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

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JUL -7 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: MB 46513, Fipronil Metabolite - Review of Three Toxicity Studies

P.C. Code: 129121
DP Barcode: D204322
Case: 285247
Submission: S467761

FROM: Virginia A. Dobozy, V.M.D., M.P.H., Veterinary Medical Officer Virginia A Dobozy 7/5/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

TO: Robert Brennis/Daphne Waldo/PM 10
Registration Division (7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y.M. Ioannou 7/5/94
Review Section I, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (7509C) Marcia van Gemert 7/6/94

Registrant: Rhone Poulenc AG Company

Action Requested: Review Three Toxicity Studies with MB 46513, Fipronil Metabolite

Recommendation: Toxicology Branch II has reviewed the studies. The two acute toxicity studies are acceptable; the 14-day oral toxicity study is not a guideline requirement and thus was classified as Supplementary. Other toxicity studies with this metabolite and others referred to in the registrant's May 11, 1994 letter should be submitted for our review when they are finalized.

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DATA REVIEW

Acute Oral Toxicity/Rats (81-1): MRID # 432354-01

Material Tested: MB 46513 (98.6% a.i.)

The acute oral $LD_{50}$ was calculated as 18 mg/kg for males, 15 mg/kg for females and 16 mg/kg for the combined sexes.

Classification: Acceptable

Acute Dermal Toxicity/Rats (81-2): MRID # 432354-02

Material Tested: MB 46513 (98.6% a.i.)

The acute dermal $LD_{50}$ was greater than 2000 mg/kg.

Classification: Acceptable

14-Day Oral Toxicity/Rats: MRID # 432354-03

Material Tested: MB 46513 (98.6% a.i.)

In this exploratory 14-day oral toxicity study, five Sprague Dawley rats/sex/group were administered MB 46513 at dosages of 0, 0.3, 1, 3 and 10 mg/kg/day. All of the animals in the 10 mg/kg/day group and one female in the 3 mg/kg/day group either died or were sacrificed in a moribund condition at Days 5-8 of the study. Clinical signs of toxicity were observed in the 10 mg/kg/day group males and females and in the 3 mg/kg/day group females. Body weight gain and food consumption were markedly decreased in the 10 mg/kg/day group animals prior to death. In the 3 mg/kg/day group males and females, body weight gain over the course of the study was decreased; food consumption was decreased at the two time points evaluated. In hematology and clinical chemistry evaluations prior to the terminal sacrifice, WBC counts and total bilirubin were decreased and total protein was increased in the 3 mg/kg/day group females; WBC counts were also decreased in the 1 mg/kg/day group females. On gross pathology examination, pale livers were noted in the females in the 1, 3 and 10 mg/kg/day groups. Spots in the glandular stomach were also noted in a few animals in the 3 and 10 mg/kg/day groups that were unscheduled deaths. On histological examination, there was an increase in the number of atrophic follicles in the thyroid of males and females treated at 3 mg/kg and above.

The No Observed Effect Level (NOEL) = 1 mg/kg/day for males and 0.3 mg/kg/day for females

The Lowest Observed Effect Level (LOEL) = 3 mg/kg/day for males

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(based on decreased body weight gain, food consumption and post-mortem findings) and 1 mg/kg/day for females (based on decreases in WBC count and gross necropsy findings)

Classification: Supplementary

May 11, 1994 Letter and Attachment

The registrant's May 11, 1994 letter refers to toxicity studies conducted with metabolites MB 45950 and RPA 105048. Attachment 1 to the letter summarizes the findings of the acute oral toxicity studies with these metabolites. The finalized reports for these studies should be submitted for review by Toxicology Branch II.

Attachment 1 also summarizes the findings of studies conducted with MB 46513 which were not submitted at this time and compares the toxicity of the metabolite to the parent compound. The metabolite appears to be more toxic than the parent in most of the comparisons, however any conclusions are premature without review of the actual studies.

