

Spinosad and Spinetoram

Human-Health Risk Assessment

D376415





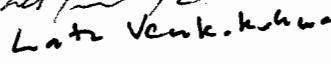
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OFFICE OF
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MEMORANDUM**Date:** 12-October-2010**Subject:** **Spinetoram.** Human-Health Risk Assessment for Cat/Kitten Spot-On Use.

PC Code: 110008	DP Barcode: D376415
Decision No.: 422561	Registration No.: 72642-O-L899 Insecticide
Petition No.: not applicable	Regulatory Action: nonfood use
Risk Assessment Type: aggregate	Case No.: 7448
TXR No.: not applicable	CAS No.: 187166-40-1 and 187166-15-0
MRID No: none	40 CFR: 180.635

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RD of the Office of Chemical Safety and Pollution Prevention (OCSPP) requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from all registered and proposed uses of spinosad and spinetoram. A summary of these findings is provided in this document. The hazard assessment was provided by Chester Rodriguez of RABI; the risk assessment, residue chemistry review, and dietary exposure analysis were provided by Tom Bloem of RABI; the occupational/residential exposure and risk assessment were provided by Lata Venkateshwara of RABI; and the drinking water assessment was provided by Ronald Parker of the Environmental Fate and Effects Division (EFED).

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1.0 Executive Summary

Background: Spinetoram and spinosad are nearly identical structurally (see Attachment 1 for structures) and were determined to be toxicologically identical (see below). Both are fermentation products of *Saccharopolyspora spinosa* and were developed for the control of lepidopterous larvae, leafminers, and thrips. Each product consists of two closely related active ingredients: spinetoram - XDE-175-J and XDE-175-L (3:1 ratio (J:L)) and spinosad - spinosyn A and D (85:15 ratio (A:D)). The mode of action for both is disruption of nicotinic/gamma amino butyric acid (GABA)-gated chloride channels. Spinosad and spinetoram are registered for application to numerous crops and for application to ornamentals, tree farms/plantations, turfgrass, home gardens, lawns, and/or aquatic application. The current action pertains to the proposed spinetoram cat/kitten spot-on use.

Elanco indicated in a meeting on 21-July-2010 with OCSPP that they will discontinue by voluntary cancellation the spinosad cattle feed-through and ear-tag registrations and that products for these uses were never produced (these uses were not registered/proposed for spinetoram or for other livestock); the exposure assessments presented in this document do not include these uses.

Hazard Assessment: The HED Hazard Assessment and Policy Committee (HASPOC) concluded that spinosad and spinetoram should be considered toxicologically identical (D340521, P. Shah, 18-Jun-2007). This conclusion was based on the following: (1) spinetoram and spinosad are large molecules with nearly identical chemical structures and (2) the toxicological profiles for each are similar (general systemic toxicity) with similar doses and endpoints chosen for human-health risk assessment. The HASPOC noted that this is not a 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 parent. The following are summaries of the spinosad and spinetoram hazard assessments.

Spinosad Hazard Assessment: Spinosad is classified as Toxicity Category III for acute oral and dermal toxicity and Toxicity Category IV for acute inhalation toxicity, primary eye irritation, and primary skin irritation. It is not a dermal sensitizer. No toxicity was seen at the limit dose in a 21-day dermal toxicity study in rabbits. The primary toxic effect observed with spinosad was multi-organ histopathology (perhaps due to systemic inflammation as with the structurally related compound spinetoram). For example, following subchronic exposure to spinosad, the primary effects seen in the mouse were increased vacuolation of cells of the lymphoid organs, liver, kidney, stomach, female reproductive tract, and epididymis, and less severely in the heart, lung, pancreas, adrenal cortex, bone marrow, tongue, pituitary gland, and anemia. In rats, thyroid follicle epithelial cell vacuolation, anemia, multifocal hepatocellular granuloma, cardiomyopathy and splenic histiocytosis were observed following subchronic exposure, in dogs microscopic changes in a variety of tissues, anemia, and possible liver damage were seen with short-term repeated dosing. In a chronic feeding study in dogs, increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid) were seen. Vacuolation of thyroid follicular cells, increased absolute and relative thyroid weights were observed in a chronic oral toxicity study in rats. Spinosad was negative for carcinogenicity in rats and mice and negative for mutagenicity in various mutagenicity assays.

Although spinosad operates via a neurotoxic mode of action in target pests, no neurotoxic effects were seen at the limit dose in an acute neurotoxicity study in rats and at doses up to 42.7 mg/kg/day in a subchronic neurotoxicity study. No developmental effects were seen in the spinosad rat and rabbit developmental toxicity studies. In the 2-generation reproductive toxicity study, spinosad produced reproductive toxicity at the highest dose tested that was characterized by an increased incidence of dystocia and/or vaginal bleeding after parturition with associated increases in mortality in the dams resulting in decreases in litter size, survival (F₂ litters only) and body weights in the offspring, whereas parental male rats exhibited chronic active inflammation of the prostate gland. Reproductive toxicity was also observed with the structurally related pesticide, spinetoram, which produced reproductive effects in the female rat in the reproduction/fertility study. Because decreased litter size and survival were observed in the presence of maternal toxicity (deaths) in the 2-generation reproduction study with spinosad and maternal and offspring toxicities were equally severe, this study provides no evidence of increased offspring susceptibility.

There were no major differences in the bioavailability, routes or rates of excretion or metabolism following a single low oral dose, single high oral dose, or repeated oral doses of spinosad in rats. The feces were the major route of excretion. Approximately 70-80% of the dose was absorbed with approximately 20% of the dose eliminated unabsorbed in the feces. The excreted metabolites were the glutathione conjugates of the parent and O-demethylated spinosyn A. Metabolites in the tissues were the N- and O-demethylated spinosyn A. Biliary excretion was rapid. Metabolites in the bile included the glutathione conjugates of parent as well as N- and O-demethylated forms of spinosyn D.

Spinetoram Hazard Assessment: 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 rats, mice and dogs, spinetoram produced multi-organ toxicity. Treatment had no adverse effects on survival but decreases in body weight, body-weight gain and/or food consumption was observed in all three species. Treatment-related findings include 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 marrow). 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 hematopoietic 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 numerous organs with necrosis of the bone marrow leading to regenerative anemia was 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 arteritis and necrosis of the arterial 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, there is no evidence of increased susceptibility following *in utero* exposures in rats and rabbits.

Spinetoram produced reproductive effects in the female rat in the 2-generation reproductive toxicity study (NOAEL=10 mg/kg/day). The effects were characterized by evidence of 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 in the 2-generation reproductive toxicity study.

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.

Dose-Response Assessment and Food Quality Protection Act (FQPA) Decision: The toxicological databases for spinosad and spinetoram were evaluated and endpoints were selected; these endpoints were then compared and, as stated above, the dose and endpoints were similar. However, due to variations in dosing levels used in the spinetoram and spinosad toxicological studies, the resulting doses/endpoints were not identical. Since HED has concluded that spinosad and spinetoram are toxicologically identical, for each scenario the spinosad and spinetoram doses chosen for risk assessment were compared and the lower of these was selected. Based on evaluation of the spinosad and spinetoram toxicological databases and the residue assumptions used in the dietary and residential exposure analyses, the risk assessment team concludes that the FQPA safety factor (SF) may be reduced to 1x. Table 1.0.1 is a summary of the toxicological endpoints relevant to the current assessment.

HED notes the following concerning the spinosad/spinetoram toxicological databases: (1) 40 CFR Part 158 was revised in 2007 to require an immunotoxicity test for registration of a pesticide (food and non-food uses). The immunotoxicity test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. These data have not been submitted and are required for either spinosad or spinetoram and (2) based on the available toxicity database and the Agency's current practices, the inhalation risk for spinosad/spinetoram was assessed using an oral toxicity study. The Agency sought expert advice and input on issues related to this route to route extrapolation approach (i.e. the use of oral toxicity studies for inhalation risk assessment) from its Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The Agency is in the process of evaluating the SAP report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route-to-route extrapolation of toxicity data. If any new policies or procedures are developed, the Agency may revisit the need for an inhalation toxicity study for spinosad/spinetoram and/or a re-examination of the inhalation toxicity risk assessment.

Table 1.0.1. Toxicological Endpoints for Spinosad and Spinetoram.		
Exposure Scenario	Dose Used for Risk Assessment – PoD	Study and Toxicological Effects
Acute Dietary (all populations)	Toxicological effect attributable to a single dose was not identified in the spinosad and spinetoram databases. This risk assessment is not necessary.	
Chronic Dietary	Oral NOAEL = 2.49 mg/kg/day chronic RfD and cPAD = 0.0249 mg/kg/day	Chronic Toxicity Study in Dogs (spinetoram); LOAEL = M/F 5.36/5.83 mg/kg/day; based on arteritis and necrosis of the arterial walls of the epididymides in males and the thymus, thyroid, larynx, and urinary bladder in females.
Short-Term Incidental Oral	Oral NOAEL = 4.9 mg/kg/day LOC for MOEs <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.
Short-Term Inhalation	Oral NOAEL = 4.9 mg/kg/day LOC for MOEs <100; 100% absorption	
Intermediate-term Incidental Oral	NOAEL = 2.49 mg/kg/day LOC for MOEs <100	Chronic Toxicity Study in Dogs (spinetoram); LOAEL = M/F 5.36/5.83 mg/kg/day; 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.	
Cancer - Oral, Dermal, Inhalation	Classification: "Not likely to be Carcinogenic to Humans" based on carcinogenicity studies in spinosad and spinetoram.	

NOAEL = no-observable adverse-effect level; LOAEL = lowest-observable adverse-effect level; RfD = reference dose; cPAD = chronic population-adjusted dose; LOC = level of concern; MOE = margin of exposure.

Dietary (food and water) Exposure and Risk Assessment: The chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID™, ver. 2.03). DEEM-FCID™ incorporates food consumption data from the United States Department of Agriculture (USDA) Continuing Surveys of Food Intakes by Individuals (CSFII; 1994-1996 and 1998). The chronic analysis assumed 100% crop treated for all food crop commodities; average field-trial residues, average USDA Pesticide Data Program (PDP) detected residue, or tolerance-level residues for crop commodities; spinosad residue estimates for fish/shellfish (residues of spinetoram in fish/shellfish are expected to be insignificant); experimental processing factors when available; refined milk, egg and ruminant/hog/poultry tissue residue estimates; and modeled drinking water estimates. The resulting chronic exposure estimates do not exceed HED's LOC ($\leq 24\%$ cPAD; children 1-2 years old were the most highly exposed subpopulation).

Residential and Non-Occupational Exposure and Risk Assessment: Based on the proposed cat/kitten spot-on use, the registered spinosad use for homeowner application to turfgrass and ornamentals (granular formulation), and the registered spinetoram use for homeowner application to gardens, lawns/ornamentals, and turfgrass, residential handler/applicator and post-application exposures to both spinosad and spinetoram are expected. The paragraphs below are summaries of the residential exposure resulting from the proposed/registered uses.

