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Office of Prevention, Pesticides
and
Toxic Substances

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January 24, 2000

MEMORANDUM

SUBJECT: Fipronil - Review of Incident Reports for Three Products

DP Barcodes: D261920, D261922 and D261923

PC Code: 129121

Cases: 014261, 046906 and 060305

Submissions: S572744, S572746 and S572747

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Cheryl L. Phin for
1/27/00

Action Requested: Review incident data on rabbits and fipronil labels to determine if additional language is appropriate.

Recommendations: 1. The details of all incidents of death (D-A) included in incident summary reports for 1999 should be submitted to the Agency. The following information on each death should be included: registration number or identity of fipronil product, species of animal, age, sex, date of treatment, amount of fipronil product applied, clinical signs, date and time of onset of clinical signs, date of death and treatment for adverse reaction (if any).

2. Based on the consistency of the reports of neurological signs and subsequent death in rabbits

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in which fipronil is misused, it is recommended that the labels for all products be revised to warn against use on this species. It is recommended that the phrase "**DO NOT USE ON RABBITS**" should be placed at multiple locations of the labels for the actual product, box and any accompanying package insert. It should appear at minimum under Directions for Use and Hazards to Domestic Animals. It is also recommended that the registrant propose a strategy for disseminating this warning to the veterinary profession since the sale of fipronil products is limited to distribution through veterinarians.

Background

Reviews of fipronil incident data have been conducted in two previous memoranda dated April 16, 1997 and April 29, 1998. The 1998 memo included an analysis of data in the Incident Data System (IDS) from March 17, 1997 to April 13, 1998. It was noted in the EPA review that incidents of neurological signs were reported after rabbits were treated with one of the fipronil products. The products are registered only for use on dogs and cats. The review recommendations indicated that misuse in rabbits should be monitored and if it continues, the label should warn against such practices.

Review of Incidents from April 15, 1998 to July 29, 1999

Incidents reported to IDS were reviewed for **adverse reactions to fipronil products in rabbits only**. Individual incident reports were submitted in 1998 prior to the finalization of the 6(a)(2) Rule, which allowed summary reporting of domestic animal incidents by registrants. In 1999, the registrant's summary reports gave the number of incidents in the following severity categories:

- D-A - domestic animal died or was euthanized
- D-B - domestic animal exhibited or was alleged to have exhibited signs which may have been life-threatening or resulted in residual disability
- D-C - domestic animal exhibited or was alleged to have exhibited signs which are more pronounced, more prolonged or of a more systemic nature than minor signs
- D-D - domestic animal exhibited or was alleged to have exhibited signs but they were minimally bothersome
- D-E - signs are unknown or not specified

In 1998, there was one individual incident report in IDS involving rabbits. One rabbit was treated with the Frontline Top Spot (9.7% a.i.) for a medium dog (44 lbs.) containing 1.34 ml. The rabbit developed status epilepticus (repeated seizures) two days post treatment and died. The amount of product applied is unknown.

In 1999, summary reports were submitted for April-June and July-September. Both of these reports grouped incidents from the U.S. and outside the U.S. The U.S. summaries contain only the number of animals within each of the severity categories and do not identify the species involved, whereas the data from outside the U.S. identify species, age, symptoms, comments and EPA classification.

In the April-June summary, there was one report in the D-A category in the U.S for Frontline Top Spot for Dogs (Registration No. 65331-3). From outside the U.S., there was one rabbit in the United Kingdom that developed strange, hyperexcitable behavior then fits (interpreted by this reviewer as seizures). This animal recovered with treatment.

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In the July-September summary, the following number of D-A incidents were reported:

Frontline Spray (Registration No. 65331-1) - 5
Top Spot for Cats (Registration No. 65331-2) - 7
Top Spot for Dogs (Registration No. 65331-3) - 0

From outside the U.S., there were reports in 13 rabbits, all of which died. Neurological signs were reported in 11 of the 13 animals prior to death.

Reports from Australia

The third Annual Report for the National Registration Authority's (NRA) Adverse Experience Reporting Program for veterinary chemicals was obtained from Internet web site. For the years 1997 and 1998, there were two reports of fipronil used on rabbits. In both cases, the rabbits showed neurological signs of jaw champing and seizures within 48 hours of fipronil treatment and died despite being washed with soap and water and being treated with a sedative. The Annual Report concluded that a warning should be issued to the veterinary profession, through various publications, on the possible risk to rabbits from fipronil.

Conclusions/Recommendations

1. The details of all incidents of death (D-A) included in incident summary reports for 1999 should be submitted to the Agency. The following information on each death should be included: registration number or identity of fipronil product, species of animal, age, sex, date of treatment, amount of fipronil product applied, clinical signs, date and time of onset of clinical signs, date of death and treatment for adverse reaction (if any).
2. Based on the consistency of the reports of neurological signs and subsequent death in rabbits in which fipronil is misused, it is recommended that the labels for all products be revised to warn against use on this species. It is recommended that the phrase "DO NOT USE ON RABBITS" should be placed at multiple locations of the labels for the actual product, box and any accompanying package insert. It should appear at minimum under Directions for Use and Hazards to Domestic Animals. It is also recommended that the registrant propose a strategy for disseminating this warning to the veterinary profession since the sale of fipronil products is limited to distribution through veterinarians.