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

JUL 20 1987

006004

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 7F3488. Karate®. Petition for Tolerance of PP321 on Soybeans.

Tox. Chem. No. 725C
Related Tox. Chem. No. 271F
Project No. 7-0466

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c) 7/15/87

William Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769c) 7/19/87

Background:

ICI Americas Inc. is requesting a permanent tolerance for PP321 on soybeans. This pesticide chemical is an ingredient of the insecticide, Karate®. PP321 is also one of two enantiomeric pairs which comprise the pesticide, cyhalothrin (PP563). The formulation, Karate® will be used with either air or ground equipment. No more than 0.05 pounds a.i./acre/season is to be applied. The treated areas are not to be used for grazing or for harvesting for forage or hay.

ICI has provided subchronic, acute and metabolism data on both PP321 and cyhalothrin to support the use of the chronic studies that have been conducted on cyhalothrin is partially fulfilling the toxicity data required for the tolerance petition on PP321. In addition, [illegible] chronic study on PP321 in dogs has been submitted.

The substance identification and technical data for PP321 and Karate® are given in a previous Experimental Use Permit Petition (10182-EUP-[illegible]), memorandum to George LaRocca, dated May 8, 1986.

Comments:

1. The following toxicity studies are required to be submitted in support of the tolerance petition (preceded by a (*)). Additional studies required for registration of the product are preceded by a (**) (ref. Fed. Reg. 40 CFR Part 158, October 24, 1984).

Technical Product	Required	Satisfied
**Acute oral LD_{50}	Yes	Yes
**Acute dermal LD_{50}	Yes	Yes
*90-day feeding studies		
rodent	Yes	Yes
nonrodent	Yes	Yes (comment 2)
**21-day dermal	Desirable	Pending (comment 3)
*Chronic feeding		
rodent	Yes	Yes (comment 4)
nonrodent	Yes	Yes
*Oncogenicity - rat & mouse preferred	Yes	Yes (comment 4)
*Teratogenicity - 2 species	Yes	Yes (comment 4)
*Reproduction, 2 generation	Yes	Yes (comment 4)
*Mutagenicity		
Gene mutation	Yes	Yes
Struct. chrom. aberration	Yes	Yes
Other genotoxic effects	Yes	Yes
End Use Product		
**Acute oral LD_{50}	Yes	Yes
**Acute dermal LD_{50}	Yes	Yes
**Acute inhalation LD_{50}	Yes	Yes
**Primary eye irritation	Yes	Yes
**Primary dermal irritation	Yes	Yes
**Dermal sensitization	Yes	Yes
Pure Active Ingredient		
*General Metabolism	Yes	Yes (comments 4,5)

2. A satisfactory chronic (1 year oral) dog study has been conducted on PP321. This study satisfies the requirement for a subchronic 90-day nonrodent feeding study.

3. The 21-day dermal study in rabbits was classified as core supplementary because of the possibility that the animals had coccidiosis. This petition will not be held up because of the data gap in this area. However, The Toxicology Branch has already requested additional slides from this study in a previous memorandum (EUP Petition 53218-EUP-1,2) and that the slides be submitted for evaluation.

4. ICI has requested that the long term studies conducted on cyhalothrin be used in partial fulfillment of the toxicity data required for the tolerance petition for PP321. PP321 consists of 2 of the 4 enantiomers of cyhalothrin. On the basis of structural considerations, metabolism and subchronic data on both PP321 and cyhalothrin, and on the fact that the data from the chronic dog study conducted on PP321 does not contradict the data from the 6-month dog study conducted on cyhalothrin, the Toxicology Branch accepts the long term data on cyhalothrin as partial fulfillment of the toxicity studies required for the tolerance petition on PP321.

5. Extensive metabolism studies have been conducted on the purified form of cyhalothrin. A comparative study between cyhalothrin and PP321 has indicated that their absorption, distribution, metabolism and excretion patterns are identical following a single 1 mg/kg dose in the male rat. Therefore, the Toxicology Branch is accepting the metabolism studies conducted on cyhalothrin along with the comparison study mentioned above in fulfillment of the metabolism studies required for the tolerance petition for PP321.

