



Pesticide Fact Sheet

Name of Chemical: Spinosad
Reason for Issuance: New Chemical/First Food Use (Cotton)
Date Issued:
Fact Sheet Number:

DESCRIPTION OF CHEMICAL

Chemical Name:

(Spinosyn A) 2-[(6-deoxy-2,3,4-tri-O-methyl- α -L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-methyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, [2R-[2R*,3aS*,5aR*,5bS*,9S*,13S*(2R*,5S*,6R*),14R*,16aS*,16bR*]] (9CI)

(Spinosyn D) 2-[(6-deoxy-2,3,4-tri-O-methyl- α -L-mannopyranosyl)oxy]-13-[[5-(dimethylamino)tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-4,14-dimethyl-1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, [2S-[2R*,3aS*,5aR*,5bR*,9R*,13R*(2S*,5R*,6S*),14S*,16aR*,16bR*]] (9CI)

Common Name: Spinosad

Trade Name: XDE-105, Tracer

CAS Nos.: 131929-60-7 (spinosyn A) and
131929-63-0 (spinosyn D)

Empirical Formula: C₄₁ H₆₅ NO₁₀ (spinosyn A) C₄₂ H₆₇ NO₁₀
(spinosyn D)

Chemical Family: Spinosyns (macrocyclic lactone isolated from soil organism *Saccharopolyspora spinosa*)

Year of Initial Registration: 1997

U.S. Registrant: DowElanco

USE PATTERNS AND FORMULATION

Registered Use: Insect control on cotton

Pests Controlled: Tobacco budworm, Cotton bollworm, Cotton leafperforator, European corn borer, Armyworms, Loopers, Saltmarsh caterpillar, and Thrips

Types of Formulations: 90.4% Technical and 44.2% Suspension Concentrate

Types and Method of Application: Foliar application to cotton using air or ground equipment equipped for conventional insecticide spraying

Application Rate: 0.04 to 0.09 pounds of active ingredient per acre per application up to 0.45 pounds of active ingredient per acre per growing season

I. SCIENCE FINDINGS

A. Summary Science Statements:

Spinosad is a new active ingredient with a unique mode of action against insect pests and is the first of a new class of spinosyn products developed for commercial use. Both technical spinosad (XDE-105) and end use product (Tracer) are classified as a Toxicity Category III pesticides and are labeled with the signal word "Caution" based on the acute dermal study. With respect to subchronic toxicity spinosad was evaluated in 13-week dietary studies and showed NOEL's of 4.9 mg/kg/day in dogs, 6 mg/kg/day in mice, and 8.6 mg/kg/day in cats. No dermal toxicity or systemic toxicity occurred in a 21-day repeated dose dermal toxicity study in rabbits given 1000 mg/kg/day (limit dose). Based on chronic toxicity testing with spinosad in the dog, the most sensitive species tested, a RfD of 0.0268 mg/kg/day is being established based on a NOEL of 2.68 mg/kg/day and an uncertainty factor of 100. There was no evidence of carcinogenicity in two rodent species at all dosages tested. Mutagenicity studies showed no mutagenic activity associated with spinosad. There was no developmental effects observed in two oral developmental toxicity studies in rats and rabbits up to the highest dose tested (HDT). The NOEL found for maternal and pup effects was 10 mg/kg/day (HDT). Neonatal effects at 100 mg/kg/day were attributed to maternal toxicity. Spinosad did not cause neurotoxicity in rats in acute, subchronic or chronic toxicity studies. Animal metabolism studies showed no major differences in the bioavailability, routes or rates of excretion or metabolism of spinosyn (Factor A) or spinosyn (Factor D) following oral administration in rats. Urine and fecal excretions were almost completed at 48 hours post dosing.

Sufficient data are available to characterize Spinosad from an ecological and environmental fate standpoint. Laboratory data indicate spinosad is highly toxic to bees. There are no acute or chronic levels of concern (LOC) exceeded for birds, terrestrial and freshwater aquatic organisms or acute LOC's exceeded for estuarine organisms. Spinosad is relatively short-lived in the field and photodegrades rapidly, half-lives less than one day. Leaching data show that Spinosad and its aged residues are unlikely to leach in most soils, are relatively immobile and poses little threat to groundwater.

