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

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

30 November 2006

MEMORANDUM

Subject:	Name of Pesticide Product:	Promeris Spot-On for Dogs
	EPA Reg. No. /File Symbol:	80490-E
	DP Barcode:	D332930
	Decision No.:	351841
	PC Codes:	106201 (Amitraz: 14.34%)
		281250 & 281251 (Metaflumizone: 14.34%)

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

Byron T. Backus 11-30-2006

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

Registrant: FORT DODGE ANIMAL HEALTH

FORMULATION FROM LABEL:

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

ACTION REQUESTED: The Risk Manager requests:

Attn Byron Backus: Please see Fort Dodge's response (submitted 7/6/05; with "Reference: EPA letter dated 27 May 2005" at top of first page) to your original companion animal safety review (completed on 5/27/05). Given that the supporting data have been reviewed, can you please go through the rebuttal point by point? Also, could you comment on the feasibility of an adult dog label vs. a label that includes treatment on puppies? If you think this is feasible based on the original data/studies would it be possible to let me know before you complete this review? Included is information from the registrant on the registration of the product in the EU (see "Committee for Medicinal Products for Vet Use, Summary of Opinion"). Please comment on the EU's decision to register the product. I am trying to get copies of DERs for the EU review.

Finally, I originally thought the end of Nov. for a review turnaround. Could that be moved up to the first of the month..."

BACKGROUND:

TRB's electronic files contain six previous actions for 80490-E. The first three are: 1) a memorandum dated 29 December 2004 from E. McAndrew to Ann Hanger with reviews of 6 acute toxicity studies conducted on the formulation; 2) a memorandum dated 27 May 2005 (B. Backus to Ann Hanger/John Hebert) with reviews of two companion animal safety studies (young adult beagles: MRID 46401003; and eight-week old beagle puppies, MRID 46401004); 3) a memorandum dated September 16, 2005 (B. Backus to Ann Hanger/John Hebert) addressing the registrant's response to the review of 27 May 2005. The recommendations made in this memorandum included the following comments: "As part of the registrant's response to the original TRB review, the registrant has cited (and summarized) four additional studies conducted on dogs with ProMeris Spot-On. Complete copies of these additional studies should be submitted to the Agency... TRB recommends that this registrant's response, along with the copies of the four additional studies, be referred to HED in order to conduct a primary review and risk assessment for the proposed use(s) of the ProMeris Spot-On formulation. Hopefully, after review of the four additional studies the significance of the glucose and BUN elevations seen in the original companion animal (adult dog & puppy) studies will be addressed as part of the risk assessment process."

The four studies were submitted to the Agency, and were referred to RAB1 in HED. These studies were sent out for contract review, however, at the request of Karen Whitby, Branch Chief of RAB1, it was agreed that the secondary reviews would be done by TRB.

There were two (the fourth and fifth TRB actions for 80490-E) subsequent memoranda by TRB covering the secondary reviews of these four studies. The first was dated 21 August 2006 (B. Backus to John Hebert) for MRIDs 46672102 [Evaluation of the toxicity in Chihuahua breed dogs of an insectidal spot on for dogs containing R-28153, 150 mg and amitraz, 150 mg/L], 46672103 [Safety evaluation study of oral exposure from auto- or allogrooming R-28153/amitraz spot-on formulation in dogs], and 46672104 [Safety evaluation study of repeated treatments with a topically applied spot-on formulation of R-28153 and amitraz in dogs]. In this review it was stated that: "Overall, the findings from these studies do not indicate that an adequate margin of safety exists between the companion animal (dog) use exposure and that at which symptoms of toxicity occur. This is particularly evident in the Chihuahua study...in which possible indications of toxicity occurred at 1X." The second review was also dated 21 August 2006 (B. Backus to John Hebert) covering the secondary review of a fourth study, MRID 46672101 (Pharmacokinetics of R-28153 and amitraz after a single topical application to dogs at 20 mg/kg of R-28153 and amitraz).

The sixth TRB review for 80490-E (also dated 21 August, 2006, B. Backus to John Hebert) largely consisted of comments on the Australian Pesticides & Veterinary Medicines Authority (APVMA) report on this product.

COMMENTS AND RECOMMENDATIONS:

1. As previously stated in the TRB review of 21 August 2006 with respect to the findings of three dog studies (MRIDs 46672102, 46672103, and 46672104): "Overall, the findings from

these studies do not indicate that an adequate margin of safety exists between the companion animal (dog) use exposure and that at which symptoms of toxicity occur. This is particularly evident in the Chihuahua study (MRID 46672102), in which possible indications of toxicity occurred at 1X."

2. While the European Medicines Agency Committee for Medicinal Products for Veterinary Use made a positive recommendation to grant a marketing authorization for the Metaflumizone-Amitraz product (copy available at www.emea.eu.int/pdfs/vet/press/pr/39100906.pdf) the report includes the following: "The most common side effects are effects typical for amitraz such as sedation, lethargy, CNS depression, hyperglycaemia, bradycardia and slow, shallow breathing and these may be observed in a small number of animals. Most of these signs are due to alpha-2-adreno-receptor agonist effects. Signs are usually transitory and generally resolved without treatment within 24 hours. If symptoms are severe or persist the alpha-2-adreno-receptor antagonist atipamezole hydrochloride may be used at a dose of 0.2 mg/kg bodyweight by intramuscular injection to reverse these side-effects..."

3. The proposed product 80490-E also gave positive results in a guinea pig dermal sensitization study (MRID 46395810).

4. Based on the findings (consistent with the known effects of amitraz) and lack of a 5X safety factor in the companion animal safety studies, the comments regarding amitraz side effects from the European Medicines Agency Committee, and the potential for dermal sensitization, TRB's concern is that registration of this proposed product will result in a significant number of adverse incidents involving treated dogs. As a result, TRB is unable to make a recommendation for registration. TRB asks the PM to defer to HED to conduct a risk assessment based on the exposure risks and to make recommendations as to possible label use restrictions.

5. HED can more adequately address the feasibility of an adult versus puppy label after the risk assessment has been completed.