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

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

Date: 26-June-2008

Subject: **Spinosad.** Residue Chemistry Summary for Ear Tag Use on Beef and Dairy Cattle.

PC Code: 110003	**DP Barcode:** 354012
Decision No.: 382212	**Registration No.:** 72642-T - Spinosad Ear TAG
Petition No.: none	**Regulatory Action:** Section 3
Risk Assessment Type: not applicable	**Case No.:** none
TXR No.: not applicable	**CAS No.:** Spinosyn A and D: 131929-60-7 and 131929-63-0
MRID No: 47197604	**40 CFR:** 180.495

From: Tom Bloem, Chemist
Registration Action Branch 1, Health Effects Division (RAB1/HED); 7509P

Through: William Donovan, Ph.D., Chemist
Reregistration Branch 3/HED (7509P)

To: George Larocca/Bonaventure Akinlosotu (RM 13)
Registration Division (7505P)

Elanco Animal Health (Greenfield, IN) requested the registration of SPINOSAD EAR TAG (15% spinosad; EPA Reg. No. 72642 -x) as an end-use product for the control of horn flies and face flies on beef and dairy cattle. The proposal concludes that the currently-available livestock magnitude of the residue studies and the currently-established livestock tolerances are sufficient for the proposed use.

Executive Summary

Background: Spinosad is a fermentation product of *Saccharopolyspora spinosa*, a naturally-occurring soil organism. The product consists of two related active ingredients: spinosyn A and spinosyn D. The two active ingredients differ by one methyl group and are typically present at an 85:15 ratio (A:D). The registrant indicated that the exact mode of action is not known but is characterized by excitation of the insect nervous system, leading to involuntary muscle contractions, prostration with tremors, and paralysis (effects are consistent with excitation of the nicotinic acetylcholine receptors). Spinosad is currently registered for application to numerous crops with tolerances for the combined residues of spinosyn A and D ranging from 0.01-200 ppm (40 CFR 180.495).

Direction for Use: The petitioner is requesting registration of SPINOSAD EAR TAG (15% spinosad; 2.51 g ai/ear tag; EPA Reg. No. 72642 -x) as an end-use product for the control of horn flies (*Haematobia irritans*) and face flies (*Musca autumnalis*) on beef and dairy cattle. The label states the following: **(1)** do not apply to animals <6 months of age; **(2)** use one ear tag per animal; and **(3)** ear tags remain effective for up to 5 months.

Nature of the Residue - Livestock: The nature of the residue in livestock is adequately understood based on metabolism studies conducted on ruminants (oral and dermal), and poultry (oral). The metabolic pathway involved either the loss of a single methyl group from the N-methyl moiety on the foroamine sugar and/or the hydroxylation of the macrolide at several different positions. HED concluded that the residue of concern in livestock for risk assessment and tolerance enforcement purposes are spinosyns A and D (D243816, G. Herndon, 3-Mar-1998; D264984, W. Donovan, 14-Jun-2002).

Magnitude of the Residues - Livestock: Residues in/on beef/dairy cattle commodities are currently derived from dietary exposure (consumption of treated feed and feed through use), dermal application, and premise treatment. The petitioner is requesting an ear tag use for the control of horn flies and face flies. Based on the mass of spinosad present in each ear tag (2.51 grams) and since the label states that each ear tag is effective for up to 5 months (one ear tag per cow), a theoretical dermal deposition rate of 16.73 mg ai/day can be calculated (assumes a linear deposition and 0 g ai after 5 months). The petitioner submitted a summary of a depletion study which indicated average depletion rates from ear tags of 7.5-13.5 mg ai/day (n=5; overall average of 10.8 mg ai/day; 122-165 days; MRID 47197604).

In support of the registered dermal application use to beef/dairy cattle, the registrant submitted a dermal magnitude of the residue study. This study indicated that the registered pour-on treatment yielded the highest residues (5 applications at 2 mg ai/kg body weight; retreatment interval of 14 days). Based on the pour-on dermal magnitude of the residue data, the theoretical deposition rate from the ear tag use (16.73 mg ai/day), residue estimates derived from the ear tag use were calculated. These estimates were then combined with the residue estimates resulting from consumption of treated feed (including the feed through use) and pour-on/premise treatment. Based on a comparison of the expected total residue and the current tolerance and the conservative nature of this assessment (assumes that all methods of treatment are conducted simultaneously; each treatment results in the maximum residue), HED concludes that revised livestock tolerances are unnecessary.

Analytical Methods: Adequate livestock methods are available for tolerance enforcement. Method RES 94094 (GRM 95.03) is a HPLC/UV method suitable for determination of spinosad residues in ruminant commodities. Method GRM 95.03 has undergone successful ILV and EPA laboratory validation, and has been forwarded to the FDA for inclusion in the Pesticide Analytical Manual II (PAM Volume II; G. Herndon, 6-Apr-1999). Method RES 95114, an immunoassay method for determination of spinosad residues in ruminant commodities underwent a successful ILV and EPA laboratory validation and has been submitted to FDA for inclusion in PAM Volume II (G. Herndon, 5-Jan-1999).

