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OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

DATE: **7/1/2010**

SUBJECT: **Spinetoram:** Occupational and Residential Exposure/Risk Assessment for use as a Spot-on on Cats and Kittens

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Petition No.:

Risk Assessment Type: ORE
TXR No.: NA
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DP Barcode: D376658
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Regulatory Action: Section 3 Registrations
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Registration Division

Elanco Animal Health, a division of Eli Lily and Company, has requested a registration of the active ingredient (ai) spinetroram for use as a spot-on on cats and kittens. This document contains an occupational and residential exposure/risk assessment for the requested uses. An aggregate human risk assessment for these new uses is presented in a separate Health Effects Division (HED) memorandum.

1.0 Executive Summary

This document presents an occupational and residential exposure/risk assessment of a new spinetoram use. The formulated end-use product is labeled under the trade name

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L899 Insecticide. The proposed product is formulated as a spot-on for flea control for cats and kittens.

Hazard Identification

The Agency identified adverse effects from exposure to spinetoram at durations of exposure ranging from short-term (up to 30 days) to intermediate-term durations (1 to 6 months) to long-term (chronic) durations (more than 6 months). No dermal endpoint was selected and, therefore, quantification of dermal risk is not required. Short-term inhalation and incidental oral risks were assessed using a No Observable Adverse Effect Level (NOAEL) of 4.9 mg/kg/day from a subchronic feeding study in dogs. Intermediate-term inhalation and incidental oral risks were assessed using a NOAEL of 2.49 mg/kg/day from a chronic toxicity dog study. An assumption of equivalent toxicity from the oral and inhalation routes of exposure was made (i.e., 100% inhalation absorption). A body weight of 70 kg was used in the risk assessment. Exposure from the use of spot-on products is expected to occur for short and intermediate durations. The level of concern (LOE) for exposure is a margin of exposure (MOE) greater than or equal to 100.

Use Profile

Spinetoram (XDE-175) is a multicomponent tetracyclic macrolide developed for the control of various insects. It consists of two closely related active ingredients, XDE-175-J and XDE-175-L, present in an approximate 3:1 ratio. Spinetoram is a fermentation product of *Saccharopolyspora spinosa* and is an analogue of the insecticide spinosad (PC code 110003; registered for application to numerous crops); its mode of action is disruption of nicotinic/gamma amino butyric acid (GABA)-gated chloride channels. Spinetoram is currently registered as liquid, dry flowable, and water-dispersible granule formulations for use on agricultural crops, commercial aquatic plants, ornamentals, tree farms/plantations, turfgrass, home gardens and lawns, and for the control of red imported fire ants. The proposed use is as a spot-on for flea control. L899 Insecticide is proposed as a monthly topical solution for the prevention and treatment of flea infestations for cats and kittens eight weeks of age and older. Spinetoram can be used by homeowners and by commercial applicators.

Occupational Handler Exposure/Risk

HED determined there is a potential for short- and intermediate-term exposure in occupational settings during the application of products containing spinetoram. Proposed domestic pet spot-on use of spinetoram could be performed by professional animal care workers; however, exposure/risk from application to cats was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-contained, as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

Occupational Post-application Exposure/Risk

Occupational post-application activities associated with spot-on products are either not expected to occur or are expected to be significantly less than residential post-application exposures (i.e., minimal involvement by a professional animal care worker with the animal is assumed to occur after such treatment occurs). EPA believes that the residential post-application exposure/risk assessment is reasonably protective for occupational post-application exposures/risks.

Residential Handler Exposure/Risk

Spinetoram is proposed for residential use in the control of fleas on domestic pets; however, exposure/risk from spinetoram application to domestic pets was not assessed because residential handler contact is expected to be negligible. EPA believes that the residential post-application exposure and risk assessment is reasonably protective for both occupational and residential handler exposures/risks. The spot-on product is designed to be self-contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

Spinetoram is currently registered for residential uses, including homeowner applications to home gardens, home lawn/ornamentals, turfgrass and fire ant mounds. These uses were assessed in previous reviews. (See Memo K. Lowe, DP Code 325865, and Spinetoram: Occupational and Residential Exposure/Risk Assessment for the New Use on Agricultural Crops, Commercial Aquatic Plants, Ornamentals, Tree Farms/Plantations, Turfgrass, Home Gardens and Lawns, and for the Control of Red Imported Fire Ants.)

