID # 43559501

Material Tested: M&B 46513 (97.5% a.i.)

M&B 46513 was administered in the diet to groups of ten male and ten female CD rats at dosages of 0, 0.5, 3, 10 or 30 ppm (males: 0, 0.029, 0.177, 0.594 and 1.772 mg/kg/day; females: 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day, respectively) daily for 90 days.

There were four deaths in both sexes of the 30 ppm group during the treatment period. There was an increased incidence of clinical signs of neurotoxicity (aggressivity, irritability to touch, increased motor activity and curling up on handling) in the 10 and 30 ppm group males and females. One male in the 3 ppm group was also observed to display these signs. Mean body weights were statistically decreased in the 30 ppm group males and females and the 10 ppm group males at multiple weekly measurements during the study. Overall mean body weight gains for the 10 and 30 ppm group males was decreased 15.4 and 12.9, respectively. Mean weekly food consumption and food conversion efficiency for the 30 ppm group males and females were lower than the controls during the first two weeks of the study only. There were no treatment-related changes in hematology or urinalysis parameters. Alterations in clinical chemistry parameters were of no toxicological significance. Treatment-related decreases were seen in T_4 at weeks 2 and 10 in the 30 ppm group males and in the 30 ppm group females at week 10. There was also a decrease in T_3 in the 30 ppm group males at week 10. However, there were no changes in the thyroid gland on macroscopic or microscopic examination. Therefore, the toxicological significance of the hormone alterations is questionable. There were no treatment-related macroscopic or microscopic necropsy changes.

The No Observed Effect Level (NOEL) was 3 ppm (0.177 and 0.210 mg/kg/day for males and females, respectively). The Lowest Observed Effect Level (LOEL) was 10 ppm (0.594 and 0.709 mg/kg/day for males and females, respectively) based on an increased incidence of clinical signs of toxicity in both sexes and decreased body weight and body weight gain in males. The study demonstrates that the metabolite is more toxic than the parent chemical (MB 46030) when administered to rats for 90 days.

Classification: Acceptable

Toxicity Comparisons - Parent vs. Metabolite

In both the subchronic and acute studies, the dosage at which the fipronil metabolite was toxic has been lower than for the parent .

In a subchronic rat study with the parent, the LOEL was 30 ppm for males (1.93 mg/kg/day) and females (2.28 mg/kg/day) based on alterations in serum protein values and increased weight of the liver and thyroid. The NOEL was 5 ppm for males (0.33 mg/kg/day) and females (0.37 mg/kg/day). As described above, in the subchronic study with the metabolite, the signs of toxicity (clinical signs of toxicity and decreased body weight and body weight gain in males) at the LOEL, 10 ppm (0.594 and 0.709 mg/kg/day for males and females, respectively), were more severe than those observed at the LOEL for the parent. The NOEL was 3 ppm (0.177 and 0.210 mg/kg/day for males and females, respectively)

In the acute oral study (MRID # 42918628) with the parent technical, the LD_{50} was 97 mg/kg for the combined sexes (Toxicity Category II). For the metabolite technical, the LD_{50} was 16 mg/kg for the combined sexes (Toxicity Category I).

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 9/13/95
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. J M Ioannou 10/17/95
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Toxicity/Rats (82-1)

EPA I.D. NUMBERS: P. C. CODE: 129121
MRID NUMBER: 435595-01

TEST MATERIAL: M&B 46513
Synonym: Fipronil Metabolite

STUDY NUMBER: SA 93226

TESTING FACILITY: Rhone-Poulenc-Secteur Agro
Sophia Antipolis Cedex

SPONSOR: Rhone-Poulenc Ag Company

TITLE OF REPORT: M&B 46513: 90-Day Toxicity Study in the Rat by Dietary Administration

AUTHOR(S): M. Dange

REPORT ISSUED: June 17, 1994

EXECUTIVE SUMMARY: In this subchronic rat study (MRID # 435595-01), M&B 46513 was administered in the diet to groups of ten male and ten female CD rats at dosages of 0, 0.5, 3, 10 or 30 ppm (males: 0, 0.029, 0.177, 0.594 and 1.772 mg/kg/day; females: 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day, respectively) daily for 90 days.