B. Chemical Characteristics

Color - Light gray to white

Physical State - Solid

Odor - Slightly stale water

Melting Point - 84 C to 99.5C (spinosyn A) and 161.5 C to 170 C (spinosyn D)

Density, Bulk Density or Specific Gravity - 0.512 (s.g. at 20C)

Solubility (technical) - Water = 89.4 ppm (spinosyn A) and 0.495 ppm (spinosyn D)

Acetone = 16.8 g/mL (spinosyn A) and 1.01 g/mL (spinosyn D)

Acetonitrile = 13.4 g/mL (spinosyn A) and 0.255 g/mL (spinosyn D)

Dichloromethane = 52.5 g/mL (spinosyn A) and 44.8 g/mL (spinosyn D)

Hexane = 0.448 g/mL (spinosyn A) and 743 ppm (spinosyn D)

Methanol = 19.0 g/mL (spinosyn A) and 0.252 g/mL (spinosyn D)

1-Octanol = 0.926 g/mL (spinosyn A) and 0.127 g/mL (spinosyn D)

Toluene = 45.7 g/mL (spinosyn A) and 15.2 g/mL (spinosyn D)

Vapor Pressure at 25C = 3.0×10^{-11} kPa (spinosyn A) and 2.0×10^{-11} kPa (spinosyn D)

Octanol/Water Partition Coefficient = pH 5 buffer - 2.8

(spinosyn A) 3.2 (spinosyn D)

log Kow at 23C) pH 7 buffer - 4.0 (spinosyn A) 4.5

(spinosyn D) pH 9 buffer - 5.2 (spinosyn A) 5.2 (spinosyn D)

pH = 7.74 (10% slurry of spinosad technical in water)

Stability - Spinosad technical is stable after 28 days at ambient, 1220F, and in contact with stainless steel, brass, and ferric chloride (metal ions). [Active ingredient degrades photolytically under artificial sunlight.]

C. Toxicology Profile and Exposure Assessment

Acute toxicity: (90.4% spinosad technical) (XDE-105)

-Acute oral LD50 rat: 3738 mg/kg (males) and >5000 mg/kg (females). Toxicity Category IV.

-Acute dermal LD50 rabbit: >2000 mg/kg. Toxicity Category III.

-Acute inhalation LC50 rat: >5.18 mg/l. Toxicity Category IV.

-Primary eye irritation rabbit: Slight conjunctival irritation. Toxicity Category IV.

- Primary dermal irritation rabbit: No erythema and edema. Toxicity Category IV.
- Dermal sensitization guinea pig: Not a sensitizer.
- Acute neurotoxicity rat: No observed effect level >2000 mg/kg.

Acute toxicity: (44.2% suspension concentrate formulation) (Tracer)

- Acute oral LD50 rat: >5000 mg/kg. Toxicity Category IV.
- Acute dermal LD50 rabbit: >2000 mg/kg. Toxicity Category III.
- Acute inhalation LC50 rat: >5 mg/l. Toxicity Category IV.
- Primary eye irritation rabbit: Slight conjunctival irritation. Toxicity Category IV.
- Primary dermal irritation rabbit: Slight transient erythema and edema. Toxicity Category IV.
- Dermal sensitization guinea pig: Not a sensitizer.

Subchronic toxicity (spinosad technical)

- 21-day dermal rabbit: NOEL 1000 mg/kg/day.
- 13-week rat: NOEL 8.6 mg/kg/day (males) and 10.4 mg/kg/day (females). LOEL 42.7 mg/kg/day (males) and 52.1 mg/kg/day (females) based on thyroid vacuolation.
- 13-week mouse: NOAEL 7.5 mg/kg/day. LOAEL 22.5 mg/kg/day based on vacuolation multiple tissues, stomach glandular dilatation, and increased organ weights.
- 13-week dog: NOEL 4.89 mg/kg/day (males) and 5.38 mg/kg/day (females). LEL 9.73 mg/kg/day (males) and 10.47 mg/kg/day (females) based on microscopic changes in a variety of tissues, clinical signs of toxicity, decreases in mean body weights and food consumption and biochemical evidence of anemia and possible liver damage.
- 13-week neurotoxicity rat: NOEL >42.7 mg/kg/day (males) and >52.1 mg/kg/day (females). Highest dose tested.

