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DATA EVALUATION REPORT - AMENDMENT II[1]

STUDY TYPE: Subchronic Oral Toxicity (dietary -rat); OPPTS 870.3100; [§82-1a] ✓

DP BARCODE: D261080 ✓ SUBMISSION: S571151
P.C. CODE: 129121 ✓

TEST MATERIAL (PURITY): MB 46513 (Fipronil photometabolite)

SYNONYMS: Fipronil-desulfinyl

CITATION: Dange, M (1994) MB 46513 90-Day Toxicity Study in the Rat by Dietary Administration. Rhone-Poulenc Secteur Agro. SA93226, June 17, 1994. MRID 43559501. Unpublished

Dange, M (1999) MB 46513 90-Day Toxicity Study in the Rat by Dietary Administration. Rhone-Poulenc Secteur Agro. SA93226, June 17, 1994, amended on October 15, 1999. MRID 44963501. Unpublished

Blacker, A (1998) Historical Control Data (1991 to 1997) for Clinical Signs Observed in Rats from 90-Day Studies. Rhone-Poulenc Secteur Agro. No study number, December 17, 1998. MRID 44963502. Unpublished.

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EXECUTIVE SUMMARY: In this subchronic rat study (MRID 43559501, 44963501, 44963502), MB 46513 was administered in the diet to groups of ten male and ten female CD rats at concentrations 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 have aggressivity on one occasion (Day 41), irritability on three occasions (Days 50-84) and excessive vocalization on one occasion (Day 70). However, based on historical control data from 12 studies in Sprague-Dawley rats from this laboratory*

[1]The HED document numbers for the original review and first amendment are 011714 and 012509, respectively.

(44963502), it was determined that irritability and aggressivity can be reported in control animals at a comparable incidence. In addition, in the chronic toxicity/carcinogenicity study (MRID 44615301), at a dose comparable to the 3 ppm dose, the earliest time point at which the signs were observed was day 209 of the study. Therefore, it was concluded that the clinical signs in the one male at 3 ppm were not supported by the chronic toxicity/carcinogenicity study. 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 TSH, or 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 NOAEL is 3 ppm (0.18 and 0.21 mg/kg/ day in males and females, respectively). The LOAEL is 10 ppm (0.594 and 0.709 mg/kg/day in males and females, respectively) based on clinical signs of toxicity in both sexes and decreased body weight and body weight gain in males.

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

Review of MRID 44963501

The final report for Study SA 93226 (MRID 43559501) was amended following the examination of 17 studies in the Sprague-Dawley rat performed between 1991 and 1997 at Rhone-Poulenc Agro. The study author concluded that it appeared a proportion of male and female control animals spontaneously exhibited signs of aggressivity and/or irritability. In Study SA 93226, one male at 3 ppm presented these signs. The author retrospectively considered this single observation to be within the incidence of the historical control data. Thus, the NOAEL was changed to 3 ppm for both sexes.

Review of MRID 44963502

Data on the incidence of irritability, aggressivity and increased motor activity from 17 90-day studies conducted at Rhône-Poulenc Agro, Sophia Antipolis, France, from June 5, 1991 to December 16, 1997 were submitted. Thirteen of the studies were conducted in compliance with GLP. Four of the studies were not conducted in full compliance in that they were not audited by Quality Assurance; one of the studies was performed by gavage. Therefore, these five studies were eliminated from the data base by this reviewer. In the remaining 12 studies, the rats used were either Sprague-Dawley Crl:CD(SD)BR strain from Charles River France (5 studies) or Sprague-Dawley Ico:OFA.SD.(IOPS Caw) strain from Iffa-Credo (7 studies). Data from the individual laboratories will be considered separately. The rats in the 90-day study with fipronil-desulfinyl were from the Charles River strain. In the 5 studies (total of 50 animals) using this supplier, irritability and aggressivity were reported in only one study, SA 96277 (irritability in 4/10 males and 4/10 females, aggressivity in 0/10 males and 2/10 females). In the 7 studies (total of 70 animals) using the strain from Iffa-Credo, there were 3 studies in which aggressivity and/or irritability were reported; increased motor activity was reported in another study. The data from studies in which either irritability or aggressivity were reported are presented in Table 1 below, along with separate total incidences in the Charles River France and Iffa-Credo rats and in the complete data base. Since increased motor activity was not observed in the 3 ppm male in question in the 90-day fipronil-desulfinyl study, those data are not included the table.

