CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022408Orig1s000

PHARMACOLOGY REVIEW(S)

Memorandum

To: NDA 22408

From: Jianyong Wang, Ph.D., Pharmacology/Toxicology Reviewer

Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date:	07/26/2010
Serial No:	SDN 18
Submission type:	Resubmission
Drug:	Natroba Suspension (0.9% Spinosad)
Drug class:	Insecticide
Indication:	Head lice infestation in adults and children
Route:	Topical
Sponsor:	ParaPRO Pharmaceuticals, LLC

Clinical formulation: See previous nonclinical review for Original NDA submission entered into DARRTS on 09/03/2009.

Introduction:

The sponsor submitted the original NDA on 01/22/2009. The nonclinical review was entered into DARRTS on 09/03/2009. On 11/18/2009 a complete response letter was issued to the sponsor, stating that the Agency cannot approve the NDA in its present form for a number of reasons, including that the drug ingredient benzyl alcohol is considered a second active ingredient, which would require additional nonclinical information to support its safety. Afterwards a post-action meeting was held with the sponsor on 03/25/2010, during which the Agency informed the sponsor that a consensus has not been reached on whether benzyl alcohol is an active ingredient, and requested additional information for the determination. Subsequently the sponsor resubmitted the NDA (Class 2) on 07/26/2010.

Review of nonclinical toxicology study reports:

The sponsor did not provide any new nonclinical information in this resubmission.

Discussion and conclusions:

The Chemistry reviewer, Dr. Zhengfang Ge, informed me that some degradation products were noted during her review that were not shown in the primary drug product batches. An information request was sent to the sponsor to clarify this issue. Subsequently the sponsor provided specification data, showing that each unspecified degradation product (b) (4) of the drug substance and total unspecified degradation products (b) (4) of the final drug product (per the conversation with Dr. Ge). Per the ICH Q3B guidance, the identification threshold for degradation products is 0.2% of drug substance or 2 mg, whichever is lower, for new drug products that have a maximum daily dose between 10 mg to 2 g. Considering the short term use of Natroba product, the very low systemic exposure under maximum use clinical conditions, and that no significant toxicity was observed in repeat dose dermal animal studies, the degradation

products at the reported levels do not elicit a safety concern and are acceptable from a pharmacology/toxicology perspective.

The Agency has determined that benzyl alcohol, (b) (4) in the Natroba product, is not a second active ingredient. No new nonclinical information is required at this time. The NDA for Natroba Suspension (0.9% spinosad) is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label discussed in the next section are incorporated into the Natroba Suspension label. No nonclinical postmarketing studies are recommended for this drug product.

It is noted that the Maternal Health Team proposed further changes to the suggested wording for Section 8.1 of the Natroba label. An additional sentence was added and became the second sentence in the first paragraph of Section 8.1: "Studies in humans did not assess for the absorption of benzyl alcohol contained in Natroba Suspension." This proposed change obtained concurrence from clinical during the final labeling meeting and it is also acceptable from a pharmacology/toxicology perspective.

Recommendations:

It is recommended that the suggested labeling changes provided in the next section be incorporated into the Natroba Suspension label.

Suggested labeling:

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the Natroba Suspension label reproduced below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled studies with topical spinosad suspension in pregnant women. Reproduction studies conducted in rats and rabbits were negative for teratogenic effects. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study *[see Clinical Pharmacology (12.3)]* which did not allow for the determination of human AUC values that could be used for this calculation.

Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 10, 50 and 200 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 6 – 15) to pregnant female rats. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 200 mg/kg/day. Oral doses of 2.5, 10 and 50 mg/kg/day spinosad were administered during the period of organogenesis (gestational days 7 – 19) to pregnant female rabbits. No teratogenic effects were noted at any dose. Maternal toxicity occurred at 50 mg/kg/day.

A two-generation dietary reproduction study was conducted in rats. Oral doses of 3, 10, and 100 mg/kg/day spinosad were administered to male and female rats from 10-12 weeks prior to mating and through the mating, parturition, and lactation period. No reproductive/developmental toxicity was noted at doses up to 10 mg/kg/day. In the presence of maternal toxicity, increased dystocia in parturition, decreased gestation survival, decreased litter size, decreased pup body weight, and decreased neonatal survival were noted at a dose of 100 mg/kg/day.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Spinosad causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die.

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 (b) (4) Carcinogenesis, Mutagenesis, Impairment of Fertility

In an oral (diet) mouse carcinogenicity study, spinosad was administered to CD-1 mice at doses of 0.0025, 0.008, and 0.036% in the diet (approximately 3.4, 11.4, and 50.9 mg/kg/day for

males and 4.2, 13.8, and 67.0 mg/kg/day for females) for 18 months. No treatment-related tumors were noted in the mouse carcinogenicity study up to the highest doses evaluated in this study of 50.9 mg/kg/day in male mice and 13.8 mg/kg/day in female mice. Female mice treated with a dose of 67.0 mg/kg/day were not evaluated in this study due to high mortality.

In an oral (diet) rat carcinogenicity study, spinosad was administered to Fischer 344 rats at doses of 0.005, 0.02, 0.05, and 0.1% in the diet (approximately 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) for 24 months. No treatment-related tumors were noted in the rat carcinogenicity study in male or female rats up to the highest doses evaluated in this study of 24.1 mg/kg/day in male rats and 30.1 mg/kg/day in female rats. Rats in the highest dose group in this study were not evaluated due to high mortality.

Spinosad revealed no evidence of mutagenic or clastogenic potential based on the results of four *in vitro* genotoxicity tests (Ames assay, mouse lymphoma L5178Y assay, Chinese hamster ovary cell chromosome aberration assay, and rat hepatocyte unscheduled DNA synthesis assay) and one *in vivo* genotoxicity test (mouse bone marrow micronucleus assay).

Oral administration of spinosad (in diet) to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction, at doses up to 10 mg/kg/day *[see Pregnancy (8.1)]*.

(b) (4)

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/s/

JIANYONG WANG
09/30/2010

BARBARA A HILL
09/30/2010
I concur

Memorandum

To: NDA 22-408

From: Norman R. Schmuff, Branch Chief, DPA II, Branch 4

(in lieu of Elaine Morefield, Division Director, DPA II)

Date: 9/23/2009

Re: Tertiary Review of (b) (4) (Spinosad) Suspension 0.9%

Summary

This is a 505(b) (1) New Drug Application (NDA) submitted by ParaPRO LLC for the prescription use of (b) (4) (spinosad) (b) (4) The proposed indication is treatment of human head lice (b) (4)

The drug substance, spinosad, is a new molecular entity, a fermentation product produced by the actinomycete, Saccharopolyspora spinosa. Spinosad contains two components, spinosyn A and D. The applicant makes a reference to DMF 17795 held by Dow AgroSciences LLC (Michigan, USA) for CMC information of spinosad. The proposed drug product, (b) (4) is a suspension of the spinosad in cetostearyl alcohol.

Recommendation

The reviewer has recommended that the NDA not be approved on the grounds described in 21 CFR 314.125 (b)(1), specifically that the application failed to provide adequate information to assure the identity, strength, purity, and quality of the drug product. Based on my assessment, I concur with the reviewer's recommendation.

The deficiencies are described in the Chemistry Review, and are summarized on pages 52 and 53. These include, but are not limited to:

- failure to include in the application, a specification for acceptance of the drug substance
- failure to comply with a previous agreement drug product impurities
- an inadequate analytical procedure for the assay of drug product.

APPEARS THIS WAY ON ORIGINAL

Unexplained phase separation was also noted in samples provided to the Agency in May 2009.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

NORMAN R SCHMUFF
09/23/2009
ONDQA Tertiary Review

Pharmacology/Toxicology Supervisory Memorandum

NDA number: 22-408
Sequence number/date/type of submission: 1 / January 22, 2009/ New NDA
Sponsor: ParaPRO Pharmaceuticals LLC
Supervisor name: Barbara Hill
Division name: Division of Dermatology and Dental Products
Date: September 4, 2009
Drug: (b) (4) (spinosad) suspension, 0.9%
Drug class: Insecticide, Pediculicide
Indication: Treatment of head lice in patients (b) (4)

General comments:

I concur with the conclusions contained in Dr. Jianyong (Jerry) Wang's nonclinical review for this drug product.
I concur that there are no nonclinical approval issues for this drug product.
I concur with the suggested nonclinical labeling changes proposed by Dr. Wang for this drug product including that the appropriate Pregnancy Category is B.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

BARBARA A HILL
09/04/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-408**
SERIAL NUMBER:	**1**
DATE RECEIVED BY CENTER:	**1-22-2009**
PRODUCT:	(b) (4) **Spinosad)**
INTENDED CLINICAL POPULATION:	**Children and adults with head lice**
SPONSOR:	**ParaPRO Pharmaceuticals, LLC**
DOCUMENTS REVIEWED:	**Electronic CTD NDA submission**
REVIEW DIVISION:	**Division of Dermatology and Dental Products (HFD-540)**
PHARM/TOX REVIEWER:	**Jianyong Wang, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barbara Hill, Ph.D.**
DIVISION DIRECTOR:	**Susan Walker, M.D.**
PROJECT MANAGER:	**Dawn Williams**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability – The NDA for drug product (b) (4) Spinosad) is approvable from a pharmacological/toxicological perspective.

B. Recommendation for nonclinical studies – None

C. Recommendations on labeling – Recommended wording for the nonclinical portions of the label are provided in the "Suggested Labeling" section located at the end of this review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Major signs of systemic toxicity observed in repeat dose oral toxicology studies in mice, rats, and dogs include: vacuolation in a variety of tissues, chronic inflammation and necrosis of thyroid gland, anemia with compensatory hematopoiesis, lymph node necrosis, liver cytomegaly and necrosis, skeletal muscle myopathy, arteritis, chronic inflammation, hyperplasia and hyperkeratosis of stomach mucosa, and lymphoid organ histiocytosis. Administration of spinosad in the diet at up to 0.1% for 12 months did not appear to be neurotoxic in rats. No dermal toxicity or systemic toxicity was noted after application of moistened spinosad (0.6 mL water added per gram of XDE-105) up to 1000 mg/kg to the skin of rabbits for 6 hours a day for 21 days. Topical daily application of 0.5, 1.0 and 2.0% spinosad (b) (4) to minipigs for 28 days did not produce significant dermal or systemic toxicity.

Spinosad was evaluated in Ames test, mouse lymphoma assay, chromosome aberration test, UDS assay, and micronucleus test, and it does not appear to be genotoxic. Spinosad was evaluated in an 18-month oral carcinogenicity study in mice and in a 2-year oral carcinogenicity study in rats. No statistically significant neoplastic findings were observed in these two studies.

Spinosad was evaluated for effects upon reproduction. Spinosad is not teratogenic in rats at oral doses up to 200 mg/kg or in rabbits at oral doses up to 50 mg/kg. In a two-generation dietary reproduction study in rats, at the high dose of 100 mg/kg, which was clearly a maternally toxic dose, spinosad appeared to have an effect on parturition with increased dystocia observed in both P1 and P2 generations. Decreased gestation survival, decreased litter size, decreased pup body weight and decreased neonatal survival were also noted at 100 mg/kg.

Spinosad 2% (b) (4) was not irritating to the skin of minipig but produced relatively mild irritation in the rabbit eye and the irritation was reversible with time. Spinosad 2% (b) (4) did not induce a phototoxic reaction in mice when irradiated with an

essentially all UVA light source. Spinosad did not appear to be a skin sensitizer in guinea pigs.

B. Pharmacologic activity - Spinosad is an insecticide. It causes paralysis of insects by over-exciting the nervous system.

C. Nonclinical safety issues relevant to clinical use – None at this time.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-408
Review number: 1
Sequence number/date/type of submission: 1 / 01-22-09 / Original NDA submission
7 / 07-09-09 / Nonclinical information
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: ParaPRO Pharmaceuticals, LLC, Carmel, Indiana
Manufacturer for drug substance: Dow AgroSciences, Harbor Beach, Michigan

Reviewer name: Jianyong Wang
Division name: Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 8-7-09

Drug:

Trade name: (b) (4) Spinosad)
Generic name: (b) (4) Spinosad
Code name: LY232105, DE-105, XDE-105 or PP105
Chemical name:

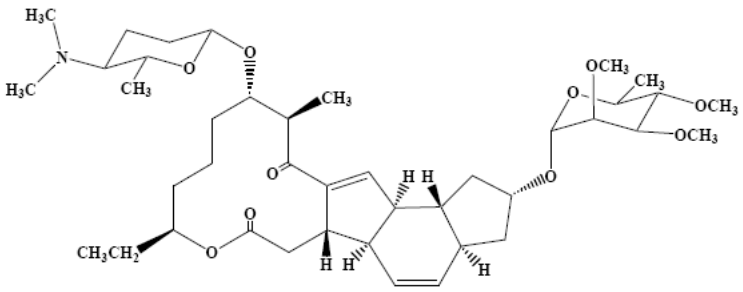
Spinosyn A: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,a5-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-L-mannopyranosyl)oxy]-13-[[2R,5S,6R)-5-(dimethylamino) tetrahydro-6-methyl-2H-pyran-2-yl]oxy]-9-ethyl-2,3,3a,5a,5b,6,9,10,11,12,13,14,16a,16b-tetradecahydro-14-metyl-,(2R,3aS,5aR,5bS,9S,13S,14R,16aS,16bR)-

Spinosyn D: 1H-as-Indaceno[3,2-d]oxacyclododecin-7,15-dione, 2-[(6-deoxy-2,3,4-tri-O-methyl-alpha-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-dimetyl-,(2S,3aSR,5aS,5bS,9S,13S,14R,16aS,16bS)-

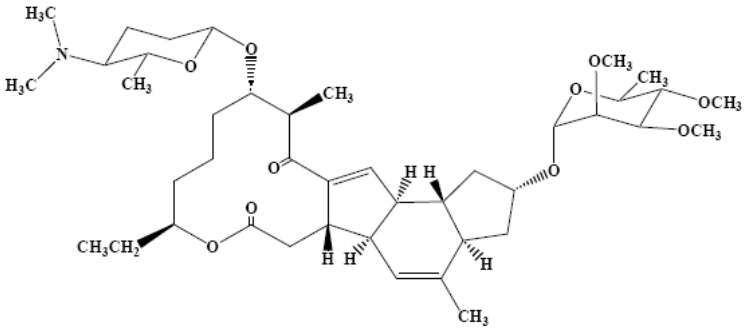
(*Note:* These chemical names are taken from the submission. Spinosad is a mixture of factors, primarily Spinosyn factor A and Spinosyn factor D. Spinosyn factor A accounts for about (b) (4) of Spinosad and Spinosyn factor D accounts for about (b) (4). Spinosyn factor B accounts for about (b) (4) of Spinosad and other factors account for about (b) (4)

CAS registry number: Spinosyn A: 131929-60-7, Spinosyn D: 131929-63-0
Molecular formula/molecular weight: Spinosyn A: $C_{41}H_{65}NO_{10}$ / 731.461
Spinosyn D: $C_{42}H_{67}NO_{10}$ / 745.477

Structure:
Spinosyn A:



Spinosyn D:



Relevant INDs/NDAs/DMFs:

1) The Active Pharmaceutical Ingredient (API) is prepared by Dow AgroSciences, LLC. The API data are referenced in the DowAgroSciences Drug Master File (DMF) (DMF 17795, 09/19/2004). A reference authorization letter is included in the submission.
2) IND 66,657 (b) (4) Spinosad (b) (4) head lice, HFD-540)

Drug class: Insecticide, Pediculicide

Intended clinical population: children and adults with head lice

Clinical formulation:

The composition of the (b) (4) formulation is listed in the following table. The concentration of spinosad should be fixed at (b) (4) (chemistry has designated that amount is now 0.9% based on Spinosyn Factors A and D only, and recommends the name (b) (4) be changed to suspension). Two minor changes are noted in the ingredient concentrations when compared with the composition previously submitted to IND 66,657 (hydroxyethyl cellulose (b) (4) hexylene glycol (b) (4) The new levels of the two ingredients are still below the approved levels in the CDER inactive ingredient database. The changes of the two ingredient concentrations are not considered significant regarding the toxicity profile of the drug product.

Ingredient	Concentration (% w/w)	Function
Spinosad	0.5-2	active ingredient
Hydroxyethyl cellulose	(b) (4)	
Cetearyl alcohol		
Propylene glycol		
Ceteareth-20		
Stearalkonium chloride 4.2		
Benzyl alcohol		
Hexylene glycol		
Isopropyl alcohol		
Butylated hydroxytoluene		
FD&C Yellow #6		
Water		
Sodium hydroxide		
Hydrochloric acid		

Reviewer's comments:

Benzyl alcohol (b) (4) in the formulation at the concentration (b) (4) Benzyl alcohol 5% lotion (Ulesfia) has approved under NDA 22-129 on 04/09/2009 for the treatment of head lice infestation in patients 6 months of age and older. Intravenous administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome. Therefore, it is recommended the description of the neonatal toxicity of benzyl alcohol be included in the Warnings and Precautions section of the label for (b) (4) similar to the description contained in the Ulesfia label.

The Chemistry reviewer (Dr. Zhengfang Ge) identified three impurities in the DMF of spinosad that have a quantity higher than the qualification threshold: (b) (4)

(b) (4)

(b) (4)

The CMC reviewer informed me that the DMF sponsor has provided impurity data of 9 batches of the drug substance used in clinical studies and the data showed that all the quantities of impurities were below the specification limit and consistent. The manufacturing process of the drug substance has not been changed, therefore the drug substance used in nonclinical studies is expected to have the same impurity profile as specified in the DMF.

