United States
Environmental Protection Agency
Office of Prevention, Pesticides and Toxic Substances (7505P)

Pesticide Fact Sheet

Name of Chemical: **Spinetoram**
Date Issued: **October 2009**

DESCRIPTION OF CHEMICAL

Common Name: Spinetoram (mixture of XDE-175-J and XDE-175-L)

Generic Name: **XDE-175-J:** (2*R*,3a*R*,5a*R*,5b*S*,9*S*,13*S*,14*R*,16a*S*,16b*R*)-13-{[(2*R*,5*S*,6R)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9-ethyl-14-methyl-7,15-dioxo-2,3,3a,4,5,5a,5b,6,7,9,10, 11,12,13,14,15,16a,16b-octadecahydro-1*H*-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-*O*-ethyl-2,4-di-*O*-methyl-alpha-L-mannopyranoside;

XDE-175-L: (2*S*,3a*R*,5a*S*,5b*S*,9*S*,13*S*,14*R*, 16a*S*,16b*S*)-13-{[(2*R*,5*S*,6*R*)-5-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yl]oxy}-9-ethyl-4,14-dimethyl-7,15-dioxo-2,3,3a,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-hexadecahydro-1*H*-as-indaceno[3,2-*d*]oxacyclododecin-2-yl 6-deoxy-3-*O*-ethyl-2,4-di-O-methyl-alpha-L-mannopyranoside

EPA Chemical Code: 110008 and 110009

Chemical Abstracts Service (CAS) Number: XDE-175-J: 187166-40-1
XDE-175-L: 187166-15-0

Pesticide Type: Insecticide

Chemical Class: Fermentation product of *Saccharopolyspora spinosa*, and an analogue of spinosad, a spinosyn

Year of Initial Registration : 2007

U.S. Technical Registrant: Dow AgroSciences, LLC
9330 Zionsville Road
Indianapolis, IN 46268-1053

Spinetoram received reduced risk status on March 6, 2006 and has been registered for use since September 28, 2007. This is the first issuing of a fact sheet for this chemical and the following information is current as of the publication date.

Use Patterns and Formulations

Pests Controlled: Lepidoptera larvae (e.g., worms, caterpillars), various Diptera, thrips, sawfly larvae, certain beetles and psyllids, some Orthoptera, fleas, and red imported fire ants

Application Sites: Spinetoram is registered for use on numerous agricultural crops; as well as home gardens; commercial aquatic plant production (restricted to commercial facilities which utilize fully contained pools or containers); ornamentals grown outdoors, in nurseries, or in greenhouses; tree farms or plantations; turfgrass and lawns.

Types of Formulations:
62719-539 Technical (manufacturing concentrate)
62719-540 GF-1640 WG-NC (suspension concentrate)
62719-541 Delegate WG (water dispersible granule)
62719-544 GF-1587 SC-NC (suspension concentrate)
62719-545 Radiant SC (soluble concentrate)
62719-596 GF-1629 SC (suspension concentrate)

Application Methods and Rates: Spinetoram controls or suppresses Lepidoptera larvae (e.g., worms, caterpillars), various Diptera, thrips, sawfly larvae, certain beetles and psyllids, some Orthoptera, fleas, and red imported fire ants. Foliar spray applications can be made by aerial, ground or chemigation application on all crops as needed for insect control. Up to 0.0156-0.438 lb. a.i./A can be applied annually, with single applications ranging from 3-6 times per year. Pre-harvest intervals (PHIs) range from 1 to 60 days. The reentry interval (REI) is 4 hrs. 62719-540 GF-1640 WG-NC is a 25% a.i. water soluble concentrate. 62719-541 Delegate WG is a 11.7% a.i. water dispersible granule. 62719-544 GF-1587 SC-NC is a 11.7% water soluble concentrate. 62719-545 Radiant SC is a 25% a.i. soluble concentrate. 62719-596 GF-1629 SC is a 5.9% a.i. water soluble concentrate.

The use of emulsified crop oils or methylated crop oil plus organosilicone combination products as spray adjuvants are recommended. For resistance management purposes, the use of the same ingredient or products with the same mode of action on consecutive generations of insects should be avoided.

SCIENCE FINDINGS

Spinetoram (XDE-175) is a multicomponent tetracyclic macrolide developed for the control of Lepidoptera larvae, leafminers, and thrips on a variety of crops. 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). Spinetoram and spinosad are considered toxicologically equivalent. Its mode of action is disruption of nicotinic/gamma amino butyric acid (GABA)-gated chloride channels.