Residential Post-application Exposure/risks

HED has determined that exposure to spinetoram is likely following residential use on cats and kittens. Individuals of varying ages can potentially be exposed when they have contact with pets treated with the spot-on product. It is assumed that most residential uses of spinetoram will result in short- and intermediate-term post-application dermal (adults and children 3 to <6 years old) and oral/hand-to-mouth (3 to <6 year olds) exposures. Only oral/hand-to-mouth exposures were assessed for spinetoram, since no dermal endpoint was selected.

Short-term incidental oral (hand-to-mouth) exposures to treated cats for children 3 to <6 years old resulted in estimated MOEs > 100 and, therefore, are not of concern to HED. Intermediate-term incidental oral (hand-to-mouth) exposures to treated cats for children 3 to <6 years old resulted in estimated MOEs > 100 and, therefore, are not of concern to HED.

Review of Human Research

This risk assessment does not rely on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical and, therefore, does not require review of ethical conduct.

2.0 Hazard and Toxicity Profile

Spinetoram has low acute toxicity via the oral, dermal and inhalation routes of exposure (Toxicity Category IV). It is a dermal sensitizer, but not an eye or dermal irritant.

The acute toxicity categories for spinetoram are summarized in Table 1. Spinetoram is a relatively new active ingredient. It was determined by HAZPOC, on 6/14/07, that spinetoram is toxicologically similar to another chemical, spinosad, which has been assessed for various uses by HED in previous risk assessments. HED has concluded that spinosad and spinetoram are toxicologically identical. As a result, HED picked the lowest of the spinosad and spinetoram endpoints for each scenario. Table 2 summarizes endpoints chosen by HED for spinetoram.

Adverse effects were identified at durations of exposure ranging from short-term (up to 30 days) to intermediate-term durations (1 to 6 months) to long-term (chronic) durations (more than 6 months). No dermal endpoint was selected and, therefore, quantification of dermal risk is not required. Short-term inhalation and incidental oral risks were assessed using a NOAEL of 4.9 mg/kg/day from a subchronic feeding study in dogs based on microscopic changes in a multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage. Intermediate-term inhalation and incidental oral risks were assessed using a NOAEL of 2.49 mg/kg/day from a chronic toxicity dog study based on vacuolation in glandular cells (parathyroid) and lymphatic tissues, arteritis, and increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels. An assumption of equivalent toxicity from the oral and inhalation routes of exposure was made (i.e., 100% inhalation absorption). A body weight of 70 kg was used in the risk assessment.

Structure-activity-relationship (SAR) analysis would indicate that spinetoram, like spinosad, would not be likely to be carcinogenic to humans. (HED's Hazard Assessment and Policy Committee (HAZPOC) June 18, 2007.)

Table 1. Acute Toxicity Profile – Spinetoram

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral rat	46695031	LD_{50} (F) > 5000 mg/kg	IV
870.1200	Acute dermal rat	46695034	$LD_{50} \geq 5000$ mg/kg	IV
870.1300	Acute inhalation rat	46695037	$LC_{50} > 5.50$ mg/L	IV
870.2400	Acute eye irritation rabbit	46695040	Slight eye irritant	IV
870.2500	Acute dermal irritation rabbit	46695043	not a dermal irritant	IV
870.2600	Skin sensitization mouse	46695046	Positive	-

Exposure Scenario	Point of Departure	Uncertainty/ FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short-Term (1-30 days)	NOAEL = 4.9 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	rLOC for MOE < 100 oLOC for MOE < 100	**Subchronic toxicity in dogs (spinosad);** LOAEL = 9.73 mg/kg/day based on microscopic changes in multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage.
Incidental Oral Intermediate-Term (1-6 months)	NOAEL = 2.49 mg/kg/day[1]	UF_A = 10x UF_H = 10x FQPA SF = 1x	rLOC for MOE < 100 oLOC for MOE < 100	**Chronic toxicity in dogs (spinetoram);** LOAEL = 5.36 mg/kg/day in males/5.83 mg/kg/day in females based on arteritis and necrosis of the arterial walls of the epididymides in males, and the thymus, thyroid, larynx, and urinary bladder in females.
Dermal (all durations)	Short-, Intermediate-and Long-Term dermal risk assessments are not required for the following reasons: 1) lack of concern for pre and/or post natal toxicity; 2) the combination of molecular structure and size as well as the lack of dermal or systemic toxicity at 1000 mg/kg/day in a 21-day spinosad and spinetoram dermal toxicity studies in rats which indicates poor dermal absorption; and 3) the lack of long-term exposure based on the current use pattern.			
Inhalation Short-Term (1-30 days)	NOAEL = 4.9 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	rLOC for MOE < 100 oLOC for MOE < 100	**Subchronic Feeding Study in Dogs (spinosad);** LOAEL = 9.73 mg/kg/day based on microscopic changes in multiple organs, clinical signs of toxicity, decreases in mean body weights and food consumption, and biochemical evidence of anemia and possible liver damage.
Inhalation Intermediate-Term (1-6 months)	NOAEL = 2.49 mg/kg/day	UF_A = 10x UF_H = 10x FQPA SF = 1x	rLOC for MOE < 100 oLOC for MOE < 100	**Chronic toxicity dog (spinetoram);** LOAEL = 5.36 mg/kg/day in males/5.83 mg/kg/day in females based on arteritis and necrosis of the arterial walls of the epididymides in males, and the thymus, thyroid, larynx, and urinary bladder in females.
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans" based on carcinogenicity studies in spinosad and spinetoram.			