Considering that (1) the proposed use (b) (4) is a single topical treatment with short duration (2) there is very low systemic exposure to the drug substance (see Section 2.6.4.8) (3) spinosad was tested negative in two oral carcinogenicity studies (4) the impurity profile of the drug substance used in nonclinical studies is likely the same as specified in the DMF and (5) the low toxicity potential of the three identified impurities, there are no significant safety concerns for impurities (b) (4)

Spinosad is a mixture of factors, primarily Spinosyn factor A and Spinosyn factor D. Spinosyn factor A accounts for about (b) (4) of Spinosad and Spinosyn factor D accounts for about (b) (4) Spinosyn factor B accounts for about (b) (4) of Spinosad and other factors (b) (4) account for about (b) (4). In the response to Chemistry's information request (letter dated 08/07/2009), the sponsor listed the ingredient composition of the nonclinical lots and clinical lots of spinosad (part of the list is cited in the following table). Although quantitative information of each individual minor Spinosyn factor was not provided for nonclinical lot ACD13651, the quantity of combined minor factors is similar in the nonclinical lots and clinical lots. From a pharmacology/toxicology perspective, the variations in the ingredient composition between nonclinical lots and clinical lots appear acceptable. In addition, clinical pharmacokinetic studies showed that the systemic exposure to spinosad was very low under maximum use conditions (see Section 2.6.4.8). Therefore, the nonclinical studies conducted with the nonclinical lots of spinosad are considered acceptable to support the clinical development of the (b) (4) drug product.

API Analytical Characterization					
PII Lot No.	NA	03-0463	04-0288	06-0171	06-0170
Dow Lot No.	ACD13651	RH25160W06	SE27160W11	UB04160W02	UB04160W03
	Dow Toxicology	Preclinical	Phase 1,2 Studies	Phase 3	Phase 3
Manufacture Date	1/1/1991	1/1/2003	6/7/2004	2/4/2006	2/6/2006
	(b) (4)				
Factor A					
Factor D					
A+D					
Combined Minor Factors					
Total, all factors					

Route of administration: Topical

Proposed use:

(b) (4) Spinosad) should be applied as a single treatment to dry scalp and hair. Up to 120 mL (b) (4) may be used to adequately cover the scalp and hair. (b) (4) must be left on the scalp and hair for 10 minutes and then should be rinsed thoroughly with warm water. If reinfestation occurs after treatment, (b) (4) can be applied again according to the Directions for Use. Therefore the maximum single dose of spinosad will be 1200 mg. This would be a dose of 20 mg/kg in a 60 kg adult or 60 mg/kg in a 20 kg child.

Background:

Spinosad is used as an agricultural insecticide. A variety of nonclinical studies have been conducted with Spinosad to support this use. Many of these studies were conducted by the oral route and included long term studies. In most of these studies the drug substance was the mixture of various spinosyn factors, primarily A and D.

A preNDA meeting was conducted with the sponsor on 11/04/2008. Three issues were identified from a pharmacology/toxicology perspective: (1) No nonclinical cardiovascular safety pharmacology studies were submitted. EKG evaluation was not performed in the toxicology studies in dogs. (2) No toxicokinetic data for oral diet toxicology studies in rats or dogs or for reproductive/developmental toxicology studies were submitted. (3) No juvenile animal toxicology studies were submitted. The sponsor addressed these issues in the response to the 74-day filing letter (response letter dated 04/24/2009).

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. *In vitro* evaluation of a new pediculicidal active ingredient against the eggs and crawling stages of the head louse, Study No. 344-0030.
2. XDE-I05: 18-month dietary oncogenicity study in CD-1mice, Study No. DERBI-29837
3. XDE-105: 2-year chronic toxicity, chronic neurotoxicity and oncogenicity study in Fischer 344 rats, Study No. DERBI-29838

Studies not reviewed within this submission:

The following studies have been reviewed under IND 66,657 by Dr. Paul Brown:

Safety pharmacology:
1. XDE-105: 13-week dietary toxicity, 4-week recovery, and 13 week neurotoxicity studies in Fischer 344 rats (Neurotoxicity portion), Study No. DERBI-4246

Pharmacokinetics/Toxicokinetics:
1. XDE-105 (Factor A): metabolism and tissue distribution of ^{14}C-labeled XDE-105 (Factor A) in Fischer 344 rats, Study No. DERBI-29220
2. XDE-105 (Factor D): metabolism and tissue distribution of ^{14}C-labeled XDE-105 (Factor D) in Fischer 344 rats, Study No. DERBI-29140
3. Bile elimination of XDE-105 (Factor D) in Fischer 344 rats, Study No. DERBI-29221
4. XDE-105: comparison of the metabolism and tissue distribution of ^{14}C-labeled XDE-105 (Factor A) and ^{14}C-labeled XDE-105 (Factor D) in Fischer 344 rats., Study No. DERBI-29848
5. Spinosyn A: Probe study, dermal absorption of 14C-labeled Spinosyn A in Fischer Rats, Study No. DERBI-44495
6. Bioaccumulation of ^{14}C-Spinosyn A in female Fischer 344 rats following repeated oral administration with ^{14}C-Spinosyn A, Study No. DERBI-47511
7. A ten-day GLP pharmacokinetic study of spinosad administered orally or dermally to rats, Study No. 0456-05307
8. *In vitro* dermal absorption/percutaneous penetration assay in human donor skin, Study No. 04AA92.630008

   (Note: Studies 1 and 2 listed above were also further discussed in the report of Study 4. The report of Study 4 contained no new data.)

Single-dose toxicity:
1. Acute dermal toxicity study in New Zealand White rabbits, Study No. DERBI-24283 (DR-0323-1194-017D)
2. Acute dermal toxicity study in New Zealand White rabbits, Study No. DERBI-24929 (DR-0323-1194-017D1)
3. DE-105: Acute oral toxicity study in Fischer 344 rats and CD-1 mice, Study No. DERBI-43749
4. XDE-105: Acute oral toxicity study in Fischer 344 rats and CD-1 mice, Study No. DERBI-24289
5. The acute toxicity of XDE-105 administered orally to Fischer 344 rats, Study No. DERBI-15440

6. The acute toxicity of XDE-105 administered intraperitoneally to Fischer 344 rats, Study No. DERBI-15438
7. XDE-105: acute neurotoxicity study in Fischer 344 rats, Study No. DERBI-8344

Repeat-dose toxicity:

1. A 28-day study of a test article when administered topically to swine, Study No. 766C-602-232-03
2. XDE-105: Probe and 21-day repeated dose dermal toxicity study in New Zealand White rabbits, Study No. DERBI 24045
3. A subchronic toxicity studying CD-1 mice administered XDE-105 in the diet for 3 months, Study No. DERBI-15445
4. Spinosad: 4-week dietary toxicity and recovery study in Fischer 344 rats, Study No. DERBI-68163
5. XDE 105, Factor A and Factor D: 28-day dietary toxicity study in Fischer 344 rats, Study No. DERBI-24273
6. A subchronic toxicity study in Fischer 344 rats administered XDE-105 in the diet for 3 months, Study No. DERBI-40760
7. XDE-105: 13 week dietary toxicity and 4 week recovery studies in Fischer 344 rats, Study No. DERBI-24277
8. XDE-105: 13-week neurotoxicity studies in Fischer 344 rats, Study No. DERBI-4246
9. XDE105: 13-week oral subchronic toxicity study in dogs, Study No. DERBI-24388
10. A 21-day subchronic dermal toxicity study of XDE-105 in New Zealand white rabbits, Study No. DERBI-15442
11. XDE-105: chronic neurotoxicity study in Fischer 344 rats, Study No. DERBI-40187
12. XDE-105: 12-month oral chronic toxicity study in dogs, Study No.:DERBI-40188. Another report numbered DERBI-68690 was also submitted which included neurological examinations on the dogs used in this study.

Genetic toxicology:

1. The effect of XDE-105 on the induction of reverse mutations in *Salmonella typhimurium* and *Escherichia coli* using the Ames test, Study No. DERBI-15447
2. Mutagenicity test on XDE-105 in the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay preincubation method with a confirmatory assay, Study No. DERBI-45425
3. Mutagenicity test on XDE-105 Factor B in the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay preincubation method with a confirmatory assay, Study No. DERBI-47406
4. The effect of XDE-105 on the induction of forward mutation at the thymidine kinase locus of L5178Y mouse lymphoma cells, Study No. DERBI-1467
5. The effect of XDE-105 on the in vitro induction of chromosome aberrations in Chinese hamster ovary cells, Study No. DERBI-1474
6. The effect of XDE-105 on the induction of unscheduled DNA synthesis in primary cultures of adult rat hepatocytes, Study No. DERBI-1469
7. The effect of XDE-105 on the in vivo induction of micronuclei in bone marrow in ICR mice, Study No. DERBI-1468

Reproductive and developmental toxicology:

1. Oral gavage teratology study in Sprague-Dawley rats, Study No. DERBI-15453
2. XDE-105: oral gavage teratology study in New Zealand white rabbits, Study No. DERBI-7543
3. XDE-105: Two-generation dietary reproduction study in Sprague-Dawley rats, Study No. DERBI-27238

Local tolerance:

1. A primary dermal irritation study of test article when administered to swine, Study No. 766B-601-211-03
2. A primary ocular irritation study of test article administered to rabbits, Study No. 766A-301-912-03
3. A 2-week acute dermal irritation and toxicity study in New Zealand white rabbits following a single topical application and 24 hour exposure of XDE-105, Study No. DERBI-1471
4. XDE-105: primary eye irritation study in New Zealand white rabbits, Study No. DERBI-24282

Special toxicology:

1. Dermal phototoxicity screening test in mice, Study No. MB 04-12544.30
2. Assessment of skin sensitization potential using the local lymph node assay in the mouse, Study No. LMK 001/042794/LN
3. A skin sensitization study of DE-105 in guinea pigs (Maximization test), Study No. DERBI-49901
4. XDE-105: dermal sensitization potential in the Hartley albino guinea pigs, Study No. DERBI-24280

The following studies have not been reviewed under IND 66,657:

(b) (4)

The sponsor also submitted the following literatures to this NDA. These literatures were not summarized in this review because they do not add significant information to the database that was captured in the review.

1. Salgado VL. 1998. Studies on the mode of action of Spinosad: insect symptoms and physiological correlates. Pesticide Biochemistry and Physiology 60:91-102.

2. Lüllmann H, Lüllmann-Rauch R, and Wassermann O. 1978. Lipidosis induced by amphiphilic cationic drugs. Biochem Pharmacol 27:1103-8.
3. Schneider P. 1992. Drug-induced lysosomal disorders in laboratory animals: new substances acting on lysosomes. Arch Toxicol 66:23-33.
4. Reasor MJ. 1989. A review of the biology and toxicologic implications of the induction of lysosomal lamellar bodies by drugs. Toxicol Appl Pharmacol 97:47-56.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Spinosyn A appears to cause the excitation of the nervous system in insects by altering the function of nicotinic and gamma amino butyric acid-gated ion channels. Paralysis of the insect appears to be caused by this prolonged over excitation of the nervous system. Concentrations of 0.5 to 2% Spinosad have been tested *in vitro* against live head lice and eggs (nits). The mixture was 100% effective at killing the lice and nits at all concentrations. The exact vehicle used in these studies is not clear and the vehicle itself appeared to have significant activity against the lice and nits.

2.6.2.2 Primary pharmacodynamics:

Study #1:

Study title *In vitro* evaluation of a new pediculicidal active ingredient against the eggs and crawling stages of the head louse

Study no.: 344-0030
Sponsor study no.: N/A
Volume #, and page #: eCTD
Conducting laboratory: (b) (4)
Date of study initiation: not known (Date of study completion: 03/22/2004)
GLP compliance: No
QA reports: No
Drug, lot #, and % purity: Spinosad, lot # and purity are not provided
Vehicle: not provided
Positive control: Nix® Permethrin Lice Treatment

Methods

Three concentrations of Spinosad (0.5%, 1.0%, and 2.0%), placebo, water, and Nix® Permethrin Lice Treatment were tested for mortality against both the crawling stages (crawlers) and eggs (nits) of head lice (*pediculis humanus capitis*). Five replications of 25 crawlers and 48 total eggs were tested. The crawlers were immersed in each solution for 10 minutes then rinsed and placed in petri dishes with hair. Mortality counts were taken every hour until 20% mortality was reached in the controls. The nits were immersed in each solution for 10 minutes, then rinsed and placed in petri dishes. Nits were evaluated 17 days post treatment.

Results:

Figure 1. Mortality of crawlers

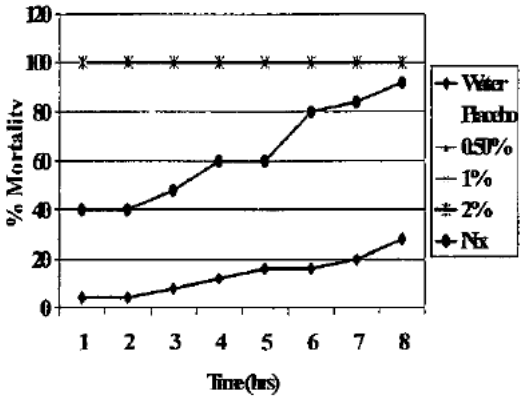
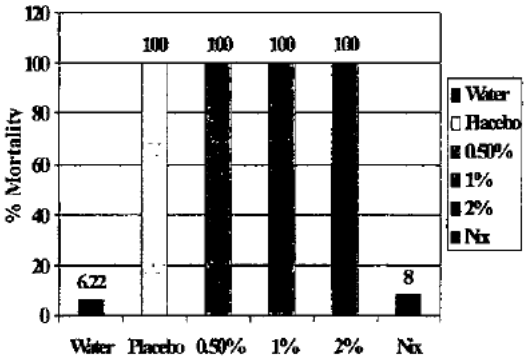


Figure 2. Mortality of nits.



The crawlers showed 100% mortality with all three spinosad formulations from 1 to 8 hours post-treatment. The water control reached 20% mortality at 7 hours post-treatment, and both the placebo and Nix® reached 80% mortality at 6 hours post-treatment. The nit mortality was 100% for the placebo and all three spinosad formulations. The mortality for the water control and Nix® was 6.2% and 8%, respectively.

2.6.2.3 Secondary pharmacodynamics: N/A

2.6.2.4 Safety pharmacology

Neurological effects:

The neurological effects were evaluated in a 13-week neurotoxicity study in Fischer 344 rats (Study No. DERBI-4246), which is a part of a 13-week dietary study in Fischer 344 rats (Study No. DERBI-24277).

Male and female rats (10/sex) were fed diets containing 0, 0.003, 0.006, 0.012 or 0.06% XDE-105 for 13 weeks. These were equivalent to doses of 0, 2.2, 4.3, 8.6 and 42.7 mg/kg/day in males and 0, 2.6, 5.2, 10.4 and 52.1 mg/kg/day in females. A functional observational battery, grip performance, hindlimb landing foot splay and a motor activity test were conducted before treatment and monthly during treatment. At the end of the 13-week treatment period a neuropathological evaluation was conducted on 5 animals/sex/group. The brain was cut into nine sections and the following other nervous tissues were prepared: trigeminal ganglion, pituitary gland, eyes with optic nerves, spinal cord, nasal tissues with olfactory epithelium, skeletal muscles, sciatic nerve, tibial nerve and sural nerve. These tissues were only examined in the control and high dose animals. No treatment related effects were noted in the handheld and open field observations. No differences were noted in gait or posture, muscle tone or hind limb extensor thrust response. Sensory responses and overall activity and reactivity were judged to be normal. Hindlimb and forelimb grip performance and hindlimb landing foot splay were not affected. Motor activity as measured by photobeam breaks in a circular motor activity cage was not affected by treatment. There were a few microscopic findings in nervous tissues such as swollen axons and degeneration of individual nerve fibers in the medulla oblongata and swollen

axons in the par nervosa area of the pituitary and some individual nerve fiber degeneration in the spinal cord but these appeared to occur with a similar incidence and severity in the control and high dose groups. Essentially no neurological effects were noted in rats fed up to 0.06% XDE-105 in the diet for 13 weeks. No toxicokinetic data was available for this study.

Cardiovascular effects: Not assessed.

Pulmonary effects: Not assessed.

2.6.2.5 Pharmacodynamic drug interactions: N/A

2.6.3 PHARMACOLOGY TABULATED SUMMARY: N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Relatively small amounts of spinosad penetrated into human skin *in vitro* (1.44% with one hour of contact, 16% with 24 hours of contact). When rats were treated with Spinosyn A under occlusion in a vehicle of dipropylene glycol monoethyl ether, about 10 to 14% of the total dose was in the skin after 24 hours while about 1% was absorbed systemically. In rat studies, approximately 70-80% of Factor A and 60% of Factor D was absorbed after oral administration in an aqueous methylcellulose vehicle. There does not appear to be accumulation over 10 days of dosing in the rat.

In rats, Spinosyn A was rapidly distributed to tissues. C_{max} plasma levels were lower than tissue C_{max} values. At C_{max} the highest concentrations of drug were observed in the GI tract and the duodenum was the segment with the highest in the GI tract. Other tissues that also had relatively high levels included the liver, lung, adrenals, thyroids, lymph nodes, peri-renal fat, kidneys, spleen, heart and thymus. The brain had relatively low levels.