Spinetoram Proposed Cat/Kitten Spot-On Use: 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. Based on this, residential handler/applicator exposure is anticipated to be negligible.

Based the proposed cat/kitten spot-on use, short-/intermediate-term post-application dermal (all populations) and hand-to-mouth incidental oral (children) exposures may occur. However, dermal assessments are unnecessary as no dermal endpoints have been identified for spinetoram; post-application inhalation exposures are anticipated to be negligible based on the low spinetoram vapor pressure ($\leq 1.6 \times 10^{-7}$ mm Hg). HED evaluated incidental oral exposures for children 3-<6 years old (children 3-<6 years old are the representative population for incidental oral exposure). 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). The resulting MOEs are ≥ 130 and, therefore, do not exceed HED's LOC.

Spinetoram Registered Residential Uses: Spinetoram is registered for homeowner application to gardens, lawns/ornamentals, and turfgrass. Since no dermal endpoints were identified, only short-term inhalation risks were assessed for the residential handlers. The resulting MOEs ranged from 4,300,000-8,400,000 and, therefore, do not exceed HED's LOC. Post-application inhalation exposures are anticipated to be negligible based on the low spinetoram vapor pressure ($\leq 1.6 \times 10^{-7}$ mm Hg). HED concluded that there is a potential for toddler short-term incidental oral exposures (hand-to-mouth, object-to-mouth, and soil ingestion). The resulting combined short-term incidental oral MOE was 970 and, therefore, does not exceed HED's LOC. Since toxicological effects attributable to a single dose were not identified, episodic ingestion of granules was not assessed.

Spinosad Registered Residential Uses: Spinosad is registered for homeowner application to turfgrass and ornamentals. Since no dermal endpoints were identified and based on the granular formulation and low spinosad vapor pressure ($\leq 1.5 \times 10^{-10}$ mm Hg), residential handler/applicator/post-application dermal and inhalation assessment were not conducted. HED concluded that there is a potential for toddler short-term incidental oral exposures (hand-to-mouth, object-to-mouth, and soil ingestion). The resulting combined short-term incidental oral MOE was 640 and, therefore, does not exceed HED's LOC. Since toxicological effects attributable to a single dose were not identified, episodic ingestion of granules was not assessed.

HED notes that the registered spinosad fruit fly bait application scenario permits application to non-crop vegetation and this use may result in residential exposures. Based on the application rates (fruit fly bait - 0.0003 lbs ai/acre; turf/ornamental - 0.41 lbs ai/acre), HED concludes that residential exposure resulting from the fruit fly application will be insignificant when compared to the exposure resulting from the turf/ornamental application. Therefore, quantitative analysis of the residential exposure resulting from the fruit fly bait application was not performed.

Aggregate Exposure and Risk Assessment: In general, aggregate exposures are calculated by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Based on the anticipated residential exposure scenarios and since acute and cancer risk assessments are not required, only short-term, intermediate-term, and chronic aggregate exposure assessments were conducted.

Short-Term Aggregate Risk Assessment: Based on the proposed/registered uses, the following short-term residential exposure are anticipated: (1) short-term incidental oral exposures to children from the proposed spinetoram cat/kitten spot-on use and from the registered spinosad and spinetoram turf and ornamental application scenarios and (2) short-term inhalation exposure to adults (handler/applicators) from the registered spinetoram garden, turf, lawns, and ornamental application scenarios. Because the pests controlled for the spinetoram pet-care product and the spinosad/spinetoram homeowner plant-care products (garden, turfgrass, lawn, and/or ornamentals) differ, it is not likely that these types of exposures will co-occur on the same day. Therefore, the short-term aggregate assessment combines dietary exposure with the single highest potential residential exposure.

For children, short-term aggregate exposure includes chronic dietary (food and water) and incidental oral exposure resulting from the proposed spinetoram pet use (highest exposure of all possible scenarios). For adults, short-term aggregate exposure includes chronic dietary exposure (food and water) and inhalation exposure from registered spinetoram turf use (highest exposure of all possible scenarios). Since the aggregate MOEs are ≥ 200 , short-term aggregate exposure to spinosad does not exceed HED's LOC.

Intermediate-Term Aggregate Risk Assessment: Based on the proposed/registered uses, only intermediate-term incidental oral exposures to children from the proposed spinetoram cat/kitten spot-on use is anticipated with the intermediate-term aggregate exposure combining chronic dietary (food and water) and the incidental oral exposures. The aggregate MOE is at the LOC of 100. For the following reasons, HED concludes that aggregate intermediate-term assessment is conservative: (1) the dietary exposure analysis assumed 100% crop treated for all food commodities; (2) the dietary exposure analysis assumed the modeled estimated drinking water concentration (EDWC) resulting from the turf application scenario (turf use yielded the highest EDWC); the model assumed that 87% of the water basin is covered with crops and 100% of these crops are treated using the turf application scenario (maximum application rates and no degradation assumed); and (3) the dietary exposure analysis assumed all livestock are exposed to the premise (ruminants) or premise/dermal (poultry) application scenarios and consume water which has been treated with spinosad (mosquito larvicide application scenario).

HED notes that the aggregate intermediate-term MOE is at the LOC. The following measures may be taken by the petitioner to refine the risk assessment: (1) submission of information concerning the magnitude of total spinosad residues in water following the mosquito larvicide application scenario (total spinosad residues) (2) restricting the minimum weight of cats that may be treated to 6 lbs (since the greater potential for exposure results from contact with smaller sized cats, and since the current assessment assumes (based on the proposed label) that cats as small as 4 lbs may be treated) or decreasing the amount applied to younger cats; and/or (3) submission of a hand-wipe petting study (protocol guidance available upon request).

Chronic Aggregate Risk: Since there are no registered/proposed uses which result in chronic residential exposures, the chronic aggregate exposure assessment consists of exposure from food and water. The chronic dietary exposure estimates were $\leq 24\%$ cPAD and, therefore, do not exceed HED's LOC

Occupational Exposure and Risk Assessment: Spinetoram is proposed for use as spot-on application to cats 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.

Occupational post-application exposure to treated animals is not expected. Domestic pets are expected to be treated and returned to their owners such that post-application contact will be negligible. Further, HED believes that the residential post-application exposure/risk assessment is protective for potential occupational post-application exposures/risks. Since the residential post-application MOEs were all >100 , HED does not have concerns for occupational post-application exposures.

Environmental Justice Considerations: Potential areas of environmental justice concerns, to the extent possible, were considered in this human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (<http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under CSFII and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

HED notes that since both spinosad and spinetoram are 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 from the spinosad mosquito larvicide application scenario (spinetoram not registered for direct application to water); the water residue assumed that the entire water body is treated and a uniform 1 meter depth (no inflow/outflow). Since mosquito larvae inhabit areas protected from wind/wave action treatment of the entire water body is not expected and dilution of treated water with untreated water is likely. In addition, HED notes that the fish bioaccumulation

study included residue dissipation data which indicated that TRRs dropped very quickly when fish were placed in untreated water. Therefore, HED concludes that potential exposure to spinosad and spinetoram from the consumption of fish/shellfish has been adequately considered.

Recommendations for Tolerances/Registration: HED concludes that the toxicological, residue chemistry, and occupational/residential exposure databases support a conditional registration for the proposed spot-on application of spinetoram to cats/kittens. An unconditional registration may be established upon submission of an immunotoxicity study conducted with spinosad or spinetoram in accordance with the revised 40 CFR Part 158.

Summary of Deficiencies:

- In accordance with the revised 40 CFR Part 158 data requirements, an immunotoxicity study is required for all food and non-food use chemicals. Since spinosad and spinetoram are considered toxicologically identical and since the toxicity data of these pesticides can be used interchangeably the immunotoxicity study is required on only one of the compounds.

2.0 Ingredient Profile

Spinetoram is nearly structurally identical to spinosad (see Attachment 1 for structures). Both are fermentation products of *Saccharopolyspora spinosa* and were developed for the control of lepidopterous larvae, leafminers, and thrips. Each product consists of two closely related active ingredients: spinetoram - XDE-175-J and XDE-175-L (3:1 ratio (J:L)) and spinosad - spinosyn A and D (85:15 ratio (A:D)). The mode of action for both is disruption of nicotinic/GABA-gated chloride channels.

2.1 Summary of Registered Uses

Spinosad and spinetoram are registered for application to numerous crops with tolerances for the combined residues of spinosyn A and D (spinosad) or XDE-175-J, XDE-175-L, ND-J, and NF-J (spinetoram) ranging from 0.01-200 ppm (spinosad - 40 CFR 180.495; spinetoram 40 CFR 180.635). Spinosad and spinetoram are also registered for application to ornamentals, tree farms/plantations, turfgrass, home gardens, lawns, and/or aquatic application.

2.2 Summary of Proposed Uses

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 2.2.1 presents the proposed spot-on use as labeled for application to cats or kittens.

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

2.3 Structure and Nomenclature

Tables 2.3.1 and 2.3.2 are summaries of the spinosad nomenclature and physical/chemical properties; Tables 2.3.3 and 2.3.4 are summaries of the spinetoram nomenclature and physical/chemical properties.

Table 2.3.1. Spinosad Nomenclature.	
Chemical Structure	<p style="text-align: center;">Spinosyn A: R = H Spinosyn D: R = CH₃</p>
Common name	Spinosad
Company experimental name	XDE-105
IUPAC name	Spinosyn A: (2 <i>R</i> ,3 <i>aS</i> ,5 <i>aR</i> ,5 <i>bS</i> ,9 <i>S</i> ,13 <i>S</i> ,14 <i>R</i> ,16 <i>aS</i> ,16 <i>bR</i>)-2-(6-deoxy-2,3,4-tri- <i>O</i> -methyl- α -L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetra-deoxy- β -D-erythro-pyranosyloxy)-9-ethyl-2,3,3 <i>a</i> ,5 <i>a</i> ,5 <i>b</i> ,6,7,9,10,11,12,13,14,15,16 <i>a</i> ,16 <i>b</i> -hexadecahydro-14-methyl-1 <i>H</i> -8-oxacyclododeca[<i>b</i>]as-indacene-7,15-dione; Spinosyn D: (2 <i>S</i> ,3 <i>aR</i> ,5 <i>aS</i> ,5 <i>bS</i> ,9 <i>S</i> ,13 <i>S</i> ,14 <i>R</i> ,16 <i>aS</i> ,16 <i>bR</i>)-2-(6-deoxy-2,3,4-tri- <i>O</i> -methyl- α -L-mannopyranosyloxy)-13-(4-dimethylamino-2,3,4,6-tetra-deoxy- β -D-erythro-pyranosyloxy)-9-ethyl-2,3,3 <i>a</i> ,5 <i>a</i> ,5 <i>b</i> ,6,7,9,10,11,12,13,14,15,16 <i>a</i> ,16 <i>b</i> -hexadecahydro-4,14-dimethyl-1 <i>H</i> -8-oxacyclododeca[<i>b</i>]as-indacene-7,15-dione
CAS name	Spinosyn A: 2-[(6-deoxy-2,3,4-tri- <i>O</i> -methyl- α -L-manno-pyranosyl)oxy]-13-[[5-(dimethylamino)-tetrahydro-6-methyl-2 <i>H</i> -pyran-2-yl]oxy]-9-ethyl-2,3,3 <i>a</i> ,5 <i>a</i> ,5 <i>b</i> ,6,9,10,11,12,13,14,16 <i>a</i> ,16 <i>b</i> -tetradecahydro-14-methyl-1 <i>H</i> -as-Indaceno[3,2- <i>d</i>]oxacyclododecin-7,15-dione; Spinosyn D: 2-[(6-deoxy-2,3,4-tri- <i>O</i> -methyl- α -L-manno-pyranosyl)oxy]-13-[[5-(dimethylamino)-tetrahydro-6-methyl-2 <i>H</i> -pyran-2-yl]oxy]-9-ethyl-2,3,3 <i>a</i> ,5 <i>a</i> ,5 <i>b</i> ,6,9,10,11,12,13,14,16 <i>a</i> ,16 <i>b</i> -tetradecahydro-4,14-methyl-1 <i>H</i> -as-Indaceno[3,2- <i>d</i>]oxacyclododecin-7,15-dione
CAS #	Spinosyn A: 131929-60-7; Spinosyn D: 131929-63-0