Recommendation

The acute oral and acute dermal toxicity studies with MB 46513 are acceptable. The 14-day oral toxicity study is not a guideline requirement and therefore is classified as Supplementary. The studies with the metabolites referred to in the registrant's May 11, 1994 letter and Attachment 1 should be submitted for review by Toxicology Branch II.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/5/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M. Ioannou 7/5/94
Section I, Toxicology Branch II (7509C)

## DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Acute Oral Toxicity/Rats (81-1) |
| EPA ID NUMBERS: | P. C. CODE: 129121<br>MRID NUMBER: 432354-01 |
| TEST MATERIAL: | MB 46513<br>Synonym: Fipronil Metabolite |
| STUDY NUMBER: | SA 93074 |
| TESTING FACILITY: | Rhone-Poulenc-Secteur Agro<br>Sophia Antipolis Cedex, France |
| SPONSOR: | Rhone-Poulenc, Ltd. |
| TITLE OF REPORT: | MB 46513 Acute Oral $LD_{50}$ in Rats |
| AUTHOR(S): | M. Dange |
| REPORT ISSUED: | September 7, 1993 |

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID # 432354-01), a single dose MB 46513 in corn oil was administered orally to five male and five female Sprague Dawley rats per group at dosages of 3, 10, 20 and 30 mg/kg. The animals were observed for 14 days post-treatment for mortality. **The acute oral $LD_{50}$ was calculated as 18 mg/kg for males, 15 mg/kg for females and 16 mg/kg for the combined sexes.**

The study is classified as **Acceptable** with a **TOXICITY CATEGORY I** and **satisfies** the guideline requirements (81-1) for an acute oral toxicity study in rats.

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## I. MATERIALS

### A. Test Material

Name: MB 46513
Synonym: Fiprönil metabolite
Chemical Name: Not provided
Purity: 98.6%
Lot Number: 33 RJ 0108
Description: Yellow powder
Storage Conditions: Air-tight, light-resistant container in a refrigerator at 4°C

The chemical was prepared at various (w/v) concentrations in corn oil and administered at a volume of 10 ml/kg.

### B. Test Animals

Species: Sprague Dawley rats
Source: Charles River France, St Aubin-les-Elbeuf, France
Age: Eight weeks
Weight: 305 to 382 g for males; 204 to 267 g for females
Housing: Individually in stainless steel, wire mesh cages
Food and Water: Certified Rodent Pellet diet A04C and water *ad libitum*
Environmental Conditions: Temperature: 22 ± 2°C
Relative humidity: 55 ± 15%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Acclimation Period: 5 days

## II. METHODS

In a preliminary experiment, 9/10 animals died at a dose of 30 mg/kg, whereas 10 mg/kg produced no mortality.

In the definitive study, male and female rats were administered the test substance orally at the dosages indicated below.

| Group | Dose (mg/kg) | No. of Rats M | F |
|---|---|---|---|
| 1 | 3 | 5 | 5 |
| 2 | 10 | 5 | 5 |
| 3 | 30 | 5 | 5 |
| 4 | 20 | 5 | 5 |

The animals were checked for clinical signs, moribundity and mortality one hour after dosing and at least once more on Day 1. Thereafter, the rats were observed once daily during the 14-day observation period. Body weight was recorded on Days 1 (day of dosing), 8 and 15. At the end of the observation period, the

surviving animals were sacrificed and necropsied. $LD_{50}$ values were calculated by the method of Dragstedt and Lang.[1]

III. RESULTS

Death occurred at doses of 20 and 30 mg/kg. The number of deaths per group is summarized below:

| Dose Level (mg/kg) | Number of Deaths | |
|---|---|---|
| | Males | Females |
| 3 | 0 | 0 |
| 10 | 0 | 0 |
| 20 | 3 | 4 |
| 30 | 5 | 5 |

The deaths occurred between Days 2 and 4 post-dosing. The $LD_{50}$ values were calculated as 18 mg/kg for males, 15 mg/kg for females and 16 mg/kg for the combined sexes.

Convulsions (clonic and/or tonic) were observed before death in all animals in the 30 mg/kg group and in one female in the 20 mg/kg group. All the treated animals appeared hyper-reactive to noise. Animals in all except the lowest dose group had reduced motor activity, dyspnea and bradypnea. Nasal discharges were observed in males in the 10, 20 and 30 mg/kg groups and in females in the 20 and 30 mg/kg groups. Females in the highest two groups also had hypersalivation. The clinical signs were observed during the first 5 days post-dosing.