Spinosad appears to be largely eliminated in the feces in the rat. Some of this (36%) is via the bile. Spinosyn A appears to be largely metabolized since only 6% of the parent compound was found in the feces whereas approximately 50% of the parent compound Spinosyn D was found in the feces. Metabolism of the Spinosyns included O-demethylation, N-demethylation, hydroxylation and glutathione conjugation of the parent and phase I metabolites. Although sufficient information for reliable PK parameters was not collected, the estimated terminal half-life for Spinosyn A in the rat was between 25 to 44 hours and 29 to 33 hours for Factor D.

In a ten-day GLP pharmacokinetic study, spinosad was administered to SD rats via oral gavage at a dose of 10 mg/kg/day for 10 days. The PK parameters are as the following:

Table 3. Mean Pharmacokinetic Parameters for Spinosyn A and Spinosyn D Following Oral Delivery on Study Day 1 and Study Day 10.

Test Article	Route	Dose (mg/kg)	Study Day	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng*hr/mL)
Spinosyn A	Oral	10	1	2	159	1024
Spinosyn A	Oral	10	10	1	213	1176

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Test Article	Route	Dose (mg/kg)	Study Day	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng*hr/mL)
Spinosyn D	Oral	10	1	2	15	108
Spinosyn D	Oral	10	10	1	20	146

In another study, Fischer 344 rats was dosed orally with either 10 or 100 mg/kg of radiolabeled spinosad (Study DR-0323-1194-012), with PK parameters listed below:

Table 2B. Mean Pharmacokinetic Parameters for Spinosyn A Following Oral Delivery on Study Day 1. From DR-0323-1194-012

Test Article	Route	Target Dose (mg/kg)	Study Day	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24\ hr)}$ (ng*hr/mL)
Spinosyn A	Oral	10	1	1	702	6849
Spinosyn A	Oral	100	1	2	3903	67941

2.6.4.2 Methods of Analysis: liquid chromatography (LC) and mass spectroscopy (MS) methods

2.6.4.3 Absorption: refer to the brief summary above.

2.6.4.4 Distribution: refer to the brief summary above.

2.6.4.5 Metabolism: refer to the brief summary above.

2.6.4.6 Excretion: refer to the brief summary above.

2.6.4.7 Pharmacokinetic drug interactions: N/A

2.6.4.8 Other Pharmacokinetic Studies

Clinical pharmacokinetic study brief summary:

Three Phase 1 clinical studies have been conducted to evaluate the pharmacokinetics of spinosad (b) (4):

1. Study SPN-101-04: Spinosad 2.0% (b) (4) was applied once (single application) for10 minutes to23 healthy subjects (21-60 years of age)
2. Study SPN-103-05: Spinosad 2.0% (b) (4) was applied once (single application) for10 minutes to 14 pediatric patients (4-15 years of age) with head lice
3. Study SPN-106-06: Spinosad 1.0% (b) (4) was applied once (single application) for 10 minutes to 8 healthy pediatric subjects (6-23 months of age)

In all the blood samples obtained from these studies (614 samples in Study SPN-101-04, 136 samples in Study SPN-103-05, and 48 samples in Study SPN-106-06), spinosad/spinosad metabolite concentration was below the limit of quantification (BLQ: 3 ng/mL). These studies have been reviewed by the clinical pharmacology reviewer (Dr. Dennis Bashaw) and Dr. Bashaw determined that these studies were adequate for the evaluation of pharmacokinetics (b) (4) under maximal use conditions.

2.6.4.9 Discussion and Conclusions

The cardiovascular safety of spinosad was not evaluated in safety pharmacology studies, and ECG was not assessed in repeat dose toxicology studies in dogs or minipigs. However, due to a very low systemic exposure to spinosad (below the limit of quantification) under the maximal use conditions in humans, no additional safety pharmacology studies are recommended at this time.

No toxicokinetic data were available for the conducted repeat dose oral toxicology studies, carcinogenicity studies, or reproductive toxicology studies, which are summarized in the following Toxicology sections. In those studies, significant systemic toxicities have been observed in the animals, indicating that adequate systemic exposure has been achieved in those studies.

Because the systemic exposure to spinosad after the maximal use conditions in humans is so low that it is impossible to make calculation of pharmacokinetic parameters, the animal to human dose ratios used in the labeling will not be calculated based on either AUC comparisons or total dose comparisons. There will be no multiples of human exposure calculated for this label. The following wording will be used in the label for (b) (4):

"No comparisons of animal exposure with human exposure are provided in this labeling due to the low systemic exposure noted in the clinical pharmacokinetic study *[see Clinical Pharmacology (12.3)]* which did not allow for the determination of human AUC values that could be used for this calculation."

No additional nonclinical pharmacokinetic/toxicokinetic studies are recommended at this time.

2.6.4.10 Tables and figures to include comparative TK summary: N/A

2.6.5 PHARMACOKINETICS TABULATED SUMMARY: N/A

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

A single dose of XDE-105 administered orally at up to 1800 mg/kg (actual dose) did not appear to be neurotoxic in rats. Body weights were slightly decreased in the mid and high dose on Day 2. No behavioral effects or effects on motor activity were noted. The lesions noted in the neural tissues were observed at similar incidence in vehicle and drug treated animals and appear to be general background lesions. No toxicokinetic data was collected in this study so the systemic levels of exposure are not known.

In a 3-month oral (diet) toxicity study, diet containing 0, 0.005, 0.015, 0.045 or 0.12% of XDE-105 was given to CD-1 mice. The highest dose of XDE-105 (0.12%) was not tolerated. Significant body weight decreases were observed in the 0.12% group. Body weight gain decreased 230% and 165% in the 0.12% males and females, respectively after 6 weeks. Body weight and body weight gain in the 0.045% group were also decreased compared to control although to a lesser degree than in the 0.12% group. There was no change in body weight or body weight gain relative to control in the 0.015% and 0.005% groups. The primary lesion that occurred in many tissues in a dose-dependent manner was vacuolation. Electron microscopic evaluation revealed cytoplasmic lamellar inclusion bodies. The report concludes that this is consistent with phospholipidosis which results from the accumulation of polar lipids in lysosomes. Other findings include anemia with compensatory hematopoiesis and lymph node necrosis. There was also significant liver cytomegaly and necrosis. The liver toxicity was also apparent in the clinical chemistry findings at both 0.045% and 0.12%. The dietary level of 0.005% appears to be the NOAEL. The vacuolation of the ovary at 0.005% was similar in incidence and severity to control and the kidney vacuolation at 0.005% occurred in only one animal and was slight. Limitations of this study include an ad lib presentation of the diet with no quantitation of food consumption and no toxicokinetic evaluation. Therefore, accurate quantitation of dose or exposure is not possible.

In a 3-month oral (diet) toxicity study, diet containing 0, 0.05, 0.1, 0.2, or 0.4% of XDE-105 was given to Fischer 344 rats. The 0.4% level of XDE-105 in the diet was not tolerated. High dose males and females were sacrificed on Day 44 due to high mortality and poor health. By the end of the study, body weight gain was reduced 18% and 26% in males and females, respectively, in the 0.2% group. Body weight and body weight gain in the 0.1 and 0.05% groups were similar to control. The most pronounced effect in this study was widespread vacuolation in a variety of tissues. The presence of cytoplasmic lamellar inclusion bodies makes these lesions consistent with phospholipidosis. Some observed effects may not be directly related to the phospholipidosis such as the splenic hematopoiesis, gastric hyperkeratosis, cecal changes, hypospermatogenesis and skeletal muscle myopathy. Effects tended to be more severe in

females than males. Some of the hematology and histology changes suggest blood loss although this was not grossly observed. Clinical chemistry changes suggest some hepatic toxicity. A NOAEL was not established in this study since some of the effects such as increased liver weights, lymphoid organ histiocytosis and follicular cell vacuolation in the thyroid were noted even at the lowest dose of 0.05%. One shortcoming of this study is that no toxicokinetic data was collected so the systemic exposure to XDE-105 or its metabolites is unknown.

In a subsequent study, XDE-105 was well tolerated by rats when fed in the diet at up to 0.06% for 13 weeks. The primary effect at this dose appeared to be thyroid vacuolation. Some alveolar histiocytosis in the lung was also observed. There appeared to be a slight effect on liver and heart weight although there was no histological correlation to those effects. The NOAEL for XDE-105 in the diet for the Fisher 344 rat appears to be 0.012% under the conditions of this study.

Administration of XDE-105 in the diet at up to 0.1% (46 and 57 mg/kg/day for males and females, respectively) for 12 months did not appear to be neurotoxic in rats (this study was part of the 2-year carcinogenicity study described in the carcinogenicity section). One male animal receiving the 0.1% diet died between month 9 and month 12 and no explanation was provided. No behavioral effects or effects on motor activity were noted. The lesions noted in the neural tissues were observed at similar incidence in vehicle and drug treated animals and appear to be general background lesions. No toxicokinetic data was collected in this study so the systemic levels of exposure are not known.

Dogs fed diets containing 1350/900 ppm XDE-105 (~ 45/30 mg/kg/day) for 13 weeks appear to exhibit anemia and some hepatotoxicity according to hematologic and clinical chemistry parameters. Histopathologic lesions related to XDE-105 included widespread cytoplasmic vacuolation especially in lymph tissues. Arteritis also appeared to be a widespread XDE-105 related finding. Similar toxicity although at lower incidence was observed with a diet containing 300 ppm XDE-105. A diet containing 150 ppm XDE-105 (~ 5 mg/kg/day) appeared to be a NOAEL in the dog. No toxicokinetic data or reversibility information was collected in this study.

An oral dose of XDE-105 of 9 mg/kg/day (300/600 ppm in the diet) administered for 12 months was associated with increased clinical chemistry parameters indicative of possible hepatotoxicity and with increased vacuolation in several tissues including lymphoid tissues in dogs. This dose was also associated with some focal occurrences of arteritis. No neurological behavioral or reflex changes were noted in the treated animals. The middle dose of 3 mg/kg/day administered for 12 months (100/120 ppm in the diet) appeared to be a NOAEL in the dog.

No dermal toxicity was noted after application of moistened XDE-105 (0.6 mL water added per gram of XDE-105, up to 1000 mg/kg) to the skin of rabbits for 6 hours a day for 21 days (5 daily applications per week for a total of 15 applications). Essentially no systemic toxicity was noted in this study; however, it was not conclusive for systemic toxicity since no toxicokinetic data were available.

Application of the (b) (4) vehicle and formulations containing 0.5, 1.0 and 2.0% spinosad to minipigs for 28 consecutive days did not produce significant local or systemic toxicity (There is no mention of removal of the test article in the study report). Systemic exposure to spinosyn A and D was demonstrated in this study by the plasma level data (see the following table). A full toxicokinetic profile was not obtained in this study due to limited blood sampling times. The highest dose appears to be the NOAEL in this study. This dose is the 2% (b) (4) which is 40 mg/kg. This is a human equivalent dose (HED) of 20 mg/kg based on 7 kg swine body weight and 60 kg human weight and is calculated with the equation:
HED=40 mg/kg x $(7 \text{ kg}/60 \text{ kg})^{1/3}$ = 20 mg/kg.
Reviewer's comment: Because the minipigs used in this study were small (with body weights around 7 kg, compared with an average body weight of 40 kg for adult minipigs), the above equation was used for the HED calculation, instead of using a conversion factor of 0.946 for minipig.

Day 28 spinosyn A and D levels (ng/mL)		
Group	Males	Females
0 hour		
10 mg/kg (0.5%)	17.6	19.7
20 mg/kg (1.0%)	9.3	51.0
40 mg/kg (2.0%)	55.9	111.4
8 hour		
10 mg/kg (0.5%)	13.4	21.9
20 mg/kg (1.0%)	35.1	54.3
40 mg/kg (2.0%)	86.9	178.5

Genetic toxicology:

In one Ames assay, XDE-105 appeared to produce a significant increase in revertants. The report suggested that the growth of colonies may have been supported by the drug substance since trace amounts of histidine and other amino acids had been discovered in the test article. It is noted that the XDE-105 tested was listed as only 88.0% pure. However, when colony replicates were grown it appeared that some of the colonies from the drug treated plates were true revertants. A subsequent Ames test conducted in a different laboratory with apparently the same lot number of drug showed no increase in mutation. The material used in this second assay was put through an additional filtration process since bacterial contamination was noted upon preliminary dose range finding studies.

XDE-105 showed no evidence of mutagenicity at the thymidine kinase locus in L5178Y mouse lymphoma cells in the presence or absence of metabolic activation. XDE-105 showed no evidence of inducing chromosomal aberrations in CHO cells in the presence or absence of metabolic activation. XDE-105 did not cause any increase in unscheduled DNA synthesis in primary rat hepatocyte cultures at nontoxic or toxic doses. XDE-105 showed no evidence of consistently inducing micronuclei in bone marrow erythrocytes when administered to rats.

An Ames assay with purified Factor B, which makes up about 2% of Spinosad, was negative.

Carcinogenicity:

In an 18-month oral mouse carcinogenicity study, doses (in diet) of 0, 0.0025, 0.0080, and 0.0360% of XDE-105 (0, 3.4, 11.4, and 50.9 mg/kg/day for males and 0, 4.2, 13.8, and 67.0 mg/kg/day for females) were given to CD-1 mice. There were no significant treatment-related findings in low or middle dose group mice. Due to a high mortality rate, high dose females were terminated early on Day 455. Body weights were lower in high dose males (3-11.2%) and females (4.6-11.1%), compared with control. Spleen weights were higher in high dose males and females at the 3 months sacrifice only, which was consistent with the histological finding of increased extramedullary hematopoiesis noted in spleen. Thickening of the glandular portion of stomach was noted in the majority of high dose animals. Histologically, increase in vacuolation in various tissues, sinus histiocytosis in lymph nodes, skeletal muscle myopathy, chronic inflammation and hyperplasia of the glandular mucosa of stomach, and hyperplasia and hyperkeratosis of the nonglandular mucosa of stomach, were noted in high dose males and females. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria, however, high dose females were not evaluated.

The NOAEL is considered to be the middle dose in the study, 0.008% of XDE-105. The high dose (0.036%) reached the MTD in males and exceeded the MTD in females, while the middle dose is below the MTD in females. It would be preferable to have a dose between 0.036% and 0.008% in dosing females. However, the overall study design appears acceptable.

In a 2-year oral rat carcinogenicity and chronic toxicity study, doses (in diet) of 0, 0.005, 0.02, 0.05, and 0.10% of XDE-105 (0, 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 0, 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) were given to Fischer 344 rats. Due to a high mortality rate, high dose males and females were terminated early on Days 714 and 611, respectively. Body weights were lower in high dose males (3-17.8%) and females (2.1-9.9%), compared with control. Gross pathology and histology were not evaluated in high dose males and females at 24-month sacrifice due to early termination. An increase in organ weights was noted in heart, kidney, liver, spleen, and thyroid gland in high dose animals; an increase in organ weights was also noted in heart (male), kidney (female), thyroid gland in animals at 0.05% dose, in a lesser degree compared to high dose group. At the 12 months sacrifice, histological findings noted in high dose group included: heart degeneration, vacuolation in kidney (females), skeletal muscle degeneration, slight aggregation of reticuloendothelial cells in liver, spleen, and mesenteric lymph nodes, slight increase of extramedullary hematopoesis in spleen (females), slight subacute to chronic inflammation in lung, degeneration/regeneration of the glandular mucosa of stomach, vacuolation and subacute to chronic inflammation in thyroid gland. Similar findings were also observed in the liver, mesenteric lymph node, and thyroid gland of females at 0.05% dose and the thyroid gland of males at 0.05% dose. At the 24-month sacrifice, histological findings noted in animals at 0.05% dose included: vacuolation, subacute to chronic inflammation, and necrosis of thyroid gland, slight subacute to chronic inflammation in lung (females), and slight aggregation of reticuloendothelial cells in lymph nodes. Vacuolation in thyroid glands was also noted in a number of male and female rats at 0.02% dose. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria.

The NOAEL is considered to be the low dose of the study, 0.005% of XDE-105, considering histological findings in animals at 0.02% dose. The high dose (0.10%) exceeded the MTD in both males and females, indicated by high mortality and toxicity. The dose of 0.05% XDE-105 produced some toxicity in both male and female rats, indicated by organ weight increase and histological findings (mainly in thyroid gland, lung, and lymph nodes). Thyroid gland is considered a target organ of oral toxicity of XDE-105 in Fischer 344 rats.

The 2-year oral rat carcinogenicity study is considered adequate. It would be preferable to test a dose between the tested high dose and middle dose for female mice in the 18-month oral mouse carcinogenicity study. However, the 18-month oral mouse carcinogenicity study is considered adequate. No additional carcinogenicity testing is recommended at this time.

Reproductive toxicology:

A teratogenicity study in rats was conducted with oral administration of 10, 50 and 200 mg/kg by gavage. Pregnant female rats were treated once daily on Days 6 through 15 of gestation. The NOEL for teratogenicity in this study appeared to be 200 mg/kg, although this was only a minimal maternally toxic dose. No toxicokinetic information was collected so no information on exposure was available for this study.

A teratogenicity study in rabbits was conducted with oral administration of 2.5, 10 and 50 mg/kg by gavage. Pregnant female rabbits were treated once daily on Days 7 through 19 of gestation. The NOEL for teratogenicity in this study appeared to be 50 mg/kg, and this was a maternally toxic dose. No toxicokinetic information was collected so no information on exposure was available for this study.