There were four deaths in both sexes of the 30 ppm group during the treatment period. There was an increased incidence of clinical signs of neurotoxicity (aggressivity, irritability to touch, increased motor activity and curling up on handling) in the 10 and 30 ppm group males and females. One male in the 3 ppm group was also observed to display these signs. Mean body weights were statistically decreased in the 30 ppm group males and females and the 10 ppm group males at multiple weekly measurements during the study. Overall mean body weight gains for the 10 and 30 ppm group males was decreased 15.4 and 12.9, respectively. Mean weekly food consumption and food conversion efficiency for the 30 ppm group males and females were lower than the controls during the first two weeks of the study only. There were no treatment-related changes in hematology or urinalysis parameters. Alterations in clinical chemistry parameters were of no toxicological significance. Treatment-related decreases were seen in T_4 at weeks 2 and 10 in the 30 ppm group males and in the 30 ppm group females at week 10. There was also a decrease in T_3 in the 30 ppm group males at week 10. However, there were no changes in the thyroid gland on macroscopic or microscopic examination. Therefore, the

toxicological significance of the hormone alterations is questionable. There were no treatment-related macroscopic or microscopic necropsy changes.

The No Observed Effect Level (NOEL) was 3 ppm (0.177 and 0.210 mg/kg/day for males and females, respectively). The Lowest Observed Effect Level (LOEL) was 10 ppm for females (0.594 and 0.709 mg/kg/day for males and females, respectively) based on an increased incidence of clinical signs of toxicity in both sexes and decreased body weight and body weight gain in males. The study demonstrates that the metabolite is more toxic than the parent chemical (MB 46030) when administered to rats for 90 days.

This study is classified as **Acceptable** and **satisfies** the data requirements for a subchronic rat study (82-1).

I. MATERIALS

A. Test Material

Name: M&B 46513
Synonym: Fipronil metabolite
Chemical Name: 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylpyrazole
Purity: 97.5% (99.7% on re-analysis)
Batch Number: 10 DGM 22
Description: Cream-colored solid
Storage Conditions: In air-tight, light resistant container at room temperature

B. Administration: dietary

C. Test Animals

Species: Sprague-Dawley rats
Source: Charles River France, St Aubin-les-Elbeuf, France
Age: approximately three to four weeks upon arrival at testing facility
Weight: 259 to 296 g for males; 176 to 223 g for females at start of exposure
Housing: Individually in stainless steel cages
Environmental Conditions: Temperature: 22 ± 2°C
Relative humidity: 55% ± 15%
Photoperiod: 12 hours light/dark
Air changes: 15 per hour
Food and Water: Complete rodent diet A04C P1 and tap water *ad libitum*
Acclimation Period: 21 days

II. METHODS

A. Diet Preparation and Analysis

M&B 46513 was dissolved in acetone and sufficient amounts were mixed into the basal diet to provide the required dietary concentrations. Acetone was also added to the control diets. The test diets were prepared every three weeks and stored at approximately -18° C when not in use.

The lowest and highest concentrations were analyzed to verify that the diets were homogeneous. The concentrations of the test material were verified at each level following the first, third and last of the five dietary preparations. In a preliminary study (SA 93138), the stability of the test substance was verified in 0.5 and 100 ppm diets after a 52-day freezing period. Samples of the lowest and highest concentrations were taken from the food pots at the end of weeks 4, 8 and 12.

B. Dosage and Administration

The animals were assigned to the following treatment groups using an "automatic procedure".

Group	Treatment	Dietary Concentration (ppm)	Number of Animals Males	Females
1	Control	0	10	10
2	M&B 46513	0.5	10	10
3	M&B 46513	3	10	10
4	M&B 46513	10	10	10
5	M&B 46513	30	10	10

The diets were administered continuously for at least 90 days.