The body weight of the animals in the 3 and 10 mg/kg groups was not affected by treatment. The animals in the 20 mg/kg group which survived had a body weight decrease on Day 8 but gained weight over the course of the study. The only significant findings at necropsy were pale livers in two males and two females in the 30 mg/kg group and evidence of hypersalivation in five females in this group.

IV. COMPLIANCE

Signed statements submitted by the sponsor indicated that the study was conducted in accordance with GLP regulations and Quality Assurance inspections were conducted. A Statement of No Data Confidentiality Claim was submitted by the sponsor.

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[1] Dragstedt C.A. and Lang V.F. (1928): Respiratory stimulants in acute cocaine poisoning in rabbits, *J. Pharmacol. Exp. Ther.*, 96, pp 99-113.

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## V. CONCLUSIONS

The $LD_{50}$ was calculated as 18 mg/kg for males, 15 mg/kg for females and 16 for the combined sexes.

The study is classified as **Acceptable** with a **TOXICITY CATEGORY I** and satisfies the guideline requirements (81-1) for an acute oral toxicity study in rats.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. Virginia A Dobozy 7/5/94
Section I, Toxicology Branch II (7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. Y.M. Ioannou 7/5/94
Section I, Toxicology Branch II (7509C)

## DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | Acute Dermal Toxicity/Rats (81-2) |
| EPA ID NUMBERS: | P. C. CODE: 129121<br>MRID NUMBER: 432354-02 |
| TEST MATERIAL: | MB 46513<br>Synonym: Fipronil Metabolite |
| STUDY NUMBER: | SA 93095 |
| TESTING FACILITY: | Rhone-Poulenc-Secteur Agro<br>Sophia Antipolis Cedex, France |
| SPONSOR: | Rhone-Poulenc, Ltd. |
| TITLE OF REPORT: | MB 46513 Acute Dermal $LD_{50}$ in the Rat |
| AUTHOR(S): | M. Dange |
| REPORT ISSUED: | December 2, 1993 |

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID # 432354-02), a single dose of MB 46513 moistened with saline was administered topically to five male and five female Sprague Dawley rats at a dosage of 2000 mg/kg. The animals were observed for 14 days post-treatment for mortality. The death of one female seven days post-treatment was attributed to the chemical. The acute dermal $LD_{50}$ was greater than 2000 mg/kg.

The study is classified as **Acceptable** with a **TOXICITY CATEGORY III** and satisfies the guideline requirements (81-2) for an acute dermal toxicity study in rats.

## I. MATERIALS

### A. Test Material

Name: MB 46513
Synonym: Fipronil metabolite
Chemical Name: Not provided
Purity: 98.6%
Lot Number: 33 RJ0 108
Description: Yellow powder
Storage Conditions: Air-tight, light-resistant container in a refrigerator at 4°C

### B. Test Animals

Species: Sprague Dawley rats
Source: Charles River France, St Aubin-les-Elbeuf, France
Age: Seven to nine weeks old at arrival
Weight: 233 to 249 g for males; 230 to 250 g for females
Housing: Individually in stainless steel, wire mesh cages
Food and Water: Certified Rodent Pellet diet A04C and water *ad libitum*
Environmental Conditions: Temperature: 22 ± 2°C
Relative humidity: 55 ± 15%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Acclimation Period: 6 days

## II. METHODS

Approximately one day before dosing, the dorsum and flanks of five male and five female rats were clipped. On the day of dosing, a single dose of 2000 mg/kg of the test chemical moistened with 1 ml of 0.9% saline on a gauze pad was applied to an area corresponding to approximately 10% of the animal's body surface. The pad was then held in place with a bandage for 24 hours. At the end of the exposure period, the bandage was removed and the residual test substance was washed off with water.

The animals were checked for clinical signs and mortality one hour after dosing and at least once more on Day 1. The treated area was checked for signs of irritation when the bandage was removed. Thereafter, the rats were observed once daily during the 14-day observation period. Body weight was recorded on Days 1 (day of dosing), 8 and 15. At the end of the observation period, the surviving animals were sacrificed and necropsied.