6. The inert ingredients in the product Karate® have been cleared for use under 180.1001.

7. The draft label (12/86) precautionary statement should be changed to reflect that the formulation is corrosive to the skin. The registrant should also include a statement that the formulation is a potential sensitizer.

8. A copy of the proposed tolerances (Section F) is attached.

9. The Toxicology Branch has no objection to granting the petition for a permanent tolerance for PP321 on soybeans, once the label has been modified. An 8-point document is attached.

[NOT AVAILABLE ON FILM]

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SECTION F

PROPOSED TOLERANCES

It is proposed that tolerances be established for residues of (±)-α-cyano-(3-phenoxyphenyl)methyl(±)-cis-(Z-2-chloro-3,3,3-trifluoroprop-2-enyl)-2,2-dimethylcyclopropanecarboxylate in or on the following raw agricultural commodities:

Commodity	Parts Per Million
Soybeans	0.01
Poultry, meat	0.01
Poultry, fat	0.01
Poultry, meat byproducts	0.01

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8-Point Review

[Prepared for 7F3488, PP321 on soybeans, July, 1987]

1. Toxicity data with technical grade PP321 and with technical grade cyhalothrin (justification given in point #8 of this document) considered in support of this tolerance (selected studies).

Acute oral LD_{50}, rats PP321	79 mg/kg in males 56 mg/kg in females
90-day feeding, rats PP321	NOEL 50 ppm, LOEL 250 ppm based on reduced body wt gain
26-week oral, dogs Cyhalothrin	NOEL 1 mg/kg/day LOEL 2.5 mg/kg/day (liquid feces)
Chronic feeding, rat Cyhalothrin	NOEL 50 ppm, LOEL 250 ppm (reduced body wt gain. No onco. effects)
Chronic oral, dog PP321	NOEL 0.5 mg/kg/day, LOEL 3.5 mg/kg/day (clinical signs of neurotoxicity)
Chronic/Onco, mouse Cyhalothrin	NOEL 100 ppm, LOEL 500 ppm (decreased body wt gain. No onco. effects)
Teratology, rabbit Cyhalothrin	NOEL maternal tox. 10 mg/kg/d, LOEL 30 mg/kg/d (decreased body wt gain). NOEL fetotox. 30 mg/kg/d Not teratogenic.
Teratology, rat Cyhalothrin	NOEL maternal tox. 10 mg/kg/d, LOEL 15 mg/kg/d (reduced body wt). NOEL embryo-leth. & fetotox. 15 mg/kg/d. Not teratogenic.

Reproduction - 3 gen., rat Cyhalothrin	NOEL parental tox. 10 ppm, LOEL 30 ppm (decr. bw gain). Offspring: NOEL 10 ppm, LOEL 30 ppm (decreased bw gain).
Metabolism, rats Cyhalothrin and PP321	55% oral absorption. Extensively metabolized when absorbed; cleavage of ester to cyclopropylcarboxylic acid & phenoxybenzyl derivatives. Accumulation of [illegible] cmpd. in fat upon chronic administration.
Mutagenicity - Ames Gene Mutation (PP321)	Not mutagenic
Mutagenicity - Chrom. Aberr. in rodents (PP321)	Did not induce micronuclei
Mutagenicity - Gene mutation in Lymphoma cells (PP321)	Not mutagenic
Mutagenicity - In Vitro Cytogenetics (PP321)	Not a clastogen in human lymphocytes

2. Additional toxicity data considered desirable:
None

3. Not applicable

4. No other tolerances have been published, although some tolerances are pending in review.

5. The relationship of these tolerances on the contribution to the diet and the MPI must be addressed by the Residue Chemistry Branch and the TAS system.

6. The 3-generation reproduction study on cyhalothrin in the rat with a safety factor of 100 was used to calculate the ADI. The NOEL was 0.5 mg/kg/day (10 ppm). The ADI is calculated to be 0.0050 mg/kg/day and the MPI is 0.3000 mg/day (60 kg).