Multiresidue Methods (MRMs) Testing: Data pertaining to multiresidue methods testing of spinosyns B and K and N-demethyl spinosyn D in conjunction with PP#6F4761/6H5754 which were previously submitted and forwarded to Food and Drug Administration (FDA) for review (S. Willett, 23-Jan-1997). Data pertaining to the multiresidue methods testing of spinosyns A and D were submitted in conjunction with PP#6G04692 and were also forwarded to FDA (G. Herndon, 1-May-1996).

Recommendation: HED concludes that the residue chemistry database supports an unconditional registration for the proposed ear tag use. Based on the currently-available data, revised livestock tolerances are unnecessary. A human-health risk assessment will be prepared as a separate document.

HED notes that a summary of the depletion data for spinosad from the ear tags were provided in MRID 47197604 and these data are reviewed in the current document. MRID 47197604 also includes waiver requests for acute oral and acute dermal toxicity tests. Since these data are not relevant to the residue chemistry review, they are not reviewed in this document.

Detailed Considerations

Background

Spinosad is a fermentation product of *Saccharopolyspora spinosa*, a naturally-occurring soil organism. The product consists of two related active ingredients: Spinosyn A and Spinosyn D. The two active ingredients differ by one methyl group and are typically present at an 85:15 ratio (A:D). The registrant indicated that the exact mode of action is not known but is characterized by excitation of the insect nervous system, leading to involuntary muscle contractions, prostration with tremors, and paralysis (effects are consistent with excitation of the nicotinic acetylcholine receptors). Spinosad is used for the control of many foliage feeding pests including lepidopterous larvae, leafminers, and thrips.

Table 1. Test Compound Nomenclature

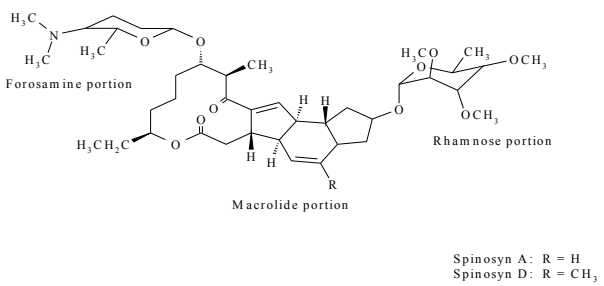
Chemical Structure	
Common name	Spinosad
Company experimental name	XDE-105
IUPAC name	**Spinosyn A:** (2*R*,3a*S*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-14-methyl-1*H*-8-oxacyclododeca[*b*]*as*-indacene-7,15-dione **Spinosyn D:** (2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-2-(6-deoxy-2,3,4-tri-*O*-methyl-α-L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetradeoxy-β-D-erythropyranosyloxy)-9-ethyl-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-4,14-dimethyl-1*H*-8-oxacyclododeca[*b*]*as*-indacene-7,15-dione
CAS name	**Spinosyn A:** 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-manno-pyranosyl)oxy]-13-[[5-(dimethylamino)-tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1*H*-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione **Spinosyn D:** 2-[(6-deoxy-2,3,4-tri-O-methyl-α-L-manno-pyranosyl)oxy]-13-[[5-(dimethylamino)-tetrahydro-6-methyl-2*H*-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-methyl-1*H*-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione
CAS #	**Spinosyn A:** 131929-60-7; **Spinosyn D:** 131929-63-0

Table 2. Physicochemical Properties of the Technical Grade Test Compound

Melting range	Spinosyn A: 84-99.5°C; Spinosun D: 161.5-170°C	EPA Fact Sheet
pH (10% slurry of spinosad in water)	7.74	
Density at 20°C	0.512	
Water solubility (ppm)	Spinosyn A: 89.4; Spinosyn D: 0.495	
Vapor pressure at 25°C (kPa)	Spinosyn A: 3.0×10^{-11}; Spinosyn D: 2.0×10^{-11}	
Dissociation constant (pK_a)	not available	
Octanol/water partition coefficient $Log(K_{OW})$	**Spinosyn A** - 2.8 (pH 5), 4.0 (pH 7), and 5.2 (pH 9); **Spinosyn D** - 3.2 (pH 5), 4.5 (pH 7), and 5.2 (pH 9)	
UV/visible absorption spectrum	not available	

OPPTS GLN 860.1200 Directions for Use

The petitioner is requesting registration of SPINOSAD EAR TAG (15% spinosad; 2.51 g ai/ear tag; EPA Reg. No. 72642 -x) as an end-use product for the control of horn flies (*Haematobia irritans*) and face flies (*Musca autumnalis*) on beef and dairy cattle. The label states the following: **(1)** do not apply to animals <6 months of age; **(2)** use one ear tag per animal; and **(3)** ear tags remain effective for up to 5 months.