## III. RESULTS

The death of one female found the morning after the application was suspected to be due to a bandage wrapped too tightly. Another female was found dead on Day 7; this death was attributed to treatment with the test chemical. Clinical signs of toxicity

observed on Days 1 and 2 included chromodachryorrhea, piloerection, polypnea and subdued behavior in the males and lacrimation, piloerection, reduced motor activity and tremors in the females. The signs subsided on Day 3, however from Days 4 to 10, one female curled up at handling and had soiled fur. Traces of blood were also observed in the cage of this animal on Days 4, 5, 6, 7 and 8.

The majority of the surviving animals had decreased body weights on Day 8 but regained weight by the end of the study. The only changes on necropsy were found in the female that died on Day 7. Microscopic examination of the liver in this animal showed the presence of foci of necrosis accompanied by hemorrhage and early fibrosis and minimal inflammatory infiltration in addition to a mild multifocal liver cell macrovacuolation. The relationship of these changes to treatment is unknown.

IV. COMPLIANCE

Signed statements submitted by the sponsor indicated that the study was conducted in accordance with GLP regulations and Quality Assurance inspections were conducted. A Statement of No Data Confidentiality Claim was submitted by the sponsor.

V. CONCLUSIONS

The $LD_{50}$ was greater than 2000 mg/kg for males and females.

The study is classified as **Acceptable** with a **TOXICITY CATEGORY III** and **satisfies** the guideline requirements (81-2) for an acute dermal toxicity study in rats.

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Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

| | |
|---|---|
| STUDY TYPE: | 14-Day Oral Toxicity/Rats |
| EPA ID NUMBERS: | P. C. CODE: 129121<br>MRID NUMBER: 432354-03 |
| TEST MATERIAL: | MB 46513<br>Synonym: Fipronil Metabolite |
| STUDY NUMBER: | SA 93063 |
| TESTING FACILITY: | Rhone-Poulenc-Secteur Agro<br>Sophia Antipolis Cedex, France |
| SPONSOR: | Rhone-Poulenc, Ltd. |
| TITLE OF REPORT: | MB 46513 Exploratory 14-Day Toxicity Study in the Rat by Gavage |
| AUTHOR(S): | M. Dange |
| REPORT ISSUED: | April 11, 1994 |

EXECUTIVE SUMMARY: In an exploratory 14-day oral toxicity study (MRID # 432354-03), five Sprague Dawley rats/sex/group were administered MB 46513 at dosages of 0, 0.3, 1, 3 and 10 mg/kg/day. All of the animals in the 10 mg/kg/day group and one female in the 3 mg/kg/day group either died or were sacrificed in a moribund condition at Days 5-8 of the study. Clinical signs of toxicity observed in the 10 mg/kg/day group males and females and in the 3 mg/kg/day group females included convulsions (resulting in death in the 10 mg/kg/day group), emaciation (mostly females), piloerection, chromodachryorrhea, prostration, excessive reaction to noise, hunched posture, nasal discharge, few feces and a curled up reaction when handled. Body weight gain and food consumption were markedly decreased in the 10 mg/kg/day group animals prior to death. In the 3 mg/kg/day group males and females, body weight gain over the course of the study was decreased; food consumption was decreased at the two time points evaluated. In hematology and clinical chemistry evaluations prior to the terminal sacrifice, WBC counts and total bilirubin were decreased and total protein was increased in the 3 mg/kg/day group females; WBC counts were also decreased in the 1 mg/kg/day group females. On gross pathology examination, pale livers were noted in the females in the 1, 3 and 10 mg/kg/day groups. Spots in the glandular stomach were also noted in a few animals in the 3 and 10 mg/kg/day groups that were unscheduled deaths. On histological examination, there was an increase in the number of atrophic follicles in the thyroid of

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males and females treated at 3 mg/kg and above.

The No Observed Effect Level (NOEL) = 1 mg/kg/day for males and < 3 mg/kg/day for females

The Lowest Observed Effect Level (LOEL) = 3 mg/kg/day for males (based on decreased body weight gain, food consumption and post-mortem findings) and 1 mg/kg/day for females (based on decreases in WBC count and gross necropsy findings)

The study is classified as **Supplementary** as it is not a required guideline study.

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## I. MATERIALS

### A. Test Material

Name: MB 46513
Synonym: Fipronil metabolite
Chemical Name: Not provided
Purity: 98.6%
Lot Number: 33RJ0108
Description: Yellow solid
Storage Conditions: Air-tight, light-resistant container in a refrigerator at 4°C

The dosing formulation was prepared fresh daily by suspending the test chemical in 0.5% methylcellulose in distilled water.