In a two-generation dietary reproductive toxicology study, doses of 0, 3, 10, and 100 mg/kg (approximately 0, 0.005, 0.02, and 0.2% XDE-105 in diet, the concentration in diet was adjusted to provide a constant mg/kg dose) were tested in rats. P1 animals (30 males, 30 females) were treated from Week 6 of age. After 10 weeks of treatment P1 animals were mated one to one within dose groups to produce F1a litters. During gestation the females were fed with the same diet as before breeding. Following weaning of the F1a litters at 3 weeks of age, 30 male and 30 female offspring from each treatment group were selected to be the second parental group (P2). F1a animals received the same diet as the mothers during weaning until all litters were weaned. Approximately one week after weaning the last F1a litter, the P1 adults were again mated to produce the F1b litters. Following weaning of the last F1a litter, P2 animals were treated for 12 weeks and then bred to produce the F2 litters. Litters were weaned on Day 21 postpartum. The high dose (100 mg/kg) appeared to have an effect on parturition with increased dystocia observed in both parental generations. Decreased gestation survival, decreased litter size, decreased pup body weight and decreased neonatal survival were noted at 100 mg/kg. The 100 mg/kg dose was clearly toxic to the parental generations, while 10 and 3 mg/kg doses were essentially not toxic. The NOAEL for parental and reproductive/developmental toxicity in this study appears to be 10 mg/kg/day in the diet.

Local tolerance:

A 4-hour exposure to the 2% spinosad (b) (4) under semi-occlusive dressing was not irritating to the skin of minipigs. A 24-hour exposure to a dose of 5000 mg/kg of XDE-105 applied to 10% BSA under semi-occlusive dressing was not irritating to the skin of rabbits. The 2% spinosad (b) (4) produced relatively mild irritation in the rabbit eye and the irritation was reversible with time.

Special toxicology:

The spinosad 2% (b) (4) did not induce a phototoxic reaction in mice when irradiated with an essentially all UVA light source. The sponsor originally submitted an absorption spectrum of highly dilute drug product, which made it difficult to determine if the drug product absorbed UV or visible radiation. It does not appear that a new spectrum has been submitted with less dilute drug product. Therefore, it is difficult to determine if this study is appropriate. However, since the current planned application time of the drug is short (10 min) followed by washing off from the hair, additional nonclinical phototoxicity information is not considered necessary from a pharmacology/toxicology perspective.

A local lymph node assay was conducted in mice with the 2% spinosad (b) (4). While this study would have been more informative if it also included a positive control group with the (b) (4) vehicle, it did not show any indication that spinosad caused cell proliferation in the local lymph nodes. The (b) (4) vehicle induced a greater dpm value than acetone/olive oil although this did not reach the 3 fold ratio required to consider the results a positive finding. It would have been more informative to compare this increase with that induced by a positive control. The spinosad (b) (4) did not induce an increase in dpm value that was significantly greater than the dpm value obtained for the (b) (4) vehicle. Sensitization tests in guinea pigs with the active ingredient in water did not show any evidence that spinosad was a contact sensitizer.

2.6.6.2 Single-dose toxicity – refer to the summary above.

2.6.6.3 Repeat-dose toxicity – refer to the summary above.

2.6.6.4 Genetic toxicology – refer to the summary above.

2.6.6.5 Carcinogenicity

Study #1

Study title: XDE-105: 18-month dietary oncogenicity study in CD-1 mice

Key study findings:

Oral doses (in diet) of 0, 0.0025, 0.0080, and 0.0360% of XDE-105 (0, 3.4, 11.4, and 50.9 mg/kg/day for males and 0, 4.2, 13.8, and 67.0 mg/kg/day for females) were administered to mice for 18 months. There were no significant treatment-related findings in low or middle dose group mice. Due to a high mortality rate, high dose females were terminated early on Day 455 and no histological evaluations were performed for high dose females. No significant differences were noted in overall mortality pattern in males at all dose levels or in low or middle

dose females. Body weights were lower in high dose males (3-11.2%) and females (4.6-11.1%); body weight gains were also lower in high dose males (21.1-50%) and females (20.3-42.3%), compared with control. Absolute and relative mean spleen weights were higher in high dose males and females at the 3 months sacrifice only (64% and 76% in males, 56% and 47% in females). This finding is consistent with the increased extramedullary hematopoiesis of the spleen noted in histology examination. Thickening of the glandular portion of stomach was noted in the majority of high dose males and females from the 12 months and 18 months necropsies. Histologically, increase in vacuolation in various tissues, sinus histiocytosis in lymph nodes, skeletal muscle myopathy, chronic inflammation and hyperplasia of the glandular mucosa of stomach, and hyperplasia and hyperkeratosis of the nonglandular mucosa of stomach, were noted in high dose males and females. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria, however, high dose females were not evaluated due to early sacrifice.

The NOAEL is considered to be the middle dose in the study, 0.008% of XDE-105. The high dose (0.036%) reached the MTD in males and exceeded the MTD in females, while the middle dose is below the MTD in females. It would be preferable to have a dose between 0.036% and 0.008% in dosing females.

Adequacy of the carcinogenicity study and appropriateness of the test model:
This study is considered adequate to test the oral carcinogenicity of XDE-105 in male CD-1 mice. It would be preferable to test a dose 2 fold lower than the high dose (0.036%) in female mice. However, the overall study design appears acceptable.

Evaluation of tumor findings:
There were no significant neoplastic findings under the study conditions.

Study No.: DR-0323-1l94-006 (Sponsor's reference No.: DERBI-29837)
Volume #, and page #: eCTD
Conducting laboratory and location: (b) (4)

Date of study initiation: 09/25/1992
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: XDE-105 (mixture of Factors A and D), Lot# ACD 13651, purity 88% (76.1% Factor A and 11.9% Factor D)
CAC concurrence: There is no record of CAC concurrence on the protocol. The study appeared to have been conducted to support the use of Spinosad as an agricultural insecticide.

Methods

Doses: 0, 0.0025, 0.0080, and 0.0360% in diet. The time weighted average dosages ingested, based upon mean feed consumption and mean body weight data were 0, 3.4, 11.4, and 50.9 mg/kg/day for males, and 0, 4.3, 13.8, and 67.0 mg/kg/day for females.

Basis of dose selection: MTD. The sponsor stated the following dose selection rationale: "The high dose (0.036%) was expected to produce clear evidence of toxicity in multiple organs based upon the results of a previously conducted subchronic study. There were body weight differences noted at a treatment level of 0.045% following 90 days of exposure. In addition, multiple organ systems were shown to be affected upon histopathological examination and numerous clinical chemistry and hematologic parameters were altered. The repeated-dose subchronic studies suggested that the effects progressed markedly from 2 to 13 weeks. Therefore, the potential existed that at the high-dose proposed for this study, there would be an effect on survivability as a result of the broad range of effects in these animals after 90 days of exposure. The remaining dose levels were expected to provide dose-response data for the treatment-related effect(s) observed in the high-dose group and to ensure definition of a NOEL for the test material."

Reviewer's comments: The subchronic study appears to be the 3-month diet study in CD-1 mice that was summarized in the general toxicology section above. The space between the high dose and middle dose was 4 fold. It would be preferable if the space between the high dose and middle dose was 2 fold. However, the overall design of the study appears acceptable.

Species/strain: CD-1 mice

Number/sex/group (main study): 50/sex/group

Dose Levels (percent)	3-Month Sacrifice No. of Mice/Sex/Dose	12-Month Sacrifice No. of Mice/Sex/Dose	18-Month Sacrifice No. of Mice/Sex/Dose
0	9 or 10	10	50
0.0025	10	10	50
0.0080	10	10	50
0.0360	10	10	50
TOTAL	79	80	400

Route, formulation, volume:

The administration route is oral (diet). Test diets were prepared by serially diluting a premix (test material-feed concentrate). Test material was administered as a constant fixed percent in the diet. Test material intake was calculated based on mean feed consumption and mean body weight data collected throughout the study.

Frequency of dosing: Diet was available ad libitum.

Satellite groups used for toxicokinetics or special groups:

Ten mice/sex/group were designated for interim sacrifice after 3 months and 12 months, respectively. There were no toxicokinetics groups.

Age: Approximately 5-6 weeks

Animal housing: Suspended, stainless steel cages with wire-mesh floors and catch pans lined with animal cageboards (b) (4) to minimize odor and maintain a clean environment.

Restriction paradigm for dietary restriction studies: None.

Drug stability/homogeneity: Analyses to verify the concentration of the test material in the diets were conducted at the start of the study and at least quarterly thereafter. Analysis for active

ingredients showed that the formulations contained the expected concentrations throughout the study.

Dual controls employed: No.

Interim sacrifices: Yes. At 3 months and 12 months.

Deviations from original study protocol: None remarkable.

Observation times:

Mortality: twice daily

Clinical signs: twice daily

Body weights: weekly for the first 13 weeks, monthly thereafter

Food consumption: weekly for the first 13 weeks, a 1-week period each month thereafter

Ophthalmology: at prestudy and sacrifices

Clinical pathology: 3-, 12-, and 18-month, including hematology and clinical chemistry

Gross pathology: Necropies at the interim and final sacrifices. Weights of the brain, heart, liver, kidneys, testes (males), and spleen were recorded and the organ weight to final body weight ratios calculated for all animals.

Histopathology: Peer review: yes ( ), no (X)

In animals from the 18-month sacrifice, all tissues listed in the following table from control group males and females, middle dose (0.008%) females, and high dose (0.036%) males, were evaluated (exception - joint). High dose (0.036%) females were terminated on Day 455 due to markedly lower body weight gains and excessive mortality indicative of exceeding the MTD. The tissues from high dose females were saved but not evaluated.

TISSUES COLLECTED AND PRESERVED AT NECROPSY

ADRENALS	JEJUNUM	PITUITARY
AORTA	KIDNEYS	PROSTATE
BONE (INCLUDING JOINT)	LACRIMAL/HARDERIAN GLANDS	RECTUM
BONE MARROW	LARYNX	SALIVARY GLANDS
BRAIN (CEREBRUM, BRAINSTEM, CEREBELLUM)	LIVER	SEMINAL VESICLES
CECUM	LUNGS	SKELETAL MUSCLE
CERVIX	MAMMARY GLAND	SKIN AND SUBCUTIS
COAGULATING GLANDS	MEDIASTINAL LYMPH NODE	SPINAL CORD (CERVICAL, THORACIC, LUMBAR)
COLON	MEDIASTINAL TISSUES	SPLEEN
DUODENUM	MESENTERIC LYMPH NODE	STOMACH
EPIDIDYMIDES	MESENTERIC TISSUES	TESTES
ESOPHAGUS	NASAL TISSUES	THYMUS
EYES	ORAL TISSUES	THYROID GLAND
GALLBLADDER	OVARIES	TONGUE
GROSS LESIONS	OVIDUCTS	TRACHEA
HEART	PANCREAS	URINARY BLADDER
ILEUM	PARATHYROID GLANDS	UTERUS
	PERIPHERAL NERVE	VAGINA

The following tissues from low and middle dose males and females from the 3-month and 12-month sacrifices, and from low dose males and females and middle dose males from the 18-month sacrifice, were examined: cervix (females), epididymides (males), kidneys, liver, lungs, mesenteric and mediastinal lymph nodes, ovaries (females), oviducts (females), pancreas, parathyroids, skeletal muscle, spleen, stomach, thymus, tongue, uterus (females), vagina (females) and gross lesions.

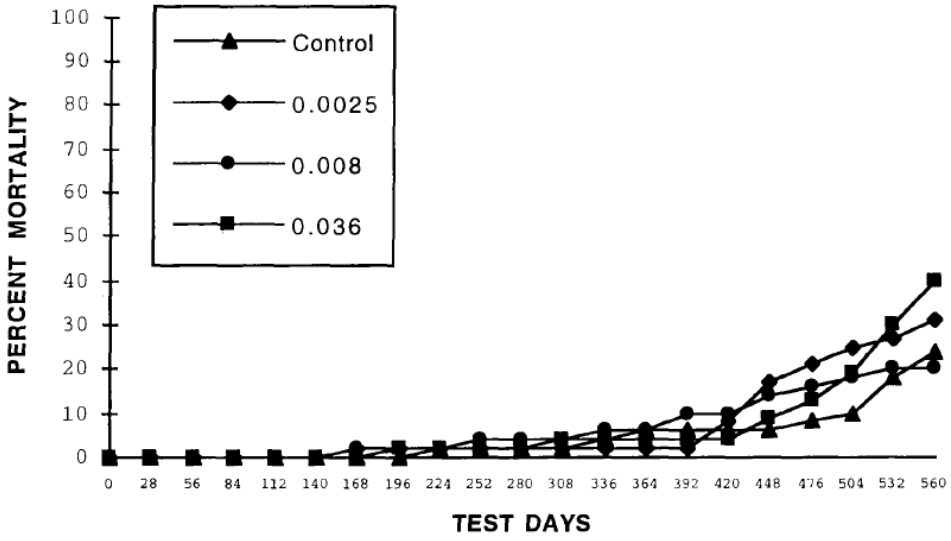
Toxicokinetics: Not evaluated.

Results:

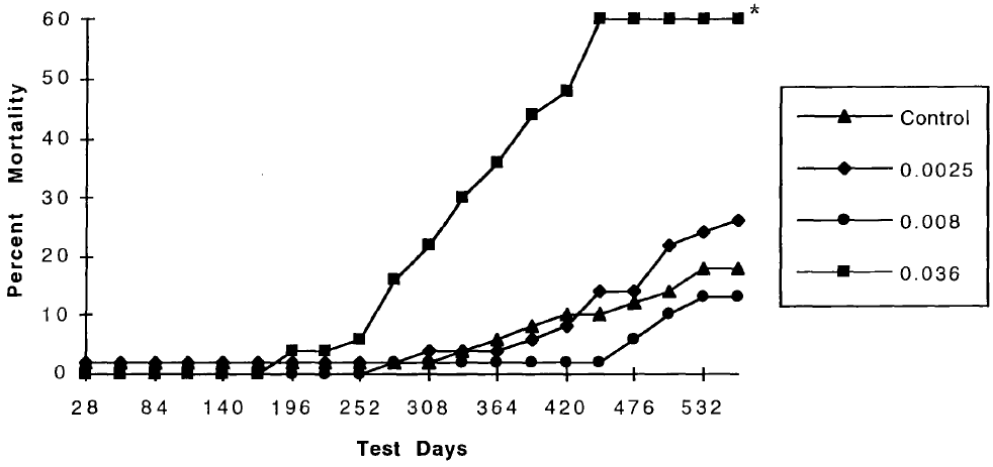
Mortality:

There were no statistically significant differences in overall mortality pattern in low, middle, or high dose male mice or low or middle dose female mice. Mortality rates at the end of the study were 24%, 35%, 29%, and 44% for control, low dose, middle dose, and high dose male mice and 18%, 26%, and 13% for control, low dose, and middle dose female mice, respectively. Mortality rates of high dose females were 60% at Week 54 of the study as compared with 10% in the concurrent controls. The sponsor stated that due to the excessive toxicity noted, the high-dose females were terminated as per agreement with the US EPA on Day 455.

Cumulative mortality rates in male mice:



Cumulative mortality rates in female mice:



Ophthalmology: No treatment-related effects on ophthalmology were noted.

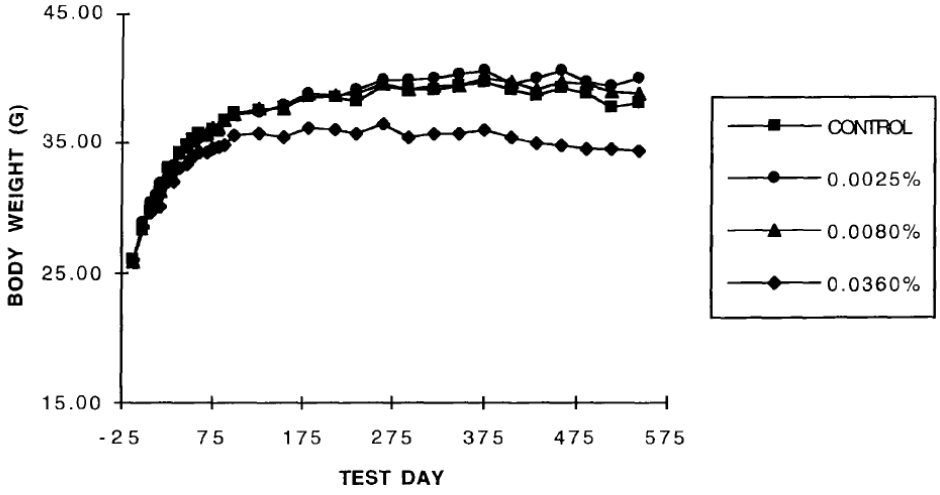
Clinical signs:

Perineal soiling was noted in high dose males. Dermatitis of the ear, lacrimation, thin appearance, perineal soiling, and roughened haircoat were noted in high dose females. There were no significant treatment-related observations in the low and middle dose males and females.

