



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Bayer Report No. 106743 entitled "Evaluation of Potential Exposures to Pet Owners and Veterinary Professionals During Application of Advantage (Imidacloprid) to Control Fleas on Cats and Dogs."

FROM: Carol Lang, Biologist *Carol Lang*
Special Review and Registration Section I

TO: Dennis Edwards, Jr., and Portia Jenkins (7505C)
Registration Division

THRU: Mark I. Dow, Ph.D., Section Head *Mark I. Dow*
Special Review and Registration Section II

Larry C. Dorsey, Chief *Larry Dorsey*
Occupational and Residential Exposure Branch
Health Effects Division (7509C)

DP Barcode: D219370

Pesticide Chemical Code: 129099

EPA Reg. No.:

PHED: No.

I. INTRODUCTION

A. Purpose

The Registration Division (RD) has requested that the Occupational and

Residential Exposure Branch (OREB) review the above-cited report submitted by Bayer Corp. regarding potential exposures to pet owners and veterinary professionals during application of the end-use product Advantage (active ingredient imidacloprid) to control fleas on cats and dogs. Bayer's cover letter accompanying the submitted report indicates that a user risk assessment is not required, however, Bayer prepared this report and submitted it for information purposes.

B. Background

Bayer Animal Health has developed a 9.1% imidacloprid solution (Advantage) as a method to control fleas on cats and dogs. The product is intended to be applied topically to the pet by parting the hair on the back and applying a small volume of solution contained in a prefilled plastic applicator tube directly on the skin. A single treatment is claimed to provide effective flea control for 4 weeks on dogs and 2 weeks on cats. Advantage is marketed under various names and in tubes containing different amounts of the topical solution, dependent on the type of animal to be treated (cat or dog), and on the size of the animal (by weight). The various end-use products are listed in Table 1, below (information derived from labels submitted by Bayer Corp.).

Table 1. Advantage Products to Control Fleas

Product Name	Animal Treated	Animal Weight	Tube Contents (ml end-use product)*
Advantage 9	Cats and kittens	9 lbs. and under	0.4
Advantage 18	Cats	> 9 lbs.	0.8
Advantage 10	Small dogs and puppies	10 lbs. and under	0.4
Advantage 20	Dogs	11-20 lbs.	1.0
Advantage 55	Dogs	> 20 lbs.	2.5
Advantage 110	Dogs	> 55 lbs.	5.0

Note: Intended treatment for cats is every two weeks; for dogs, once a month. In all treatment scenarios, the label states that the entire contents of the tube are to be used at the time of each treatment.

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Bayer Corp. surveyed, by telephone, their Animal Health Sales personnel representing four geographic regions in the United States, to identify anticipated use patterns for the Advantage products. Basing projected use patterns for Advantage on the Bayer sales personnel's knowledge of reported usage for another Bayer flea-control product (Pro Spot), an attempt was made to identify typical and worst-case scenarios for applications at home by pet owners and in clinics by a veterinarian or technician.

Of note in the scenarios described by Bayer, are the following issues: 1) the scenarios cited are based totally on testimonial opinions provided by Bayer staff; 2) neither the typical nor worst case scenarios assume treatment of the largest pets, i.e., the pets on which the largest quantity of topical solution would be administered and in which the greatest acute exposure to humans might be expected; and, 3) in the exposure calculations provided by Bayer, it was assumed that only 1.0% of the total amount of product/active ingredient applied would contact and adhere to the skin of the applicator's hand.

OREB has completed prior assessments on end-use products containing imidacloprid. There is a Toxicology Endpoint Selection Document for imidacloprid dated April 18, 1994 (attached). No systemic toxicity was observed at dose levels up to 1000 mg/kg/day in a 21-day dermal toxicity study. The value of 1000 mg/kg/day is used by OREB in this review (per personal communication with Beth Doyle, DRES, on October 26, 1995). Of significance, the Toxicology Endpoint Selection Document states under the sections entitled "Short-Term Occupational or Residential Exposure" and "Intermediate-Term Occupational or Residential Exposure" that risk assessment is not required. Also stated in this document is the fact that imidacloprid is not an inhalation or dermal toxicant and that, while dermal absorption data ^{is} not available, imidacloprid is not considered to present a hazard via the dermal route.

II. DETAILED CONSIDERATIONS

OREB's exposure assessment is based on the assumptions in Table 2.

Table 2. Assumptions for Worker Exposure Assessments

Factors	Quantities/Units
Applicator body weight	60 kg
Pet treated	Dog over 55 lbs.
End-use product applied	5 ml
Active ingredient in end-use product	Imidacloprid, 9.1% w/w equivalent to 0.091 gm/ml
NOEL	1000 mg/kg BW/d
Dermal absorption ¹	100%
Dermal exposure ²	Entire contents of tube (5 ml)
Personal protective equipment	None

III. CONCLUSIONS

Table 3, below, summarizes the OREB estimate for total acute exposure for applicators of imidacloprid, the active ingredient in Advantage products to control fleas on dogs and cats, as it might be applied one time to a dog over 55 lbs. The estimate is based on the assumptions outlined in Table 2.

Table 3. Worker Exposure to Imidacloprid*

Job Function	Absorbed Daily Dose	Margin of Exposure
Applicator	7.6 mg ai/kg BW/d	132

* Calculations attached as Appendix A.

OREB notes that the Less Than Lifetime Committee in the Toxicology Endpoint Document on imidacloprid stated that no risk assessment was required for short or intermediate term exposure. There is neither exposure data on which to base an assessment of repetitive use of the end-use products nor objective

¹ In the absence of dermal absorption data, an absorption factor of 100% is assumed.

² In the absence of data to show the actual quantity of topical solution in a 5 ml tube that an applicator may be exposed to, and for purposes of a conservative estimate of exposure; it is assumed that the applicator is exposed to the entire contents of a 5 ml tube of topical solution.

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information on which to generate exposure scenarios. OREB notes that there is no data to support the assumption made by Bayer Corp. that only 1% of the topical solution in a tube of end-use product is likely to contact and adhere to an applicator during treatment.

Having reviewed the Toxicology Endpoint Selection Document on imidacloprid and Bayer Report Number 106743, and having estimated the absorbed daily dose and margin of exposure resulting from a one-time exposure to 5 ml of end-use products containing 9.1% imidacloprid, OREB concludes that exposure to this quantity of imidacloprid yields a margin of exposure that is greater than 100. No further exposure assessment is required for the Advantage products at this time.

Attachment

cc: C. Lang, OREB
Correspondence File
Chemical File, Imidacloprid (129099)

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APPENDIX A. CALCULATIONS

Absorbed Daily Dose (ADD) = 5 ml (w/w equivalent to 0.091 gm/ml) = 0.455 gm imidacloprid X 1000mg/gm = 455 mg imidacloprid divided by 60 kg BW = 7.6 mg imidacloprid/kg BW/d

Margin of Exposure (MOE) = NOEL* divided by the ADD = 1000 mg/kg BW/d divided by 7.6 mg imidacloprid/kg BW/d = 132

* Toxicology Endpoint Selection Document on Imidacloprid dated April 18, 1994.

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