### B. Test Animals

Species: Sprague Dawley rats
Source: Iffa-Credo, L'Arbresle, France
Age: Six to seven weeks old on arrival
Weight: 245 to 294 g for males; 191 to 222 g for females
Housing: Individually in stainless steel, wire mesh cages
Food and Water: Certified Rodent Pellet diet A04C and water *ad libitum*
Environmental Conditions: Temperature: 22 ± 2°C
Relative humidity: 55 ± 15%
Photoperiod: 12 hours light/dark
Air Changes: 15/hour
Acclimation Period: 15 days

## II. METHODS

### A. Dosage and Administration

Male and female rats were administered the test substance orally by gavage at the dosages indicated below.

| Group | Test Substance | Dose (mg/kg) | No. of Rats M | No. of Rats F |
|---|---|---|---|---|
| 1 | Vehicle | 0 | 5 | 5 |
| 2 | MB 46513 | 0.3 | 5 | 5 |
| 3 | MB 46513 | 1 | 5 | 5 |
| 4 | MB 46513 | 3 | 5 | 5 |
| 5 | MB 46513 | 10 | 5 | 5 |

### B. Experimental Design

The following observations and measurements were made at the indicated times and frequencies.

Clinical signs, moribundity and mortality - twice daily
Body weight - day of dosing and then on Days 5, 8, 12, 14 and before necropsy
Food consumption - weekly
Hematology and clinical chemistry - Day 15
Necropsy - all animals on Day 15
Histopathology - liver and thyroid gland

C. Pathological Parameters

Hematology

Blood was drawn from the retro-orbital venous plexus under ether anesthesia. The following hematology parameters were measured.

| | |
|---|---|
| Hematocrit (HCT) | Total plasma protein (TP) |
| Hemoglobin (HGB) | Leukocyte differential count |
| Leukocyte count (WBC) | Mean corpuscular HGB (MCH) |
| Erythrocyte count (RBC) | Mean corpuscular HGB conc. (MCHC) |
| Platelet count | Mean corpuscular volume (MCV) |

Clinical Chemistry

The following clinical chemistry parameters were measured.

| | |
|---|---|
| Total bilirubin | Urea |
| Total protein | Albumin |
| Aspartate aminotransferase | Alkaline phosphatase |
| Alanine aminotransferase | |

Post-mortem Examinations

All animals found dead or sacrificed during the study were subjected to a gross necropsy examination. Those surviving until Day 15 were sacrificed by exsanguination under pentobarbital anesthesia and then necropsied. The kidney, liver, ovary, spleen, testis and thyroid gland (with parathyroid) were weighed and fixed at the terminal sacrifice only. Histological examinations were done on the liver and thyroid gland for all animals.

D. Statistical Analyses

A description of the statistical analyses from the study report is attached to the DER.

III. RESULTS

A. Mortality

Four males and four females in the 10 mg/kg/day group and one female in the 3 mg/kg/day group died during the study. The deaths occurred between Days 5 and 8. One male and one female in the 10

mg/kg/day group were sacrificed in a moribund condition.

B. Clinical Signs

Convulsions were observed in two males in the 10 mg/kg/day group on Day 5 approximately 4 to 5 hours post-dosing, in another male in this group on Day 6 approximately 2 hours post-dosing and in one female in the 10 mg/kg/day group on Day 5 approximately four hours post-dosing. All of these animals died shortly after the convulsions were observed. Other clinical signs of toxicity observed in males and females of this group included: emaciation (mostly females), piloerection, chromodachryorrhea, prostration, excessive reaction to noise, hunched posture, nasal discharge, few feces and a curled up reaction when handled. Females in the 3 mg/kg/day group were also observed to be emaciated, have reduced motor activity, to curl up when handled and to have few feces.

No treatment-related signs were observed in the 0.3 and 1 mg/kg/day groups.

C. Body Weight and Body Weight Gain

Animals in the 3 mg/kg/day group had a slight decrease in body weight, whereas those in the 10 mg/kg/day group which died between Days 5 and 8 had a significant decrease. Body weight gain was significantly reduced in the 3 mg/kg/day group males and females at some of the time points. The 0.3 and 1 mg/kg/day groups were not affected. Table 1 presents the body weight and weight gain data at selected time points.