Table 2: Incidence of Irritability and Aggressivity in Historical Control Data Base (Blacker, 1998b)*

Study Number	Study Start Date	Incidence of irritability		Incidence of aggressivity	
		Males	Females	Males	Females
SA 96097[b]	21 March 1996	0/10	1/10	0/10	0/10
SA 96277[a]	17 July 1996	4/10	4/10	0/10	2/10
SA 97004[b]	20 February 1997	3/10	1/10	1/10	0/10
SA 97078[b]	09 April 1997	1/10	1/10	0/10	0/10
Total Incidence in Charles River France rats		4/50 (8%)	4/50	0/50	2/50
Total Incidence in Iffa-Credo rats		4/70 (5.7%)	3/70	1/70	0/70
Total Incidence in Data Base		8/120[c] (6.7%)	7/120	1/120	2/120

* Only studies in which either irritability or aggressivity were reported are included in the table.
a Sprague-Dawley Crl:CD (SD) BR rats from Charles River France, St. Aubin-les-Elbeuf, France
b Sprague-Dawley Ico:OFA.SD.(IOPS Caw) rats from Iffa-Credo, L'Arbresle, France
c Denominator based on total number of animals in 12 studies considered acceptable for the historical control data base.

Conclusions

Thirteen of the studies were conducted in compliance with GLP; four of the studies were not conducted in full compliance in that they were not audited by Quality Assurance. One of the studies was performed by gavage. Therefore, five studies were eliminated by the reviewer, giving a total of 120 animals in the historical control data base.

In the 90-day study with fipronil-desulfinyl, aggressivity was observed on one occasion (Day 41), irritability on three occasions (Days 50-84) and excessive vocalization on one occasion (Day 70) in one male at 3 ppm. With the format of the individual animal data in the study report, it can be determined that the single occasion of aggressivity occurred alone, but it cannot be determined if irritability and excessive vocalization occurred on the same day.

The historical control data demonstrate that irritability and aggressivity can be observed in control animals at an incidence comparable to that of the 3 ppm group males in the fipronil-desulfinyl study. In addition, there are data from the chronic toxicity/carcinogenicity study from the same testing facility using the same strain of rat (supplier: Iffa-Credo) at near comparable doses which can also be used to support or refute the NOAEL in the 90-day study. In the chronic toxicity/carcinogenicity study (MRID 44615301), the 2 ppm dose in males was equal to 0.098

mg/kg bw per day as a time-weighed average for the 104-week study. Given that the mg/kg bw dose would have been higher at the beginning of the study, the 0.098 dose is fairly comparable to the 0.18 mg/kg bw per day dose for males in the 90-day study. Examination of the individual animal data of the 2 ppm males from the chronic toxicity/carcinogenicity study demonstrated that 8 of 70 animals had signs of aggressivity or irritability to touch, however the earliest time point at which the signs were observed was day 209 of the study. Therefore, based on this line of analysis, it can be concluded that the clinical signs in the one male at 3 ppm in the 90-day study are not supported by the chronic toxicity/carcinogenicity study. The NOAEL in the 90-day study should be increased to 3 ppm (0.18 and 0.21 mg/kg/ day in males and females, respectively). The LOAEL is 10 ppm (0.594 and 0.709 mg/kg/day in males and females, respectively) based on clinical signs of toxicity in both sexes and decreased body weight and body weight gain in males.

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