Table 2.3.2. Spinosad Physicochemical Properties.		EPA Fact Sheet
Melting points	Spinosyn A: 84-99.5°C; Spinosyn D: 161.5-170°C	
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 x 10 ⁻¹¹ ; Spinosyn D: 2.0 x 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); 5.2 (pH 9) Spinosyn D: 3.2 (pH 5); 4.5 (pH 7); 5.2 (pH 9)	
UV/visible absorption spectrum	not available	

Spinosad and Spinetoram

Human-Health Risk Assessment

D376415

Table 2.3.3. Spinetoram Nomenclature.

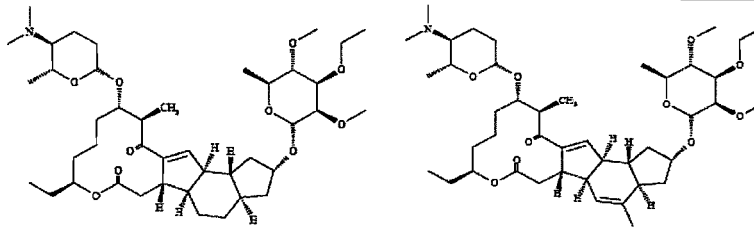
Chemical Structure	
Common name	Spinetoram (mixture of XDE-175-J and XDE-175-L)
Company experimental name	XDE-175-J (TSN104472; 3'-O-ethyl 5,6-dihydro spinosyn J; 175-J); XDE-175-L (TSN104480; 3'-O-ethyl spinosyn L; 175-L)
IUPAC name	XDE-175-J: (2R,3aR,5aR,5bS,9S,13S,14R,16aS,16bR)-13-[[[(2R,5S,6R)-5-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yl]oxy]-9-ethyl-14-methyl-7,15-dioxo-2,3,3a,4,5,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-octadecahydro-1H-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2,4-di-O-methyl-alpha-L-mannopyranoside; XDE-175-L: (2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)-13-[[[(2R,5S,6R)-5-(dimethylamino)-6-methyltetrahydro-2H-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-1H-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2,4-di-O-methyl-alpha-L-mannopyranoside
CAS name	XDE-175-J: 1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-3-O-ethyl-2,4-di-O-methyl-a-L-mannopyranosyl)oxy]-13-[[[(2R,5S,6R)-5-(dimethylamino)tetrahydro-6-methyl 2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,4,5,5a,5b,6,9,10,11,12,13,14,16a,16b-hexadecahydro 14-methyl- (2R,3aR,5aR,5bS,9S,13S,14R,16aS,16bR) XDE-175-L: 1H-as-indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-3-O-ethyl-2,4-di-O-methyl-a-L-mannopyranosyl)oxy]-13-[[[(2R,5S,6R)-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-(2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)
CAS #	XDE-175-J: 187166-40-1; XDE-175-L: 187166-15-0

Table 2.3.4. Spinetoram Physicochemical Properties.

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 x 10 ⁻⁵ Pa at 20°C, 6.0 x 10 ⁻⁵ Pa at 25°C XDE-175-L: 2.1 x 10 ⁻⁵ Pa at 20°C, 4.2 x 10 ⁻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:	Wavelength (λ_{max} , 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:		
	Neutral	243	11100
	Basic (pH 12.6)	244	11200
	Acidic (pH 1.04)	202	9800

3.0 Hazard Characterization

Detailed hazard characterizations for spinetoram and spinosad were presented in a previous HED risk assessments (spinosad - D284803, D. Vogel *et al.*, 15-Aug-2002; spinetoram - D331741, P. Shah *et al.*, 20-Sep-2007) and a summary of the spinetoram and spinosad hazard assessments are provided in the Executive Summary. The toxicity profile for spinosad and spinetoram are presented in Attachments 2 and 3 respectively.

HED notes the following concerning the spinosad/spinetoram toxicological databases: (1) 40 CFR Part 158 was revised in 2007 to require an immunotoxicity test for registration of a pesticide (food and non-food uses). The immunotoxicity test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. These data have not been submitted and are required for either spinosad or spinetoram and (2) based on the available toxicity database and the Agency's current practices, the inhalation risk for spinosad/spinetoram was assessed using an oral toxicity study. The Agency sought expert advice and input on issues related to this route to route extrapolation approach (i.e. the use of oral toxicity studies for inhalation risk assessment) from its FIFRA SAP in December 2009. The Agency received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The Agency is in the process of evaluating the SAP report and may, as appropriate, re-examine and develop new policies and procedures for conducting inhalation risk assessments, including route-to-route extrapolation of toxicity data. If any new policies or procedures are developed, the Agency may revisit the need for an inhalation toxicity study for spinosad/spinetoram and/or a re-examination of the inhalation toxicity risk assessment.

3.1 FQPA Assessment

Excluding the lack of spinosad and spinetoram immunotoxicity studies, the toxicology databases for spinosad and spinetoram are adequate for evaluation of the FQPA SF; the following acceptable studies are available for spinosad and spinetoram: developmental toxicity study in rats, developmental toxicity study in rabbits, and two-generation reproduction study in rats. Based on the currently-available data, HED concludes that a FQPA SF of 1x is appropriate for the following reasons (Table 3.1.1 is a summary of the toxicological endpoints for spinosad and spinetoram):

- There is no evidence of increased susceptibility of rat and rabbit fetuses to *in-utero* exposure to spinosad or spinetoram. In the spinosad and spinetoram rat and rabbit developmental toxicity studies, developmental toxicity was not observed at any dose level. In the spinosad two-generation reproduction studies, maternal and offspring toxicity were equally severe, indicating no evidence of increased susceptibility. In the spinetoram 2-generation reproduction study, no adverse effects were observed on the offspring at dose levels that produced parental toxicity. Therefore, there is no evidence of increased susceptibility and there are no concerns or residual uncertainties for pre and/or post-natal toxicity. In addition, there was no evidence of neurotoxicity in the acute, subchronic and chronic toxicological studies.

- Excluding the immunotoxicity test, the spinosad and spinetoram toxicological databases are complete. There was evidence of histopathology in the organs of the immune system in several studies with either spinosad or spinetoram. However, in every study, these effects were observed in at least one other non-immune organ at the same dose (e.g., thyroid, liver, intestine, heart, epididymides, or others), and in many studies these effects were observed in several organs at the same dose, thereby indicating general systemic toxicity that was not limited to the immune organs. In addition, leukocyte counts (an indicator of immune function) were unaffected in any study. Therefore, the data are not consistent with an immunosuppressive effect, and in the case of spinetoram are more consistent with a systemic inflammatory reaction. Because the required guideline immunotoxicity study measures immunosuppression, and there is no evidence of immunosuppression in the database with either chemical, HED does not believe that conducting a functional immunotoxicity study will result in a lower POD than that currently used for overall risk assessment, and therefore, a database uncertainty factor (UF_{DB}) is not needed to account for the lack of this study.
- Spinosad was negative in both acute and subchronic neurotoxicity studies. An acute spinetoram neurotoxicity study showed no treatment-related changes at the limit dose (2000 mg/kg/day). In addition, there is no evidence of clinical signs of neurotoxicity or neuropathology observed in adult animals in any of the available studies with spinetoram. Based on these observations and since spinosad and spinetoram are considered toxicologically identical and do not belong to the class of compounds that would be expected to be toxic to the nervous system (e.g., organophosphates, synthetic pyrethroids), a waiver was granted for the spinetoram subchronic neurotoxicity study.
- The dietary exposure analysis is conservative in that modeled drinking water estimates; average spinosad field-trial residue, average spinosad USDA PDP detected residue, or tolerance-level residues for crop commodities; and 100% crop treated were assumed for all commodities excluding milk and cattle tissue (cattle dietary burdens refined through incorporation of average residues and projected percent crop treated estimates). The residential exposure analysis is conservative since it is based on the residential Standard Operating Procedures (SOPs). The dietary and residential risk assessments are thus conservative and are not expected to underestimate risk.

As stated above, the doses and endpoints for spinosad and spinetoram were similar. However, due to variations in dosing levels used in the spinetoram and spinosad toxicological studies, the resulting doses/endpoints were not identical. Since HED has concluded that spinosad and spinetoram are toxicologically identical, for each scenario the spinosad and spinetoram doses chosen for risk assessment were compared and the lower of these was selected.

Table 3.1.1. Summary of Toxicological Doses and Endpoints for Spinetoram and Spinosad for Use in Dietary, Non-Occupational, and Occupational Human Health Risk Assessments¹.

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	Toxicological effect attributable to a single dose was not identified in the spinosad and spinetoram databases. This risk assessment is not required.			
Chronic Dietary (All Populations)	NOAEL = 2.49 mg/kg/day	UF _A = 10x UF _H = 10x FQPA SF = 1x	cRfD = 0.0249 mg/kg/day cPAD = 0.0249 mg/kg/day	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.
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	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.
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	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.
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; 100% absorption	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; 100% absorption	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 the spinosad carcinogenicity studies. Based on the structural similarity of spinetoram and spinosad and the similarity of the toxicological database for the currently-available studies, HED concluded that in the interim, the conclusions concerning the spinosad chronic oral carcinogenicity studies will be translated to spinetoram (petitioner indicated they will be submitting spinetoram carcinogenicity studies in the fall of 2007).			

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.

3.2 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Neither spinosad nor spinetoram were among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: <http://www.epa.gov/endo/>.

3.3 Recommendation for Aggregate Risk Assessment

Since inhalation and incidental oral endpoints (all durations) are based on the same oral study, dietary and inhalation exposures may be aggregated for all populations (dermal endpoints were not selected).

4.0. Dietary Exposure/Risk Characterization

4.1 Metabolism in Primary Crops, Livestock, and Rotational Crops

The spinosad and spinetoram residues of concern, for tolerance expression and risk assessment purposes, are as defined in Tables 4.1.1 and 4.1.2, respectively. For further information refer to the documents referenced in Tables 4.1.1 and 4.1.2.