7. There are no pending regulatory actions from the Toxicology Branch against registration of the pesticide.

8. The registrant has requested that the long term studies conducted on cyhalothrin be used in partial fulfillment of the toxicity data required for the tolerance petition

for PP321 (Karate). PP321 consists of 2 of the 4 enantiomers of cyhalothrin. On the basis of structural considerations, metabolism and subchronic data on both PP321 and cyhalothrin, and on the fact that data from the chronic dog study conducted on PP321 does not conflict with the data from the 6-month dog study conducted on cyhalothrin, the Toxicology Branch (TB) accepts the long term data on cyhalothrin as partial fulfillment of the toxicity studies required for the tolerance petition on PP321. TB has also decided that both cyhalothrin and PP321 will be considered to be the same chemical for the purpose of establishing the ADI and TMRC (see attached memorandum from R. Engler to Pam Hurley, dated July 10, 1986). Any future tolerance petitions for either cyhalothrin, PP321 or any other mixtures of the 16 possible isomers of the chemical structure (provided that the appropriate toxicological data are provided) will be treated as if they are the same chemical and the proposed tolerances will be added to the percent ADI calculated for PP321 in this action.

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JUL 10 1986

MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: ADI/RfD for Cyhalothrin and Karate
Caswell Nos. 271F and 725C

FROM: Toxicology Branch ADI Committee

TO: Pam Hurley
Section II, Toxicology Branch/HED (TS-769)

and

Residue Chemistry Branch/HED (TS-769)

Background:

The RfD/ADI documents for these "two" chemicals were presented to the Toxicology Branch ADI Committee. The following facts were presented to the Committee:

1. Cyhalothrin and Karate are basically the same chemical, the differences are found in their stereo chemistry.

2. Cyhalothrin consists of four (4) stereo isomers and Karate of two (2). The two Karate isomers are contained in Cyhalothrin, they represent 40% of Cyhalothrin.

3. At present, it appears that the use of Cyhalothrin focuses on using it on cattle (meat and milk tolerances) and Karate is intended for food crops (rac tolerances).

4. The major studies supporting an ADI/RfD were performed on Cyhalothrin, but the registrants intend to use these studies in support of either chemical.

5. While there might be some difference between the two "chemicals" especially with respect to efficacy, 90-day studies in rats have shown that there is no significant difference in their biological effects on mammals.

6. The reproduction study (3 generation) for Cyhalothrin shows the most sensitive toxicological endpoint (NOEL = 0.5 mg/kg/day).

Options: Essentially three options were discussed.

1. To establish an ADI for Cyhalothrin at 0.005 mg/kg/day (NOEL/100) and to establish a separate ADI for Karate at 0.002 mg/kg/day (NOEL/100/2.5) accounting for the fact that only 40% of the Cyhalothrin fed was actually Karate.

2. To establish an ADI on Cyhalothrin (as option 1) and require all the long-term data on Karate to establish a separate ADI.

3. To establish an ADI for Cyhalothrin/Karate based on the Cyhalothrin data (i.e., 0.005 mg/kg/day).

Consensus:

The consensus of the ADI committee was to use option 3 for the following reasons:

(1) All information, particularly the 90 day rat studies, show that there is no significant difference in the toxicity of the different stereo isomeric mixtures of this chemical.

(2) Establishing two ADIs for essentially the same chemical would provide the opportunity to expose the population to excessive levels of the Cyhalothrin/Karate complex, especially under the present use practices where meat and milk tolerances would be evaluated against the "Cyhalothrin ADI" and other tolerances against the "Karate ADI."

(3) Separate tolerances for stereo-isomers of the same chemicals would be inconsistent with the practice of setting combined tolerances on salts, esters and acids of the same chemical; the basic toxicological properties remain the same even though these are not identical chemicals, in the strictest sense.

(4) To prorate the combined Cyhalothrin/Karate ADI/RfD by a factor of 0.4 was not considered necessary since comparative toxicity tests did not show differences which would support this type of amortization.

(5) Referral to RCB: The committee, as a result of the above consensus concluded that residue evaluations and expressions for either Cyhalothrin or Karate must include any and all stereo isomers.

LAMBDA - CYHALOTHRIN 128897

Page _____ is not included in this copy.