CHEMICAL CHARACTERISTICS

Property	**Technical**
Melting points	**XDE-175-J:** 143.4°C; **XDE-175-L:** 70.8°C
pH	6.46 at 23.1°C for 1% w/w aqueous solution
Density	1.1485 g/cm^3 at 20°C
Water solubility (20°C)	**XDE-175-J:** 10.0 mg/L (purified water); 423 mg/L (pH 5 buffer); 11.3 mg/L (pH 7 buffer); ~8 mg/L (pH 9 buffer); 6.27 mg/L (pH 10 buffer) **XDE-175-L:** 31.9 mg/L (purified water); 1630 mg/L (pH 5 buffer); 46.7 mg/L (pH 7 buffer); 1.98 mg/L (pH 9 buffer); 0.706 mg/L (pH 10 buffer)
Solvent solubility (20°C)	Methanol - >250 g/L; Acetone - >250 g/L; n-Octanol - 132 g/L; Ethyl Acetate - >250g/L; 1,2-dichloromethane - >250 g/L; Xylene - >250 g/L; Heptane - 61.0 g/L
Vapor pressure	**XDE-175-J:** 5.3 x10^{-5} Pa at 20°C, 6.0 x10^{-5} Pa at 25°C **XDE-175-L:** 2.1 x10^{-5} Pa at 20°C, 4.2 x10^{-5} Pa at 25°C
Dissociation constant (pKa)	**XDE-175-J:** pKa = 7.86; **XDE-175-L:** pKa = 7.59
Octanol/water partition coefficient (20°C)	**XDE-175-J:** 2.44 (pH 5); 4.09 (pH 7); 4.22 (pH 9) **XDE-175-L:** 2.94 (pH 5); 4.49 (pH 7); 4.82 (pH 9)
UV/visible absorption spectrum	**XDE-175-J:** Solution / Wavelength λmax, nm / Extinction coefficient ε, L/(mol*cm) Neutral 245 12200 Basic (pH 12.6) 246 11700 Acidic (pH 1.04) 247 12400 **XDE-175-L:** Solution / Wavelength λmax, nm / Extinction coefficient ε, L/(mol*cm) Neutral 243 11100 Basic (pH 12.6) 244 11200 Acidic (pH 1.04) 202 9800 245 11400

HUMAN HEALTH ASSESSMENT

Hazard Characterization: The toxicological database for spinetoram was evaluated and compared to that of spinosad. The Agency concluded that spinosad and spinetoram should be considered toxicologically identical. This conclusion was based on the following: (1) spinetoram and spinosad are large molecules with nearly identical structures and (2) the toxicological profiles for each are similar (generalized systemic toxicity) with similar doses and endpoints chosen for human-health risk assessment. This is not a consideration for cumulative assessment where the concepts of mechanism of toxicity and potency are evaluated; rather, spinosad and spinetoram should be considered toxicologically identical in the same manner that metabolites are generally considered toxicologically identical to the parent.

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

In subchronic toxicity studies conducted in mice, rats, and dogs, spinetoram produced no adverse effects on survival, but decreases in body weight, body weight gain, and/or food consumption were observed. Spinetoram was shown to produce anemia in multiple species (rats, mice and dogs) with the presence of histiocytic aggregates of macrophages in various organs and tissues (lymph nodes, spleen, thymus, and bone morrow). Aggregation of macrophages was indicative of immune stimulation in response to insults of the chemical exposure and was considered secondary effects of the toxic effect to the hematopoetic system.

Dogs appear to be the most toxicologically sensitive species to spinetoram exposure. In the subchronic study with dogs, lower thymus weights, atrophy of the thymic cortex, arteritis and/or

perivascular inflammation in several organs with necrosis of the bone marrow leading to regenerative anemia were seen. These effects were seen in the presence of general systemic toxicity. In the chronic study with dogs, there were no treatment-related effects on survival, body weight, hematology, clinical chemistry or gross pathology. Treatment-related changes were limited to areteritis and necrosis of the areterial walls of the epididymides in one male dog and thymus, thyroid, larynx, and urinary bladder in one female at the high dose. It is postulated that chronic treatment exacerbated the spontaneous arteritis in genetically predisposed Beagle dogs ("Beagle Pain Syndrome"). In developmental toxicity studies in rats and rabbits no developmental effects were found. Both acute and subchronic neurotoxicity studies demonstrated no neurotoxic effects.

Spinetoram was shown to produce reproductive effects in parental female rats. The effects were characterized by treatment-related depletion of primordial and/or "growing" ovarian follicles, dystocia and other parturition abnormalities, late resorptions/retained fetuses and increased postimplantation loss. However, no adverse effects were observed on the offspring at dose levels that produced parental toxicity. The developmental toxicity and reproduction studies indicated no evidence of increased susceptibility of the offspring with pre and/or postnatal exposures.

No indication of neurotoxicity was observed in the acute neurotoxicity screening battery in rats, or in the subchronic and chronic toxicity studies conducted on spinetoram. All the mutagenicity studies conducted on spinetoram were negative. The NOAEL derived from the chronic dog study (2.49 mg/kg/day) is well characterized, and together with the traditional uncertainty/safety factors will provide adequate protection for effects observed in laboratory animals.

Since spinetoram is toxicologically identical to spinosad, and spinosad is classified as "not likely to be carcinogenic to humans" based on lack of evidence for carcinogenicity in mice and rats, the same classification will be applied to spinetoram.