Matrix	Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants ¹	XDE-175-J, XDE-175-L, ND-J, and NF-J	XDE-175-J, XDE-175-L, ND-J, and NF-J
Ruminant ^{1,2}	XDE-175-J, XDE-175-L, ND-J, and NF-J	XDE-175-J, XDE-175-L, ND-J, and NF-J
Hen ^{1,3}	XDE-175-J, XDE-175-L, ND-J, NF-J, 3'-O-deethyl-175-J, 3'-O-deethyl-175-L, and O-demethyl-175-L ³	XDE-175-J, XDE-175-L, ND-J, and NF-J
Rotational Crops ¹	Cannot be determined from the available data.	
Drinking Water ¹	Since identified or partially identified degradates in the fate studies contained the major ring structures of the parent compound, a total residue method was used in modeling.	--

¹ See D331741 (P. Shah *et al.*, 20-Sep-2007) for more information.

² HED notes that feeding studies should employ dosing with parent only (XDE-175-J and XDE-175-L) and should monitor for the residues of concern for risk assessment.

³ O-demethyl-175-L is either 2'-O-demethyl-175-L or 4'-O-demethyl-175-L or a mixture of both.

Matrix	Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants ¹	spinosyn A and D	spinosyn A and D
Hog and Ruminants (oral and dermal) ¹	oral and dermal - spinosyn A and D	oral and dermal - spinosyn A and D
Poultry (oral and dermal) ^{1,2}	oral - spinosyn A and D dermal (excluding liver) - spinosyn A and D; dermal (liver) - spinosyns A, B, D, J, N-demethyl D, and N-demethyl J	spinosyn A and D
Rotational Crops ¹	spinosyn A and D	spinosyn A and D
Drinking Water ³	total spinosad	--
Fish/Shellfish ⁴	adjustment of the TRRs in the edible tissues from the spinosyn A bioconcentration study (19 ppb data) for the water concentration resulting from the mosquito larvicide use	spinosyn A and D

¹ See D243816 (G. Herndon, 03-Mar-1998) and D264984 (W. Donovan, 14-Jun-2002) for more information.

² See D374794 (T. Bloem, 25-Mar-2010) for more information.

³ See D316077 (T. Bloem *et al.*, 02-Aug-2006) for more information.

⁴ HED notes that these conclusions are appropriate for this mosquito larvicide petition only and will be reevaluated if the petitioner alters the aquatic application scenario; see D316077 (T. Bloem *et al.*, 02-Aug-2006) for more information.

4.2 Toxicity Profile of Major Metabolites and Degradates

No toxicological data are available on the metabolites of spinosad and spinetoram. The identified metabolites for spinosad/spinetoram are structurally similar. Since the metabolites (identified and unidentified) were found to be more polar than parent and, therefore, are likely to be rapidly excreted, it is unlikely that the metabolites will be more toxic than the parent.

4.3 Drinking Water Residue Profile

EDWCs were provided by EFED. EFED concluded that the previously provided spinetoram (D325409, L. Liu, 14-May-2007) and spinosad (D331271, R. Parker, 28-Jul-2006) estimates were acceptable for the current use. EFED generated the surface and ground water estimates using the FQPA Index Reservoir Screening Tool (FIRST) and Screening Concentration In Ground Water (SCIGROW) models, respectively. Table 4.3.1 is a summary of the modeled water concentrations. Based on these estimates, the chronic dietary analysis assumed a water residue estimate of 10.5 ppb. The models and descriptions are available at the EPA internet site: <http://www.epa.gov/oppefed1/models/water/>.

Water Source	Acute	Chronic	Long-Term Average
Spinosad (turf application scenario; 4 x 0.4 lb ai/acre; RTI = 7 days; 87% of the watershed is treated)			
surface	34.5	10.5	--
ground	1.1	1.1	1.1
Spinetoram (turf and fire ant mound application; 1 x 0.454 lb ai/acre; 100% of the watershed is treated)			
surface	14.419	6.171	--
ground	0.072	0.072	0.072

4.4 Food Residue Profile

There are no issues associated with residues in/on food/feed commodities as a result of the proposed spinetoram cat/kitten spot-on use.

4.5 Dietary Exposure and Risk

D380915, T. Bloem, 18-Aug-2010

The chronic dietary risk assessment was conducted using DEEM-FCID™ (ver. 2.03). DEEM-FCID™ incorporates food consumption data from the USDA CSFII (1994-1996 and 1998). The chronic analysis assumed 100% crop treated for all food crop commodities; average field-trial residues, average USDA PDP detected residue, or tolerance-level residues for crop commodities; spinosad residue estimates for fish/shellfish (residues of spinetoram in fish/shellfish are expected to be insignificant); experimental processing factors when available; refined milk, egg and ruminant/hog/poultry tissue residue estimates; and modeled drinking water estimates. The resulting chronic exposure estimates do not exceed HED's LOC ($\leq 24\%$ cPAD; children 1-2 years old were the most highly exposed subpopulation).

Population Subgroup	cPAD (mg/kg/day)	Chronic	
		Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.0249	0.002430	10
All Infants (<1 year old)		0.003034	12
Children 1-2 years old		0.005915	24
Children 3-5 years old		0.004932	20
Children 6-12 years old		0.003119	12
Youth 13-19 years old		0.001922	7.7
Adults 20-49 years old		0.002184	8.8
Adults 50+ years old		0.001859	7.5
Females 13-49 years old		0.001848	7.4

5.0 Residential (Non-Occupational) Risk Assessment

D376658, L. Venkateshwara, 1-Jul-2010

Based on the proposed cat/kitten spot-on use, the registered spinosad use for homeowner application to turfgrass and ornamentals (granular formulation; D284802, M. Dow and D. Vogel, 15-Aug-2002), and the registered spinetoram use for homeowner application to gardens, lawns/ornamentals, and turfgrass (D325865, K. Lowe, 10-Jul-2007), residential handler/applicator and post-application exposures to both spinosad and spinetoram are expected. The subsections below and Table 5.0.1 are summaries of the residential exposure resulting from these proposed/registered uses (the resulting exposure do not exceed HED's LOC).

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for spinosad/spinetoram. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at <http://www.epa.gov/opp00001/factsheets/spraydrift.htm>). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT[®] computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift. HED notes that residential exposure to spinosad/spinetoram resulting from the turf uses do not exceed HED's LOC (see below) and it is unlikely that spray drift from the registered agricultural uses will result in exposures higher than these.

Table 5.0.1. Summary of Proposed/Registered Spinosad/Spinetoram Residential Exposures and Risks.		
Activity	Exposure (mg/kg/day)	MOE ¹
Proposed Spinetoram Cat/Kitten Spot-on Use		
toddler/child - post-application - short-term incidental oral	0.019	260
toddler/child - post-application - intermediate-term incidental oral	0.019	130
Registered Spinetoram Residential Uses (gardens, lawns, ornamentals, and turfgrass)		
adult - loader/applicator - short-term inhalation	0.000001	4,300,000
toddler/child - post-application - short-term incidental oral	0.00762	640
Registered Spinosad Residential Uses (turfgrass and ornamentals)		
toddler/child - post-application - short-term incidental oral	0.005014	970

Spinetoram Proposed Cat/Kitten Spot-On Use: The proposed use is as a monthly topical spot-on application to cats eight weeks of age or older for the control of fleas. The label notes only one size treatment (231 mg ai/ treatment) for all cats/kittens. Application by homeowners is permitted. The following is a summary of the applicator and post-application residential risk assessments.

Handler/Applicator: 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. Based on this, residential handler/applicator exposure is anticipated to be negligible.

Post-Application: The proposed use of spinetoram on cats/kittens may result in dermal exposure to all ages and hand-to-mouth exposure from contact with treated pets for children. However, dermal assessments are unnecessary as no dermal endpoints have been identified for spinetoram; post-application inhalation exposures are anticipated to be negligible based on the low spinetoram vapor pressure ($\leq 1.6 \times 10^{-7}$ mm Hg).

Based on the label instructions short-term and intermediate-term incidental oral exposures are anticipated (one application per month is permitted). HED evaluated incidental oral exposures for children 3-<6 years old (children 3-<6 years old are the representative population for incidental oral exposure). The following 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): (1) even loading of residues across the entire surface of the treated animal; (2) a representative (average) cat size was assumed to be 10 lbs; estimated exposure to a smaller (4 lb) and larger (16 lb) than average size cat were also assessed; (3) 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); (4) post-application activities are assessed on the same day that the pesticide is applied because it is assumed that individuals could handle/touch their pets immediately after application; (5) one pet is contacted per day; and (6) saliva extraction efficiency is 50% (i.e., every time the hand goes in the mouth approximately half of the residues on the hand are removed). A summary of child (3 to <6 years old) incidental oral exposure is presented in Table 5.0.2. The resulting MOEs are ≥ 130 and, therefore, do not exceed HED's LOC.

App. Rate (AR; mg ai/treatment) ¹	Cat Weight (lb)	Surface Area (SA) Cat (cm ²) ²	Salivary Ext. Factor (SAL)	SA Hands (cm ²)	Freq	PDR (mg/kg/day) ³	Short-term MOE ⁴	Intermediate-term MOE ⁵
231	4	1620	0.5	20	1	0.019	260	130
	10 (Avg.)	2930				0.010	490	250
	16	3980				0.0077	640	320

¹ AR calculated from proposed label.

² Surface Area (cm²) = ((12.3 x ((cat weight (lb) x 454)^{0.65}))

³ PDR (mg/kg/day) = potential dose rate = [(AR x F_{AR} ÷ SA_{pet}) x (SAL) x SA_{hands} x Freq] ÷ Body Weight (15 kg); F_{AR} = fraction available as transferable residue = 0.20.

⁴ Short-term MOE = Short-term NOAEL (4.9 mg/kg/day) ÷ PDR (mg/kg/day)

⁵ Intermediate-term MOE = Intermediate-term NOAEL (2.49 mg/kg/day) ÷ PDR (mg/kg/day)

Spinetoram Registered Residential Uses: Spinetoram is registered for homeowner application to gardens, lawns/ornamentals, and turfgrass. Since no dermal endpoints were identified, only short-term inhalation risks were assessed for the residential handlers. The resulting MOEs ranged from 4,300,000-8,400,000 and, therefore, do not exceed HED's LOC (D325865, K. Lowe, 10-Jul-2007). Post-application inhalation exposures are anticipated to be negligible based on the low spinetoram vapor pressure ($\leq 1.6 \times 10^{-7}$ mm Hg). HED concluded that there is a potential for toddler short-term incidental-oral exposures (hand-to-mouth, object-to-mouth, and soil ingestion). The resulting combined short-term incidental oral MOE was 970 and, therefore, does not exceed HED's LOC (D325865, K. Lowe, 10-Jul-2007). Since toxicological effects attributable to a single dose were not identified, episodic ingestion of granules was not assessed.