C. Experimental Design

The study protocol required the following observations and examinations at the indicated times or frequencies.

physical examinations - detailed weekly examinations
moribundity, mortality and clinical signs of toxicity - checked twice daily; recorded once daily
body weights - once during acclimatization period, on first day of dosing and then weekly throughout the treatment period
food consumption - weekly intervals during the treatment period
food conversion - calculated at weekly intervals
ophthalmoscopic examinations - all animals before treatment; groups 1 and 5 after 12 weeks of treatment
hematology and clinical chemistry - on day 85, 86 or 87
thyroid hormone assays - during weeks 2 and 10
urinalysis - on day 91, 92, 93 or 94
gross necropsy - all animals
organ weights - designated organs from all animals
histopathology - designated organs and tissues from all animals

D. Pathological Parameters

For hematology and clinical chemistry evaluations, blood was drawn from the retro-orbital sinus under ether anesthesia after an overnight fast. The CHECKED (X) hematology parameters were examined.

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Prothrombin Time
__Total plasma protein (TP)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc. (MCHC)
X Mean corpuscular volume (MCV)
__Reticulocyte count

* EPA guideline requirement

The CHECKED (X) clinical chemistry evaluations were done.

Electrolytes:
X Calcium*
X Chloride*
__Magnesium*
X Phosphorus*
X Potassium*
X Sodium*

Enzymes:
X Alkaline phosphatase
__Cholinesterase
X Creatine phosphokinase*
__Lactic acid dehydrogenase
X Serum alanine aminotransferase (also SGPT)*
X Serum aspartate aminotransferase (also SGOT)*

Other:
X Albumin*
X Blood creatinine*
X Blood urea nitrogen*
X Cholesterol*
__Globulins
X Glucose*
X Total Bilirubin*
X Total Protein*
X Triglycerides
X Protein electrophoresis

* EPA guideline requirement

The CHECKED (X) urinalysis parameters were measured.

__Appearance*
X Volume*
X Specific gravity*
X pH
X Sediment (microscopic)*
X Protein*
X Urobilinogen
X Glucose*
X Ketones*
X Bilirubin*
X Blood*
__Nitrite
__Total reducing substances

* EPA guideline requirement

At the end of the treatment period (day 91, 92, 93 or 94), the animals were exsanguinated under deep anesthesia. An approximately equal number of animals were sacrificed each day. All animals found dead or euthanized in a moribund condition were also necropsied. The following CHECKED (X) tissues were preserved; the (XX) organ(s) in addition were weighed.

Digestive System	Cardiovasc./Hemat. System	Neurologic System
X Tongue	X Aorta*	XXBrain*
X Salivary glands*	XXHeart*	X Periph. nerve*
X Esophagus*	X Bone marrow*	X Spinal cord
X Stomach	X Lymph nodes*	XXPituitary*
X Duodenum*	XXSpleen*	X Eyes (Optic n.)*
X Jejunum*	XXThymus*	Glandular
X Ileum*	Urogenital System	XXAdrenals*
X Cecum*	XXKidneys*	X Lacrimal gland
X Colon*	X Urinary bladder*	X Mammary gland*
X Rectum*	XXTestes*	XXParathyroids*
XXLiver*	XXEpididymides	XXThyroids*
__Gall bladder*	XXProstate/urethra	Other
X Pancreas*	X Seminal vesicle	X Bone*
Respiratory System	XXOvaries	X Skeletal muscle*
X Trachea*	XXUterus*	X Skin
X Lung*	X Vagina	__All gross lesions and masses

In addition, femoral bone marrow smears were taken, fixed and stained but not examined because no significant hematology changes were found.

Histological examinations were done on the following: 1) preserved tissues listed above from all rats in Groups 1 and 5; 2) the liver, lung and kidney of all animals.

E. Statistical Analyses

A description of the statistical methods from the study report is attached.

F. Compliance

Signed statements of Quality Assurance and compliance with Good Laboratory Practice regulations were submitted by the testing facility. The sponsor submitted a statement claiming no data confidentiality. A signed "Flagging Statements" indicates that the study neither meets nor exceeds the criteria of 40 CFR 158.34. However, the study does raise concern about the toxicity of this metabolite as compared to the parent chemical.

III. RESULTS

A. Achieved Dosages

The following actual mean dosages were received during the course of treatment (extracted from Table 6, Page 65 of the study report).