FQPA Safety Factor for Infants and Children: The 10X Food Quality Protection Act (FQPA) safety factor for the protection of infants and children was reduced to 1X. The completeness of the toxicity database for spinetoram and the lack of residual uncertainties for pre-/post-natal toxicity, in conjunction with the database available on spinosad, is adequate for the risk assessment. No neurotoxicity has been demonstrated in acute and subchronic neurotoxicity screening studies and the assumptions used in the exposure assessment are unlikely to underestimate exposure.

Occupational Exposure: Standard conservative assumptions were used for estimating occupational risks; the level of concern for occupational inhalation exposure is a Margin of Exposure (MOE) of at least 100. There were no short- or intermediate-term risks of concern identified for occupational handlers (i.e., all MOEs $\geq$100). Long-term handler exposures are not expected; therefore, a long-term assessment was not conducted.

An occupational postapplication risk assessment was not performed because a dermal endpoint was not selected for spinetoram and inhalation exposures are expected to be minimal and less than the application exposures. In lieu of a postapplication risk assessment, a restricted-entry interval (REI) of 12 hours is assumed based on the default of 12 hours in the Worker Protection Standard for Agricultural Pesticides for active ingredients classified as category III or IV for acute dermal toxicity, skin irritation potential, and eye irritation potential. Based on review of the toxicological database, spinetoram is a candidate for a reduced-risk active ingredient and a 4-hour REI. However, each end-use product must meet the criteria of PR Notice 95-3 to qualify for an REI of 4 hours.

Residential Exposure: Short-term residential inhalation risks were estimated for adult residential handlers, as well as short-term postapplication incidental oral risks for toddlers, based on applications to

home lawns, home gardens and ornamentals. Risks were not of concern for either residential handler or postapplication activities (MOEs >970).

Aggregate Exposure and Risk Characterization: In accordance with the FQPA, the Agency considered aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. The dose and endpoints for spinetoram and spinosad were similar but not identical due to variation in the dosing regimen used in the toxicological studies. Since it has concluded that spinosad and spinetoram are toxicologically identical, the most sensitive of the spinosad and spinetoram endpoints were picked for each scenario.

The toxicological endpoints relevant to this risk assessment are summarized below:

Acute Dietary	Toxicological effects attributable to a single dose was not identified in the spinosad and spinetoram databases, thus, a risk assessment is not required.
Chronic Dietary (Dog)	No Observable Adverse Effect Level (NOAEL) = 2.49 mg/kg/day Chronic Reference Dose Value (RfD) and chronic Population Adjusted Dose (cPad) = 0.0249mg/kg/day
Short-term Oral and Inhalation (Dog)	NOAEL = 4.9 mg/kg/day Target MOE = 100 (residential)(occupational)
Intermediate and Long-term Oral and Inhalation (Dog)	NOAEL = 2.49 mg/kg/day Target MOE = 100(residential)(occupational)

Dietary Exposure and Risk Assessment: As previously stated, EPA concluded that spinosad and spinetoram are toxicologically equivalent; therefore, dietary exposure to these compounds was aggregated. Since both products control the same pest species, EPA concludes that it is unlikely that spinetoram and spinosad will be applied to the same crop simultaneously. Therefore, the dietary exposure analysis did not calculate a combined spinetoram and spinosad residue for crops. Based on the side-by-side spinetoram and spinosad residue data, which indicated that spinetoram residues were less than or equal to spinosad residues, EPA concludes that the spinosad residue data were an adequate surrogate for spinosad or spinetoram in/on crops.

Acute Risk: An effect of concern attributable to a single exposure (dose) was not identified from the oral toxicity studies including the developmental toxicity studies in rats and rabbits.

Chronic Risk: Since there are no registered/proposed uses which result in chronic residential exposures, the chronic aggregate exposure assessment is concerned only with exposure from food and water. The chronic analysis assumed 100% crop treated for all food crop commodities and modeled drinking water estimates. Residues in livestock were refined through the incorporation of a refined dietary burden (average feed crop residues and projected percent crop treated estimates) and through the incorporation of average residues from the feeding and dermal magnitude of the residue studies. The resulting chronic exposure estimates are not of concern to EPA (≤81% cPAD; children 1-2 years old were the most highly exposed population).