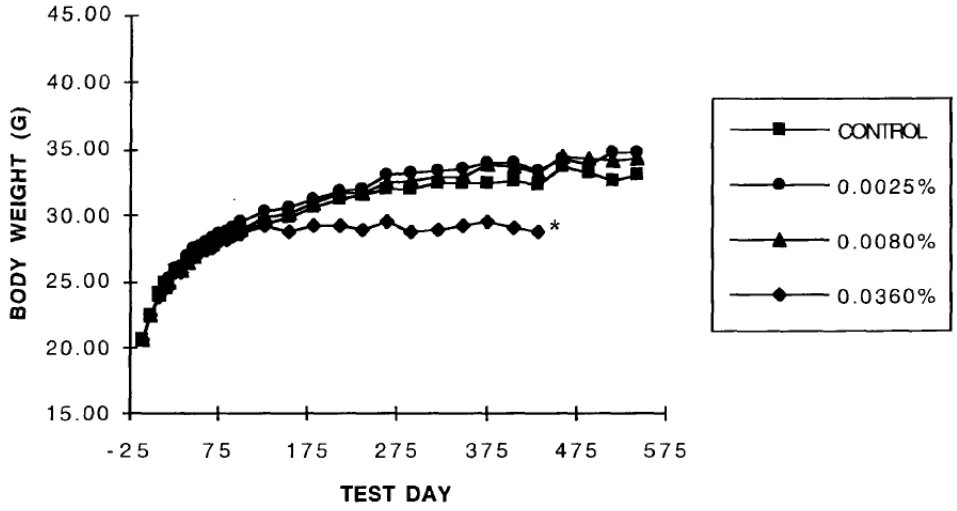
Body weights:

The mean body weights of high dose males were statistically lower than those of controls by 3.0 to 11.2%, starting at Day 19 and continued for the remainder of the dosing period. The mean body weight gains of high dose males were 21.1 to 50.0% lower than controls. No significant differences in body weights or body weight gains were noted in low or middle dose males. The mean body weights of high dose females were statistically lower than controls by 4.6 to 11.1%, beginning on Day 182 and continued for the remainder of their dosing period (to Day 455). The mean body weight gains of high dose females were 20.3 to 42.3% lower than controls. No significant differences in body weights or body weight gains were noted in low or middle dose females.

Male mice body weights:



Female mice body weights:



Food consumption:

Consistent with the decreases in body weight gains, mean feed consumption in high dose males and females were lower than concurrent controls (no statistical evaluation conducted). No significant changes were noted in low or middle dose groups.

Clinical pathology:

Hematology: Mean hemoglobin concentration and mean hematocrit levels were slightly lower in high dose males at all evaluation intervals and in high dose females at the 3-month interval, compared with controls. Mean leukocyte count of high dose males and females was higher than controls at the 12-month interval (~ 2 fold) but not at the 3- or 18-month intervals.

Clinical chemistry: No remarkable treatment-related findings.

Gross pathology:

Organ weights: Absolute and relative mean spleen weights were higher in high dose males and females at the 3 months sacrifice only (64% and 76% in males, 56% and 47% in females). This finding is consistent with the increased extramedullary hematopoiesis of the spleen noted in histology examination. Absolute and relative mean liver weights were higher in high dose females at the 3-month sacrifices (38% and 32%). Mean relative liver weights were higher in high-dose males at 3, 12, and 18 months (21%, 21%, and 5%) and in high dose females at 12 months (27%, high dose females were not evaluated at 18 months). There were no histopathological findings correlated to the elevated liver weights. No remarkable findings were noted in low or middle dose group mice.

Mice from the 3 months necropsy had no treatment-related gross lesions. Thickening of the glandular portion of stomach was noted in the majority of high dose males and females from the 12 months and 18 months necropsies. No remarkable findings were noted in low or middle dose group mice.

Histopathology: Mice that died before scheduled sacrifice, or were euthanized in a moribund condition, were included in the examination.

Non-neoplastic:

There were no treatment-related histopathological findings in low or middle dose groups. High dose females at 18 months sacrifice were not examined. Increases in vacuolation in the epididymides (males), pancreas, parathyroid glands, cervix (females), uterus (females), and ovaries (females), were observed in high dose group at all sacrifices. Very slight or slight degeneration/regeneration of renal tubules was noted in high dose males and females at the 3 months sacrifice. Sinus histiocytosis in the mesenteric and mediastinal lymph nodes was noted in high dose males and females at all sacrifices. Myopathy of skeletal muscle was noted in high dose males and females at all sacrifices. Increased extramedullary hematopoiesis in spleen was noted in high dose males and females at the 3 months sacrifice. An increased incidence and severity of hyperplasia of the glandular mucosa of the stomach was noted in high dose males and females at all sacrifices. Chronic inflammation of the glandular mucosa, hyperplasia of the nonglandular mucosa, and hyperkeratosis of the nonglandular mucosa were also noted in the stomach of high dose males and females.

Neoplastic:

High dose females at 18 months sacrifice were not examined. No significant neoplastic findings were noted in mice from the 3 months and 12 months sacrifices. The neoplastic findings in mice from the 18 months sacrifice are presented in the following tables:

SEX	MALES					FEMALES			
DOSE IN %	0	.0025	.008	.036		0	.0025	.008	.036#
NUMBER OF MICE EXAMINED	50	50	50	50		50	50	50	0
BONE (NO. OF TISSUES EXAMINED)	50	19	15	50		50	13	50	0
OSTEOGENIC SARCOMA, RIB, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1		0	0	0	-
BONE MARROW (NO. OF TISSUES EXAMINED)	50	19	15	50		50	13	50	0
HEMANGIOMA, BENIGN, PRIMARY:	0	0	0	0		0	0	1	-
CERVIX (NO. OF TISSUES EXAMINED)	-	-	-	-		50	50	50	0
SQUAMOUS CELL CARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-		0	1	0	-
FIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-		0	1	0	-
HEMANGIOMA, BENIGN, PRIMARY:	-	-	-	-		1	1	0	-
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-		1	1	1	-
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, METASTASIS:	-	-	-	-		2	0	1	-
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	-	-	-	-	**	3	1	2	-
JEJUNUM (NO. OF TISSUES EXAMINED)	50	19	16	50		50	13	50	0
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	1	0		0	0	0	-
LACRIMAL/HARDERIAN GLAND(S) (NO. OF TISSUES EXAMINED)	50	19	15	50		50	13	50	0
ADENOMA, BENIGN, PRIMARY:	1	0	0	2		1	0	3	-
LIVER (NO. OF TISSUES EXAMINED)	50	50	50	50		50	50	50	0
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY:	10	6	2*	1*		0	1	3	-
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: (TWO)	0	1	1	1		0	0	0	-

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SEX	MALES					FEMALES			
DOSE IN %	0	.0025	.008	.036		0	.0025	.008	.036#
NUMBER OF MICE EXAMINED	50	50	50	50		50	50	50	0
LIVER (CONTINUED)									
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: (ONE OR TWO)	10	7	3*	2*	**	0	1	3	-
HEMANGIOMA, BENIGN, PRIMARY:	0	0	0	1		0	1	2	-
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0		0	0	0	-
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0		1	0	0	-
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	1	0	0	0	**	1	0	0	-
LUNGS (NO. OF TISSUES EXAMINED)	50	50	50	50		50	50	50	0
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	2	0		0	0	1	-
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, METASTASIS:	1	0	0	0		1	0	0	-
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	1	0	2	0	**	1	0	1	-
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY:	11	6	13	13		7	11	5	-
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (TWO)	1	0	2	0		3	1	0	-
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (THREE)	0	0	2	0		0	1	0	-
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (ONE, TWO OR THREE)	12	6	17	13	**	10	13	5	-
TOTAL ANIMALS WITH ADENOMA AND/OR ADENOCARCINOMA	13	6	19	13		11	13	5	
RHABDOMYOSARCOMA, (THORAX), MALIGNANT, SECONDARY:	0	0	0	0		0	0	1	-
LYMPH NODE - MEDIASTINAL (NO. OF TISSUES EXAMINED)	50	50	50	50		50	50	50	0
ADENOCARCINOMA, (LUNGS), MALIGNANT, SECONDARY:	0	0	0	0		1	0	0	-
LYMPHOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0		1	0	0	-
LYMPH NODE - MESENTERIC (NO. OF TISSUES EXAMINED)	49	48	49	50		50	49	50	0
HEMANGIOMA, BENIGN, PRIMARY:	0	0	0	0		0	2	1	-

SEX	MALES					FEMALES			
DOSE IN %	0	.0025	.008	.036		0	.0025	.008	.036#
NUMBER OF MICE EXAMINED	50	50	50	50		50	50	50	0
LYMPH NODE - MESENTERIC (CONTINUED)									
HEMANGIOSARCOMA, (LIVER), MALIGNANT, SECONDARY:	0	0	0	0		1	0	0	-
MAMMARY GLAND (NO. OF TISSUES EXAMINED)	13	1	2	14		50	9	49	0
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0		1	0	0	-
ADENOMA, BENIGN, PRIMARY:	0	0	0	0		2	0	0	-
TOTAL ANIMALS WITH ADENOMA AND/OR ADENOCARCINOMA	0	0	0	0		3	0	0	-
MEDIASTINAL TISSUES (NO. OF TISSUES EXAMINED)	50	19	15	50		50	13	50	0
ADENOCARCINOMA, (LUNGS), MALIGNANT, SECONDARY:	1	0	0	0		1	0	0	-
MULTIPLE ORGANS (NO. OF TISSUES EXAMINED)	4	5	4	1		8	5	4	0
STROMAL CELL SARCOMA, (CERVIX), MALIGNANT, SECONDARY:	0	0	0	0		2	0	0	-
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY:	0	0	0	1		0	0	0	-
HISTIOCYTIC SARCOMA, MALIGNANT, PRIMARY:	0	0	0	0		0	1	0	-
HISTIOCYTIC SARCOMA, (INGUINAL SUBCUTIS), MALIGNANT, SECONDARY:	1	0	0	0		0	0	0	-
LEUKEMIA - LYMPHOID CELL, MALIGNANT, PRIMARY:	0	2	2	0		3	0	0	-
LYMPHOSARCOMA, MALIGNANT, PRIMARY:	0	1	0	0		2	3	3	-
OVARIES (NO. OF TISSUES EXAMINED)	-	-	-	-		50	50	50	0
ADENOMA, BENIGN, PRIMARY:	-	-	-	-		0	0	2	-
ADENOMA, BENIGN, PRIMARY: (TWO)	-	-	-	-		1	0	0	-
ADENOMA, BENIGN, PRIMARY: (ONE OR TWO)	-	-	-	-	**	1	0	2	-
HEMANGIOMA, BENIGN, PRIMARY:	-	-	-	-		1	0	0	-

SEX	MALES					FEMALES			
DOSE IN %	0	.0025	.008	.036		0	.0025	.008	.036#
NUMBER OF MICE EXAMINED	50	50	50	50		50	50	50	0
OVARIES (CONTINUED)									
LEIOMYOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-		1	0	0	-
LUTEOMA, BENIGN, PRIMARY:	-	-	-	-		0	0	1	-
PANCREAS (NO. OF TISSUES EXAMINED)	50	50	50	50		50	50	50	0
ADENOMA, ISLETS, BENIGN, PRIMARY:	0	0	0	0		0	0	1	-
PITUITARY (NO. OF TISSUES EXAMINED)	48	18	13	49		49	12	47	0
ADENOMA, ANTERIOR (PARS DISTALIS), BENIGN, PRIMARY:	0	0	0	1		1	0	2	-
RECTUM (NO. OF TISSUES EXAMINED)	50	19	15	50		50	13	50	0
STROMAL CELL SARCOMA, (CERVIX), MALIGNANT, SECONDARY:	0	0	0	0		0	0	1	-
SKIN AND SUBCUTIS (NO. OF TISSUES EXAMINED)	50	25	23	50		50	20	50	0
HEMANGIOMA, BACK, BENIGN, PRIMARY:	0	0	0	0		0	1	0	-
RHABDOMYOSARCOMA, THORAX, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0		0	0	1	-
HISTIOCYTIC SARCOMA, INGUINAL, MALIGNANT, PRIMARY, METASTASIS:	1	0	0	0		0	0	0	-
SPLEEN (NO. OF TISSUES EXAMINED)	50	50	50	50		50	50	50	0
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0		1	0	3	-
HISTIOCYTIC SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1		0	0	0	-
SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0		0	1	0	-
TESTES (NO. OF TISSUES EXAMINED)	50	19	15	50		-	-	-	-
SCHWANNOMA, BENIGN, PRIMARY:	0	0	0	1		-	-	-	-

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SEX	MALES				FEMALES			
DOSE IN %	0	.0025	.008	.036	0	.0025	.008	.036#
NUMBER OF MICE EXAMINED	50	50	50	50	50	50	50	0
THYROID GLAND (NO. OF TISSUES EXAMINED)	49	19	15	50	50	13	50	0
ADENOMA, FOLLICLE(S), BENIGN, PRIMARY:	0	0	0	0	1	0	0	-
UTERUS (NO. OF TISSUES EXAMINED)	-	-	-	-	50	50	50	0
HEMANGIOMA, BENIGN, PRIMARY:	-	-	-	-	1	1	4	-
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-	0	1	0	-
STROMAL CELL SARCOMA, ENDOMETRIUM, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-	0	1	0	-
DECIDUOMA, BENIGN, PRIMARY:	-	-	-	-	1	0	0	-
VAGINA (NO. OF TISSUES EXAMINED)	-	-	-	-	49	49	50	0
POLYP, BENIGN, PRIMARY:	-	-	-	-	0	1	0	-
COMBINED NEOPLASMS								
TOTAL ANIMALS WITH HISTIOCYTIC SARCOMA - ANY SITE:	1	1	0	0	0	1	0	-
TOTAL ANIMALS WITH LYMPHOSARCOMA AND/OR LEUKEMIA/LYMPHOID CELL -ANY SITE:	0	3	2	0	6	3	3	-
TOTAL ANIMALS WITH HEMANGIOMA AND/OR HEMANGIOSARCOMA - ANY SITE:	1	0	0	1	4	6	9	-

Tissues that might have potentially significant neoplastic findings were selected for targeted statistical analysis (Biostatistics reviewer Dr. Min Min). The results are listed in the following table:

	Tissue	Neoplastic findings				p-trend	p-comparison with control		
		0%	0.0025%	0.008%	0.036%		low	med	high
Male	Lung adenoma (benign)	12	6	17	13	0.242	0.904	0.189	0.500
	Lymphosarcoma and/or Leukemia (combined)	0	3	2	0	0.815	0.121	0.248	--
Female	Liver adenoma (benign)	0	1	3	--	0.060	0.500	0.121	--
	Lung adenoma (benign)	10	13	5	--	0.947	0.318	0.869	--
	Hemangioma and/or hemangiosarcoma (combined, any site)	4	6	9	--	0.079	0.370	0.117	--

According to Dr. Min, the statistical evaluation criteria are briefly described as: "Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level a=0.025 for rare tumors and a=0.005 for common tumors for a submission with two species, and a significance level a=0.05 for rare tumors and a=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than or equal to 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of a significance level a=0.05 for rare tumors and a=0.01 for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%". The neoplastic findings in mice administered XDE-105 for 18 months were not statistically increased relative to controls.

Toxicokinetics:

Toxicokinetic analysis was not performed in this study.

Study #2

Study title: XDE-105: 2-year chronic toxicity, chronic neurotoxicity and oncogenicity study in Fischer 344 rats

Key study findings:

Oral doses (in diet) of 0, 0.005, 0.02, 0.05, and 0.10% of XDE-105 (0, 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 0, 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) were administered to rats for 24 months. Due to a high mortality rate, high dose males and females were terminated early on Days 714 and 611, respectively. Tissues of high dose males and females were not evaluated at 24-month sacrifice. No significant differences were noted in overall mortality pattern in males or females at other doses. Body weights were lower in high dose males (3-17.8%) and females (2.1-9.9%), compared with control. Gross pathology and histology were not evaluated in high dose males and females at 24-month sacrifice due to early termination. An increase in organ weights was noted in heart, kidney, liver, spleen, and thyroid gland in high dose animals. An increase in organ weights was also noted in heart (male), kidney (female), thyroid gland in animals at 0.05% dose, to a lesser degree compared to high dose group. Histological alterations in females were greater in incidence and/or severity than in males at the same dose level. At the 12 months sacrifice, histological findings noted in high dose group included: heart degeneration, vacuolation in kidney (females), skeletal muscle degeneration, slight aggregation of reticuloendothelial cells in liver, spleen, and mesenteric lymph nodes, slight increase of extramedullary hematopoesis in spleen (females), slight subacute to chronic inflammation in lung, degeneration/regeneration of the glandular mucosa of stomach, vacuolation and subacute to chronic inflammation in thyroid gland. Similar findings were also observed in the liver, mesenteric lymph node, and thyroid gland of females at 0.05% dose and the thyroid gland of males at 0.05% dose. At the 24-month sacrifice, histological findings noted in animals at 0.05% dose included: vacuolation, subacute to chronic inflammation, and necrosis of thyroid gland, slight subacute to chronic inflammation in lung (females), and slight aggregation of reticuloendothelial cells in lymph nodes. Vacuolation in thyroid glands was also noted in a number of male and female rats at 0.02% dose. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria.

The NOAEL is considered to be the low dose of the study, 0.005% of XDE-105, considering histological findings in animals at 0.02% dose. The high dose (0.10%) exceeded the MTD in both males and females, indicated by high mortality and toxicity. The dose of 0.05% XDE-105 produced some toxicity in both male and female rats, indicated by organ weight increase and histological findings (mainly in thyroid gland, lung, and lymph nodes). Thyroid gland is considered a target organ of oral toxicity of XDE-105 in Fischer 344 rats.

Adequacy of the carcinogenicity study and appropriateness of the test model:
This study is considered adequate to test the oral carcinogenicity of XDE-105 in Fischer 344 rats. The high dose (0.10%) exceeded the MTD for both males and females; while the second high dose (0.05%), which is 2 fold lower than the high dose, produced significant toxicity in Fischer 344 rats.

Evaluation of tumor findings:
There were no significant neoplastic findings under the study conditions.