Chronic toxicity and carcinogenicity (spinosad technical)

- 1-year chronic feeding dog: Dietary levels (mg/kg/day) - 0, 1.44, 2.68, and 8.46 (males) and 0, 1.33, 2.72, and 8.22 (females). NOEL 2.68 mg/kg/day (males) and 2.72 mg/kg/day (females). LOEL 8.46 mg/kg/day (males) and 8.22 mg/kg/day (females) based on vacuolation multiple tissues and increased liver enzymes and triglycerides.
- 1-year chronic neurotoxicity rat: Dietary levels (mg/kg/day) - 0, 2.5, 9.9, 24.9, 50.7 (males) and 0, 3.1, 12.4, 31, 63.8 (females). NOEL 50.7 mg/kg/day (males) and 63.8 mg/kg/day (females).
- 18-month carcinogenicity mouse: Dietary levels (mg/kg/day) - 0, 3.4, 11.4, 50.9 (males) and 0, 4.2, 13.8, and 67 (females). NOEL 11.4 mg/kg/day (males) and 13.8 mg/kg/day (females). MTD was exceeded at highest dose tested. No tumor indication at any dose level.
- 2-year chronic feeding and carcinogenicity rat: Dietary levels (mg/kg/day) - 0, 2.4, 9.5, 24.1, 49.4 (males) and 0, 3,

12, 30.3, and 62.8 (females). NOEL 2.4 mg/kg/day (males) and 3.0 mg/kg/day (females). LOEL 9.5 mg/kg/day (males) and 12 mg/kg/day (females) based on thyroid vacuolation. MTD was exceeded at highest dose tested. No tumor induction at any dose level.

Developmental and reproductive toxicity (spinosad technical)

- Developmental toxicity rat: Dietary levels (mg/kg/day) - 0, 10, 50, and 200. Maternal NOEL 50 mg/kg/day. Maternal LOEL 200 mg/kg/day based on decreased body weight. Developmental NOEL 200 mg/kg/day.
- Developmental toxicity rabbit: Dietary levels (mg/kg/day) - 0, 2.5, 10, 50. Maternal NOEL 10 mg/kg/day. Maternal LOEL 50 mg/kg/day based on decreased body weight and feed consumption and abortions. Developmental NOEL 50 mg/kg/day.
- Reproductive toxicity rat: Dietary levels (mg/kg/day) - 0, 3, 10, 100. Developmental NOEL 10 mg/kg/day. Developmental and parental LOEL 100 mg/kg/day based on decreased gestation survival, body weight, and litter size (neonatal). Developmental effects were due to maternal toxicity.

Mutagenicity (spinosad technical)

- Ames test reverse mutation assay (Salmonella typhimurium and Escherichia coli) with or without metabolic activation showed no mutagenic activity. In Vitro induction of chromosome aberrations in Chinese hamster ovary cells. Spinosad did not induce chromosomal aberrations in vitro in CHO cells.
- In Vitro induction of forward mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells. Test conducted with and without metabolic activation showed spinosad was not mutagenic.
- In Vitro induction of micronuclei in bone marrow of ICR mice. Spinosad did not induce micronuclei.
- In Vitro induction of unscheduled DNA synthesis in primary cultures of adult rat hepatocytes. Spinosad did not induce DNA repair synthesis in cultured rat hepatocytes and thus was not mutagenic.

Metabolism

- Metabolism in rat. Spinosad is rapidly absorbed and extensively metabolized. There were no major differences in the bioavailability, routes or rates of excretion, or metabolism of spinosyn A and spinosyn D following oral administration in rats. In addition, the routes and rates of excretion were not affected by repeated administration.

Carcinogenicity

- Based on the available carcinogenicity studies in two rodent species Spinosad has not been determined to be a human carcinogen. A final cancer classification using the Guidelines

for Carcinogen Risk Assessment published September 24, 1986 (51 FR 33992) is pending however the current data does not indicate that a cancer risk assessment will be necessary.

D. Ecological Effects Profile

- Acute oral LD50 northern bobwhite quail and mallard duck: >1333 mg/kg. Slightly toxic.
- Acute dietary LC50 northern bobwhite quail and mallard duck: >5156 ppm. Practically nontoxic.
- Avian one-generation reproduction study in northern bobwhite quail and mallard duck: NOEC 550 ppm and LOEC 1100 ppm.
- Acute 96-hour LC50 rainbow trout: 30 ppm. Slightly toxic.
- Acute 96-hour LC50 bluegill sunfish: 5.94 ppm. Moderately toxic.
- Freshwater fish early life-stage rainbow trout: NOEC 0.498 ppm, LOEC 0.962 ppm, and MATC 0.692 ppm.
- Acute 48-hour EC50 daphnid: 14 ppm. Slightly toxic.
- Freshwater aquatic invertebrate life-cycle daphnid: NOEC 0.0006 ppm, LOIC 0.0012 ppm, MATC 0.0008 ppm.
- Acute estuarine 96-hour LC50 sheepshead minnow: 7.9 ppm. Moderately toxic.
- Acute estuarine 96-hour LC50 grass shrimp: >9.76 ppm. Moderately toxic.
- Acute estuarine 96-hour EC50 eastern oyster: 0.3 ppm. Very highly toxic.
- Nontarget aquatic plant toxicity EC50: 10.6 ppm (duckweed/*Lemna gibba*), >105.5 ppm (green algae/*Selenastrum capricornutum*), 0.23 ppm (marine diatom/*Skeletonema costatum*), 0.09 ppm (freshwater diatom/*Navicula pelliculosa*), and 8.9 ppm (blue-green algae/*Anabaena flos-aquae*).
- Nontarget terrestrial plants EC25: > 25% detrimental effects at 0.18 lb a.i./acre.
- Honey bee acute contact 48-hour LD50 : 0.0029 ug/bee. Highly toxic.