Aggregate Risk: Since there are no registered/proposed uses which result in chronic residential exposures, the chronic aggregate exposure assessment is concerned only with exposure from food and water. Since the dietary exposure analysis included drinking water, the discussion and exposure estimates represent aggregate chronic exposure. Currently, short-term incidental oral exposures to

toddlers are anticipated from the registered turf and ornamental application scenarios for spinosad and spinetoram and short-term inhalation exposure to handler/applicators is anticipated for the proposed home garden, turf, and ornamental application scenarios for spinetoram (no handler/applicator exposure to spinosad is anticipated). Since spinosad and spinetoram control the same pests, EPA concludes that these products will not be used in combination with each other and incidental oral exposure from spinosad and spinetoram do not need to be combined. For aggregate short-term assessment, EPA selected the incidental oral exposure resulting from application of spinosad, as this was higher than the incidental oral exposure resulting from application of spinetoram. The incidental oral and inhalation exposures were each combined with chronic dietary (food and water) exposure for determination of aggregate short-term exposure. EPA uses chronic dietary exposure when conducting short-term aggregate assessments, as it has been determined that this will more accurately reflect exposure from food over the EPA-defined short-term interval (1-30 days) than will acute exposure. The resulting aggregate MOEs are ≥180 and are, therefore, not of concern to the Agency.

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

The EPA notes that since spinetoram is thought to be persistent in water and bioaccumulate in fish, the dietary exposure analysis included residues estimates for fish/shellfish. The fish/shellfish residue estimates were based on the total radioactive residues (TRRs) from a bioaccumulation study corrected for an estimated water residue derived assuming 10 cm water depth and no inflow/outflow (no degradation of the compound was assumed). The dietary assessment assumed that every fish/shellfish consumed has these conservative residue estimates. In addition, EPA notes that the fish bioaccumulation study included residue dissipation data which indicated that TRRs dropped very quickly when the fish was placed in water without any residues. Therefore, EPA concludes that potential exposure to spinosad and spinetoram from the consumption of fish as been adequately accounted.

Residue Chemistry: Based on the turnip, apple, and lettuce metabolism studies conducted with XDE-175-J or XDE-175-L uniformly labeled throughout the macrolide ring, EPA concludes that the residue of concern in primary crops for purposes of tolerances enforcement and risk are spinetoram (XDE-175-J and XDE-175-L), N-demethyl-175-J, and N-formyl-175-J.

Based on the goat and hen metabolism studies conducted with XDE-175-J or XDE-175-L uniformly labeled throughout the macrolide ring, EPA concludes the following: **(1)** residues of concern for tolerance enforcement and risk assessment in ruminants and for tolerance enforcement in poultry are spinetoram (XDE-175-J and XDE-175-L), N-demethyl-175-J, and N-formyl-175-J and **(2)** the residues of concern in hens for purposes of risk assessment are spinetoram (XDE-175-J and XDE-175-L), N-demethyl-175-J, N-formyl-175-J, 3'-O-deethyl-175-J, 3'-O-deethyl-175-L, and O-demethyl-175-L.

The submitted confined rotational crop study conducted with XDE-175-J or XDE-175-L uniformly labeled throughout the macrolide ring are inadequate to determine the residues of concern in rotational crops. However, the study does demonstrate that TRRs in rotational crops planted 30 days after application are low (≤0.027 ppm) and that qualitatively residues in rotational crops are not likely to be more toxic than parent. Therefore, EPA concludes that the available data support the following rotational crop restrictions: treated field may only be rotated to a labeled crop.

Tolerances have been established in 40 CFR 180.635 in or on the following food commodities: Acerola (0.30 ppm); Almond, hulls (9 ppm); Amaranth grain, grain (1.0 ppm); Apple, wet pomace (0.50 ppm);