Study No.: DR-0323-1l94-005 (Sponsor's reference No.: DERBI-29838)

Volume #, and page #: eCTD
Conducting laboratory and location: (b) (4)

Date of study initiation: 05/14/1992
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: XDE-105 (mixture of Factors A and D), Lot# ACD 13651, purity 88% (76.1% Factor A and 11.9% Factor D)
CAC concurrence: There is no record of CAC concurrence on the protocol. The study appeared to have been conducted to support the use of Spinosad as an agricultural insecticide.

Methods

Doses: 0, 0.005, 0.02, 0.05, and 0.10% in diet. The time weighted average dosages ingested, based upon mean feed consumption and mean body weight data were 0, 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 0, 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females.

Basis of dose selection: MTD. The sponsor stated the following dose selection rationale: "The high dosage (0.10%) was expected to produce clear evidence of toxicity in multiple organs based upon the results of previously conducted subchronic studies. While there were no body weight differences noted at this treatment level following 90 days of exposure, multiple organs were histologically affected. In addition, numerous clinical chemistry and hematologic parameters were altered. The repeated-dose and subchronic studies suggested that the effects progressed markedly from 2 to 13 weeks. Therefore, the potential existed that at the high dose proposed for this study, there would be an effect on survivability. The remaining lower dose levels (0.005%, 0.02% and 0.05%) were expected to provide dose-response data for the treatment-related effect(s) observed in the high-dose group and to ensure definition of a NOEL for the test material."
Reviewer's comments: The subchronic study appears to be the 3-month diet study in Fischer 344 rats that was summarized in the general toxicology section above. This dose selection rationale appears reasonable.

Species/strain: Fischer 344 rats
Number/sex/group (main study): 50/sex/group

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STUDY DESIGN

Dose Levels (percent)	12-Month Sacrifice No. of Rats/Sex/Dose#	24-Month Sacrifice No. of Rats/Sex/Dose
0	15	50
0.005	15	50
0.02	15	50
0.05	15	50
0.1	15	50
TOTAL	150	500

Study Parameters	6 Months	12 Months	18 Months	24 Months
	No. of Rats/Sex/Dose Group@			
Hematology*	10	10	10	20
Clinical Chemistry*	10	10	10	20
Urinalysis*	10	10	10	20
Necropsy	--	10	--	50
Organ Weights	--	10	--	50
Histopathology **	--	10	--	50

Route, formulation, volume:
The administration route is oral (diet). Test diets were prepared by serially diluting a premix (test material-feed concentrate). Test material was administered as a constant fixed percent in the diet. Test material intake was calculated based on mean feed consumption and mean body weight data collected throughout the study.

Frequency of dosing: Diet was available ad libitum.

Satellite groups used for toxicokinetics or special groups:
Fifteen mice/sex/group were designated for interim sacrifice after 12 months of dosing. There were no toxicokinetics groups.

Age: Approximately 5 weeks

Animal housing: Suspended, stainless steel cages with wire-mesh floors and catch pans lined with animal cageboards (b) (4) to minimize odor and maintain a clean environment.

Restriction paradigm for dietary restriction studies: None.

Drug stability/homogeneity: Analyses to verify the concentration of the test material in the diets were conducted at the start of the study and at least quarterly thereafter. Analysis for active ingredients showed that the formulations contained the expected concentrations throughout the study.

Dual controls employed: No.

Interim sacrifices: Yes. At 12 months.

Deviations from original study protocol: None remarkable.

Observation times:

Mortality: twice daily

Clinical signs: twice daily

Clinical evaluation: weekly

Functional Observational battery: A functional observational battery was conducted on a pre-selected subset of 10 rats/sex/dose group at prestudy and 3, 6, 9 and 12 months after test initiation. The animals were sacrificed after 12 months of dosing. The functional observational battery and motor activity evaluation were addressed in a separate chronic neurotoxicity report.

Body weights: weekly for the first 13 weeks, monthly thereafter
Food consumption: weekly for the first 13 weeks, a 1-week period each month thereafter
Ophthalmology: at prestudy and sacrifices
Clinical pathology: At 6, 12, 18, and 24 months, including hematology, clinical chemistry, and urinalysis
Gross pathology: Necropies at interim and final sacrifices. Weights of the brain, heart, adrenal glands, liver, kidneys, thyroid with parathyroid glands (fixed), spleen, ovaries and testes were recorded and the organ weight to final body weight ratios calculated for all animals.
Histopathology: Peer review: yes ( ), no (X)

The tissues listed in the following table from control group and high dose (0.1%) group animals in 12-month sacrifice and from control group and 0.05% dose group in 24-month sacrifice were evaluated (exception - auditory sebaceous glands and bone joint). High dose (0.1%) males and females were terminated on Days 714 and 611, respectively, due to excessive mortality indicative of exceeding the MTD. The tissues from high dose group animals were saved but not evaluated.

TISSUES COLLECTED AND PRESERVED AT NECROPSY

ADRENALS	KIDNEYS	PROSTATE
AORTA	LACRIMAL/HARDERIAN GLANDS	RECTUM
AUDITORY SEBACEOUS GLANDS	LARYNX	SALIVARY GLANDS
BONE (INCLUDING JOINT)	LIVER	SEMINAL VESICLES
BONE MARROW	LUNGS	SKELETAL MUSCLE
BRAIN (CEREBRUM, BRAINSTEM, CEREBELLUM)	MAMMARY GLAND	SKIN AND SUBCUTIS
CECUM	MEDIASTINAL LYMPH NODE	SPINAL CORD (CERVICAL, THORACIC, LUMBAR)
CERVIX	MEDIASTINAL TISSUES	SPLEEN
COAGULATING GLANDS	MESENTERIC LYMPH NODE	STOMACH
COLON	MESENTERIC TISSUES	TESTES
DUODENUM	NASAL TISSUES	THYMUS
EPIDIDYMIDES	ORAL TISSUES	THYROID GLAND
ESOPHAGUS	OVARIES	TONGUE
EYES	OVIDUCTS	TRACHEA
GROSS LESIONS	PANCREAS	URINARY BLADDER
HEART	PARATHYROID GLANDS	UTERUS
ILEUM	PERIPHERAL NERVE	VAGINA
JEJUNUM	PITUITARY	

The following tissues from the 0.005% and 0.02% dose levels were evaluated: liver, kidneys, lungs, mesenteric lymph node (with adjacent tissue), thyroid with parathyroid glands, heart, skeletal muscle, tongue, stomach, mammary glands with skin, larynx, spleen, prostate and gross lesions [the sponsor states that stomach, skeletal muscle, tongue, spleen, prostate, larynx (males), and heart (males) were not histologically examined from the 24-month sacrifice because the incidence and severity of lesions were similar between 0 and 0.05% group rats].

Toxicokinetics: Not evaluated.

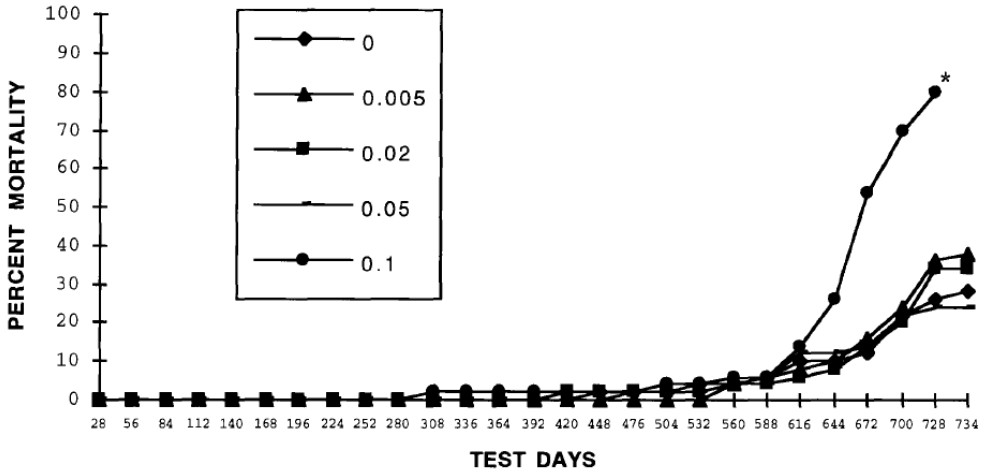
Results:

Mortality:

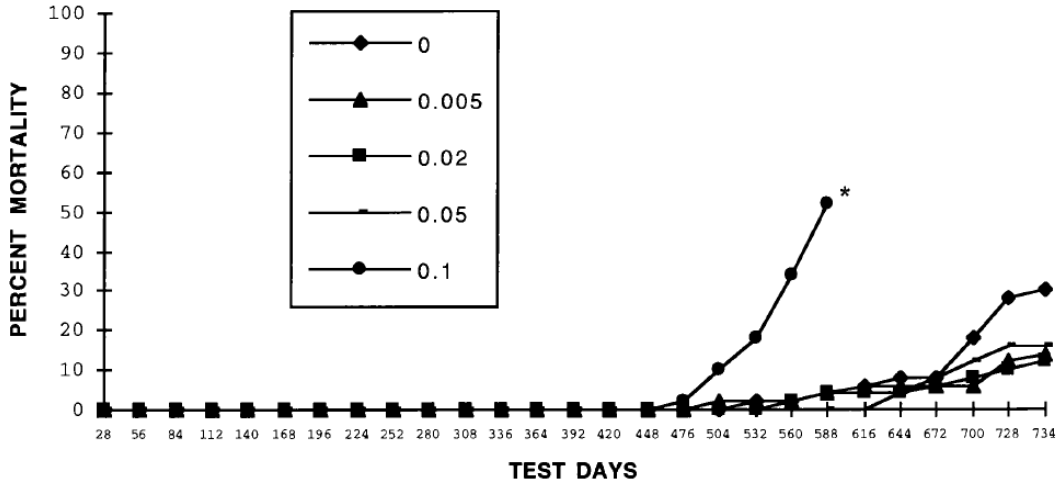
There were no statistically identified differences in overall mortality pattern in male or female rats of the 0.005%, 0.02% or 0.05% groups. Mortality rates at the end of the study were 28%, 38%, 34%, and 24%, for male rats and 30%, 14%, 12%, and 16% for female rats ingesting 0, 0.005, 0.02 or 0.05% XDE-105, respectively. The mortality rate was 80% for the 0.10% males

at Week 102 and 60% for the 0.10% females at Week 88, compared to 26% and 6% for the concurrent controls, respectively. The sponsor stated that the high dose males and females were terminated on Days 714 and 611, respectively, due to excessive mortality.

Cumulative mortality rates in male rats:



Cumulative mortality rates in female rats:



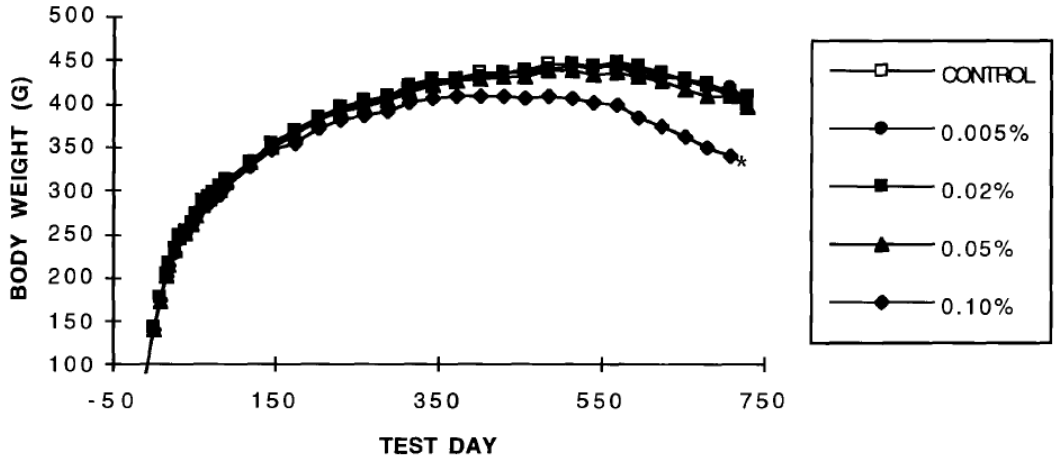
Ophthalmology: No treatment-related effects on ophthalmology were noted.

Clinical signs:

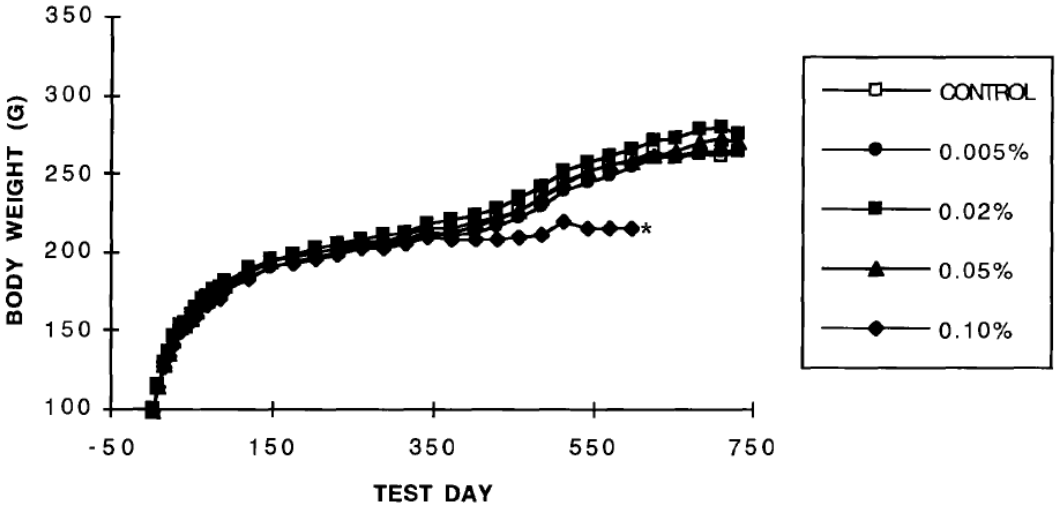
Thin appearance, rapid respiration, and perineal soiling were noted in high dose animals. There were no significant treatment-related observations in the 0.005, 0.02, or 0.05% dose groups.

Body weights:

Male rats body weights:



Female rats body weights:



The mean body weights of high dose (0.10%) males were lower than those of controls by 3.0 to 17.8%, starting on Day 175 and continued for the remainder of their dosing period. Similarly, the mean body weights of high dose females were lower than those of controls by 2.1 to 9.9%, starting on Day 27 and thereafter. The mean body weight gains were lower in high dose males and females, in the range of 3.9 to 27.2% when compared with the controls. No remarkable treatment-related findings in body weights or body weight gains were noted in 0.005%, 0.02, or 0.05% dose groups.

Food consumption:

There were no meaningful differences noted in feed consumption in all dose groups, compared with control.

Clinical pathology:

Hematology: Mean leukocyte count was 39% higher in high dose females than controls at 18-month interval. This was considered consistent with the thyroid and lung inflammation identified in these animals. No other treatment-related significant findings were noted.

Urinalysis: No significant treatment-related findings were noted.

Clinical chemistry: Mean aspartate aminotransferase (AST) levels were higher in high dose males at 12- and 18-months (35% and 42%) and in high dose females at 18-months (54%). A number of statistically significant changes are either considered not treatment-related or considered of no toxicological significance.

Gross pathology: High dose males and females were not evaluated at 24-month sacrifice due to early termination.

Organ weights: Absolute and relative mean heart weights of high dose males and females were higher than concurrent controls at 12-month sacrifice (10% and 17% for males, 16% and 24% for females). Female rats at 0.05% dose also had higher absolute and relative mean heart weights at 12- and 24-month sacrifices (7% and 8% at 12-month, 8% and 8% at 24-month); while male rats at 0.05% dose had higher relative mean heart weights at 12-month (6%). Absolute and relative mean kidney weights were higher in high dose males and females at 12-month (10% and 17% for males, 18% and 27% for females) and in females at 0.05% dose at 24-month (9% and 9%). Absolute and relative mean liver weights were higher in high dose females at 12-month (15% and 24%); relative mean liver weights were higher in high dose males at 12-month (12%). Absolute and relative mean spleen weights were higher in high dose males and females at 12 months (31% and 39% for males, 56% and 67% for females). Absolute and relative mean thyroid weights were higher in high dose males and females at 12-month (266% and 292% for males, 195% and 220% for females) and in 0.05% dose group males and females at 24-month (14% and 16% for males, 100% and 107% for females). There were no significant differences in organ weights in male or female rats at 0.02% or lower doses.

12-month sacrifice: The lungs of 8 of 10 high dose females and 1 of 10 high dose males had multiple pale foci.

24-month sacrifice: High dose males and females had a greater incidence of gross pathologic observations in the following: increased thyroid gland size, heart lesions (pale foci, mottled atrium or thrombi in the heart), lung lesions (pale foci, area or mass/nodule in the lungs), and hydrothorax - thoracic cavity.

Histopathology: Tissues of high dose males and females were not evaluated at 24-month sacrifice due to early termination, except for lungs in 9 high dose female rats to resolve specific gross pathologic findings.

Non-neoplastic:

12-month sacrifice: In general, alterations in the tissues of female rats were greater in incidence and/or severity than those of male rats at the same dose level. Histological findings noted in high

dose group included: heart degeneration, vacuolation in kidney (females), skeletal muscle degeneration, slight aggregation of reticuloendothelial cells in liver, spleen, and mesenteric lymph nodes, slight increase of extramedullary hematopoesis in spleen (females), slight subacute to chronic inflammation in lung, degeneration/regeneration of the glandular mucosa of stomach, vacuolation and subacute to chronic inflammation in thyroid gland. Similar histological effects were also observed in the liver, mesenteric lymph node, and thyroid gland of females at 0.05% dose and the thyroid gland of males at 0.05% dose.