Pages 10 through 14 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

X A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

eviewed by: Pamela Hurley
ection 2 , Tox. Branch (TS-769C)
econdary Reviewer: Edwin Budd
ection 2 , Tox. Branch (TS-769C)

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DATA EVALUATION REPORT

STUDY TYPE: Chronic dog study (83-1) TOX. CHEM. NO.: 725C

ACCESSION NUMBER: 400279-02

TEST MATERIAL: PP321

SYNONYMS: Karate

STUDY NUMBER(S): PDO583

REPORT NUMBER: CTL/P/1316

SPONSOR: ICI Americas Inc., Macclesfield, England

TESTING FACILITY: ICI, PLC Central Toxicology Laboratory, Alderly, Park, Macclesfield, UK

TITLE OF REPORT: PP321: 1 Year Oral Dosing Study in Dogs

AUTHOR(S): Hext PM, Brammer A, Chalmers DT, Chart IS, Gore CW, Pate I, Banham PB

REPORT ISSUED: 1/22/86

IDENTIFYING VOLUME: Vols. 1 and 2

CONCLUSION: The NOEL for chronic effects is 0.5 mg/kg/day in beagle dogs, based upon clinical signs of neurotoxicity, including ataxia, convulsions and muscle tremors. There was an increase in fluid feces in all animals at 3.5 mg/kg/day and in one animal at 0.5 mg/kg/day (the latter was not considered to be toxicologically significant). The dose levels tested were 0.1, 0.5 and 3.5 mg/kg/day.

Classification: CORE GUIDELINE

A. MATERIALS AND METHODS:

1. Test Compound(s):

Chemical Name: (Z)-(1R, 3R), S-ester and (Z)-(1S, 3S), R-ester of alpha-cyano-3-phenoxybenzyl,3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropane carboxylate
Description: buff-colored powder
Batch #(s), Other #(s): batch ref. P13, CTL Ref. YO2537/001/005
Purity: 96.5% w/w PP321
Source: ICI, PLC, Plant Protection Div., Jealotts Hill, Berkshire, UK
Vehicle (if applicable): corn oil

2. Test Animals and/or Other Test System (if applicable):

Species and Strain (sexes): male and female beagle dogs
Age: 16-21 weeks (20-25 weeks at start)
Source(s): ICI, PLC, Alderly Park, Macclesfield, UK

3. Procedure:

a. Dosing Preparation : Animals administered the compound orally via gelatin capsule. Quantities corrected for purity and dissolved in corn oil. 0.25 ml/kg administered daily. Animals fed standard laboratory diet.
Frequency of preparation: 5 week intervals
Storage conditions: In the dark at room temperature
Stability Analyses: Stability studies done in previous studies; stable over a period of 6-7 weeks
Concentration Analyses: all solutions analyzed for PP321 content prior to use in study

b. Basis For Selection of Dosage Levels: Based upon a six-week dose-range finding study. Clinical signs of neurotoxicity and fluid feces seen at 2.5 mg/kg/day and above.

c. Animal Assignment and Dose Levels:

Test Group	Dose Administered mg/kg/day	Main Study 12 months male	female
Contr.	0	6	6
1	0.1	6	6
2	0.5	6	6
3	3.5	6	6

d. Clinical Observations and Mortality: All animals observed routinely 3 times daily during the week and 2 times daily on weekends and holidays. Full clinical exams at pre-study and at 3-monthly intervals. Exams included cardiac and pulmonary auscultation and indirect ophthalmoscopy.

e. Body Weight Determinations: Weekly

f. Food and/or Water Consumption: Daily

g. Ophthalmological Examinations (if applicable): 3-monthly intervals

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h. Clinical Pathology: (*) recommended by Guidelines

1) Hematology:

Collection times for blood (including # of animals): prestudy, weeks 4, 13, 26, 39 and 52

The following CHECKED (X) parameters were examined:

X		X	
x	Hematocrit (HCT)*	x	Mean corpustular HGB (MCH)
x	Hemoglobin (HGB)*	x	Mean corpustular HGB conc.(MCHC)
x	Leukocyte count (WBC)*	x	Mean corpustular volume (MCV)
x	Erythrocyte count (RBC)*	x	Kaolin-cephalin
x	Platelet count*	x	Prothrombin times
	Total plasma protein (TP)		
x	Leukocyte differential count*		

2) Clinical Chemistry:

The following CHECKED (X) parameters were examined:

X	Electrolytes:	X	Other:
x	Calcium*	x	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
	Phosphorus*	x	Cholesterol*
x	Potassium*		Globulins
x	Sodium*	x	Glucose*
	Enzymes:		Total bilirubin*
x	Alkaline phosphatase	x	Total protein*
	Cholinesterase	x	Triglycerides
	Creatinine phosphokinase*		
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
x	Plasma creatine kinase		

3) Urinalysis:

Collection times for urine (including # of animals):
pre-experimentally and weeks 25 and 51

The following CHECKED (X) parameters were examined:

X		X	
	Appearance*	x	Glucose*
	Volume*	x	Ketones*
x	Specific gravity*	x	Bilirubin*
x	pH	x	Blood*
x	Sediment (microscopic)*		Nitrate
x	Protein*	x	Urobilinogen

i. Gross Necropsy:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to end of exposure period and were subjected to complete gross pathological examinations:

All

Animals (groups) sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations:

All

j. Histopathology:

Animals (groups) which died or were sacrificed in moribund condition and/or were sacrificed as part of an interim group prior to the end of the exposure period and were subjected to microscopic examination:

All

Animals (groups) which were sacrificed at the end of the treatment/observation period and were subjected to microscopic examination:

All

CHECKED (x) tissues were preserved for histopathological examination and (xx) tissues were weighed upon removal from the animal. The (*) tissues were recommended by the Guidelines.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*	x	Eyes (optic n.)*
x	Jejunum*	x	Thymus*		Glandular
x	Ileum*		Urogenital	xx	Adrenals*
x	Cecum*	xx	Kidneys*		Lacrimal gland
x	Colon*	x	Urinary bladder*	x	Mammary gland*
x	Rectum*	xx	Testes*	x	Parathyroids*
xx	Liver*		Epididymides	xx	Thyroids*
x	Gall bladder*	x	Prostate		Other
x	Pancreas*		Seminal vesicle	x	Bone*
	Respiratory	xx	Ovaries	x	Skeletal muscle*
x	Trachea*	x	Uterus*	x	Skin
x	Lung*			x	All gross lesions and masses
				x	Bone marrow smears
				x	Epididymides
				x	Tibia/femur (stifle joint)

k. Statistical Analyses: Body weight gains were considered by analysis of variance. Hematological and biochemical data were considered by analysis of covariance on pre-experimental values. Organ weights were considered by analysis of variance and analysis of covariance on final body weight. Student's t-test was also used.

B. RESULTS:

1. Dosing Preparation: 11 samples were analyzed for PP321 concentration. The mean values were as follows: for the 0.4 mg/ml concentration, the mean concentration range was 0.37-0.43 mg/ml; for the 2.0 mg/ml concentration, the mean concentration range was 1.85-2.08 mg/ml and for the 14.0 mg/ml concentration, the mean concentration range was 12.6-15.2 mg/ml. The concentrations were within 10% of nominal for all preparations. The mean concentrations of dosing solutions administered over the whole of the study were within 5% of the intended concentrations.

2. Clinical Observations and Mortality: In week 46, 1 male from the highest dose level (3.5 mg/kg/day) was killed because of severe ataxia and convulsions which persisted over a period of 2 days, even though dosage was withheld during this period. No other animals either died or were killed in extremis during the study.

   At 3.5 mg/kg/day, the principal clinical observations following dosing were neurological effects. These included ataxia, muscle tremors and convulsions (see attached table). Subdued behavior was also observed in many of these animals. For individual animals, usually on single days only, dosing at this level was suspended to allow recovery from the neurotoxic effects. Worn, broken or bleeding claws were observed in 3 dogs, and on 3 occasions appeared to be associated with the signs of neurotoxicity. On 3 other occasions with 1 female dog, it was unknown whether or not this accompanied neurotoxic effects. Regurgitation of food was seen occasionally during the first 2 weeks of the study from 7/12 dogs. Thereafter, there was only a moderate incidence in this group. An increased incidence in fluid feces was observed in all the dogs from this dose group thoughout the study.

   At 0.5 mg/kg/day, 2 dogs were observed to have gait abnormalities (2 times in 1 animal and 4 times in the other animal). Convulsions were observed in 2 other dogs (both males); the convulsions appeared to be precipitated by the stress of handling or noise. Blood stains on the pen floor with no obvious cause were seen in 2 dogs. The frequency of fluid feces was clearly increased in 1 dog at this dose level and the overall incidence in this group suggested a slight treatment-related effect.