Artichoke, globe (0.30 ppm); Asparagus (0.04 ppm); Atemoya (0.30 ppm); Avocado (0.30 ppm); Banana (0.25 ppm); Beet, sugar, molasses (0.75 ppm); Biriba (0.30 ppm); Brassica, head and stem, subgroup 5A (2.0 ppm); Brassica, leafy greens, subgroup 5B (10 ppm); Bushberry, subgroup 13B (0.25 ppm); Caneberry, subgroup 13A (0.70 ppm); Canistel (0.30 ppm); Cattle, fat (5.5 ppm); Cattle, liver (0.85 ppm); Cattle, meat (0.20 ppm); Cattle, meat byproducts (except liver) (0.60 ppm); Cherimoya (0.30 ppm); Citrus, dried pulp (0.50 ppm); Citrus, oil (3.0 ppm); Corn, sweet, kernel plus cob with husks removed (0.04 ppm); Cotton, gin byproducts (1.5 ppm); Cotton, undelinted seed (0.04 ppm); Cranberry (0.04 ppm); Custard apple (0.30 ppm); Date (0.10 ppm); Egg (0.04 ppm); Feijoa (0.30 ppm); Fig (0.10 ppm); Fruit, citrus, group 10 (0.30 ppm); Fruit, pome, group 11 (0.20 ppm); Fruit, stone, group 12 (0.20 ppm); Goat, fat (5.5 ppm); Goat, liver (0.85 ppm); Goat, meat (0.20 ppm); Goat, meat byproducts (except liver) (0.60ppm); Grain, aspirated fractions (20 ppm); Grain, cereal, group 15, except rice, sorghum, pearl millet and proso millet (0.04 ppm); Grain, cereal, group 16, forage (3.5 ppm); Grain, cereal, group 16, hay (10 ppm); Grain, cereal, group 16, stover (10 ppm); Grain, cereal, straw, group 16, except rice (1.0 ppm); Grape (0.50 ppm); Grape, raisin (0.70 ppm); Guava (0.30 ppm); Herb, dried, subgroup 19A (22 ppm); Herb, fresh, subgroup 19A (3.0 ppm); Hog, fat (0.40 ppm); Hog, meat (0.04 ppm); Hog, meat byproducts (0.04 ppm); Hop, dried cones (22 ppm); Horse, fat (5.5 ppm); Horse, liver (0.85 ppm); Horse, meat (0.20 ppm); Horse, meat byproducts (except liver) (0.60 ppm); Ilama (0.30 ppm); Jaboticaba (0.30 ppm); Juneberry (0.25 ppm); Lingonberry (0.25 ppm); Longan (0.30 ppm); Lychee (0.30 ppm); Mango (0.30 ppm); Milk (0.30 ppm); Milk, fat (7.5 ppm); Nut, tree, group 14 (0.10 ppm); Okra (0.40 ppm); Onion, green (2.0 ppm); Papaya (0.30 ppm); Passionfruit (0.30 ppm); Pea and bean, dried shelled, except soybean, subgroup 6C (0.04 ppm); Pea and bean, succulent shelled, subgroup 6B (0.04 ppm); Peanut (0.04 ppm); Peanut, hay (11 ppm); Peppermint, tops (3.5 ppm); Pineapple (0.04 ppm); Pineapple, processed waste (0.15 ppm); spice, subgroup 19B, except black pepper - 1.7 ppm; Pistachio (0.10 ppm); Pomegranate (0.30 ppm); Poultry, fat (0.10 ppm); Poultry, meat (0.04 ppm); Poultry, meat byproducts (0.04 ppm); Pulasan (0.30 ppm); Rambutan (0.30 ppm); Salal (0.25 ppm); Sapodilla (0.30 ppm); Sapote, black (0.30 ppm); Sapote, mamey (0.30 ppm); Sapote, white (0.30 ppm); Sheep, fat (5.5 ppm); Sheep, liver (0.85 ppm); Sheep, meat (0.20 ppm); Sheep, meat products (except liver) (0.60 ppm); Soursop (0.30 ppm); Soybean, seed (0.04 ppm); Spanish lime (0.30 ppm); Spearmint, tops (3.5 ppm); Star apple (0.30 ppm); Star fruit (0.30 ppm); Strawberry (1.0 ppm); Sugar apple (0.30 ppm); Ti, leaves (10 ppm); Vegetable, bulb, group 3, except green onion (0.10 ppm); Vegetable, cucurbit, group 9 (0.30 ppm); Vegetable, foliage of legume, group 7 (8.0 ppm); Vegetable, fruiting, group 8 (0.40 ppm); Vegetable, leafy, except Brassica, group 4 (8.0 ppm); Vegetable, leaves of root and tuber, group 2 (10 ppm); Vegetable, legume, edible podded, subgroup 6A (0.30 ppm); Vegetable, root and tuber, group 1 (0.10 ppm); Watercress (8.0 ppm); Wax jambu (0.30 ppm).

There are currently no established Codex or Mexican maximum residue limits (MRLs) for residues of spinetoram in/on the commodities listed above.

ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS CHARACTERISTICS

Spinetoram consists of two components in an approximate ratio of 3 to 1, XDE-175-J and XDE-175-L, respectively. XDE-175-J is the major component in the spinetoram mixture. These two components are not isomers. XDE-175-L is slightly heavier than XDE-175-J (molecular weight = 760 vs. 748, respectively). The only difference between XDE-175-J and XDE-175-L is that XDE-175-L contains an extra methyl group at carbon 4 on the central ring. Since these two components have very similar physical and chemical as well as fate properties, XDE-175-J was selected to represent the spinetoram mixture in the ecological risk assessment.

Risk Characterization: The Agency has determined, based on proposed uses, that the major risk concern from application of spinetoram is chronic risk to freshwater invertebrates. Other concerns include the potential for risk to listed aquatic non-vascular plants and terrestrial insects, and chronic risk to freshwater benthic invertebrates and mammals. Functionally, the estimated risks may translate to reduced survival and reproduction of impacted species with subsequent effects at higher levels of biological organization.

Acute risks to top-level carnivores via consumption of pesticide-contaminated small mammals and birds were not evaluated due to a lack of data for these receptors. Quantitative food chain exposures for aquatic and semiaquatic wildlife receptors (e.g., via consumption of contaminated aquatic plants and/or fish) were also not considered.