24-month sacrifice:

Vacuolation of the epithelial cells of the thyroid follicles in thyroid glands was noted in the majority of male and female rats at 0.05% dose and also a number of male and female rats at 0.02% dose. In addition, the majority of female rats and a few male rats at 0.05% dose had a subacute to chronic inflammation and necrosis of the thyroid gland.

An increase in the incidence of multifocal, very slight, subacute to chronic inflammation in lung was noted in females at 0.05% dose, but not in males. Prior to the removal of the high dose group from the study, the lungs of 9 female rats were histologically examined to evaluate lung lesions (8 rats had died and one rat was euthanatized due to its moribund condition). The observed alveolar histiocytosis and chronic inflammation corresponded to the gross pathologic observations noted in the lungs of these rats. The suspected nodule/masses also corresponded to focal areas of chronic inflammation and were not lung neoplasms.

Mesenteric lymph nodes of male and female rats at 0.05% dose had an increase in the incidence of slight aggregation of reticuloendothelial cells.

Neoplastic:

No significant neoplastic findings were noted in rats from the 12 months sacrifice. The neoplastic findings in rats from the 24 months sacrifice are presented in the following tables:

SEX		MALES						FEMALES				
DOSE IN %		0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#
NUMBER OF RATS EXAMINED		50	50	50	50	0		50	50	50	50	0
ADRENALS (NO. OF TISSUES EXAMINED)		50	23	20	50	0		50	10	8	50	0
ADENOMA, CORTEX, BENIGN, PRIMARY:		0	0	0	0	-		0	2	0	1	-
PHEOCHROMOCYTOMA, MEDULLA, BENIGN, PRIMARY:		8	5	3	7	-		5	0	1	0	-
PHEOCHROMOCYTOMA, MEDULLA, BENIGN, PRIMARY: (TWO)		1	0	1	0	-		0	0	1	0	-
PHEOCHROMOCYTOMA, MEDULLA, MALIGNANT, PRIMARY, NO METASTASIS:		1	1	2	0	-		1	0	0	0	-
PHEOCHROMOCYTOMA, MEDULLA, BENIGN OR MALIGNANT, PRIMARY, NO METASTASIS:		10	6	6	7	-	**	6	0	2	0	-
GANGLIONEUROMA, MEDULLA, MALIGNANT, PRIMARY, NO METASTASIS:		0	0	0	0	-		0	1	0	0	-
BRAIN (NO. OF TISSUES EXAMINED)		50	22	22	50	0		50	9	10	50	0
ASTROCYTOMA, CEREBRUM, BENIGN, PRIMARY:		0	0	0	1	-		0	0	0	0	-
OLIGODENDROGLIOMA, BENIGN, PRIMARY:		0	0	0	0	-		0	0	1	0	-
CERVIX (NO. OF TISSUES EXAMINED)		-	-	-	-	-		50	7	8	49	0
FIBROMA, BENIGN, PRIMARY:		-	-	-	-	-		1	0	0	0	-
LEIOMYOMA, BENIGN, PRIMARY:		-	-	-	-	-		1	0	0	0	-
LEIOMYOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:		-	-	-	-	-		1	0	0	0	-
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:		-	-	-	-	-		0	0	0	1	-
GANGLIONEUROMA, BENIGN, PRIMARY:		-	-	-	-	-		1	0	0	0	-
ILEUM (NO. OF TISSUES EXAMINED)		50	19	17	50	0		50	7	6	50	0
ADENOMA, BENIGN, PRIMARY:		1	0	0	0	-		0	0	0	1	-
JEJUNUM (NO. OF TISSUES EXAMINED)		50	19	18	50	0		50	6	7	50	0
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:		0	0	0	1	-		0	0	1	0	-

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SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
KIDNEYS (NO. OF TISSUES EXAMINED)	50	50	50	50	0		50	50	50	50	0	
ADENOMA, TUBULE(S), BENIGN, PRIMARY:	1	0	0	1	-		0	0	0	1	-	
CARCINOMA, TUBULE(S), MALIGNANT, PRIMARY, METASTASIS:	0	0	1	0	-		0	0	0	0	-	
LIPOMA, BENIGN, PRIMARY:	0	0	0	0	-		0	1	0	0	-	
LACRIMAL/HARDERIAN GLAND(S) (NO. OF TISSUES EXAMINED)	50	19	17	50	0		49	8	6	50	0	
NEUROFIBROSARCOMA, TRIGEMINAL GANGLION, MALIGNANT, SECONDARY:	0	0	0	0	-		0	0	1	0	-	
LARYNX (NO. OF TISSUES EXAMINED)	49	19	17	50	0		49	50	50	50	0	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, SECONDARY:	0	0	0	0	-		0	0	0	1	-	
LIVER (NO. OF TISSUES EXAMINED)	50	50	50	50	0		50	50	50	50	0	
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY:	0	1	2	1	-		0	0	0	0	-	
HEMANGIOMA, BENIGN, PRIMARY:	1	0	0	0	-		0	0	0	0	-	
LUNGS (NO. OF TISSUES EXAMINED)	50	50	50	50	0		50	50	50	50	0	
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY:	1	0	0	0	-		0	0	0	1	-	
UNDIFFERENTIATED SARCOMA, SKIN, MALIGNANT, SECONDARY:	0	0	0	0	-		0	1	0	0	-	
LYMPH NODE - MISCELLANEOUS (NO. OF TISSUES EXAMINED)	0	0	0	1	0		24	10	11	18	0	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, SECONDARY:	-	-	-	0	-		0	1	0	0	-	
MAMMARY GLAND (NO. OF TISSUES EXAMINED)	50	31	28	49	0		49	28	38	50	0	
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	0	0	-		0	1	0	0	-	

SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
MAMMARY GLAND (CONTINUED)												
ADENOMA, BENIGN, PRIMARY:	0	0	1	0	-		0	0	0	1	-	
FIBROADENOMA, BENIGN, PRIMARY:	1	4	4	3	-		8	2	6	2	-	
FIBROADENOMA, BENIGN, PRIMARY: (TWO)	0	0	0	1	-		0	0	0	0	-	
FIBROADENOMA, BENIGN, PRIMARY:	1	4	4	4	-	**	8	2	6	2	-	
MEDIASTINAL TISSUES (NO. OF TISSUES EXAMINED)	50	19	17	50	0		50	7	6	50	0	
GIANT CELL TUMOR, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	-		0	1	0	0	-	
MESENTERIC TISSUES (NO. OF TISSUES EXAMINED)	50	50	50	50	0		50	50	50	50	0	
ADENOCARCINOMA, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0	-		0	0	0	1	-	
MULTIPLE ORGANS (NO. OF TISSUES EXAMINED)	49	40	37	49	0		49	39	36	49	0	
ADENOCARCINOMA, MALIGNANT, SECONDARY:	0	0	0	0	-		0	0	0	1	-	
ADENOCARCINOMA, UTERUS, MALIGNANT, SECONDARY:	0	0	0	0	-		0	1	0	0	-	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, SECONDARY:	0	0	0	0	-		1	0	0	0	-	
CARCINOMA, KIDNEY, MALIGNANT, SECONDARY:	0	0	1	0	-		0	0	0	0	-	
CARCINOMA, UTERUS, MALIGNANT, SECONDARY:	0	0	0	0	-		0	1	0	0	-	
MESOTHELIOMA, MALIGNANT, PRIMARY:	0	2	0	2	-		0	0	0	0	-	
UNDIFFERENTIATED SARCOMA, SKIN, MALIGNANT, SECONDARY:	0	1	0	0	-		1	0	0	0	-	
LEUKEMIA - LARGE GRANULAR LYMPHOCYTE (FISCHER RAT), MALIGNANT, PRIMARY:	19	15	6	6	-		11	5	8	5	-	
ORAL TISSUES (NO. OF TISSUES EXAMINED)	50	19	17	50	0		50	7	6	50	0	
SQUAMOUS CELL CARCINOMA, HARD PALATE, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1	-		0	0	0	0	-	

SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
OVARIES (NO. OF TISSUES EXAMINED)	-	-	-	-	-		50	14	9	49	0	
GRANULOSA - THECAL CELL TUMOR, BENIGN, PRIMARY:	-	-	-	-	-		0	0	0	1	-	
PANCREAS (NO. OF TISSUES EXAMINED)	50	20	18	50	0		50	7	6	50	0	
ADENOMA, ACINI, BENIGN, PRIMARY:	1	0	0	1	-		0	0	0	0	-	
ADENOMA, ISLETS, BENIGN, PRIMARY:	8	1	2	11	-		3	0	0	1	-	
ADENOMA, ISLETS, BENIGN, PRIMARY: (TWO)	0	0	0	2	-		0	0	0	0	-	
ADENOMA, ISLETS, BENIGN, PRIMARY:	8	1	2	13	-	**	3	0	0	1	-	
PITUITARY (NO. OF TISSUES EXAMINED)	50	35	32	50	0		50	27	38	50	0	
ADENOMA, ANTERIOR (PARS DISTALIS), BENIGN, PRIMARY:	23	22	22	24	-		27	15	27	20	-	
ADENOMA, PARS INTERMEDIA, BENIGN, PRIMARY:	0	0	0	1	-		0	0	1	0	-	
CARCINOMA, ANTERIOR (PARS DISTALIS), MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1	-		0	0	0	0	-	
GANGLIONEUROMA, POSTERIOR (PARS NERVOSA), BENIGN, PRIMARY:	0	0	0	1	-		0	0	0	0	-	
SCHWANNOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	0	0	-		0	0	0	0	-	
PREPUTIAL OR CLITORAL GLANDS (NO. OF TISSUES EXAMINED)	4	2	5	8	0		1	2	3	4	0	
CARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	2	0	-		0	0	0	1	-	
SQUAMOUS CELL CARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	-		0	1	0	0	-	
SQUAMOUS PAPILLOMA, BENIGN, PRIMARY:	0	0	0	0	-		0	0	1	0	-	
RECTUM (NO. OF TISSUES EXAMINED)	50	19	17	50	0		50	6	6	50	0	
LEIOMYOMA, BENIGN, PRIMARY:	0	0	0	0	-		0	0	0	1	-	

BEST AVAILABLE COPY

SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
SKIN AND SUBCUTIS (NO. OF TISSUES EXAMINED)	50	28	30	50	0		50	30	38	50	0	
ADENOMA, SEBACEOUS GLANDS, BENIGN, PRIMARY:	0	0	2	0	-		0	0	0	0	-	
BASAL CELL ADENOMA, BENIGN, PRIMARY:	1	1	0	1	-		0	0	0	0	-	
KERATOACANTHOMA, BENIGN, PRIMARY:	0	3	4	1	-		1	0	1	0	-	
PAPILLOMA, BENIGN, PRIMARY:	1	3	0	0	-		0	0	0	0	-	
SQUAMOUS CELL CARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	0	1	-		1	0	0	0	-	
SQUAMOUS PAPILLOMA, BENIGN, PRIMARY:	0	0	0	0	-		0	0	1	1	-	
FIBROMA, BENIGN, PRIMARY:	5	6	5	5	-		0	1	1	0	-	
FIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	1	1	-		0	0	0	0	-	
LIPOMA, BENIGN, PRIMARY:	0	1	1	0	-		0	1	0	1	-	
OSTEOGENIC SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	1	0	-		0	0	0	0	-	
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	-		0	1	0	0	-	
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY, METASTASIS:	0	1	0	0	-		1	1	0	0	-	
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	0	1	0	0	-	**	1	2	0	0	-	
HISTIOCYTIC SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0	-		0	0	0	0	-	
NEUROFIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0	-		0	0	0	1	-	
SPINAL CORD (CERV, THOR & LUM) (NO. OF TISSUES EXAMINED)	50	19	17	50	0		50	7	6	50	0	
ASTROCYTOMA, BENIGN, PRIMARY:	0	0	0	0	-		1	0	0	0	-	
SPLEEN (NO. OF TISSUES EXAMINED)	50	24	23	50	0		50	11	15	50	0	
HEMANGIOMA, BENIGN, PRIMARY:	1	0	0	0	-		0	0	0	0	-	

SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
SPLEEN (CONTINUED)												
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	1	0	-		0	0	0	0	-	
LIPOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	-		1	0	0	0	-	
LEUKEMIA - LARGE GRANULAR LYMPHOCYTE (FISCHER RAT), MALIGNANT, PRIMARY, NO METASTASIS:	3	0	1	0	-		0	0	1	0	-	
TESTES (NO. OF TISSUES EXAMINED)	50	47	47	50	0		-	-	-	-	-	
ADENOMA, RETE TESTIS, BENIGN, PRIMARY:	0	0	1	0	-		-	-	-	-	-	
LEYDIG CELL TUMOR, BENIGN, PRIMARY:	6	5	10	6	-		-	-	-	-	-	
LEYDIG CELL TUMOR, BENIGN, PRIMARY: (TWO)	39	39	35	41	-		-	-	-	-	-	
LEYDIG CELL TUMOR, BENIGN, PRIMARY:	45	44	45	47	-	**	-	-	-	-	-	
THYROID GLAND (NO. OF TISSUES EXAMINED)	50	50	49	50	0		50	50	50	49	0	
ADENOMA, FOLLICLE(S), BENIGN, PRIMARY:	1	3	1	1	-		0	0	0	1	-	
ADENOMA, PARAFOLLICULAR CELLS, BENIGN, PRIMARY:	7	7	10	11	-		9	13	7	7	-	
ADENOMA, PARAFOLLICULAR CELLS, BENIGN, PRIMARY: (TWO)	2	0	0	1	-		0	0	2	0	-	
ADENOMA, PARAFOLLICULAR CELLS, BENIGN, PRIMARY:	9	7	10	12	-	**	9	13	9	7	-	
CARCINOMA, FOLLICLE(S), MALIGNANT, PRIMARY, NO METASTASIS:	0	2	0	0	-		0	0	0	0	-	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	1	1	-		1	0	1	2	-	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0	-		1	1	0	1	-	
CARCINOMA, PARAFOLLICULAR CELLS, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	0	0	1	1	-	**	2	1	1	3	-	
TRIGEMINAL GANGLIA (NO. OF TISSUES EXAMINED)	0	0	0	0	0		0	0	1	0	0	
NEUROFIBROSARCOMA, MALIGNANT, PRIMARY, METASTASIS:	-	-	-	-	-		-	-	1	-	-	

SEX	MALES						FEMALES					
DOSE IN %	0	0.005	0.02	0.05	0.10#		0	0.005	0.02	0.05	0.10#	
NUMBER OF RATS EXAMINED	50	50	50	50	0		50	50	50	50	0	
UTERUS (NO. OF TISSUES EXAMINED)	-	-	-	-	-		50	26	31	50	0	
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-	-		0	1	0	0	-	
ADENOCARCINOMA, MALIGNANT, PRIMARY, METASTASIS:	-	-	-	-	-		0	1	0	0	-	
ADENOCARCINOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	-	-	-	-	-	**	0	2	0	0	-	
ADENOMA, BENIGN, PRIMARY:	-	-	-	-	-		0	1	0	0	-	
CARCINOMA, MALIGNANT, PRIMARY, METASTASIS:	-	-	-	-	-		0	1	0	0	-	
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY:	-	-	-	-	-		12	13	21	20	-	
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY: (TWO)	-	-	-	-	-		6	3	2	2	-	
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY: (THREE)	-	-	-	-	-		0	2	0	1	-	
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY: (FOUR)	-	-	-	-	-		0	0	2	0	-	
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY:	-	-	-	-	-	**	18	18	25	23	-	
LEIOMYOMA, BENIGN, PRIMARY:	-	-	-	-	-		1	0	0	0	-	
LEIOMYOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-	-		0	0	0	1	-	
VAGINA (NO. OF TISSUES EXAMINED)	-	-	-	-	-		50	8	7	48	0	
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	-	-	-	-	-		0	1	0	0	-	

Tissues that might have potentially significant neoplastic findings were selected for targeted statistical analysis (Biostatistics reviewer Dr. Min Min). The results are listed in the following table:

	Tissue	Neoplastic findings				p-trend	p-comparison with control		
		0%	0.005%	0.02%	0.05%		low	med	high
Male	Mammary gland fibroadenoma (benign)	1	4	4	4	0.214	0.181	0.181	0.181
	Pancreas adenoma (benign)	8	1	2	13	0.005	0.985	0.954	0.163
	Skin keratoacanthoma (benign)	0	3	4	1	0.506	0.121	0.059	0.500
	Thyroid gland adenoma (benign)	9	7	10	12	0.135	0.607	0.500	0.312
	Thyroid gland carcinoma	0	2	1	1	0.421	0.248	0.500	0.500
Female	Thyroid gland adenoma (benign)	9	13	9	7	0.855	0.235	0.602	0.607
	Thyroid gland carcinoma	2	1	1	3	0.212	0.500	0.500	0.500
	Uterus adenocarcinoma	0	2	0	0	0.751	0.248	--	--
	Uterus endometrial stromal polyp (benign)	18	18	25	23	0.117	0.582	0.113	0.208

According to the Haseman-Lin-Rahman criteria, the neoplastic findings in rats administered XDE-105 for 24 months were not statistically increased relative to controls.

Toxicokinetics:

Toxicokinetic analysis was not performed in this study.