[1] NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (intraspecies). UF_H = potential variation in sensitivity among members of the human population (interspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose (a = acute, c = chronic). MOE = margin of exposure. LOC = level of concern (r = residential, o = occupational). N/A = not applicable.

3.0 Use Profile

Spinetoram is proposed for use on cats and kittens. The proposed product is formulated as a spot-on for flea control. L899 is proposed as a monthly topical solution for the prevention and treatment of flea infestations for cats and kittens eight weeks of age and older. Note only one size treatment is applied to all size kittens and cats 8 weeks and older. Spinetoram can be used by homeowners and by commercial applicators. Table 3 presents the proposed spot-on use as labeled for application to cats or kittens.

Table 3. Summary of Proposed Spot-On Product Containing Spinetoram (39.6% ai)		
EPA Reg. No.	Use Site	Application Rate
72642-0	Cats and Kittens (8 weeks or older)	0.019 fl oz or 0.55 ml: 231 mg ai/treatment

4.0 Occupational Exposure/Risk

HED has considered the potential for short- and intermediate-term dermal exposure in occupational settings during the application of products containing spinetoram.

4.1 Occupational Handler

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The anticipated use patterns and current labeling indicate occupational exposure scenarios based on the types of equipment and techniques that can potentially be used for spinetoram applications.

Spinetoram is proposed for use as a spot-on application to cats and kittens with occupational use likely occurring in a veterinary or professional pet grooming setting; however, exposure/risk from application to domestic pets was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair.

4.2 Occupational Post-application

Occupational post-application exposure to treated animals is not expected. Domestic pets are expected to be treated and immediately returned to their owners such that post-application contact will be negligible. EPA believes that the residential post-application exposure/risk assessment is reasonably protective for any potential occupational post-application exposures.

5.0 Residential (Non-Occupational) Exposure/Risk

HED has considered the potential for short- and intermediate-term dermal (adults and children 3 to <6 years old) and oral/hand-to-mouth exposures (children 3 to <6 years old) in residential settings resulting from homeowner use of the proposed products containing spinetoram. However, a dermal risk assessment is not required because there is no dermal endpoint.

5.1 Residential Handler Exposure/Risk

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The Agency believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task as was described above for occupational handlers. Residential handlers are

addressed somewhat differently by the Agency as homeowners are assumed to complete all elements of an application with little use of any protective equipment.

Spinetoram is formulated for residential use for the control of fleas on cats and kittens. Exposure/risk from spinetoram application to domestic pets was not assessed because handler contact is expected to be negligible. The spot-on product is designed to be self-contained as it is applied directly from the tube to the pet with the tip of the applicator used to part the pet's hair. In addition, a dermal endpoint was not selected so an exposure assessment was not done.

5.2 Residential Post-application Exposure/Risk

The proposed use of spinetoram on cats and kittens can result in a wide array of individuals of varying ages potentially being exposed when they have contact with treated animals. There is potential for dermal exposure to adults and children 3 to <6 years old and hand-to-mouth exposure to children 3 to <6 years old following contact with a treated cat or kitten, however, only hand-to-mouth exposure was assessed since an endpoint of concern for the dermal route was not identified.

The quantitative exposure/risk assessment developed for residential post-application is based on the following scenario:

(1) Hand-to-mouth exposure to children (3 to <6 year olds) from contact with a treated companion animal

5.2.1 Data and Assumptions for Residential Post-application Exposure Scenarios

The series of assumptions and exposure factors which serve as the basis for estimating the incidental oral (hand-to-mouth) exposures are derived from the "HED Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 19, 1997)" and the 1999 Draft Policy 13, "Post-application Exposure Assessment for Children from Treated Pets." The residential SOPs are currently undergoing further revision, but are not sufficiently developed for use in this assessment.