Spinosad Registered Residential Uses: Spinosad is registered for homeowner application to turfgrass and ornamentals. Since no dermal endpoints were identified and based on the granular formulation and low spinosad vapor pressure ($\leq 1.5 \times 10^{-10}$ mm Hg), residential handler/applicator/post-application dermal and inhalation assessment were not conducted. HED concluded that there is a potential for toddler short-term incidental-oral exposures (hand-to-mouth, object-to-mouth, and soil ingestion). The resulting combined short-term incidental oral MOE was 640 and, therefore, does not exceed HED's LOC (D284802, M. Dow and D. Vogel, 15-Aug-2002). Since toxicological effects attributable to a single dose were not identified, episodic ingestion of granules was not assessed.

HED notes that the registered spinosad fruit fly bait application scenario permits application to non-crop vegetation and this use may result in residential exposures. Based on the application rates (fruit fly bait - 0.0003 lbs ai/acre; turf/ornamental - 0.41 lbs ai/acre), HED concludes that residential exposure resulting from the fruit fly application will be insignificant when compared to the exposure resulting from the turf/ornamental application. Therefore, quantitative analysis of the residential exposure resulting from the fruit fly bait application was not performed.

6.0 Aggregate Risk Assessment

In general, aggregate exposures are calculated by summing dietary (food and water) and residential exposures (residential or other non-occupational exposures). Based on the anticipated residential exposure scenarios and since acute and cancer risk assessments are not required, only short-term (residential, food, and water), intermediate-term (residential, food, and water), and chronic (food and water) aggregate exposure assessments were conducted.

Short-Term Aggregate Risk Assessment: Based on the proposed/registered uses, the following short-term residential exposure are anticipated (see Section 5.0): (1) short-term incidental oral exposures to children from the proposed spinetoram cat/kitten spot-on use and from the registered spinosad and spinetoram turf and ornamental application scenarios and (2) short-term inhalation exposure to adults (handler/applicators) from the registered spinetoram garden, turf, lawns, and ornamental application scenarios. Because the pests controlled for the spinetoram pet-care product and the spinosad/spinetoram homeowner plant-care products (garden, turfgrass, lawn, and/or ornamentals) differ, it is not likely that these types of exposures will co-occur on the same day. Therefore, the short-term aggregate assessment combines dietary exposure with the single highest potential residential exposure.

For children, short-term aggregate exposure includes chronic dietary (food and water) and incidental oral exposure resulting from the proposed spinetoram pet use (highest exposure of all possible scenarios). For adults, short-term aggregate exposure includes chronic dietary exposure (food and water) and inhalation exposure from registered spinetoram turf use (highest exposure of all possible scenarios). Table 6.0.1 is a summary of the short-term aggregate exposures and risk estimates. Since the aggregate MOEs are ≥ 200 , short-term aggregate exposure to spinosad does not exceed HED's LOC. Short-term aggregate risk calculations were conducted for children 1-2 years old and adults 20-49 years old as these populations had the highest chronic dietary exposures for children and adults and provide the highest short-term exposures.

Population	NOAEL (mg/kg/day)	Target MOE	Chronic Food Water Exposure (mg/kg/day)	Incidental Oral Exposure (mg/kg/day) ¹	Handler Inhalation Exposure (mg/kg/day) ²	Aggregate MOE (food, water, and residential) ³
General U.S. Population	4.9	100	0.002430	--	0.000001	2000
Children 1-2 years old			0.005915	0.019	--	200
Adults 20-49 years old			0.002184	--	0.000001	2200

¹ Incidental oral exposure = 0.019; see Table 5.0.1.

² Residential inhalation exposure = 0.000001 mg/kg/day; see D325865.

³ Aggregate MOE = NOAEL ÷ (chronic dietary exposure + residential exposure).

Intermediate-Term Aggregate Risk Assessment: Based on the proposed/registered uses, only intermediate-term incidental oral exposures to children from the proposed spinetoram cat/kitten spot-on use is anticipated (see Section 5.0) with the intermediate-term aggregate exposure combining chronic dietary (food and water) and the incidental oral exposures. Table 6.0.2 is a summary of the intermediate-term aggregate exposures and risk estimates. The aggregate MOE is at the LOC of 100. Intermediate-term aggregate risk calculations were conducted for children 1-2 years as they had the highest chronic dietary exposures for children and provide the highest intermediate-term exposures.

For the following reasons, HED concludes that aggregate intermediate-term assessment is conservative: (1) the dietary exposure analysis assumed 100% crop treated for all food commodities; (2) the dietary exposure analysis assumed modeled EDWCs resulting from the turf application scenario (turf use yielded the highest EDWC); the model assumed that 87% of the water basin is covered with crops and 100% of these crops are treated using the turf application scenario (maximum application rates and no degradation assumed); and (3) the dietary exposure analysis assumed all livestock are exposed to the premise (ruminants) or premise/dermal (poultry) application scenarios and consume water which has been treated with spinosad (mosquito larvicide application scenario).

Table 6.0.2. Intermediate-Term Aggregate Risk Calculations.

Population	NOAEL ¹ (mg/kg/day)	Target MOE	Chronic Food Water Exposure (mg/kg/day)	Incidental Oral Exposure (mg/kg/day) ¹	Aggregate MOE ¹
Children 1-2 years old	2.49	100	0.005915	0.019	100

¹ Incidental oral exposure = 0.019; see Table 5.0.1; aggregate MOE = NOAEL ÷ (chronic dietary exposure + residential exposure).

HED notes that the aggregate intermediate-term MOE is at the LOC. The following measures may be taken by the petitioner to refine the risk assessment: (1) submission of information concerning the magnitude of total spinosad residues in water following the mosquito larvicide application scenario (total spinosad residues) (2) restricting the minimum weight of cats that may be treated to 6 lbs (since the greater potential for exposure results from contact with smaller sized cats, and since the current assessment assumes (based on the proposed label) that cats as small as 4 lbs may be treated) or decreasing the amount applied to younger cats; and/or (3) submission of a hand-wipe petting study (protocol guidance available upon request).

Chronic Aggregate Risk: Since there are no registered/proposed uses which result in chronic residential exposures, the chronic aggregate exposure assessment consists of exposure from food and water. The chronic dietary exposure estimates were \leq 24% cPAD and, therefore, do not exceed HED's LOC

7.0 Cumulative Risk

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for spinetoram/spinosad and any other substances and spinetoram/spinosad does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that spinetoram/spinosad has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

8.0 Occupational Exposure

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Spinetoram is proposed for use as spot-on application to cats 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.

Occupational post-application exposure to treated animals is not expected. Domestic pets are expected to be treated and returned to their owners such that post-application contact will be negligible. Further, HED believes that the residential post-application exposure/risk assessment is protective for potential occupational post-application exposures/risks. Since the residential post-application MOEs were all >100, HED does not have concerns for occupational post-application exposures.

9.0 Deficiencies/Data Needs

9.1 Toxicology

- In accordance with the revised 40 CFR Part 158 data requirements, an immunotoxicity study is required for all food and non-food use chemicals. Since spinosad and spinetoram are considered toxicologically identical and since the toxicity data of these pesticides can be used interchangeably the immunotoxicity study is required on only one of the compounds.

9.2 Residue Chemistry and Occupational/Residential

- None.

Attachment 1: Chemical Structures.

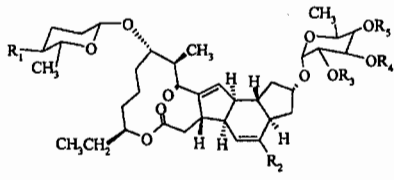
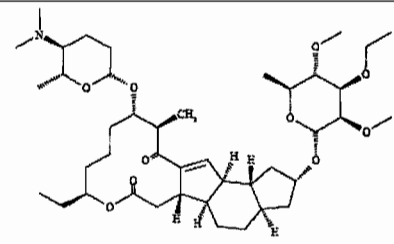
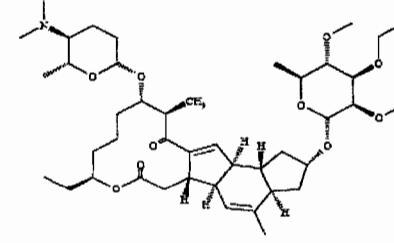
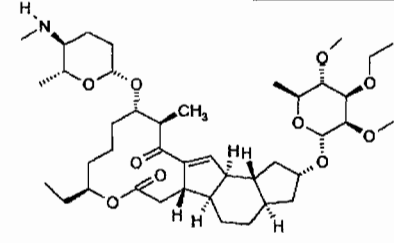
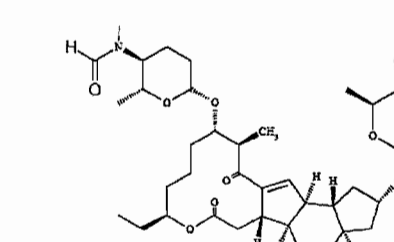
Attachment 2: Toxicity Profile for Spinosad.

Attachment 3: Toxicity Profile for Spinetoram.

RDI: RABI (18-Aug-2010)

T. Bloem:S10945:PY1:(703)-605-0217

Attachment 1: Chemical Names and Structures

Spinosad Compounds	
	
spinosyn A	parent; R ₁ = N(CH ₃) ₂ , R ₂ = H, R ₃ = CH ₃ , R ₄ = CH ₃ , R ₅ = CH ₃
spinosyn D	parent; R ₁ = N(CH ₃) ₂ , R ₂ = CH ₃ , R ₃ = CH ₃ , R ₄ = CH ₃ , R ₅ = CH ₃
spinosyn B	spinosyn A demethylated in the forosamine ring; R ₁ = N(CH ₃), R ₂ = H, R ₃ = CH ₃ , R ₄ = CH ₃ , R ₅ = CH ₃
spinosyn J	spinosyn A demethylated in the rhamose ring; R ₁ = N(CH ₃) ₂ , R ₂ = H, R ₃ = CH ₃ , R ₄ = H, R ₅ = CH ₃
N-demethyl spinosyn D	spinosyn D demethylated in the forosamine ring; R ₁ = N(CH ₃), R ₂ = CH ₃ , R ₃ = CH ₃ , R ₄ = CH ₃ , R ₅ = CH ₃
N-demethyl spinosyn J	spinosyn J demethylated in the forosamine ring; R ₁ = N(CH ₃), R ₂ = H, R ₃ = CH ₃ , R ₄ = H, R ₅ = CH ₃
Spinetoram Compounds	
Spinetoram (XDE-175-J) (2R,3aR,5aR,5bS,9S,13S,14R,16aS,16bR)-13-[[[(2R,5S,6R)-5-(dimethylamino)-6-methyltetrahydro-2H-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-1H-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2,4-di-O-methyl- α -L-mannopyranoside	
Spinetoram (XDE-175-L) (2S,3aR,5aS,5bS,9S,13S,14R,16aS,16bS)-13-[[[(2R,5S,6R)-5-(dimethylamino)-6-methyltetrahydro-2H-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-1H-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2,4-di-O-methyl- α -L-mannopyranoside	
metabolite – ND-J (N-demethyl-175-J) (2R,3aR,5aR,5bS,9S,13S,14R,16aS,16bR)-9-ethyl-14-methyl-13-[[[(2S,5S,6R)-6-methyl-5-(methylamino)tetrahydro-2H-pyran-2-yl]oxy]-7,15-dioxo-2,3,3a,4,5,5a,5b,6,7,9,10,11,12,13,14,15,16a,16b-octadecahydro-1H-as-indaceno[3,2-d]oxacyclododecin-2-yl 6-deoxy-3-O-ethyl-2,4-di-O-methyl- α -L-mannopyranoside	
Spinetoram metabolite – NF-J (N-formyl-175-J) (2R,3S,6S)-6-((2R,3aR,5aR,5bS,9S,13S,14R,16aS,16bR)-2-[[[(6-deoxy-3-O-ethyl-2,4-di-O-methyl- α -L-mannopyranosyl)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-1H-as-indaceno[3,2-d]oxacyclododecin-13-yl]oxy]-2-methyltetrahydro-2H-pyran-3-yl(methyl)formamide	

