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WASHINGTON, D.C. 20460

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JUL 15 1994

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

MEMORANDUM

**SUBJECT:** MB 46950, Fipronil Metabolite - Review of  
Acute Oral Toxicity Study

P.C. Code: 129121  
DP Barcode: D205097  
Case: 285247  
Submission: S469213

**FROM:** Virginia A. Dobozy, V.M.D., M.P.H., Veterinary  
Medical Officer *Virginia A. Dobozy 7/7/94*  
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 *J.M. Ioannou 7/11/94*  
Review Section I, Toxicology Branch II  
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D., Branch Chief *J.M. Ioannou 7/11/94*  
Toxicology Branch II  
Health Effects Division (7509C)

**Registrant:** Rhone Poulenc AG Company

**Action Requested:** Review acute oral toxicity study with MB  
45959, Fipronil metabolite and comment on  
whether this study will significantly impact  
the toxicity profile for this chemical.

**Recommendation:** Toxicology Branch II has reviewed the study  
and found it acceptable. The acute oral LD<sub>50</sub>  
values in male and female rats for this  
metabolite are slightly lower than the parent  
compound. The HED Metabolism Committee will  
consider this finding.



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DATA REVIEW

Acute Oral Toxicity/Rats (81-1): MRID # 432797-06

Material Tested: MB 45950 (98.9% a.i.)

The acute oral LD<sub>50</sub> (95% confidence interval) was calculated as 69 mg/kg (52-90 mg/kg) for males, 100 mg/kg (77-129 mg/kg) for females and 83 mg/kg (67-101 mg/kg) for the combined sexes.

Classification: Acceptable

COMPARISON OF LD<sub>50</sub> VALUES

The acute oral LD<sub>50</sub> values (95% confidence interval) for the parent compound, fipronil, were 92 mg/kg (64-128 mg/kg) for males and 103 mg/kg (73-141 mg/kg) for females. Therefore, the acute oral toxicity of the metabolite is slightly greater than the parent. (However, the LD<sub>50</sub> determination for the parent compound was done with a different strain of rat in a different laboratory.) This finding will be considered by the HED Metabolism Committee.

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Reviewed by: Virginia A. Dobozy, V.M.D., M.P.H. *Virginia A. Dobozy 7/7/94*  
Section I, Toxicology Branch II (7509C)  
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. *Y.M.I. 7/11/94*  
Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

**STUDY TYPE:** Acute Oral Toxicity/Rats (81-1)

**EPA ID NUMBERS:** P. C. CODE: 129121  
MRID NUMBER: 432797-06

**TEST MATERIAL:** MB 45950  
Synonym: Fipronil Metabolite

**STUDY NUMBER:** SA 93272

**TESTING FACILITY:** Rhone-Poulenc-Secteur Agro  
Sophia Antipolis Cedex, France

**SPONSOR:** Rhone-Poulenc, Ltd.

**TITLE OF REPORT:** MB 45950 Acute Oral LD<sub>50</sub> in the Rat

**AUTHOR(S):** M. Dange

**REPORT ISSUED:** May 31, 1994

**EXECUTIVE SUMMARY:** In an acute oral toxicity study (MRID # 432797-06), a single dose MB 45950 in corn oil was administered orally to five male and five female Sprague Dawley rats per group at dosages of 50, 65, 90 and 120 mg/kg. The animals were observed for 14 days post-treatment for mortality. Clinical signs of neurotoxicity were observed in all the groups. Deaths occurred at dosages of 65 mg/kg and higher. At necropsy, enlarged livers seen in surviving animals of the 65 and 90 mg/kg groups were attributable to treatment. The acute oral LD<sub>50</sub> (95% confidence interval) was calculated as 69 mg/kg (52-90 mg/kg) for males, 100 mg/kg (77-129 mg/kg) for females and 83 mg/kg (67-101 mg/kg) for the combined sexes.

The study is classified as Acceptable with a TOXICITY CATEGORY II 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 45950  
Synonym: Fipronil metabolite  
Chemical Name: Not provided  
Purity: 98.9%  
Batch Number: OP5502  
Description: Slightly yellow powder  
Storage Conditions: Air-tight, light-resistant container at room temperature

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: Nine to ten weeks old at arrival  
Weight: 300 to 378 g for males; 207 to 255 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: 13 days

II. METHODS

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	50	5	5
2	120	5	5
3	65	5	5
4	90	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 once during the acclimation period and on Days 1 (day of dosing), 8 and 15. At the end of the observation period, the surviving animals were sacrificed and necropsied. LD<sub>50</sub> values were calculated by the method

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of Litchfield & Wilcoxon<sup>1</sup>.

### III. RESULTS

Death occurred at doses of 65 mg/kg and above. The number of deaths per group is summarized below:

<u>Dose Level (mg/kg)</u>	<u>Number of Deaths</u>	
	<u>Males</u>	<u>Females</u>
50	0	0
65	3	0
90	4	3
120	5	3

The deaths occurred during the first week of the study. The LD<sub>50</sub> (95% confidence interval) values were calculated as 69 mg/kg (52-90 mg/kg) for males, 100 mg/kg (77-129 mg/kg) for females and 83 mg/kg (67-101 mg/kg) for the combined sexes.

Clinical signs of toxicity were observed in all the groups. At 50 mg/kg, the following signs of neurotoxicity were observed: excessive jumps in all males and two females; increased motor activity in three females; clonic convulsions in one female; tremors and curling-up behavior when handled in one female. Animals in the other treated groups curled up when handled and had soiled fur, hunched posture, tremors, fear, subdued behavior and reduced motor activity. One animal each in the 65 and 90 mg/kg groups had tonic or clonic convulsions on Day 3; three animals in the 120 mg/kg group had similar signs on Days 2-3.

One female in the 50 mg/kg group lost weight between Days 1 and 8 but gained weight thereafter. Body weight gain in the surviving animals of the other groups was unaffected.

On gross necropsy examination, enlarged livers seen in two males and three females in the 65 mg/kg group and in one male and one female in the 90 mg/kg group were considered to be treatment-related. All of these animals had survived until study termination.

### IV. COMPLIANCE

Signed statements submitted by the sponsor indicated that the study was performed 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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<sup>1</sup> LITCHFIELD J.T. and WILCOXON F. (1949): A simplified method of evaluating dose effect experiments, *J. Pharmacol. Exp. Ther.*, 96, pp 99-113.

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V. CONCLUSIONS

The acute oral LD<sub>50</sub> (95% confidence interval) was calculated as 69 mg/kg (52-90 mg/kg) for males, 100 mg/kg (77-129 mg/kg) for females and 83 mg/kg (67-101 mg/kg) for the combined sexes.

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