General assumptions and factors used in the risk calculations include:

- Daily dose is based upon the amount of active ingredient handled on the day of treatment (i.e., a single pet treatment). The Agency always considers the maximum application rates allowed by product labeling. Estimated risks are typically based on an even loading of residues across the entire surface of the animal, where Surface Area (cm^2) = ((12.3*((BW (lb)*454)^0.65)) from HED's 1993 Wildlife Exposure Factors Handbook.

- For the purposes of this assessment, a representative (average) cat size was assumed to be 10 lbs. Using the above formula, the surface area of a 10 lb cat is

2930 cm^2. The label notes only one size treatment (231 mg ai/ treatment) is applied to all size kittens and cats 8 weeks and older. Estimated exposure to a smaller (4 lb) and larger (16 lb) than average size cat were also assessed for range finding purposes. Surface areas were calculated for the 4 and 16 lb cats and an application rate of 231 mg ai/ treatment was used.

- On the day of application, it may be assumed that 20 percent (0.20) of the maximum application rate is available on the pet's body and transferred to the individual as a dislodgeable residue. This value is based on the professional judgment and experience of the OPP/HED staff from the review of company-submitted data and is believed to be an upper-percentile assumption (US EPA, 1999 SAP).

- Post-application activities must be assessed on the same day that the pesticide is applied because it is assumed that individuals could handle/touch their pets immediately after application.

- It is assumed that one pet is contacted per day.

- Children 3 to <6 years old are assumed to weigh 15 kilograms (representing an average weight from years one to six).

- Saliva extraction efficiency is 50 percent (i.e., every time the hand goes in the mouth approximately half of the residues on the hand are removed).

- The approach used to address the hand-to-mouth exposure pathway has been modified since 1999 Draft Policy 13, "Post-application Exposure Assessment for Children from Treated Pets." In the draft policy, contact with treated pets is based on 40 events per day (20 mouthing events/day for 2 hours). For each event, the palmar surface of the hands (i.e., 20cm^2/event) is placed in the mouth of the child contributing to non-dietary ingestion exposure. In the revised approach, the frequency term has been modified to an equilibrium approach analogous to the dermal exposure component (i.e., the frequency = 1 event/day). The approach was revised since the data from which the transferable residue concentrations were determined rely on a continuous contact (grooming) technique that would lead to concentrations on the hands which are anticipated to be significantly higher than would result from petting/hugging.

The following demonstrates the method used to calculate incidental oral (hand-to-mouth) exposures that are attributable to a child touching a treated cat or kitten and exhibiting mouthing behavior.

$$\text{PDR (mg/kg/day)} = \frac{[((AR * F_{AR}) / SA_{pet})) * (SAL) * SA_{hands} * Freq)]}{BW\ (kg)}$$

Where:

PDR	=	potential dose rate (mg/kg/day)
AR	=	application rate or amount applied to animal (231 mg ai/ treatment)
F_{AR}	=	fraction of the application rate available as transferable residue (0.20)
SA_{pet}	=	surface area of a treated cat or kitten (cm^2/ animal)
SA_{hands}	=	surface area of a child's hands (20 cm^2)
SAL	=	saliva extraction factor (50%)
Freq	=	frequency of hand-to-mouth events (1 event/day)
BW	=	body weight (15 kg)

And:

MOE = NOAEL (mg/kg/day) / PDR (mg/kg/day)

MOE	=	margin of exposure
NOAEL	=	no observed adverse effect level
PDR	=	potential dose rate

A summary of child (3 to < 6 years old) incidental oral exposure is presented in Table 4. Short-term incidental oral (hand-to-mouth) exposures for 3 to <6 year olds to treated cats resulted in estimated MOEs > 100 and, therefore, are not of concern to HED. Intermediate-term incidental oral (hand-to-mouth) exposures for 3 to <6 year olds to treated cats resulted in estimated MOEs > 100 and, therefore, are not of concern to HED.

Oral	231	4	1620	0.5	20	1	0.019	260	130
		10 (Avg.)	2930				0.010	490	250
		16	3980				0.0077	640	320

a. Application calculated from proposed label for spinetoram spot-on use.
b. Surface Area (cm^2) = ((12.3*((cat weight (lb)*454)^0.65))
c. PDR (mg/kg/day) = [((AR * F_{AR}, 0.20) / SA_{pet})) * (SAL) * SA_{hands} * Freq)] / BW (kg)
d. Short-term MOE = Short-term NOAEL (4.9 mg/kg/day) / PDR (mg/kg/day)
e. Intermediate-term MOE = Intermediate-term NOAEL (2.49 mg/kg/day) / PDR (mg/kg/day)

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