   On a single occasion, 1 male dosed at the lowest dose level, 0.1 mg/kg/day had slight ataxia. Blood stains on the pen floor with no obvious cause was seen with 1 female dog in week 27. The incidence of vomiting in this dose group was comparable to controls and there was no increase in either the frequency or incidence in fluid feces over the control values.

   Other clinical findings in all dose groups were considered to be incidental.

3. Body Weight Determinations: There was no evidence of any treatment-related effects on body weight gain in either sex.

4. Food and/or Water Consumption: 5/12 dogs at the highest dose level showed a slight reduction in food intake on a very small number of occasions. Since reduction in food intake, particularly for males, was a rarity for the testing laboratory, this reduction was considered to be due to PP321. There was no apparent correlation with the occurrence of neurological effects. A total of 2 dogs in the remaining 3 groups (including controls) left food uneaten.

5. Ophthalmological Examinations: No treatment-related effects were observed.

6. Hematology: Statistically significant differences in various parameters were observed during the treatment period. The majority of the findings were noted in the highest dose group. The authors considered these observations to be minor and not to be of biological or toxicological significance.

7. Clinical Chemistry: There was evidence of slightly increased plasma triglycerides accompanied by a slight decrease in plasma cholesterol in the high dose animals throughout the dosing period. Other observed changes were considered to be incidental.

8. Urinalysis: No treatment-related effects were observed.

9. Gross Pathology: No treatment-related lesions were observed.

10. Organ Weights: In the highest dose group, mean testes weights were slightly reduced after adjustment for final body weight. This was particularly evident in 2 dogs. There were also slight dose-related increases in mean liver weights at this dose level for both sexes and evidence of increased kidney weights in males, although this was mainly due to 1 animal.

11. Histopathology:

    a. Nonneoplastic lesions: No treatment-related lesions were observed.

    b. Neoplastic lesions: No treatment-related lesions were observed.

12. Quality Assurance Measures: Appropriate inspections were conducted and reports were written. As could be reasonably established, the methods described and the results given in the report accurately reflect the data produced during the study.

C. DISCUSSION:

This study appears to have been properly conducted according to the EPA Guidelines. The only significant signs of toxicity that were observed were the clinical signs of neurotoxicity and liquid feces at the highest dose level. These signs were not supported by any microscopic indications. The clinical signs of neurotoxicity were especially evident at the highest dose level, 3.5 mg/kg/day. At 0.5 mg/kg/day, the clinical signs could not be clearly attributed to neurotoxicity. Four of twelve dogs at this dose level showed some signs possibly relating to neurotoxic effects. Of the four, two animals showed slight ataxia (one time for one dog and four times during one week for another dog). The signs were so slight that little description was written of them in the individual animal data. The other two animals displayed convulsions of short duration (lasting 30 seconds to 5 minutes), one time for one animal and two times for the other animal. These convulsions occurred while the animals were either being carried or being placed in a metabolism cage. No other clinical signs of this type were observed either in these animals or in any of the other animals at this dose level throughout the duration of the study. From the clinical observation data, the NOEL for neurotoxic effects is probably very close to 0.5 mg/kg/day. The authors of the report used this dose level as the NOEL for the study. Since the data do not indicate a clear effect, 0.5 mg/kg/day is accepted as the NOEL for neurotoxic effects in dogs. The study is classified as CORE GUIDELINE.

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS

TABLE 3

INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)/

Treatment (mg PP321/kg/Day)	Sex	Animal No.	Duration (Weeks)								
			1-4			5-8			9-12		
			SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0	1	0	0	0	0	0
0.5	Male	26	0	0	0	0	0	0	0	0	0
		27	0	0	0	0	0	0	0	0	0
		28	1	0	0	0	0	0	0	0	0
	Female	34	0	0	0	0	0	0	4	0	0
3.5	Male	37	4	0	0	2	2	0	1	0	0
		38	0	0	0	2	0	0	6	1	0
		39	13	3	0	11	2	0	9	1	1
		40	4	1	0	8	0	2	12	2	4
		41	2	0	0	0	0	0	0	1	0
		42	7	0	1	0	1	0	8	0	0
	Female	43	11	3	1	4	0	0	0	0	0
		44	3	0	0	2	0	0	1	0	0
		45	4	0	0	1	0	0	1	0	0
		46	2	0	0	0	0	0	1	0	0
		47	7	2	0	0	0	1	0	0	0
		48	4	0	0	0	0	0	0	0	0