Spinosad and Spinetoram

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Attachment 2: Toxicity Profile for Spinosad

Spinosad: Acute Toxicity.				
Guideline No.	Study Type	MRID No.	Results	Tox. Category
81-1	Acute Oral-Rat	43770701; 43414515	LD50 = >2000 mg/kg	III
81-2	Acute Dermal-Rabbit	43414516	LD50 = >2000 mg/kg	III
81-3	Acute Inhalation-Rat	43414517	LC50 = >5.18 m/L	IV
81-4	Primary Eye Irritation	43414518	not an eye irritant	IV
81-5	Primary Skin Irritation	43414519	not a skin irritant	IV
81-6	Dermal Sensitization	43414520	not a skin sensitizer	n/a

Spinosad: Subchronic, Chronic, and Other Toxicity Studies.		
Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
870.3100 90-Day oral toxicity rodents-Mouse	43566602 (1992) Acceptable/guideline 0, 0.005, 0.015, 0.045, or 0.12% 0, 7.5, 22.5, 67.5, or 180 mg/kg/day	NOAEL = 7.5 mg/kg/day in males and females. LOAEL = 22.5 mg/kg/day in males and females; based on cytoplasmic vacuolation of lymphoid organs, liver, kidney, stomach, female reproductive tract, and epididymis. Other tissues less severely affected are heart, lung, pancreas, adrenal cortex, bone marrow, tongue, and pituitary gland.
870.3100 90-Day oral toxicity rodents-Rat	43566601 (1992) Acceptable/guideline 0, 0.05, 0.1, 0.2, or 0.4% 0/0, 33.9/38.8, 68.5/78.1, 133.5/151.6, or 273.1/308.2 mg/kg/day; M/F	NOAEL = 33.9 mg/kg/day in males; 38.8 mg/kg/day in females. LOAEL = 68.5 mg/kg/day in males; 78.1 mg/kg/day in females based on adrenal cortical vacuolation in males, lymph node histiocytosis in both sexes.
870.3100 90-Day oral toxicity rodents-Rat	43557502 (1994) Acceptable/guideline 0, 0.003, 0.006, 0.012, or 0.06% 0/0, 2.2/2.6, 4.3/5.2, 8.6/10.4, or 42.7/52.1 mg/kg/day; M/F	NOAEL = 42.7 mg/kg/day in males; 52.1 mg/kg/day in females (HDT). LOAEL = Not observed in males and females.
870.3150 90-Day oral toxicity nonrodents-Dog	43444102 (1994) Acceptable/guideline 0, 150, 300, or 1350/900 (males) 900 (females) ppm 0/0, 4.89/5.38, 9.73/10.47, or 33.4/29.9 mg/kg/day; M/F	NOAEL = 4.89 mg/kg/day in males; 5.38 mg/kg/day in females. LOAEL = 9.73 mg/kg/day in males; 10.47 mg/kg/day in 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.
870.3200 Repeated Dose Dermal Toxicity-Rabbit (21 days)	43557503 (1984) Acceptable/guideline 0, 100, 500, or 1000 mg/kg/day	NOAEL = 1000 mg/kg/day in males and females (HDT). LOAEL = Not observed.
870.3700a Prenatal developmental in rodents- Rat	43557505 (1993) 43770702 (1992; range finding) Acceptable/guideline 0, 10, 50, or 200 mg/kg/day	<u>Maternal</u> : NOAEL = 200 mg/kg/day (HDT). LOAEL = Not observed. <u>Developmental</u> : NOAEL = 200 mg/kg/day (HDT). LOAEL = Not observed.

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Spinosad: Subchronic, Chronic, and Other Toxicity Studies.		
Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
870.3700b Prenatal developmental in nonrodents- Rabbit	43414521 (1994) 43770703 (1992; range finding) Acceptable/guideline 0, 2.5, 10.0, or 50.0 mg/kg/day	<u>Maternal</u> : NOAEL = 50 mg/kg/day (HDT). LOAEL = Not observed. <u>Developmental</u> : NOAEL = 50 mg/kg/day (HDT). LOAEL = Not observed.
870.3800 Reproduction and fertility effects- Rat	43701506 (1994) Acceptable/guideline 0, 0.005, 0.02, or 0.2% 0, 3, 10, or 100 mg/kg/day	Parental/Systemic NOAEL = 10 mg/kg/day. LOAEL = 100 mg/kg/day based on increases in heart, kidney, liver, spleen, and thyroid weights (both sexes), corroborative histopathology in the spleen and thyroid (both sexes), heart and kidney (males only), and histopathologic lesions in the lungs and mesenteric lymph nodes (both sexes), stomach (females only), and prostate. Reproductive NOAEL = 10 mg/kg/day. LOAEL = 100 mg/kg/day based on increased incidence of dystocia and/or vaginal bleeding after parturition with associated increases in mortality in the dams. Offspring NOAEL = 10 mg/kg/day. LOAEL = 100 mg/kg/day based on decreases in litter size, survival and body weights.
870.4100b Chronic toxicity- Dog	43701504 (1995) Acceptable/guideline 0, 50/60, 100/120, or 300/360 ppm 0/, 1.44/1.33, 2.68/2.72, or 8.46/8.22 mg/kg/day; M/F	NOAEL = 2.68 mg/kg/day in males, 2.72 mg/kg/day in females. LOAEL = 8.46 mg/kg/day in males; 8.22 mg/kg/day in females based on increases in serum alanine aminotransferase, aspartate aminotransferase, and triglycerides levels, and the presence of tissue abnormalities, including vacuolated cell aggregations, arteritis, and glandular cell vacuolation (parathyroid).
870.4200 Carcinogenicity- Mouse	43701505 (1995) Acceptable/guideline 0, 0.0025, 0.008, or 0.036% 0, 25, 80, or 360 ppm 0/0, 3.4/4.2, 11.4/13.8, or 50.9/67.0 mg/kg/day; M/F	NOAEL = 11.4 mg/kg/day in males, 13.8 mg/kg/day in females. LOAEL = 50.9 mg/kg/day in males; 67.0 mg/kg/day in females based on decreased weight gains, increased mortality, the hematologic effects, and the gross finding of increased thickening of the gastric mucosa in females and the histologic changes in the stomach of males. No evidence of carcinogenicity.
870.4200 Carcinogenicity- Mouse	44123601 (1996) Acceptable/guideline 0, 0.0008, or 0.024% 0/0, 1.1/1.3, or 32.7/41.5 mg/kg/day; M/F	NOAEL not established. LOAEL = 1.1 mg/kg/day in males; 1.3 mg/kg/day in females. No evidence of carcinogenicity.
870.4300 Chronic/ Carcinogenicity- Rat	43701507, 43710503 (1995) 0, 0.005, 0.02, 0.05, or 0.1% 0/0, 2.4/3.0, 9.5/12.0, 24.1/30.3, or 49.4/62.8 mg/kg/day; M/F	NOAEL = 9.5 mg/kg/day in males, 12.0 mg/kg/day in females. LOAEL = 24.1 mg/kg/day in males; 30.3 mg/kg/day in females based on vacuolation of the epithelial follicular cells of the thyroid in both sexes. No evidence of carcinogenicity.

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Spinosad: Subchronic, Chronic, and Other Toxicity Studies.		
Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
870.5265 Reverse Mutation Assay	43414522 (1992) Unacceptable/guideline	In the Ames Test, the mutation rates observed after treatment of <i>Salmonella typhimurium</i> strains (TA1535, TA1537, TA98, and TA100) and one strain of <i>Escherichia coli</i> (WP2/uvrA) with XDE105 increased in a dose-related manner when compared to the vehicle control. The colonies were shown in a replica plate assay to be predominately auxotrophs and not revertants. No growth of auxotrophs is expected in the Ames assay, but their presence in this assay suggests that XDE-105 supported their growth. The investigators noted that trace amounts of histidine and other amino acids were present in the test substance, which is a fermentation product. Therefore, an Ames assay with XDE-105 may not be appropriate, and this assay is considered to be unacceptable.
870.5300 Mouse lymphoma cell/mammalian activation gene forward mutation assay	43414523 (1992) Acceptable/guideline 0, 1, 5, 10, 15, 20, or 35 µg/ml 15 through 50 µg/ml with metabolic activation.	In a forward mutation assay using mouse lymphoma cells, spinosad did not induce forward mutations in mouse lymphoma L5178Y Tk [±] cells at concentrations of 0, 1, 5, 10, 15, 20, or 35 µg/ml without metabolic activation or at concentrations of 15 through 50 µg/ml with metabolic activation.
870.5375 <i>In Vitro</i> mammalian cytogenetic assay	43414524 (1992) Acceptable/guideline 20, 26, or 35 µg/ml 100, 250, or 500 µg/ml with metabolic activation.	In a chromosomal aberrations assay, spinosad did not increase the number of CHO cells with chromosome aberrations at concentrations of 20, 26, or 35 µg/ml without metabolic activation or at concentrations of 100, 250 or 500 µg/ml with metabolic activation.
870.5385 Micronucleus Assay	43414525 (1992) Acceptable/guideline 0, 500, 1000, or 2000 mg/kg/day	In a mouse micronucleus test, spinosad did not increase the frequency of micronuclei in replicate assays with bone marrow cells from ICR mice treated with doses of 0, 500, 1000, or 2000 mg/kg/day for two consecutive days.
870.5550 Unscheduled DNA Synthesis	43414526 (1992) Acceptable/guideline 0.01 to 5 µg/ml 10 to 1000 µg/ml	In the unscheduled DNA synthesis assay using primary rat hepatocytes, spinosad did not induce unscheduled DNA synthesis (UDS) in adult rat hepatocytes <i>in vitro</i> at concentrations of 0.01 to 5 µg/ml. Concentrations from 10 to 1000 µg/ml of XDE-105 were cytotoxic.
870.6200 Acute Neurotoxicity -Rat	43557501 (1994) Acceptable/nonguideline 0, 200, 630, or 2000 mg/kg	NOAEL = 2000 mg/kg in males and females (HDT). LOAEL = Not established in both sexes.
870.6200b Repeat Dose Neurotoxicity-Rat	43557504 (1993) Acceptable/nonguideline 0, 0.003, 0.006, 0.012 or 0.06% 0/0, 2.2/2.6, 4.3/5.2, 8.6/10.4, or 42.7/52.1 mg/kg/day; M/F	NOAEL = 42.7 mg/kg/day in males; 52.1 mg/kg /day in females (HDT). LOAEL = Not established in both sexes.
870.6200b Repeat Dose Neurotoxicity-Rat	43701507, 43701503 (1995) Acceptable/guideline 0 or 0.1% 0/0 or 46.0/57.0 mg/kg/day, M/F	NOAEL = 46.0 mg/kg/day in males; 57.0 mg/kg/day in females (HDT). LOAEL = Not established in both sexes.