	Dosage Levels (ppm)							
	Males				Females			
	0.5	3.0	10.0	30.0	0.5	3.0	10.0	3
Mean Achieved Dosage (mg/kg/day)	0.029	0.177	0.594	1.772	0.035	0.210	0.709	2 1

B. Diet Analyses

According to the Analytical Report for homogeneity, concentra and stability in Appendix N (page 366) of the study rep essentially all analyses were within acceptable ranges.

C. Mortality

There were four deaths in the 30 ppm groups during the treat period. One male was sacrificed moribund on Day 45 and t females were found dead on Days 11, 13 and 64. See Gross Necr for a discussion of the cause of death.

D. Clinical Signs

At 10 and 30 ppm, the most frequently observed treatment-rel clinical signs of toxicity were aggressivity, irritabilit touch, increased motor activity and animals curled up at handl The incidence of these signs was highest between weeks 3 and 5. male in the 3 ppm group was observed to be aggressive, irritabl touch and to vocalize excessively between Days 41 and 84. incidence of these signs is presented in Table 1.

Table 1
Clinical Signs of Toxicity in Rats
Treated with MB 46513 in the Diet for 90 Days[a]

	Dosage Levels (ppm)									
	Males					Females				
	0	0.5	3.0	10.0	30.0	0	0.5	3.0	10.0	30.0
Increased motor activity	0	0	0	0	1	0	0	0	1	9
Aggressivity	0	0	1	1	4	0	0	0	0	0
Excessive vocalization	0	0	1	2	0	0	0	0	0	1
Curls up at handling	0	0	0	0	5	0	0	0	0	1
Irritability to touch	0	0	1	6	6	0	0	0	5	8

a Extracted from Table 1 (pages 41-44) of the study report.

E. Body Weight and Body Weight Gain

Mean body weights were statistically decreased in the 30 ppm group males and females and the 10 ppm group males at multiple weekly measurements during the study. Mean body weight gain (reported as a weekly difference, rather than cumulative) was occasionally decreased in the 30 ppm group males and females and 10 ppm group males. Table 2 summarizes body weight and body weight gain at selected times during the study.

Table 2
Body Weight and Body Weight Gain (G)
in Rats Treated with M&B 46513 for 90 Days[a]

	Dosage Levels (ppm)									
	Males					Females				
	0	0.5	3.0	10.0	30.0	0	0.5	3.0	10.0	30.0
Body Weight										
Day 1	274.3	274.7	275.4	276.5	275.2	202.4	202.1	202.0	198.0	199.0
Day 8	333.6	337.7	332.9	327.5	294.2**	226.3	225.5	226.6	219.0	201.1**
% control value	-	101.2	99.8	98.2	88.2	-	99.6	100.1	96.8	88.9
Day 90	598.6	606.2	579.3	551.0	557.7	313.4	317.9	327.5	308.6	306.7
% control value	-	101.3	96.8	92.0	93.2	-	101.4	104.5	98.5	97.9
Body weight gain										
Days 1-8	59.3	63.0	57.5	51.0	19.0	23.9	23.4	24.6	21.0	2.1
% control value	-	106	97.0	86.0	32.0	-	97.9	102.9	87.9	8.8
Days 1-90	324.3	331.5	303.9	274.5	282.5	111.0	115.8	125.5	110.6	107.7
% control value	-	102.2	93.7	84.6	87.1	-	104.0	113.1	99.6	97.0

a Extracted from Table 2 (pages 46-49) of the study report.
** Significantly different from control ($p=0.01$), using Dunnett's test or Mann-Whitney's test

F. Food Consumption and Food Conversion Ratio

Mean weekly food consumption and food conversion efficiency for the 30 ppm group males and females were lower than the controls during the first two weeks of the study only. Table 3 summarizes food consumption at selected times during the study.