2.6.6.6 Reproductive and developmental toxicology – refer to the summary above.

2.6.6.7 Local tolerance – refer to the summary above.

2.6.6.8 Special toxicology studies – refer to the summary above.

2.6.6.9 Discussion and Conclusions

Significant systemic toxicities were observed in repeat dose oral toxicology studies in mice, rats, and dogs, which include vacuolation in a variety of tissues, chronic inflammation and necrosis of thyroid gland, anemia with compensatory hematopoiesis, lymph node necrosis, liver cytomegaly and necrosis, skeletal muscle myopathy, arteritis, chronic inflammation, hyperplasia and hyperkeratosis of stomach mucosa, and lymphoid organ histiocytosis. Administration of spinosad in the diet at up to 0.1% (46 and 57 mg/kg/day for males and females, respectively) for 12 months did not appear to be neurotoxic in rats. No dermal toxicity or systemic toxicity was noted at topical doses of spinosad up to 1000 mg/kg in a 21-day rabbit study. Topical daily application of 0.5, 1.0 and 2.0% spinosad (b) (4) to minipigs for 28 days did not produce significant dermal or systemic toxicity (HED of the high dose is 20 mg/kg).

It appears that the topical absorption of spinosad in adults and children was very low (concentration of all samples below the limit of quantification of 3 ng/mL). This low absorption appears to produce systemic levels far below those observed in the 28-day dermal minipig study, in which essentially no toxicity was observed (the highest mean blood level in the minipig was 178.5 ng/mL which was measured in females after 28 days of application of the 2.0%

formulation). Since no significant neurotoxicity was observed in repeat dose studies up to 12 months in rats, an additional neurotoxicity study in juvenile animals is not considered necessary at this time.

Spinosad was evaluated in Ames test, mouse lymphoma assay, chromosome aberration test, UDS assay, and micronucleus test, and it does not appear to be genotoxic. Spinosad was evaluated in an 18-month oral carcinogenicity study in mice and in a 2-year oral carcinogenicity study in rats. No statistically significant neoplastic findings were observed in these two studies.

Spinosad was evaluated for effects upon reproduction. Spinosad is not teratogenic in rats at oral doses up to 200 mg/kg or in rabbits at oral doses up to 50 mg/kg. In a two-generation dietary reproduction study in rats, at the high dose of 100 mg/kg, which was clearly a maternally toxic dose, spinosad appeared to have an effect on parturition with increased dystocia observed in both P1 and P2 generations. Decreased gestation survival, decreased litter size, decreased pup body weight and decreased neonatal survival were also noted at 100 mg/kg.

As summarized in the PK section, systemic exposure in Sprague-Dawley rats (the same species used in the reproductive and developmental toxicity studies) and Fischer 344 rats (the same species used in the 2-year carcinogenicity study) was determined after gavage administration. Although there are some differences in the results from these studies, it is apparent that the animals experienced systemic exposure to spinosad at relatively high levels (C_{max} on Day 1 of Spinosyn A was 159 ng/mL in SD rats and 702 ng/mL in Fischer 344 rats after the oral dosing of spinosad at 10 mg/kg). In addition, animals in the reproductive and developmental toxicity studies experienced some toxicity, indicating adequate drug exposure. Therefore, although a direct comparison between the systemic exposure in humans with that achieved in the reproductive and developmental toxicity studies may not be possible, the reproductive and developmental toxicity studies appear to be adequate to assess the reproductive and developmental effects of spinosad.

Spinosad 2% (b) (4) was not irritating to the skin of minipig but produced relatively mild irritation in the rabbit eye and the irritation was reversible with time. Spinosad 2% (b) (4) did not induce a phototoxic reaction in mice when irradiated with an essentially all UVA light source. Spinosad did not appear to be a skin sensitizer in guinea pigs.

2.6.6.10 Tables and Figures – N/A

2.6.7 TOXICOLOGY TABULATED SUMMARY – N/A

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Based on the nonclinical data available for oral spinosad and spinosad (b) (4), NDA 22-408 for the treatment of head lice infestation is approvable from a pharmacology/toxicology perspective provided that the recommended changes in the label discussed in the next section are incorporated into the (b) (4) label.

Unresolved toxicology issues (if any):

There are no unresolved toxicology issues for NDA 22-408, at this time.

Recommendations:

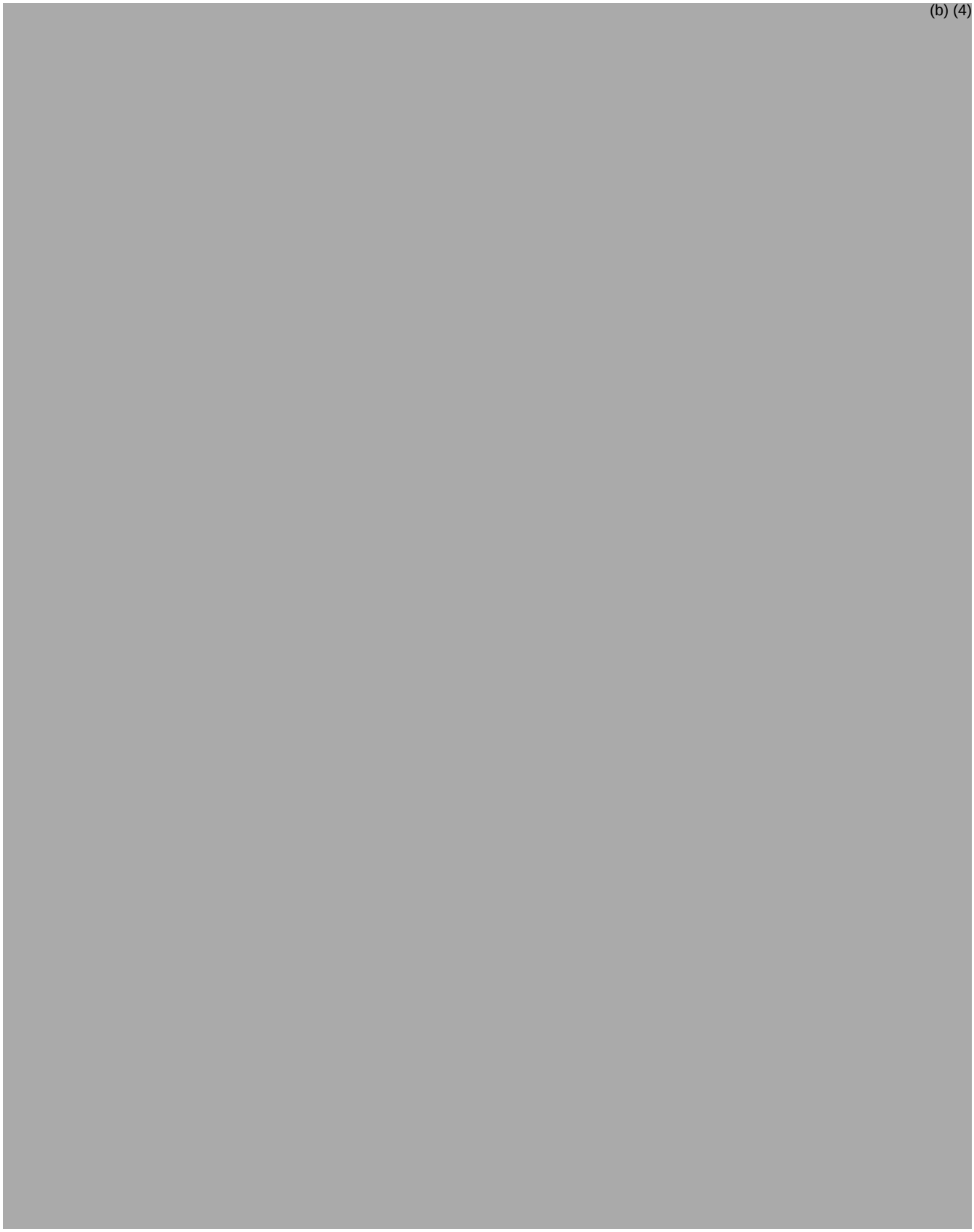
It is recommended that the suggested labeling changes provided in the next section be incorporated into the (b) (4) label.

Suggested labeling:

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the (b) (4) label reproduced below.

(b) (4)

(b) (4)



(b) (4)

APPENDIX/ATTACHMENTS

Appendix I: Executive CAC meeting minutes (Date of meeting 08/18/2009)

Executive CAC
Date of Meeting: August 18, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND, IO, Member
Todd Bourcier, Ph.D., DMEP, Alternating Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 22-408
Drug Name: (b) (4) Spinosad)
Sponsor: ParaPRO Pharmaceuticals, Carmel, Indiana

Background:

(b) (4) spinosad) is developed by the sponsor to treat head lice infestation. The proposed use of this drug product is a single topical treatment (up to 120 mL, which contains 1200 mg spinosad) on scalp and hair for 10 minutes then the drug product will be rinsed off with warm water. Clinical pharmacokinetic studies have shown that systemic exposure to spinosad/spinosad metabolites is very low (below the limit of quantification: 3 ng/mL) under maximal use conditions of the drug product. Usually carcinogenicity studies are not considered necessary to support the development of a drug product for an acute indication. However, spinosad is used as an agricultural insecticide and two oral carcinogenicity studies have been conducted to support that use. The study protocols of the two carcinogenicity studies were not submitted to the Agency for evaluation. The two oral carcinogenicity study reports were submitted to the NDA for review.

Mouse Carcinogenicity Study:

In an 18-month oral mouse carcinogenicity study, doses (in diet) of 0, 0.0025, 0.0080, and 0.0360% of spinosad (0, 3.4, 11.4, and 50.9 mg/kg/day for males and 0, 4.2, 13.8, and 67.0 mg/kg/day for females) were given to CD-1 mice. There were no significant treatment-related findings in low or middle dose group mice. Due to a high mortality rate, high dose females were terminated early on Day 455. Body weights were lower in high dose males (3-11.2%) and females (4.6-11.1%), compared with control. Spleen weights were higher in high dose males and females at the 3 months sacrifice only, which was consistent with the histological finding of increased extramedullary hematopoiesis noted in spleen. Thickening of the glandular portion of stomach was noted in the majority of high dose animals. Histologically, increase in vacuolation in various tissues, sinus histiocytosis in lymph nodes, skeletal muscle myopathy, chronic inflammation and hyperplasia of the glandular mucosa of stomach, and hyperplasia and hyperkeratosis of the nonglandular mucosa of stomach, were noted in high dose males and

females. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria. High dose females were not included in the neoplastic findings statistical evaluation due to early termination.

The NOAEL is considered to be the middle dose in the study, 0.008% of spinosad. The high dose (0.036%) reached the MTD in males and exceeded the MTD in females, while the middle dose is below the MTD in females. It would be preferable to have a dose between 0.036% and 0.008% in females. However, the overall study design appears acceptable.

Rat Carcinogenicity Study:

In a 2-year oral rat carcinogenicity and chronic toxicity study, doses (in diet) of 0, 0.005, 0.02, 0.05, and 0.10% of spinosad (0, 2.4, 9.5, 24.1 and 49.4 mg/kg/day for males and 0, 3.0, 12.0, 30.1 and 62.8 mg/kg/day for females) were given to Fischer 344 rats. Due to a high mortality rate, high dose males and females were terminated early on Days 714 and 611, respectively. Body weights were lower in high dose males (3-17.8%) and females (2.1-9.9%), compared with control. Gross pathology and histology were not evaluated in high dose males and females at 24-month sacrifice due to early termination. An increase in organ weights was noted in heart, kidney, liver, spleen, and thyroid gland in high dose animals. An increase in organ weights was also noted in heart (male), kidney (female), thyroid gland in animals at 0.05% dose, to a lesser degree compared to high dose group. At the 12 months sacrifice, histological findings noted in high dose group included: heart degeneration, vacuolation in kidney (females), skeletal muscle degeneration, slight aggregation of reticuloendothelial cells in liver, spleen, and mesenteric lymph nodes, slight increase of extramedullary hematopoesis in spleen (females), slight subacute to chronic inflammation in lung, degeneration/regeneration of the glandular mucosa of stomach, vacuolation and subacute to chronic inflammation in thyroid gland. Similar findings were also observed in the liver, mesenteric lymph node, and thyroid gland of females at 0.05% dose and the thyroid gland of males at 0.05% dose. At the 24-month sacrifice, histological findings noted in animals at 0.05% dose included: vacuolation, subacute to chronic inflammation, and necrosis of thyroid gland, slight subacute to chronic inflammation in lung (females), and slight aggregation of reticuloendothelial cells in lymph nodes. Vacuolation in thyroid glands was also noted in a number of male and female rats at 0.02% dose. There were no significant neoplastic findings according to the Haseman-Lin-Rahman criteria. High dose males and females were not included in the neoplastic findings statistical evaluation due to early termination.

The NOAEL is considered to be the low dose of the study, 0.005% of spinosad, considering histological findings in animals at 0.02% dose. The high dose (0.10%) exceeded the MTD in both males and females, indicated by high mortality and toxicity. The second high dose (0.05%) produced some toxicity in both male and female rats, indicated by organ weight increase and histological findings (mainly in thyroid gland, lung, and lymph nodes). This study is considered adequate for testing oral carcinogenicity of spinosad in rats.

Executive CAC Recommendations and Conclusions:

1) 18-month oral (diet) mouse carcinogenicity study:

- The Committee concluded that the study was acceptable, noting no prior FDA concurrence.
- The Committee concluded that the study was negative for drug-related neoplasms.

2) 2-year oral (diet) rat carcinogenicity study:

- The Committee concluded that the study was acceptable, noting no prior FDA concurrence.
- The Committee concluded that the study was negative for drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DDDP
/B. Hill, Supervisor, DDDP
/J. Wang, P/T reviewer, DDDP
/D. Williams, Project Manager, DDDP
/A. Seifried, OND IO

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22408	ORIG 1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

ADELE S SEIFRIED
08/19/2009

DAVID JACOBSON KRAM
08/20/2009

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD
NDA-22408	ORIG-1	PARAPRO PHARMACEUTICALS LLC	SPINOSAD

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/s/

JIANYONG WANG
09/02/2009

BARBARA A HILL
09/03/2009
I concur

Division of Dermatology and Dental Drug Products
Pharmacology/Toxicology Checklist for NDA Filing Meeting

Date:	2-24-2009
Reviewer:	Jianyong Wang
NDA Number:	22-408
Drug Name:	(b) (4) Spinosad)
CAS Number:	131929-60-7 for Spinosyn A
Drug Class:	Insecticide
Indication:	Treatment of human head lice (b) (4)
Route of Administration:	Topical
Date CDER Received:	1-21-2009
User Fee Date:	11-20-2009
Date of Draft Review:	9-1-2009
Sponsor:	ParaPRO Pharmaceuticals, LLC, Carmel, Indiana

Fileability:
On initial overview of the NDA application:

(1) Does the pharmacology/toxicology section of the NDA appear to be organized in a manner to allow a substantive review to be completed? YES

This is an electronic CTD NDA submission.

(2) Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner to enable a timely and substantive review? YES

(3) Is the pharmacology/toxicology section of the NDA sufficiently legible to permit a substantive review to be completed? YES

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? NO

Refer to item (7)

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? N/A

(6) Are the proposed labeling sections relative to pharm/tox appropriate? (including human dose multiples expressed in either mg/m^2 or

comparative serum/plasma levels) and in accordance with 201.57? NO

No nonclinical toxicology information was provided in Section 13 of the label. It appears that Section 13 was omitted from the label.

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? NO

Three issues were identified from a pharmacology/toxicology perspective and relayed to the sponsor during the preNDA meeting on 11/04/2008: "(a) No nonclinical cardiovascular safety pharmacology studies were submitted. EKG evaluation was not performed in the toxicology studies in dogs. (b) No toxicokinetic (TK) data for oral diet toxicology studies in rats or dogs were submitted. No TK data for reproductive/developmental toxicology studies were submitted. It would be difficult to determine the adequacy of toxicology studies without the support of TK data. (c) No juvenile animal toxicology studies were submitted." These issues were not addressed in the NDA submission. A request should be relayed to the sponsor to address these issues. The sponsor's reply will be a review issue.

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? YES

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? YES

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? N/A

No carcinogenicity studies were submitted.

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? YES

(12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. YES

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: YES

Three issues were identified from a pharmacology/toxicology perspective and relayed to you during the preNDA meeting on 11/04/2008: "(a) No nonclinical cardiovascular safety pharmacology studies were submitted. EKG evaluation was not performed in the toxicology studies in dogs. (b) No toxicokinetic (TK) data for oral diet toxicology studies in rats or dogs were submitted. No TK data for reproductive/developmental toxicology studies were submitted. It would be difficult to determine the adequacy of toxicology studies without the support of TK data. (c) No juvenile animal toxicology studies were submitted." (Please refer to the preNDA meeting minutes, additional comments for Question 2).

These three issues were not addressed in your NDA submission. Please provide either additional data or a rationale to justify the reason why additional data are not needed to support the safety of your drug product. If you believe that you have addressed these issues in your NDA submission, then specify the location of the appropriate data or rationale in your NDA submission.

It appears that Section 13 "Nonclinical Toxicology" was omitted from the submitted label in your NDA submission. You should submit a revised label that contains appropriate nonclinical toxicology information in Section 13 of the label for your drug product.

(14) Issues that should not be conveyed to the Sponsor: N/A

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/s/

Jianyong Wang
3/11/2009 12:01:25 PM
PHARMACOLOGIST

Barbara Hill
3/11/2009 12:07:18 PM
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