Spinetoram is highly toxic to terrestrial insects and aquatic invertebrates and is highly effective as it is used as an insecticide to control terrestrial insect pests. The major risk concern for spinetoram is chronic risk to freshwater invertebrates resulting in decreased survival, reproduction, and growth. Other concerns include risk to estuarine/marine invertebrates (no definitive endpoint, but risk could not be precluded), chronic risk to benthic invertebrates (reduced emergence and developmental rate), chronic risk to mammals (reproductive effects), risk to terrestrial invertebrates (mortality), and risk to listed non-vascular plants (reduced cell density). While there is the potential for bioaccumulation, spinetoram did not pose either an acute or chronic risk to mammals or birds through bioaccumulation.

Previous assessments did not identify any acute risk quotients (RQs) that exceeded the levels of concern for aquatic invertebrates. However, data supplied since the chemical was registered provide new toxicity values for the application of the parent compound and both degradates. If at the time of application, the pesticide was assumed to have toxicity equal to spinetoram at the time of the peak estimated environmental concentration (EEC), then the RQs would be less than the Level of Concern (LOC) of 0.5 for freshwater invertebrate non-listed species in each of the scenarios. However, spinetoram poses a risk to listed species in all of the scenarios regardless of application timing, as shown by the exceedence of the LOC of 0.05. A total residue method was used in estimating EEC in the ecological risk assessment.

These results may be an underestimate of the risk, however, since the toxicities of the degradates exceed the toxicity of the parent compound. A more conservative approach incorporates degradation and uses the peak EEC to represent the concentration of the primary degradate, N-demethyl-XDE-175-J. When the peak EEC is then compared to the toxicity of this degradate, the peak EEC exceeds both the freshwater invertebrate LOC of 0.5 and 0.05 for non-listed and listed species, respectively, in all of the scenarios and regardless of application timing.

The previous assessment provides a list of the outstanding data requirements and uncertainties associated with spinetoram. A subsequently submitted study on the side-by-side static acute toxicity test of three test substances (XDE-175, N-demethyl-XDE-175-J, and N-demethyl-XDE-175-L) exposed to the water flea, *Daphnia magna*, shows the degradates to be more toxic than the parent compound to freshwater invertebrates. This study highlights the need to better understand the toxicity of the degradates to other groups of organisms in order to develop a more accurate risk assessment, especially since the major degradate N-demethyl-XDE-175-J is more than an order of magnitude more toxic than the parent compound.

The study supports the need for more information on the degradation products of spinetoram related to both the environmental fate and the ecological effects; particularly to other aquatic invertebrates, benthic invertebrates, and honey bees (surrogate for pollinators and beneficial terrestrial insects). The fate of

spinetoram includes the potential for run-off into both marine and freshwater environments, so information on the toxicity of spinetoram degradates to fish is also important.

Fate: XDE-175-J has a low solubility in water (11.3 mg/L) and has a high affinity to adsorb to soil and sediment. Based on an average K_{oc} of 8,570 L/kg, XDE-175-J is expected to have low mobility in soil, and leaching to groundwater is not very likely. Volatilization is not expected to be an important environmental fate process given a vapor pressure of $5.3x10^{-5}$ Pa ($4.0x10^{-7}$ mm Hg) and Henry's Law constant of $4.0x10^{-8}$ atm-m^3/mol. XDE-175-J is not persistent in the environment, degrading through a combination of biotic and abiotic mechanisms. Although XDE-175-J is stable to hydrolysis at environmental pH (pH 5-9), it undergoes photolysis quickly, with aqueous photodegradation half-lives of <1 day. Biodegradation under aerobic conditions also appears to be important, with half-lives ranging from a few days to a few weeks. XDE-175-J is stable under anaerobic conditions.

Ecological Risk: Spinetoram has a relatively low solubility in water and high affinity for binding to organic carbon in sediment and suspended solids; thus, the bioavailability of the chemical in the water column may be limited after 24 to 48 hours. Therefore, although there is potential for acute risks to organisms living in the water column, chances of chronic exposure to freely-dissolved spinetoram and potential chronic risks to organisms strictly residing in the water column are anticipated to be lower than risks to benthic organisms. Because spinetoram is expected to quickly precipitate out of the water column, partition to sediment, and persist for extended periods of time under anoxic conditions (spinetoram degraded slowly in anaerobic aquatic degradation studies, with half-lives generally greater than 1 year), the anticipated nature of the exposure in the benthos may result in significant potential for acute and chronic risk to benthic-dwelling organisms. Additionally, given the persistent nature of the total residues (including the parent compounds and their degradates) in the aquatic environment and its bioaccumulative nature, there is potential for transport within and among these various systems and their respective compartments via food web exposure. Specifically, concentrations in predatory animals and piscivorus birds in particular, are expected to increase through bioaccumulation. However, while the KABAM (Kow(based) Aquatic BioAccumulation Model) highlighted the potential for bioaccumulation to birds and mammals that feed on aquatic food sources, spinetoram did not pose either an acute or chronic risk to mammals or birds through bioaccumulation.