Table 1
Body Weight and Weight Gain in Rats
Administered MB 46513 by Gavage for 14 Days[a]

| | Dosage Levels (mg/kg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| | 0 | 0.3 | 1 | 3 | 10 | 0 | 0.3 | 1 | 3 | 10 |
| Day 1 | 274.0 | 278.8 | 279.4 | 280.8 | 278.6 | 208.4 | 208.6 | 206.6 | 210.0 | 206.0 |
| Day 5 | 309.0 | 310.2 | 311.8 | 310.8 | 221.8* | 221.4 | 224.4 | 223.4 | 213.4 | 157.2* |
| Gain Days 1-5 | 35.0 | 31.4 | 32.4 | 30.0 | -56.8* | 13.0 | 15.8 | 16.8 | 3.4 | -48.8* |
| % control value | - | 90 | 93 | 86 | -162 | - | 122 | 129 | 26 | -375 |
| Day 14 | 376.8 | 377.6 | 376.6 | 365.4 | 0 | 239.8 | 241.8 | 244.2 | 215.0 | 0 |
| Gain Days 1-14 | 102.8 | 98.8 | 97.2 | 84.6* | 0 | 31.4 | 33.2 | 37.6 | 4.5 | 0 |
| % control value | - | 97 | 95 | 82 | - | - | 106 | 120 | 14 | - |

a Extracted from Tab. 2 and 3 (pages 28-32) of the study report; % calculated by the reviewer
* Significantly different from control, p = 0.05 with Dunnett's test

D. Food Consumption

The 3 mg/kg/day group males had a significant decrease in food consumption (average feed consumed/day) at Day 14 of the study; values for both males and females in this group were decreased at both Days 7 and 14. Food intake was markedly decreased in the 10 mg/kg/day group males and females at Day 7. The 0.3 and 1 mg/kg/day groups were not affected. The data are summarized in Table 2.

Table 2
Average Food Consumption/Day in Rats
Administered MB 46513 Orally for 14 Days[a]

| | Dosage Levels (mg/kg/day) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | Females | | | | |
| | 0 | 0.3 | 1 | 3 | 10 | 0 | 0.3 | 1 | 3 | 10 |
| Day 7 | 30.55 | 29.45 | 29.59 | 28.23 | 10.07* | 21.71 | 20.69 | 21.89 | 17.09 | 6.83* |
| % control value | - | 96 | 97 | 92 | 33 | - | 95 | 101 | 79 | 31 |
| Day 14 | 32.99 | 30.82 | 30.58 | 29.17* | 0 | 22.12 | 21.05 | 22.04 | 15.09 | 0 |
| % control value | - | 93 | 93 | 88 | - | - | 95 | 100 | 68 | - |

a Extracted from Tab. 4 (pages 34-35) of the study report; % calculated by the reviewer
* Significantly different from control, $p = 0.05$ with Dunnett's test

E. Hematology

The study report states that one of three females in the 3 mg/kg/day group had a lower white blood cell (WBC) count along with lower lymphocyte and neutrophil counts. Higher red blood cell (RBC) count, hemoglobin and hematocrit values were also noted in this rat. At 1 mg/kg/day, a lower WBC count was noted in two of the four females. At 0.3 mg/kg/day, the mean RBC count was significantly higher in the males only; this change was considered incidental since none of the higher dosage groups were affected. The study report concludes that the chemical induced lower WBC counts in the 1 and 3 mg/kg/day group females. There is no explanation for why all the surviving animals in the groups were not tested. The data for WBC counts are presented in Table 3.

Table 3
White Blood Cell Counts in Rats
Administered MB 46513 Orally for 14 Days[a]

| | Dosage Levels (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.3 | 1 | 3 | 0 | 0.3 | 1 | 3 |
| WBC Count | 13.30 | 14.30 | 12.90 | 13.50 | 8.65 | 10.28 | 6.33 | 4.87 |

a Extracted from Tab. 5 (page 44) of the study report

F. Clinical Chemistry

A significant decrease in total bilirubin and increase in total protein were seen in the 3 mg/kg/day group females. Results were presented for all of the surviving animals in the group. The data on these parameters are presented in Table 4.