In order to complete its ecological effects assessment of spinosad, EPA is requesting the registrant to conduct additional tests including: an estuarine fish early life-cycle study, an estuarine invertebrate life-cycle study, and a honey bee toxicity of residues on foliage study. These studies will be included in the conditional registration for use of spinosad on cotton.

All environmental fate data requirements have been satisfied. Additional data are still necessary regarding the mode of action on the insects nervous system and if this mode of action is the same for other organisms of concern. Additional data are also needed to see if modifications of Spinosyn D result in changes in biological activity.

E. Environmental Fate and Groundwater Profile

- Hydrolysis: No degradation at pH 5 and 7. Half lives at pH 9 of 200 days for spinosyn A and 259 days for spinosyn D. The hydrolysis products for spinosyns A and D at pH 9 are isomers formed by loss of the amino sugar and formation of a double bond within the macrolide ring system.
- Photodegradation in water: Half lives in summer sunlight and pH 7 were 0.93 day for spinosyn A and 0.82 day for spinosyn D.
- Photodegradation in soil: Half lives on Commerce silt loam soil exposed to sunlight for up to 30 days were 82 days for spinosyn A and 44 days for spinosyn D.
- Aerobic soil metabolism: Half lives were 9.4 to 17.3 days for spinosyn A and 14.5 days for spinosyn D. Spinosyn A degraded to one major metabolite identified as spinosyn B which is formed by loss of a methyl group from the nitrogen of the amino sugar. Spinosyn D produced a single major metabolite identified as mono-N-demethyl spinosyn D which is formed via the same mechanism as spinosyn B.
- Anaerobic aquatic metabolism: Half lives were 161 days for spinosyn A and 250 days for spinosyn D.
- Leaching/adsorption/desorption: spinosyn A relatively immobile to immobile with Freundlich adsorption (Kads) of 5.4 (Cecil loamy sand) to 323 (Commerce silt loam soil). Spinosyn D not determined because the lower water solubilities of spinosyn D compared to spinosyn A suggests that spinosyn D should be less mobile in soil than spinosyn A. Spinosyn B the major soil metabolite of spinosyn A is relatively immobile to immobile with Freundlich adsorption (Kads) of 4.3 (Cecil loamy sand) to 179 (Commerce silt loam soil).
- Terrestrial field dissipation: Half lives of 0.3 to 0.5 day for spinosyn A with no detectable radioactivity below 18 inches in Mississippi and 24 inches in California.
- Accumulation in fish: average BCF's for spinosyn A were 114X (whole fish), 28X (muscle tissue), and 152X (remainder of tissue). Spinosyn A does not appear to bioaccumulate nor would spinosyn D which has similar physical and chemical properties.

F. Residue and Metabolism Profile

- Plant metabolism: The metabolism of spinosad in cotton (as a result of foliar applications) is adequately understood. No trace of spinosyn A and spinosyn D and their related metabolites were found in various cotton seed fractions.
- Plant residue: Based on field trials residues of spinosad are not expected to be detectable in cottonseed at 0.01 ppm (limit of quantitation for analytical method). No concentration of residues in cottonseed process fractions at 6X maximum label rate.

-Animal metabolism: The metabolism of spinosad in goat and poultry (via an orally administered route) is adequately understood. For the use on cotton no residue tolerances are required for animal commodities.

-Confined rotational crop accumulation: No detectable residues of spinosad or related metabolites were found in rotational crops (lettuce, radish and wheat) planted 30 days after treatment.

G. Tolerance Assessment

A Section 408 tolerance under the Federal, Food, Drug and Cosmetic Act has been established for residues of Spinosad in/on the raw agricultural commodity (RAC) cottonseed at 0.02 ppm (40 CFR 180.495).

