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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

September 21, 2006

MEMORANDUM

SUBJECT: Cyphenothrin and Etofenprox: Review and Response to, "Information to Upgrade MRID 46082302, MRID 45869402, and MRID 45869401" (MRID 46874501); DP Barcode: 330745; PC Codes: Cyphenothrin: 129013; Etofenprox: 128965

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Background

This document serves as a response to Sergeant's Pet Care Products, Inc. request (MRID 46874501) to upgrade the following studies to acceptable: "Dislodgeability of Etofenprox from the Haircoat of Cats Treated with a Spot-on Formulation"(MRID 46082302), "Validation Study Comparing Dose Residue Recoverability of Etofenprox from Cotton and Latex Gloves Analysis of Data and Conclusions" (MRID 45869402), and "Amended Final Report II: Operator Exposure Assessment and Dislodgeability of Etofenprox from the Haircoat of Cats Treated with a Spot-on Formulation" (MRID 45869401). MRIDs 46082302 and 45869402 were reviewed on March 6, 2006, and the Health Effects Division (HED) determined that these studies were not suitable for risk assessment purposes due to several significant deficiencies. MRID 45869401 was reviewed on March 16, 2006 and was also determined not suitable for risk assessment purposes for many of the same deficiencies. These studies were not used in the development for the HED assessment "Etofenprox: Occupational and Residential Exposure Assessment for

Proposed Section 3 Registration on Domestic Pets (D327844)" due to deficiencies, as well as differences between certain standard assumptions in the submitted studies and those used by HED. The same Etofenprox studies were submitted by the Registrant for the HED assessment "Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Cyphenothrin on Domestic Pets (D317077)." HED also determined that the study results could not be used to support the registration of any of the cyphenothrin proposed spot-on products (2517-IL, 2517-IN, and 2517-ON). The current submission from Sergeant's Pet Care Products, Inc. is a formal request to upgrade the studies based on additional information to address the study deficiencies.

Due to the deficiencies in the aforementioned studies, the risk assessment, "Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Cyphenothrin on Domestic Pets" (D317077), used surrogate data for the estimation of residential postapplication exposure for scenarios pertaining to cyphenothrin pet spot-on products. The surrogate data were derived from a study on the dislogeability of tetrachlorovinphos from animals treated with a pump-spray treatment product (MRID 45485501). The study was previously reviewed by HED and determined to be suitable for risk assessment purposes. The dataset for this study estimates the percent available on the fur that is transferred to the hand to be approximately 5%. The 5% value from the tetrachlorovinphos dislodgeability study was used in lieu of the more conservative 20% standard value from HED's Residential Exposure SOPs 1,2,3, based on HED's determination that the tetrachlorvinphos study was more reflective of the spot-on use than the study from which the standard 20% value was derived. The 20% value was derived from a study on a shampoo product that was applied by vigorous rubbing of the treated area for an extended period of time. In using these data, HED assumed that the proposed cyphenothrin pet spot-on products are more similar to the tetrachlorovinphos product than to the shampoo product.

The residential postapplication section of the risk assessment (D317077) used the tetrachlorovinphos dislodgeability value (5%) to estimate toddler combined risk from exposures to cyphenothrin from the proposed pet spot-on uses. The combined estimated margins of exposure (MOEs) (pet hug and hand-to-mouth scenarios) for childrens' exposure to treated companion dogs are less than 100 (day zero) and, therefore, are of concern to HED. Sergeant's Pet Care, Inc. has expressed concern that the tetrachlorovinphos study, which was conducted using a pump-spray product, is not appropriate to assess the proposed spot-on formulation. If HED were to use the dislodgeability value (0.05%) from the study (MRID 45869401) submitted by Sergeant's Pet Care, Inc., the combined MOEs would be two orders of magnitude higher (well above the LOC of 100), and, therefore, not of concern to HED. However, this study, as previously mentioned, was determined not to be suitable for risk assessment purposes. While not chemical-type or use specific, the tetrachlorovinphos study was determined to be the most appropriate and protective study available for the assessment of potential risk from residential postapplication exposure to cyphenothrin from the proposed pet spot-on uses.

Previously Submitted Studies and Proposal to Upgrade the Studies

Sergeant's Pet Care, Inc. submitted dislodgeability studies (MRID 46082302 and 45869401) that were conducted with latex gloves instead of cotton gloves which would typically be used in a dislodgeability study. It is unclear to HED why the decision was made by the Registrant to perform the dislodgeability studies with a latex glove when the standard practice is the use of cotton gloves, due to their absorptive qualities. The Registrant's submitted request (MRID 46874501) cites a meeting in 2003 with the Agency in reference to this topic; however, neither the Registrant nor the Agency could locate any written documentation of the cited meeting.

Sergeant's Pet Care Products, Inc. performed a separate study, "Validation Study Comparing Dose Residue Recoverability of Etofenprox from Cotton and Latex Gloves Analysis of Data and Conclusions" (MRID 45869402) to support their decision to use a latex glove. The results of this study suggested that the use of latex gloves provided better sampling (i.e., higher recovery of residues) from the dogs than did cotton gloves; however, the study was found to be deficient. In the review completed March 6, 2006 by HED (D298228), the following limitations were described: missing information, including details regarding fortification methods; storage conditions of samples during shipping; the exact time from spike fortification to sample analysis; specific analytical methods used; the limit of quantitation (LOQ); and the sample preparation and handling of controls. Most notably, HED was concerned that both the cotton and latex glove results fell below the acceptable spike recovery range of 70-120%. Mean recovery of etofenprox ranged from 11.51% to 16.54% for cotton gloves, while mean recovery ranged from 54.47% to 67.56% for latex gloves (6 samples per matrix). Sergeant's Pet Care Products, Inc.'s submitted request (MRID 46874501) addresses a majority of the listed deficiencies. However, it does not adequately address the problem of low recoveries, a deficiency acknowledged by the Registrant. HED has determined that low mean recovery, exacerbated by a low number of samples per matrix (6 for each cotton, and latex), results in greater uncertainty than is acceptable for risk assessment purposes, particularly, since the study was conducted using latex gloves. HED's Scientific Advisory Council for Exposure (ExpoSAC) believes that cotton gloves are the most absorbent media and, therefore, should be used in this type of dislodgeability study.

