

US EPA ARCHIVE DOCUMENT



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

OFFICE OF PREVENTION,
PESTICIDES AND TOXIC
SUBSTANCES

21 August 2006

MEMORANDUM

Subject: Name of Pesticide Product: PROMERIS SPOT-ON FOR DOGS
EPA Reg. No. /File Symbol: 80490-E
DP Barcode: D331545
Decision No.: 351841
PC Codes: 106201 (Amitraz); 281250 & 281251 (Metaflumizone)

From: Byron T. Backus Ph.D., Toxicologist
Technical Review Branch
Registration Division (7505P)

Byron T. Backus
8/21/2006
RJW 8/22/2006

To: John Hebert, RM Team 07
Insecticide-Rodenticide Branch
Registration Division (7505P)

Registrant: FORT DODGE ANIMAL HEALTH

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
281250 & 281251 Metaflumizone	14.34%
106201 Amitraz	14.34%
<u>Other Ingredient(s):</u>	<u>71.32%</u>
Total:	100.00%

ACTION REQUESTED: The Risk Manager requests:

"Attn: Byron Backus

I requested this APVMA report on Promeris to assist you with the review of the domestic animal safety data. Australia has registered the product. Apparently the same domestic animal safety

studies were submitted/reviewed/accepted by Australia. Specific DERs for the studies are not available. The animal safety studies begin on page 21. Please let me know if you have any questions that could be answered by Fort Dodge."

BACKGROUND:

The material received includes summaries (p. 22-23) from five dog studies; these have also been previously reviewed by the Agency.

COMMENTS AND RECOMMENDATIONS:

1. While the statement is made on the cover sheet that: "Australia has registered the product." this is not correct. This reviewer (along with PV Shah and Rob Mitkus of HED) participated in a teleconference with representatives of APVMA on Tuesday, August 15, 2006 (our time; it was already Wednesday morning in Australia), and the representatives of APVMA stated that this product has not been accepted, and there remained a number of concerns.

2. The report states (p. 21) that: "Four hundred and fifty three dogs were treated with ProMeris[®] Spot-On for Dogs during the laboratory and field efficacy studies, with 56 adverse experiences reported. The most commonly reported adverse experiences were associated with the application site (29 cases; 52% adverse experience reports); with fourteen reports of a greasy spot remaining after treatment, six reports of scratching at the application site, with the remainder either reports of redness, scaling or pigmentation. Sixteen adverse reports (29% adverse experience reports) were consistent with the clinical signs of amitraz toxicity, including sedation/tiredness/apathy/lethargy/depression/incoordination, bradycardia, hypothermia and generalized pruritus. Five dogs (9% adverse experience reports) were reported to vomit at varying times after treatment... These results indicated that ProMeris[®] Spot-On for Dogs will generally be safe for use in dogs when used according to label directions, although it is anticipated that adverse experiences will be reported. These are most likely to involve the application site or be signs consistent with amitraz toxicity. It would be prudent to monitor the incidence of these during the first few years of use of the product."

3. EPA still has concerns regarding the death of a 3X puppy in the 8-week old beagle puppy study (MRID 46401004). According to the APVMA summary for this study: "Two puppies died – one in 3X dose group and one in 1X dose group. No deaths in 5X dose group. On necropsy deaths not linked to treatment, with findings more consistent with stress and/or anorexia." However, amitraz exposure in dogs is associated with an increased susceptibility to stress, and, in the study in MRID 46672104 (10-week old beagle puppies with repeated doses at 2-week intervals) another 3X puppy died. As noted by the (contract) reviewer: "The euthanasia of one male at the 3X dose *in extremis* and the inability to diagnose the cause of its illness are a concern. There was minimal evidence that the animal was not healthy prior to treatment. It had soft/watery feces on Day -1 and prior to dosing on Day 1. Clinical pathology values during the pretreatment period were normal. The health of the animal deteriorated by Day 32 and it was euthanized on Day 3. In a single dose study in eight-week old puppies with this R-28153/amitraz product (MRID 46401004), a female at the 3X dose was euthanized *in extremis* on Day 9. No cause of death could be determined for either animal. These deaths could be the result of including unhealthy animals in the studies; however, it cannot be ruled out that these animals

were especially sensitive to the product.”

4. Overall, the APVMA comments and summaries have not alleviated EPA’s concerns regarding the safety (or potential for adverse effects) of this product in the dog.