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Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
870.7485 Metabolism and pharmacokinetics - Rat	43701508 (1995) Acceptable/guideline 10 or 100 mg/kg (single oral dose) 10 mg/kg (repeated dose 14 days)	<p>At high (100 mg/kg) and single or multiple low (10 mg/kg) doses, there are no major differences in the bioavailability, routes or rates of excretion or metabolism of ¹⁴C-XDE-105 (Factor A) following oral administration. The feces were the major route of excretion (82 to 87% of the doses at 168 hours after dosing), and ~7-10% of the dose was excreted in the urine. Approximately 70-80% of the dose was absorbed with ~20% of the dose eliminated unabsorbed in the feces. Blood levels of ¹⁴C after the single and multiple 10 mg/kg doses were highest at 1 hour in both sexes. These levels were reduced by half 6 hours (males) and 12 hours (females) after dosing indicating that blood levels remain high for longer periods of time in female rats than in male rats. Blood levels of ¹⁴C after the 100 mg/kg dose were highest at 6 and 2 hours in males and females, respectively. Concentrations of ¹⁴C-XDE-105 at the time plasma concentrations were half the maximum value, suggested that the test material was still undergoing distribution.</p> <p>At 168 hr after administration of the low dose, the kidney, liver and fat of males and females had higher levels than other tissues. In the high dose group however, the adrenals (females only), kidney, lymph nodes, fat, and thyroids had higher levels than other tissues. The total radioactivity remaining in the tissues and carcass of the low and high dose animals was <0.6% and <3% of the administered dose, respectively. Also, at 7 days after the 100 mg/kg dose of XDE-105 (Factor A), the radioactivity observed in fat was 3-fold higher in female rats (40.978 µg equivalents/g tissue) than male rats (13.227 µg/g of tissue).</p> <p>The primary metabolites excreted were identified as the glutathione conjugates of the parent and O-demethylated XDE-105 (Factor A). Metabolites in the tissues were characterized as the N- and O-demethylated forms of Factor A. The absorption, disposition, and elimination of ¹⁴C-XDE-105 (Factor A) demonstrated no appreciable differences based on, dose or repeated dosing.</p>
870.7485 Metabolism and pharmacokinetics - Rat	43701509 (1995) Acceptable/guideline 100 mg/kg (single dose)	<p>Results of these experiments indicated that at 100 mg/kg dose, the feces were the major route of excretion (84 to 92% of the dose at 168 hours after dosing), and 3-5% of the dose was excreted in the urine. Greater than 68% of the administered radioactivity was recovered in the feces within the first 24 hours following dosing. The excretion kinetics was biphasic with the α and β excretion halftimes (t_{1/2}) of approximately 6 and 30 hours, respectively.</p> <p>The primary metabolites excreted were identified as the glutathione conjugates of the parent and O-demethylated XDE-105 (Factor D). Metabolites in the tissues were</p>

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Guideline No./Study Type	MRID No. (year)/ Classification/Doses	Results
		characterized as the N- and O-demethylated forms of Factor D. The absorption, disposition, and elimination of ¹⁴ C-XDE-105 (Factor D) demonstrated no appreciable differences based on, dose or repeated dosing.
870.7485 Metabolism and pharmacokinetics - Rat	43701510 (1995) Acceptable/guideline 100 mg/kg (single dose, bile cannulated)	<p>The feces contained from 23 to 55% of the dose (an average of 34%), and the bile had an average of approximately 36% (range of 28 to 40%) of the administered radioactivity. Approximately 21% of the dose was found in the tissues and carcass (range of 12 to 26%). The urine and CO₂ accounted for 3.3 and <0.1% of the dose. The bile excretion rate results suggested an uptake phase for the first 4 hr after dosing which preceded a biphasic decrease in the biliary excretion rate. The maximum rate of bile excretion was ~644 µg equivalents per hour at 2-4 hr; then the rate decreased to ~123 µg equivalents per hour at the 12-24 hr interval.</p> <p>The results of the study suggested that metabolites in the bile included the glutathione conjugates of the unchanged form, as well as – and O-demethylated forms of XDE-105 (Factor D).</p>

Attachment 3: Toxicity Profile for Spinetoram

Spinetoram: Acute Toxicity Studies.				
Guideline No.	Study Type	MRID	Results	Tox. Category
870.1100	Acute oral rat	46695031	LD ₅₀ (F) >5000 mg/kg	IV
870.1200	Acute dermal rat	46695034	LD ₅₀ ≥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	--

Spinetoram: Subchronic, Chronic, and Other Toxicity Studies.		
Guideline No. Study Type	MRID No. (year)/ Classification/dose	Results
870.3100 90-Day oral toxicity Rat	46695104 (2005) Acceptable/guideline 0, 120, 500, 1000, or 2000 ppm M: 0, 7.9, 32.4, 65.8, and 128 mg/kg/d F: 0, 9.5, 39.6, 79.3, 159, and 311 mg/kg/d	NOAEL (F) = 120 ppm (9.5 mg/kg/day). LOAEL (F) = 500 ppm (39.6 mg/kg/day) based on an increased incidence of very slight to slight kidney tubular vacuolization, very slight vacuolization of the follicular epithelial cells of the thyroid, and increased incidence of histiocytic aggregates of macrophages in the bone marrow, spleen and mesenteric lymph node. NOAEL (M) = 500 ppm (32.4 mg/kg/day). LOAEL (M) = 1000 ppm (65.8 mg/kg/day) based on an increased incidence of histiocytic aggregates of macrophages in lymph nodes, spleen, thymus, and ileum and jejunum (Peyer's patches), and follicular epithelial cell vacuolization of the thyroid with colloid depletion.
870.3100 90-Day oral toxicity Mouse	46695105 (2005) Acceptable/guideline 0, 50, 150, or 450 ppm M: 0, 7.5, 22.8, and 70.8 mg/kg/d F: 0, 10.2, 29.6, and 89.9 mg/kg/d 11 mg/kg/d	NOAEL (M) was not observed. LOAEL (M) = 50 ppm (7.5 mg/kg/day) based histopathology degeneration with regeneration of the tubules of the kidney. NOAEL (F) = 50 ppm (10.2 mg/kg/day). LOAEL (F) = 150 ppm (29.6 mg/kg/day) based histopathology (extramedullary hematopoiesis in the spleen) and the steepness of the dose-response curve.
870.3150 90-Day oral toxicity Dog	46568501 (2005) Acceptable/guideline 0, 150, 300 or 900 ppm M: 0, 5.73, 9.82, and 27.1 mg/kg/d F: 0, 4.97, 10.2, and 31.0 mg/kg/d	NOAEL (M) = 150 ppm [(4.975.73 (females/males)] mg/kg/day). LOAEL (M) = 300 ppm [9.8/10.2 (males/females) mg/kg bw/day in males/females, respectively], based on decreased body-weight gain (males), generalized vacuolization of macrophages within lymphoid tissue, arteritis and/or perivascular inflammation in numerous organs with necrosis of the bone marrow leading to regenerative anemia, and a decrease in thymus weights (males) with slight atrophy of the thymic cortex (males).
870.3200 21/28-Day dermal toxicity Rat	46675106 (2005) Acceptable/ guideline 0, 100, 500, and 1000 mg/kg/d	NOAEL = 1000 mg/kg/day. LOAEL was not observed.

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Guideline No. Study Type	MRID No. (year)/ Classification/dose	Results
870.3700a Prenatal developmental in Rat	46695108 (2005) Acceptable/ guideline 0, 30, 100, and 300 mg/kg/d from GD 6-20	Maternal NOAEL = 100 mg/kg/day. LOAEL = 300 mg/kg/day based on decreased body-weight gain and food consumption during gestation. Developmental NOAEL = 300 mg/kg/day. LOAEL was not determined.
870.3700b Prenatal developmental in Rabbit	46695107 (2005) Acceptable/ guideline 0, 2.5, 10, and 60 mg/kg/d from GD 7-27	Maternal NOAEL = 10 mg/kg/day. LOAEL = 60 mg/kg/day based on decreased body-weight gains, fecal output, and food consumption, and increased absolute and relative liver weights. Developmental NOAEL = 60 mg/kg/day. LOAEL was not observed.
870.3800 Reproduction and fertility effects Rat	46887501 (2006) Acceptable/ guideline 0, 3, 10, or 75 mg/kg/d	Parental/Systemic NOAEL = 10.46 mg/kg/day (M) and 9.87 mg/kg/day (F). LOAEL = 78.97 mg/kg/day (M) and 74.87 mg/kg/day (F) based on thyroid histopathology (cytoplasmic vacuolation of follicular epithelial cells) in F ₀ and F ₁ animals of both sexes and decreased serum T ₄ and/or increased serum TSH in F ₀ females and F ₁ animals of both sexes. Reproductive NOAEL (F) = 9.87 mg/kg/day LOAEL = 74.87 mg/kg/day based on dystocia/other parturition abnormalities and late resorptions/retained fetuses and increased postimplantation loss in F ₀ and F ₁ dams. Reproductive NOAEL (M) ≥78.87 mg/kg/day LOAEL (M) was not identified. Offspring NOAEL ≥78.97 mg/kg/day (M) and 74.87 mg/kg/day (F). LOAEL was not identified.
870.4100b Chronic toxicity Dog	47011901 (2006) Acceptable/ guideline 0, 50, 100, or 200 ppm M: 0, 1.57, 2.96, and 5.36 mg/kg/d F: 0, 1.31, 2.49, and 5.83 mg/kg/d	NOAEL = 100 ppm (2.49 mg/kg/day in females/2.96 mg/kg/day in males). LOAEL = 200 ppm (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.
870.4300 Chronic/carcinogenicity Rat	47212901 & 47212902 (2007) 0, 50, 250, or 750 ppm M. 0, 2.12, 10.8, 21.6, & 32.9 mg/kg/day F: 0, 2.63, 13.2, 26.6, & 40 mg/kg/day	NOAEL = 250 ppm (10.8 mg/kg/day in males/ 13.2 mg/kg/day in females). LOAEL = 500 ppm (21.6 mg/kg/day in males/26.6 mg/kg/day in females). Based on increased incidences of thyroid follicular cell vacuolation and of aggregates of macrophages/histiocytes in peyer's patches in the ileum and mediastinal lymph nodes and an increased severity of aggregates of macrophages/histiocytes in mesenteric lymph nodes.
870.5100 <i>In vitro</i> Bacterial Gene Mutation (<i>Salmonella</i> <i>typhimurium</i> / <i>E. coli</i>)/ mammalian activation gene mutation assay	466951109 (2005) Acceptable/ guideline 0, 33, 100, 333, 1000, 2500, or 5000 µg/plate (+/- S9-activation) in the <i>E. coli</i> strain ; or 0, 1, 3.33, 10, 33.3, 100, 333, and 1000 µg/plate (-S9) and 0, 3.33, 10, 33.3, 100, 333, 1000, and 5000 µg/plate (+S9) in the <i>Salmonella</i> strains	There was no evidence of induced mutant colonies over background. (Negative)