Consistent with sections 408 (b)(2)(C) & (D), EPA has reviewed the available scientific data and other relevant information in support of this tolerance. EPA has also assessed the toxicology data base for Spinosad in its evaluation of applications for registration on cotton. EPA has sufficient data to assess the hazards of Spinosad and to make a determination on aggregate exposure, consistent with section 408 (b)(2), for the conditional registration and time-limited tolerance for residues of Spinosad on cottonseed at 0.02 ppm.

-A chronic dietary exposure/risk assessment was performed for Spinosad using an RfD of 0.02 mg/kg/day based on a NOEL of 2.68 mg/kg/day from a 2-year dog feeding study with an uncertainty factor of 100. Available data do not indicate any pre-or post natal sensitivity thus no additional uncertainty factor for increased sensitivity in infant and children is warranted.

Using the conservative exposure assumptions described above and based on the completeness and reliability of the toxicity data base, EPA has concluded that dietary exposure to Spinosad from its use on cotton will utilize less than 1% of the RfD for the U.S. population and for all of the 22 population subgroups including children and infants. EPA generally has no concern for exposures below 100% of the RfD because the RfD represents the level at or below which daily aggregate dietary exposure over a life time will not pose significant risks to human health.

Because the Agency lacks specific water-related exposure data for most pesticides, EPA has commenced and nearly completed a process to identify a reasonable yet conservative bounding figure for the potential contribution of water related exposure to the aggregated risk posed by a pesticide. In developing the bounding figure, EPA estimated residue levels in water for a number of specific pesticides using various data sources. EPA

than applied the estimated residue levels, in conjunction with appropriate toxicological endpoints (RfD's or acute dietary NOEL's) and assumptions about body weight and consumption, to calculate, for each pesticide, the increment of aggregate risk contributed by consumption of contaminated water. This analysis can be found in the Special Record for the FQPA. While EPA has not yet pinpointed the appropriate bounding figure for consumption of contaminated water, the ranges EPA is continuing to examine are all well below the level that would cause Spinosad to exceed the RfD, for the tolerance on cottonseed. EPA has therefore concluded that the potential exposure associated with Spinosad in water, even at the higher levels EPA is considering as a conservative upper bound, would not prevent EPA from determining that there is a reasonable certainty of no harm with respect to the tolerance on cottonseed.

-Analytical Method: There is a practical method (HPLC with UV detection) for detecting (0.004 ppm) and measuring (0.01 ppm) levels of spinosad in or on food with a limit of detection that allows monitoring of food with residues at or above the levels set for this tolerance. The method has had a successful method tryout in EPA's laboratories.

There are no Canadian or Mexican tolerances and no Codex maximum residue levels established for residues of Spinosad on cottonseed. Therefore no compatibility problem exists.

II. SUMMARY OF REGULATORY POSITION AND RATIONALE

Spinosad meets the criteria specified in Section 3(c)(7)(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, and is eligible for conditional registration. The proposed pesticide products containing the new chemical spinosad are conditionally registered for use on cotton for the following reasons:

It has been determined that spinosad is a reduced risk product. Thus, a public interest finding is not needed for conditional registration.

Adequate toxicological, product chemistry, ecological effects, residue/metabolism and environmental fate data have been submitted and reviewed in support of a conditional registration and time-limited tolerance. Adequate data are available to assess the acute and chronic effects of spinosad to humans. The analysis of Spinosad using tolerance level residues shows that the use on cotton will not cause exposure to exceed the levels at which EPA believes there is an appreciable risk. All population subgroups examined by EPA are well below 100% of the RfD for chronic effects.

Based on exposure to aquatic organisms and terrestrial wildlife from cotton usage, adverse effects to non-target organisms and endangered species are unlikely. Likewise surface and groundwater contamination is unlikely from cotton use. Although it was not possible to complete an ecological effects (chronic assessment) for estuarine organisms, an extrapolation from the results of freshwater chronic testing indicates that chronic effects to estuarine organisms is not expected to occur.

To allow for the submittal and evaluation of the required data to meet the conditions for full registration and permanent tolerance, the conditional registration is effective until November 15, 1998, and the time-limited tolerance effective until November 15, 1999.

IV. SUMMARY OF DATA GAPS

- Estuarine fish early life-stage study
- Estuarine invertebrate life-cycle study
- Honey bee toxicity of residues on foliage study
- Cotton gin trash residue study
- Mode of action on insect nervous system

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