Table 3
Mean Food Consumption and Food Conversion Efficiency in Rats Treated with M&B 46513 for 90 Days[a]

	Dosage Levels (mg/kg/day)									
	Males					Females				
	0	0.5	3.0	10.0	30.0	0	0.5	3.0	10.0	30.0
Mean Food Consumption (g/rat/day)										
Day 8	28.5	28.8	28.5	27.8	20.5**	20.2	20.4	20.7	19.5	14.0**
% of control value	-	101.1	100	97.5	71.9	-	101.0	102.5	96.5	69.3
Day 90	25.9	25.6	25.5	25.2	24.3	16.6	17.3	16.6	15.9	16.5
% of control value	-	98.8	98.5	97.3	93.8	-	104.2	100	95.8	99.4
Mean Food Conversion Efficiency (g food consumed/g gain in body weight)										
Day 8	29.55	31.11	28.88	26.16	13.27	16.85	16.32	16.96	15.44	2.43
Day 84[b]	8.16	8.63	9.36	9.86	9.19	3.40	3.96	0.45	3.98	[c]

a Extracted from Tables 4 (pages 58-61) and 5 (page 63) of the study report.
b Body weight stasis or loss made food conversion incalculable at Day 90.
c Body weight stasis or loss made food conversion incalculable.
** Significantly different from control (p=0.01), using Dunnett's test or Mann-Whitney's test

E. Ophthalmoscopic Examinations

There were no treatment-related lesions.

F. Clinical Pathology

Hematology

There were no statistically significant differences between the treated and control animals for any of the hematology parameters.

Clinical Chemistry

Changes in the 30 ppm group females which were attributable to treatment included lower total bilirubin (-43%, $p<0.01$), total cholesterol (-24%, $p<0.05$) and triglyceride levels (-25%, $p<0.05$). All the values were within the historical control range for rats of this age and strain. These changes were not accompanied by any alterations at necropsy and therefore, were considered to be of no toxicological significance.

Thyroid Hormone-Levels

A separate report on the thyroid hormone assays is included in Appendix M (page 357) of the study report. The data are presented as individual and mean values, as well as percentage change from control mean values. Statistical analyses were done on the percentage change data. The study report states that treatment-related decreases were seen in T_4 at weeks 2 and 10 in the 30 ppm group males and in the 30 ppm group females at week 10. There was also a decrease in T_3 in the 30 ppm group males at week 10. The report states that all the values were minimal in magnitude and within the normal range for rats of this age and strain. In addition, there were no consistent macroscopic or microscopic changes in the thyroid glands at necropsy. (On gross examination, two males in the 30 ppm group had enlarged thyroids vs. 1 in the control group.) The mean levels for these hormones is presented in Table 4.

Table 4
Mean Thyroid Hormone Levels in Rats
Treated with MB 46513 in the Diet for 90 Days[a]

	Dosage Levels (ppm)									
	Males					Females				
	0	0.5	3.0	10.0	30.0	0	0.5	3.0	10.0	30.0
TSH (ng/ml)										
Week 2	5.31	5.60	5.19	5.56	5.53	3.56	3.62	3.59	3.50	3.57
Week 10	4.96	4.97	5.01	6.04	5.91	4.13	3.76	3.45	3.87	4.00
T_3 (nmol/l)										
Week 2	1.53	1.53	1.48	1.49	1.51	1.53	1.59	1.49	1.51	1.39
Week 10	1.62	1.73	1.66	1.62	1.15	1.51	1.53	1.49	1.50	1.53
T_4 (nmol/l)										
Week 2	72.13	62.51	56.36	59.57	37.56	44.59	48.34	53.18	50.01	51.20
Week 10	50.57	49.65	46.86	50.39	37.83	58.98	59.00	56.93	49.73	41.62

a Extracted from Table 2 (Appendix M, page 361-362) of the study report.

Urinalysis

There were no treatment-related changes.

G. Necropsy Findings

Gross Necropsy

There were no treatment-related changes on post-mortem macroscopic examination. Examination of the 30 ppm group animals which died or

were euthanized in a moribund condition during the study revealed changes which were thought to result from stress. All animals had enlarged adrenals. Necrotic areas were observed on the liver of two females. Focal gastric ulcerations/erosions were seen in one male and one female.

Organ Weights

There was a statistically significant increase in the relative weight of the brain in the 10 ppm (+9%, $p<0.05$) and 30 ppm (+12%, $p<0.05$) group male rats. In addition, the relative weights of the liver and the heart were increased in the 10 ppm group females and 3 ppm group males, respectively. None of these changes were considered to be toxicologically significant.