The submitted request (MRID 46874501) also specifically addresses study "Dislodgeability of Etofenprox from the Haircoat of Cats Treated with a Spot-on Formulation" (MRID 46082302). Like the cotton and latex validation study, this study was found to have multiple limitations which prohibits its use for risk assessment purposes. These include: the LOQ values were not provided and residues detected below the LOQ were reported as 0; detailed information regarding the analytical methodology including extraction procedures of etofenprox from the gloves and HPLC detection methods were not provided; laboratory and field fortification spikes were not used in the study; information regarding the storage stability of the samples was not provided; method validation results indicate that the recovery of etofenprox from spiked glove samples was very low (i.e., 47 to 54%); and latex gloves were used in the study to

monitor residue transfer from cats' fur to human hands. As was the case for the previously discussed study (MRID 45869402), the current submission addresses a majority of these deficiencies. However, again HED has determined that low mean recovery results in greater uncertainty than is acceptable for risk assessment purposes. Furthermore, the validation study (MRID 45869402), which was performed to support the use of a latex glove in study MRID 46082302, was determined not to be reliable for risk assessment purposes. Finally, in the dislodgeability study no etofenprox was recovered at all from any gloves used to stroke the cat for 4 hours, 24 hours, or 2 days after treatment. It is the opinion of HED's ExpoSAC that the absence of removable, detectable residues is unlikely following pet treatment with etofenprox.

HED has concluded that Sergeant's Pet Care Products, Inc. submitted request (MRID 46874501) also fails to adequately address the deficiencies of MRID 45869401. The results of this study give a dislodgeability value of 0.05% which the Registrant has requested HED use in the risk assessment (D317077) for the available percentage of cyphenothrin for transfer to the hands. The Registrant indicates that the deficiencies for this study are the same as those for MRID 46082302 and, therefore, did not provide any additional information addressing this study specifically. While some of the deficiencies are adequately addressed by the submitted information, additional study-specific information is needed to address the remaining deficiencies. As with the other studies, the low mean recoveries and the choice of the latex glove render the study unacceptable for risk assessment purposes.

As detailed in this document, the cyphenothrin residential postapplication risk assessment (D317077) used tetrachlorovinphos surrogate dislodgeability data (5%) to estimate toddler combined risk from exposure to cyphenothrin from the proposed pet spot-on uses. Sergeant's Pet Care, Inc. stated in the submitted request (MRID 46874501) that they did not believe that it is appropriate to use an organophosphate (OP) chemical (tetrachlorovinphos) to assess exposures to cyphenothrin. The Registrant also stated that they did not agree with the use of a pump-spray study to assess a spot-on use. The arguments presented by the Registrant are considered by HED to be valid; however, the best available data were used. In order to refine the risk assessment, HED recommends that a new study (i.e., one without the deficiencies) be conducted.

Although HED determined that the tetrachlorovinphos data were the best surrogate data available, it is likely that these data overestimate residential postapplication risk due to differences between the use patterns (spray-pump vs spot-on). When a pump-spray product is applied, it goes on wet, soaking the animal's coat in the areas of treatment, with some product eventually seeping to the skin. A spot-on is applied directly to the skin (through parted coat) in a manner which results in little contact with the animal's coat. As a result of these differences, the pump-spray treatment is presumed to result in more readily available surface residues for transfer to humans than the proposed spot-on treatments. Spot-on treatments are applied directly to the animals' skin, and thought to migrate more along the skin of the animal (i.e., not the fur). Therefore, the dislodgeability estimate of 5% used for the risk assessment may be greater than would be expected from the spot-on use; however, due to the uncertainty of the Registrant's

submitted study, the result of 0.05% dislodgeability cannot be used for risk assessment purposes.

The combined estimated margin of exposure (MOE) (pet hug and hand-to-mouth scenarios) for childrens' exposure to treated companion dogs (day zero), based on the assumption of 5% dislodgeability, is 70 ("Occupational and Residential Exposure Assessment for Proposed Section 3 Registration of Cyphenothrin on Domestic Pets" (D317077). If a slightly lower dislodgeability value (e.g., 3%) were used, the estimated combined MOE for children would be approximately 120, which is above the LOC of 100 and, therefore, not of concern to HED. While HED has provided a rationale for using the 5% value for dislodgeable residue, the most appropriate value for use in the risk assessment of the proposed spot-on uses would be determined from an acceptable cyphenothrin residue transferability study. HED understands that Sergeant's Pet Care, Inc. intends to move forward with a dog spot-on study to measure dislodgeable residues, as they have submitted a draft protocol for this study. The Registrant's draft protocol has been reviewed by HED (D330741) and suggestions have been made for how this should be performed. Furthermore, HED recognizes that the 5% value is conservative in nature and anticipates the confirmatory study may generate a value (3% or less) which would result in an acceptable combined MOE for residential postapplication risk.