Expected Mobility: Based on laboratory studies XDE-175 is expected to be generally immobile in soil. XDE-175-J and XDE-175-L were classified as having low mobility to being immobile according to McCall's Relative Mobility classification system in loamy sand, silt loam, sandy loam and loam soils from the U.S., with a K_{oc} of 1800 to 43873 mL/g. Under terrestrial field conditions, the half-life for XDE-175 (-J + -L) in loam and sandy loam soil was 23.7 days and 6.1 days, respectively, while the observed half-life was ≤1 day in each soil. XDE-175 was not detected below the 0-15 cm soil depth at any sampling intervals. Under aquatic field conditions, XDE-175 dissipated very quickly in water, with no partitioning of residues into the sediment. Total XDE-175 residues (XDE-175-J + XDE-175-L) dissipated in the water with half-lives of 18.1 to 20.4 hours. No residues of XDE-175-J or XDE-175-L were detected in any pre- or post-application sediment samples.

Persistence: Based on laboratory studies, both components of XDE-175 dissipate rapidly by photolysis in pH 7 buffer solution, with half-lives of <1 day. Other major routes of dissipation are aerobic soil metabolism, with non-linear half-lives of 3-31 days, and photolysis in soil, with environmental half-lives of 19-88 days. In aerobic and anaerobic water/sediment systems, XDE-175 rapidly associates with the sediment phase where dissipation proceeds more slowly. Half-lives in total aerobic water/sediment systems were 116-124 days, and in total anaerobic water/sediment systems were 385-1,386 days. In laboratory soil, XDE-175 was generally immobile (Kd = 84 and Koc =8,570). Under terrestrial and aquatic field conditions, XDE-175 dissipated rapidly, with observed half-lives of ≤1 day. Leaching was not significant under terrestrial field conditions, and migration into sediments was not significant under

aquatic field conditions. Transformation products were considered stable with structures similar to the parent compounds.

Since the octanol/water partitioning coefficients for XDE-175-J and XDE-175-L are high (12,303 and 30,903, respectively), these two components are expected to bioconcentrate in fish. In rainbow trout exposed to XDE-175-J at 17.3 ng/mL, the bioconcentration factors (BCFs) for edible tissue, nonedible tissue, and whole fish were 11, 53, and 46 mL/g, respectively. After 1 day of depuration, total [^{14}C]residues in the whole fish had decreased by 28.2%. After 21 days of depuration, total [^{14}C]residues had decreased by 88.7%. The elimination half-lives for [^{14}C]residues in edible tissue, nonedible tissue, and whole fish were 2.3, and 4.1, and 4.6 days, respectively. In rainbow trout exposed to XDE-175-L at 22.3 ng/mL, the BCFs for edible tissue, nonedible tissue, and whole fish were 104, 330, and 344 mL/g, respectively. After 1 day of depuration, total [^{14}C]residues in the whole fish had steadily decreased by 9.5%. After 14 days of depuration, total [^{14}C]residues had decreased by 87.4%. The elimination half-lives for [^{14}C]residues in whole fish, edible tissue, and nonedible tissue were 4.5, 3.9, and 4.1 days, respectively. XDE-175-J and XDE-175-L rapidly metabolized, yielding 2-4 more polar metabolites; correspondingly, N-dimethyl-XDE-175-J and N-dimethyl-XDE-175-L were positively identified, along with 3'-O-deethyl-XDE-175-L.

Endangered Species Concerns: There is a concern for indirect effects to listed species that may depend upon other taxonomic groups for their survival (e.g., invertebrates as a food source for listed fish, etc.). Screening-level RQs for freshwater invertebrates, estuarine/marine invertebrates, benthic invertebrates, and mammalian species exceed the chronic risk LOC. In addition, spinetoram is highly toxic to honey bees. Therefore, the nature of the toxicological endpoint, Fish and Wildlife Services-provided "species profiles," and further evaluation of the geographical and temporal nature of the exposure will need to be considered to determine if a rationale for a "not likely to adversely affect" determination is possible. There may be a potential concern for indirect effects to the following groups of organisms in the action area: terrestrial plants, aquatic plants, birds, mammals, reptiles, aquatic invertebrates, fish, amphibians, and terrestrial insects.

DATA GAPS

Toxicology

- Chronic toxicity/carcinogenicity study in rats and carcinogenicity study in the mouse

Residue Chemistry

- The orange oil residue data are not considered scientifically valid, as the measure residue was 24x higher the highest validated fortification level (MRID 474535010). The samples should be reanalyzed using control samples fortified at concentrations which encompass the measured residue.
- Analytical reference standards for XDE-175-J, XDE-175-L, ND-J, and NF-J should be supplied to the National Pesticide Standards Repository

Environmental Fate

- 835.4200 Anaerobic Soil Metabolism

Ecological Effects

- 850.1010 Aquatic Invertebrate Toxicity Test; to be conducted on parent compound and degradates
- 850.1035 Estuarine/Marine Invertebrate Acute Toxicity; to be conducted on degradates
- 850.1300 *Daphnid* Chronic Toxicity Test; to be conducted on degradates
- 850.1350 Aquatic Invertebrate Life-Cycle, Marine; to be conducted on parent compound and degradates