OPPTS GLN 860.1300 Nature of the Residue, OPPTS GLN 860.1340 Residue Analytical Method, and OPPTS 860.1360 - MRMs

See Executive Summary.

OPPTS 860.1480 Meat/Milk/Poultry/Eggs

Residues in/on beef/dairy cattle commodities are currently derived from dietary exposure (consumption of treated feed and feed through use (D347514, T. Bloem, 24-Apr-2008)), dermal application (D264984, W. Donovan, 14-Jun-2002), and premise treatment (D264984, W. Donovan, 14-Jun-2002). Based on the mass of spinosad present in each ear tag (2.51 grams) and since the label states that each ear tag is effective for up to 5 months (one ear tag per cow), a theoretical dermal deposition rate of 16.73 mg ai/day can be calculated (assumes a linear deposition and 0 g ai after 5 months; 2.51 g ai ÷ 150 days = 16.73 mg ai/day). The petitioner submitted a summary of a depletion study which indicated average depletion rates from ear tags of 7.5-13.5 mg ai/day (n=5; overall average of 10.8 mg ai/day; 122-165 days; MRID 47197604).

In support of the registration for dermal application of spinosad to beef/dairy cattle, the registrant previously submitted a dermal magnitude of the residue study (D264984, W. Donovan, 14-Jun-2002). This study indicated that the registered pour-on treatment yielded the highest residues (5 applications at 1.82 mg ai/kg body weight; retreatment interval of 14 days). Residue estimates in beef/dairy cattle commodities resulting from the ear tag use were calculated using the dermal pour-on magnitude of the residue data (D264984, W. Donovan, 14-Jun-2002) and assumed the following (see Table 3 for estimates): **(1)** theoretical deposition rate (16.73 mg ai/day); **(2)** beef/dairy cattle weigh 500/590 kg (communication from B. Schneider); **(3)** for all commodities excluding fat, the ear tag residue estimate is based on 56 days of exposure rather than 150 days (i.e., 5 months) as the dermal use is only permitted for 56 days (5 applications with a 14-day RTI) and the dermal magnitude of the residue study demonstrated a decrease in spinosad residues as the preslaughter interval increased; therefore, residue estimates as a result of the ear tag use were calculated by multiplying the residue estimate from the dermal study by 0.17 (milk; 0.17 = (16.73 mg ai/day x 56 days) ÷ (1.82 mg ai/kg/app x 590 kg x 5 app)) or 0.21 (tissues excluding fat; 0.21 = (16.73 mg ai/day x 56 days) ÷ (1.82 mg ai/kg/app x 500 kg x 5 app)); and **(4)** the residue estimate resulting from the ear tag use for fat is based on 150 days of exposure as the dermal magnitude of the residue study did not demonstrate a decrease in spinosad residue as the preslaughter interval increased; therefore, residue estimates in fat as a result of the ear tag use were calculated by multiplying the residue estimate from the dermal study by 0.55 (0.55 = (16.73 mg ai/day x 150 days) ÷ (1.82 mg ai/kg/app x 500 kg x 5 app)).

Table 3 also contains information concerning the expected residues in/on beef/dairy commodities resulting from consumption of treated feed (this includes the feed through use), dermal/premise t4reatment, and the proposed ear tag use (for derivation of the dietary and dermal premise residue estimates see D347514, T. Bloem, 24-Apr-2008). The three sources of spinosad in beef/dairy cattle commodities were added together

and compared to the current spinosad tolerances (see Table 3). Based on a comparison of the expected total residue and the current tolerance and the conservative nature of this assessment (assumes that all methods of treatment are conducted simultaneously; each treatment results in the maximum residue), HED concludes that revised livestock tolerances are unnecessary.

Table 3: Calculation of Total Residues in Ruminants.

Matrix	Residue from Diet (ppm)[1]	Residue from Pour-on (ppm)[1]	Residue from Ear Tag (ppm)[2]	Total Residue (ppm)	Current Tolerance (ppm)[3]
Muscle	6.73	0.285	0.06	7.07	7.0
Fat	31.57	2.722	1.50	35.79	50
Kidney	11.98	0.952	0.20	13.13	15
Liver	13.95	1.178	0.24	15.37	15
Milk, whole	6.22	1.77	0.31	8.30	10
Milk, fat	--	--	--	103.74[4]	100

[1] See D347514 (T. Bloem, 24-Apr-2008) for calculation of these residues.
[2] See text for derviation of these estimates.
[3] Tolerance expression for the combined residues of spinosyn A and D and recommended in D347514 (T. Bloem, 24-Apr-2008).
[4] Milk fat residue estimated as 12.5x the residue in whole milk (D249374, M. Doherty,14-Jun-1999).

OPPTS 860.1550 Proposed Tolerances

The petitioner has not proposed tolerances and HED has concluded that the currently established cattle tolerances are sufficient for the proposed use.

RDI: RAB1 chemists (25-Jun-2008)
T. Bloem:S10945:PY1:(703)-605-0217