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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Review of 6(a)(2) data on dogs

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Introduction

Toxicology Branch II has been requested to review a 6(a)(2) submission concerning the clinical observations in an exploratory two-week toxicity study in dogs, an aborted 8-week toxicity in dogs, an 8-week toxicity in dogs, and a 1-year toxicity study in dogs. The studies were conducted by International Research and Development Corp. (IRDC) and sponsored by Chemical Specialties Manufacturers Association. The submission consisted of brief descriptions of clinical observations and figures on food consumptions and body weights.

Data analysis:

In the exploratory 2-week study, 5 groups of beagle dogs (1 dog/sex/group) received DEET by capsule at doses of 0, 62.5, 125, 250, and 500 mg/kg/day for two weeks. No treatment-related effects were seen in 62.5 and 125 mg/kg groups. At 250 mg/kg, the treated



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animals showed signs of ptyalism, nodding of the head. At 500 mg/kg, the treatment induced signs of ptosis, ptyalism, nodding of the head, and ataxia. In addition, convulsion was seen in the 500 mg/kg male.

In an aborted 8-week toxicity in dogs, the data did not indicate how many doses, the number of animals, and the means of administering the compound in this study. However, all the treated animals were reported to show signs of emesis, ptyalism, abnormal biting/scratching at themselves, and head bobbing. The head movements were more pronounced in 175 and 225 mg/kg (highest dose) animals which also exhibited ataxia and ptosis. Episodes of convulsion were also seen in 125 and 225 mg/kg animals. The study was terminated 4 days after dosing.

In another 8-week toxicity study, 2 beagle dogs/sex/dose received the test material by capsule (gelatin) at doses of 0, 50, 100, 200, and 400 mg/kg/day. To avoid acute toxicity, each dose was prepared into two capsules, each of which contained 1/2 of the dose. The experimental animal were treated twice daily for 8 weeks, and the capsule was offered one hour after feeding. The control dogs received gelatin capsules containing white mineral oil. The report indicated a high incidence of emesis, relaxed nictating membranes, ptyalism, and abnormal head movements in 400 mg/kg animals. Ptyalism was occasionally seen in 200 mg/kg dogs. No treatment-related changes were seen in either macroscopic or microscopic pathology examinations. The report indicated treatment-related effects on body weight gain and food consumption, but no data were presented. Based on these results, a dose of 400 mg/kg/day was selected as the highest dose which was to be administered in capsules in 2 divided doses per day for the 1-year toxicity study in dogs.

In the 1-year toxicity, groups of beagle dogs (4/sex/dose) received DEET in capsule at doses of 0, 30, 100, and 400 mg/kg/day. Each dose was administered in capsule with two divided doses per day. The summarized results showed that tremors were seen in 2/4 females of 100 mg/kg group, and 1/4 females and 2/4 males in 400 mg/kg groups. In addition, abnormal head movement, convulsion, and ptyalism were also seen in a 400 mg/kg male which had tremors. Tremors were reported to occur not immediately following dosing. There was a significant decrease in cholesterol levels in 400 mg/kg males.

Discussion

Based on the limited data presented in the report, the dogs, which received DEET in capsule, appeared to be sensitive to the effects of DEET in producing ptyalism, tremor, abnormal head movements, and convulsion. These clinical observations were not seen in rats which received DEET in the diet at doses up to 4000

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mg/kg/day. However, some of the clinical signs seen in dogs in this submission were reminiscent of those seen in domestic animal safety studies on Blockade^R with dogs. Tox. Branch II is looking forward to receiving the complete report on these studies and to determine the toxicity of DEET in dogs.

After evaluating these preliminary results in dogs, Tox. Branch II is considering recommending additional studies to further explore (1) whether similar neurotoxic signs could be induced with repeated dermal application of DEET on dogs and (2) the reason for the difference in neurotoxicity response by dogs and rodents.