- 850.1075 Fish Acute Toxicity Test, Freshwater and Marine; to be conducted on parent compound and degradates
- 850.1740 Whole Sediment Acute Toxicity Test, Freshwater and Marine; this study has been submitted but does not address the degradates
- 850.1790 *Chironomid* Sediment Toxicity Test; to be conducted on degradates
- 850.2100 Avian Acute Oral Toxicity Test (passerines)
- 850.3020 Honey Bee Acute contact Toxicity; to be conducted on degradates
- 850.3030 Honey Bee Toxicity of Residues on foliage

REGULATORY CONCLUSION

Benefits Determination: Spinetoram received a reduced risk designation at the time of Section 3 submission. In making its reduced risk determination, the Agency raised potential concerns for persistence in aquatic environments and chronic toxicity to invertebrates. However, since the Agency determined that spinetoram is less toxic than the OP and Carbamate alternatives with regard to mammalian, avian and fish toxicity both for acute and chronic timeframes, the Agency granted reduced risk status.

Manufacturing Use Product label: The Agency requires the following statements in the Environmental Hazards section of the manufacturing use product labels: "Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA".

End Use Product label: In order to mitigate the potential risk to aquatic invertebrates, and beneficial insects the Agency requires the following label additions on end use product labels:

1. **Add the following statement to the Hazards to Humans and Domestic Animals section:**

Per the Label Review Manual, end use products classified as dermal sensitizers require following language on product labels:
"**SIGNAL WORD: CAUTION**
Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals."

2. **Add the following statements to the Environmental Hazards section:**

"This pesticide is toxic to aquatic invertebrates. Do not apply directly to water, or to areas where surface water is present or to intertidal areas below the mean high water mark. Drift and runoff from treated areas may be hazardous to aquatic organisms in neighboring areas. Do not contaminate water when disposing of equipment washwater or rinsate."

For products applied as a foliar spray:
"This product is highly toxic to bees exposed to direct treatment or residues on blooming crops or weeds. Do not apply this product or allow it to drift to blooming crops or weeds if bees are visiting the treatment area."

3. **Add the following statements to the Directions for Use:**

"Wind Direction and Speed: Only apply this product if the wind direction favors on-target deposition. Do not apply when the wind velocity exceeds 15 mph."

"Temperature Inversion: Do not make aerial or ground applications into temperature inversions. Inversions are characterized by stable air and increasing temperatures with height above the ground. Mist or fog may indicate the presence of an inversion in humid areas. The applicator may detect the presence of an inversion by producing smoke and observing a smoke layer near the ground surface."

"Droplet Size**:** Use only medium or coarser spray nozzles (for ground and non-ULV aerial application) according to ASAE (S572) definition for standard nozzles. In conditions of low humidity and high temperatures, applicators should use a coarser droplet size."

4. Additional Requirements for Ground Applications:

"Wind speed must be measured adjacent to the application site on the upwind side, immediately prior to application."

"For ground boom applications, apply using a nozzle height of no more than 4 feet above the ground or crop canopy."

"For airblast applications, turn off outward pointing nozzles at row ends and when spraying the outer two rows. To minimize spray loss over the top in orchard applications, spray must be directed into the canopy."

5. Additional Requirements for Aerial Applications:

"The spray boom should be mounted on the aircraft as to minimize drift caused by wingtip or rotor vortices. The minimum practical boom length should be used and must not exceed 75% of the wing span or 80% rotor diameter."

"Flight speed and nozzle orientation must be considered in determining droplet size."

"Spray must be released at the lowest height consistent with pest control and flight safety. Do not release spray at a height greater than 10 feet above the crop canopy unless a greater height is required for aircraft safety."

"When applications are made with a cross-wind, the swath will be displaced downwind. The applicator must compensate for this displacement at the downwind edge of the application area by adjusting the path of the aircraft upwind."

GOVERNMENT PERFORMANCE AND RESULTS ACT (GPRA)

Registering spinetoram will meet the objectives of GPRA title 3.1.1 by assuring new pesticides that enter the market are safe for humans and the environment

For More Information: Electronic copies of this fact sheet are available on the Internet. See http://www.epa.gov/opprd001/factsheets/. For the electronic copy of the spinosad fact sheet see http://www.epa.gov/opprd001/factsheets/spinosad.pdf. Printed copies of this fact sheet can be obtained from EPA's National Center for Environmental Publications and Information (EPA/NCEPI), PO Box 42419, Cincinnati, OH 45242-2419, telephone 1-800-490-9198; fax 513-489-8695. For more information about EPA's pesticide registration program, MNDA, or of individual products containing MNDA, please contact the Registration Division (7505C), OPP, US EPA, Washington, DC 20460, telephone 703-305-5446. For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, from 6:30 a.m. to 4:30 p.m. Pacific Time, or 9:30 a.m. to 7:30 p.m. Eastern Standard Time, seven days a week.

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