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Guideline No. Study Type	MRID No. (year)/ Classification/dose	Results
870.5300 <i>In Vitro</i> Gene Mutation assay in Chinese Hamster Ovary cells	4669510 (2005) Acceptable/ guideline 0, 10, 20, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, 200, 260, and 320 µg/mL (-S9), 0, 10, 20, 40, 80, 160, 200, 240, 280, and 320 µg/mL (+S9)	There was no evidence of induced mutant colonies over background in the presence or absence of S9-activation. (Negative)
870.5395 <i>In Vivo</i> Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in Mice	46695112 (2005) Acceptable/guideline 0, 500, 1000, or 2000 mg/kg	No statistically significant increases in the micronucleated polychromatic erythrocytes (MPCE) frequency or % of polychromatic erythrocytes (PCE) were observed in any treatment group when compared to controls. (Negative)
870.5375 <i>In vitro</i> Mammalian Cytogenetics (Chromosomal Aberration Assay in Rat Lymphocytes)	46695111 (2005) Acceptable/guideline 0, 2.5, 5, 10, 20, 30, 40, 50, or 100 µg/mL (-S9), 0, 5, 10, 20, 30, 40, 50, 60, 80, or 100 µg/mL (+S9).	There were no significant increases in the frequency of aberrant cells (excluding gaps) noted in the presence or absence of S9 at any exposure period. (Negative)
870.6200 Acute Neurotoxicity screening battery	46995113 (2005) Acceptable/guideline 0, 200, 630, and 2000 mg/kg	NOAEL = 2000 mg/kg. LOAEL was not observed.
870.7485 Metabolism and pharmacokinetics Rat	46695114 (2005) Acceptable/ guideline single p.o. dose 10 or 100 mg/kg 14 daily doses 10 mg/kg single i.v. dose 10 mg/kg	The orally administered doses were rapidly absorbed. The absorbed dose was 70% or greater. After 168 h, total recoveries ranged from 88.1-97.1% of the administered doses, with no differences observed between dose levels, single or multiple doses, or route of exposure. The majority of the radioactivity was recovered in the feces (77.4-89.6% of the administered dose), while urine (3.3-9.6%) was a minor route of elimination. The majority of the radioactivity in the feces was recovered during the first 24 h, while the majority of radioactivity recovered in the urine was recovered during the first 12 h. Animals given an i.v. dose of the test compound eliminated a larger proportion of radioactivity in the urine (9.0-9.6% vs. 3.3-4.7%), and elimination of radioactivity in the feces was prolonged compared to orally-dosed animals. However the total amount of radioactivity excreted in the feces was similar regardless of route of administration, suggesting that a large percentage of orally-administered XDE-175-J would be eliminated in the feces via biliary excretion. The carcass contained the highest levels of radioactivity (0.2-1.3% administered dose); no other tissue exceeded 0.4% of the administered dose. The highest concentrations of radioactivity were generally detected in fat, kidneys, liver, and lymph nodes, and in the ovaries in females. There was no evidence of bioaccumulation. The test compound was extensively metabolized regardless of the route of administration. The majority of radioactivity recovered from urine and fecal extract samples was present as parent and a total of seven metabolites, the largest proportion of which were found in the fecal extracts. Metabolic profiles were qualitatively similar for all of the experimental groups. The major route of metabolism was found to be glutathione conjugation with the parent compound, as well as glutathione conjugation with N-demethylated, O-deethylated, and hydroxylated forms of the parent compound. Parent and

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		<p>identified compounds accounted for 70.9-83.4% of the administered dose, while unidentified metabolites accounted for 9.6-17.1% of the administered dose. The total administered dose accounted for in the excreta was 86.4-94.7%. Parent compound accounted for 7.0-22.2% (40.0% in the 100 mg/kg males) of the total radioactivity eliminated, and was found almost exclusively in the fecal extracts. The majority of radioactivity (31.4-61.0% of the administered dose) was identified as the glutathione conjugate of D₅-XDE-175-J, the glutathione conjugate of XDE-175-J, and the glutathione conjugate of N-demethyl-XDE-175-J in the urine, and the glutathione conjugate of XDE-175-J and the cysteine conjugate of XDE-175-J (tentatively identified) in the feces. The other major identified metabolites were identified as the glutathione conjugate of 3'-O-deethyl-XDE-175-J and the glutathione conjugate of hydroxy-XDE-175-J (tentatively identified) in the urine, and the cysteine conjugate of 3'-O-deethyl-XDE-175-J (tentatively identified) and the cysteine conjugate of hydroxyl-XDE-175-J (tentatively identified) in the feces (2.3-20.0% total). An additional major metabolite was identified as 3'-O-deethyl-XDE-175-J (3.9-14.4%) and was found almost exclusively in the feces. In animals dosed with [¹⁴C]N-formyl-XDE-175-J (the plant metabolite), the majority of radioactivity was recovered in the feces (89-2-91.7%), while urine (3.4-4.4%) was a minor route of elimination. The radioactivity was rapidly excreted during the first 24 h, similar to the other groups. It was stated that the N-formyl plant metabolite was also highly metabolized, and that the major metabolites were tentatively identified as the parent N-formyl test material and cysteine conjugates of the N-formyl parent and N-demethyl-XDE-175-J. Based on the fecal metabolite profile, it was estimated that 21-28% of this test material was converted to metabolites that may be common with those formed from the parent compound.</p> <p>Parent compound accounted for 7.0-22.2% (40.0% in the 100 mg/kg males) of the total radioactivity eliminated, and was found almost exclusively in the fecal extracts. The majority of radioactivity (31.4-61.0% of the administered dose) was identified as the glutathione conjugate of D₅-XDE-175-J, the glutathione conjugate of XDE-175-J, and the glutathione conjugate of N-demethyl-XDE-175-J in the urine, and the glutathione conjugate of XDE-175-J and the cysteine conjugate of XDE-175-J (tentatively identified) in the feces. The other major identified metabolites were identified as the glutathione conjugate of 3'-O-deethyl-XDE-175-J and the glutathione conjugate of hydroxy-XDE-175-J (tentatively identified) in the urine, and the cysteine conjugate of 3'-O-deethyl-XDE-175-J (tentatively identified) and the cysteine conjugate of hydroxyl-XDE-175-J (tentatively identified) in the feces (2.3-20.0% total). An additional major metabolite was identified as 3'-O-deethyl-XDE-175-J (3.9-14.4%) and was found almost exclusively in the feces.</p> <p>In animals dosed with [¹⁴C]N-formyl-XDE-175-J (the plant metabolite), the majority of radioactivity was recovered in the feces (89-2-91.7%), while urine (3.4-4.4%) was a minor route of</p>

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		elimination. The radioactivity was rapidly excreted during the first 24 h, similar to the other groups. It was stated that the N-formyl plant metabolite was also highly metabolized, and that the major metabolites were tentatively identified as the parent N-formyl test material and cysteine conjugates of the N-formyl parent and N-demethyl-XDE-175-J. Based on the fecal metabolite profile, it was estimated that 21-28% of this test material was converted to metabolites that may be common with those formed from the parent compound.
870.7485 Metabolism and pharmacokinetics Rat	46695115 (2005) Acceptable/ guideline single p.o. dose 10 or 100 mg/kg 14 daily doses 10 mg/kg single i.v. dose 10 mg/kg	The orally administered doses were rapidly absorbed, as radioactivity was detected in the plasma at 15 minutes post-dosing. The calculated systemic oral bioavailable absorbed dose was 39-57% for the low dose and 73-92% for the high dose. However, the percent of the administered dose recovered as metabolite(s) in the urine and feces was much higher at both doses. Therefore, it was considered likely that the fraction of the orally administered dose absorbed was 70% or greater in both the low and high oral dose groups. After 168 h, total recoveries ranged from 90.4-94.9% of the administered doses, with no differences observed between dose levels, single or multiple doses, or route of exposure. The majority of the radioactivity was recovered in the feces (78.5-86.7% of the administered dose), while urine (2.3-3.8%) was a minor route of elimination. The majority of the radioactivity in the feces was recovered during the first 24 h, while the majority of radioactivity recovered in the urine was recovered during the first 12 h. Generally, tissues, carcass, and cage wash accounted for <8%, except for the i.v.-dosed females (13%). At 168 h, the carcass (1.3-5.8% of the administered dose) and skin (0.4-5.9%) contained the highest mean levels of radioactivity; no other tissue (excluding the gastrointestinal tract) exceeded 0.6% of the administered dose. In general, the highest concentrations of radioactivity were detected in fat, lymph nodes, skin, and adrenals in the males, and in the fat, ovaries, lymph nodes, uterus, skin, and adrenals in females. Radioactivity was detected at low levels in other tissues. Radioactivity did not partition into the RBC. Time courses of radioactivity distribution in tissues was not performed; however, relatively little radioactivity remained in the tissues or carcass at 168 h post-dosing. Therefore, there was no evidence of bioaccumulation. The test compound was extensively metabolized regardless of the route of administration. The majority of radioactivity in urine and fecal extract samples was present as parent and a total of nine metabolites. Metabolic profiles were qualitatively similar across dose levels and route of exposure, and no major differences were noted between sexes. The major route of metabolism was found to be glutathione conjugation with the parent compound, as well as glutathione conjugation with N-demethylated and O-deethylated forms of the parent compound. In excreta, parent and identified compounds accounted for 70.7-85.8% of the administered dose, while unidentified metabolites accounted for 0.8-16.1% of the administered dose. The total administered dose accounted for in the excreta was 82.0-89.1%. Parent compound accounted for 6.5-26.1% of the total radioactivity eliminated, and was found

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		almost exclusively in the fecal extracts. The majority of the radioactivity was contained in Peak 5 (50.7-66.4% of the administered dose), which consisted of the glutathione conjugate of D ₅ -XDE-175-L, the glutathione conjugate of XDE-175-L and the glutathione conjugate of N-demethyl-XDE-175-L in the urine, and the cysteine conjugate of XDE-175-L (tentatively identified) in the feces. Peak 9 (3.9-7.7%) was identified as N-demethyl-XDE-175-L and was found in the feces. The only other identified metabolite was contained in Peak 3 (0.1-1.2%), and was tentatively identified as the cysteine conjugate of 3'-O-deethyl-XDE-175-L.



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