Table 4
Selected Clinical Chemistry Parameters
in Rats Administered MB 46513 Orally for 14 Days[a]

| | Dosage Levels (mg/kg/day) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Males | | | | Females | | | |
| | 0 | 0.3 | 1 | 3 | 0 | 0.3 | 1 | 3 |
| Total Bilirubin (umol/L) | 1.70 | 1.84 | 1.50 | 1.26 | 2.38 | 2.06 | 1.62 | 1.20* |
| Total Protein (g/L) | 60.40 | 61.20 | 62.20 | 61.20 | 60.40 | 61.20 | 61.20 | 64.00* |

a Extracted from Tab. 6 (pages 50-56) of the study report
* Significantly different from control, p = 0.05 (Dunnett's test)

G. Post-mortem Examinations

Organ Weight

There were no treatment-related differences in organ weight.

Gross Pathology

Pale livers were noted in two of five females in the 10 mg/kg/day group which died or were sacrificed during the study; dark red or black spots were noted on the glandular stomach of one male and one female of this group. Pinpoint spots were noted on the glandular stomach of one female in the 3 mg/kg/day group that died or was sacrificed during the study.

At the terminal sacrifice, pale livers were noted in one of four females in the 3 mg/kg/day group and four of five females in the 1 mg/kg/day group.

Microscopic Pathology

Atrophic (inactive) follicles characterized by very flattened follicular epithelium were noted in the thyroid gland of all animals, including the control group. However, there was a dose-related increase in the number of atrophic follicles per microscopic field. The study report stated that the change was considered to be adaptive and of doubtful toxicological significance. Hepatocellular microvacuolation in the liver was correlated to the pale color of the liver in the affected animals, but all groups were affected and there was no dose-related effect. Therefore, the changes were not considered to be significant. The study report concludes that MB 46513 induced an increase in the number of atrophic follicles in the thyroid of male and female rats at 3 mg/kg/day and above.

H. Conclusions from Study Report

The study report concluded that the NOEL was 0.3 mg/kg/day. The only finding at 1 mg/kg/day that was considered treatment-related was the decrease in the WBC count of the females.

IV. Compliance

The study was a preliminary one, was not subjected to Quality Assurance inspections and does not comply with the GLP regulations. No data confidentiality is claimed.

V. CONCLUSIONS

In this exploratory 14-day oral toxicity study, five Sprague Dawley rats/sex/group were administered MB 46513 at dosages of 0, 0.3, 1, 3 and 10 mg/kg/day. All of the animals in the 10 mg/kg/day group and one female in the 3 mg/kg/day group either died or were sacrificed in a moribund condition at Days 5-8 of the study. Clinical signs of toxicity observed in the 10 mg/kg/day group males and females and in the 3 mg/kg/day group females included convulsions (resulting in death in the 10 mg/kg/day group), emaciation (mostly females), piloerection, chromodachryorrhea, prostration, excessive reaction to noise, hunched posture, nasal discharge, few feces and a curled up reaction when handled. Body weight gain and food consumption were markedly decreased in the 10 mg/kg/day group animals prior to death. In the 3 mg/kg/day group males and females, body weight gain over the course of the study was decreased; food consumption was decreased at the two time points evaluated. In hematology and clinical chemistry evaluations prior to the terminal sacrifice, WBC counts and total bilirubin were decreased and total protein was increased in the 3 mg/kg/day group females; WBC counts were also decreased in the 1 mg/kg/day

group females. On gross pathology examination, pale livers were noted in the females in the 1, 3 and 10 mg/kg/day groups. Spots in the glandular stomach were also noted in a few animals in the 3 and 10 mg/kg/day groups that were unscheduled deaths. On histological examination, there was an increase in the number of atrophic follicles in the thyroid of males and females treated at 3 mg/kg and above.

The No Observed Effect Level (NOEL) = 1 mg/kg/day for males and 0.3 mg/kg/day for females

The Lowest Observed Effect Level (LOEL) = 3 mg/kg/day for males (based on decreased body weight gain, food consumption and post-mortem findings) and 1 mg/kg/day for females (based on decreases in WBC count and gross necropsy findings)

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