Histopathology

The findings on histopathology were those common to animals of this strain and age. There were no consistent thyroid changes to account for the alterations in the thyroid hormones in some of the treated animals.

H. Conclusion from Study Report

The study report concluded that the No Observed Effect Level (NOEL) was 0.5 ppm for males and 3 ppm for females. The toxicological effects noted were: increase in clinical signs in the 10 and 30 ppm groups; decreased body weight in the 10 and 30 ppm groups; and decreased food consumption in the 30 ppm group. It is unclear why a lower NOEL was selected for males when no effects were cited for the 3 ppm group males. It is likely to be based on the clinical signs of toxicity (aggressivity, irritable to touch, excessive vocalization) observed in one male in the 3 ppm group.

IV. *DISCUSSION*

Ten male and ten female Sprague-Dawley rats per group were administered M&B 46513 in the diet at dosages of 0, 0.5, 3, 10 or 30 ppm (males: 0, 0.029, 0.177, 0.594 and 1.772 mg/kg/day; females: 0, 0.035, 0.210, 0.709, and 2.101 mg/kg/day, respectively) daily for 90 days.

There were four deaths in the 30 ppm groups during the treatment period. One male was sacrificed moribund on Day 45 and three females were found dead on Days 11, 13 and 64. Necropsy examination revealed changes which were attributable to stress. At 10 and 30 ppm, the most frequently observed treatment-related clinical signs of toxicity were aggressivity, irritability to touch, increased motor activity and curling up on handling. The incidence of these signs was highest between weeks 3 and 5. One male in the 3 ppm group was observed to be aggressive, irritable to touch and to

vocalize excessively between Days 41 and 84.

Mean body weights were statistically decreased in the 30 ppm group males and females and the 10 ppm group males at multiple weekly measurements during the study. Mean body weight gain was occasionally decreased in the 30 ppm group males and females and 10 ppm group males. Overall mean body weight gain for males and females in the 30 ppm group was decreased 12.9 and 3.0%, respectively. Weight gain for the 10 ppm males was decreased by 15.4%. Mean weekly food consumption and food conversion efficiency for the 30 ppm group males and females were lower than the controls during the first two weeks of the study only.

Clinical chemistry changes in the 30 ppm group females which were attributable to treatment included lower total bilirubin (-43%, $p<0.01$), total cholesterol (-24%, $p<0.05$) and triglyceride levels (-25%, $p<0.05$). All the values were within the historical control range for rats of this age and strain. In addition, these changes were not accompanied by any alterations at necropsy and were therefore considered to be of no toxicological significance.

Treatment-related decreases were seen in T_4 at weeks 2 and 10 in the 30 ppm group males and in the 30 ppm group females at week 10. There was also a decrease in T_3 in the 30 ppm group males at week 10. However, there were no changes in the thyroid gland on macroscopic or microscopic examination. Therefore, the toxicological significance of the hormone alterations is questionable.

There were no organ weight changes or findings on necropsy which were considered to be of toxicological significance.

In a subchronic rat study with the parent fipronil, the NOEL was 5 ppm for males (0.33 mg/kg/day) and females (0.37 mg/kg/day). The Lowest Effect Level (LOEL) was 30 ppm for males (1.93 mg/kg/day) and females (2.28 mg/kg/day) based on alterations in serum protein values and increased weight of the liver and thyroid.

V. CONCLUSIONS

The No Observed Effect Level (NOEL) was 3 ppm (0.177 and 0.210 mg/kg/day for males and females, respectively). The Lowest Observed Effect Level (LOEL) was 10 ppm for females (0.594 and 0.709 mg/kg/day for males and females, respectively) based on an increased incidence of clinical signs of toxicity in both sexes and decreased body weight and body weight gain in males. The study demonstrates that the metabolite is more toxic than the parent chemical (MB 46030) when administered to rats for 90 days.

10/27/95 Fipanil Revised

Page _____ is not included in this copy.

Pages 18 through 20 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

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