/ expressed as number of observations/4 weeks

Slight = Unsteady gait
Moderate = Incoordinated gait
Severe = Straddled gait/recumbency

There was no incidence of ataxia in control animals

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS
TABLE 3 - continued
INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)/

Treatment (mg PP321/kg/Day)	Sex	Animal No.	Duration (Weeks)								
			13-16			17-20			21-24		
			SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0	0	0	0	0	0	0
0.5	Male	26	0	0	0	0	0	0	0	0	0
		27	0	0	0	0	0	0	0	0	0
		28	0	0	0	0	0	0	0	0	0
	Female	34	0	0	0	0	0	0	0	0	0
3.5	Male	37	1	0	0	2	1	0	2	0	0
		38	7	0	0	7	0	0	8	0	0
		39	8	1	0	14	0	1	11	3	0
		40	7	2	7	13	1	7	9	0	3
		41	0	0	0	0	0	0	0	0	0
		42	4	0	0	4	0	0	1	0	0
	Female	43	4	0	0	2	1	0	0	0	0
		44	0	0	0	3	0	0	1	0	0
		45	0	0	0	0	0	0	1	0	0
		46	1	0	0	1	0	0	2	0	0
		47	2	0	0	2	0	0	1	0	0
		48	0	0	0	0	0	0	1	0	0

/ expressed as number of observations/4 weeks

Slight = Unsteady gait
Moderate = Incoordinated gait
Severe = Straddled gait/recumbency

There was no incidence of ataxia in control animals

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS
TABLE 3 - continued
INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)/

Treatment (mg PP321/kg/Day)	Sex	Animal No.	Duration (Weeks)								
			25-28			29-32			33-36		
			SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0	0	0	0	0	0	0
0.5	Male	26	0	0	0	0	0	0	0	0	0
		27	0	0	0	0	0	0	0	0	0
		28	0	0	0	0	0	0	0	0	0
	Female	34	0	0	0	0	0	0	0	0	0
3.5	Male	37	0	0	0	0	0	0	2	0	0
		38	4	0	0	2	0	0	0	0	0
		39	15	1	0	12	2	0	6	1	0
		40	17	1	1	9	1	4	9	1	7
		41	3	0	0	0	0	0	0	0	0
		42	7	0	0	10	0	0	10	0	0
	Female	43	4	0	0	3	0	0	0	0	0
		44	0	0	0	0	0	0	2	0	0
		45	2	0	0	0	0	1	0	0	0
		46	0	0	0	0	0	0	1	0	0
		47	4	0	0	3	0	0	3	0	0
		48	1	0	0	0	0	0	0	0	0

/ expressed as number of observations/4 weeks

Slight = Unsteady gait
Moderate = Incoordinated gait
Severe = Straddled gait/recumbency

There was no incidence of ataxia in control animals

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS
TABLE 3 - continued
INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)/

Treatment (mg PP321/kg/Day)	Sex	Animal No.	Duration (Weeks)								
			37-40			41-44			45-48		
			SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE	SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0	0	0	0	0	0	0
0.5	Male	26	0	0	0	0	0	0	0	0	0
		27	0	0	0	0	0	0	0	0	0
		28	0	0	0	0	0	0	0	0	0
	Female	34	0	0	0	0	0	0	0	0	0
3.5	Male	37	2	0	0	0	0	0	0	0	0
		38	1	0	0	0	0	0	0	0	0
		39	6	1	1	7	0	2	6	2	1*
		40	13	2	2	9	2	7	12	1	6
		41	0	0	0	0	0	0	0	0	0
		42	9	0	0	4	0	0	6	1	1
	Female	43	1	1	0	0	0	0	0	0	0
		44	0	0	0	0	0	0	0	0	0
		45	1	0	0	3	0	0	0	0	0
		46	0	0	0	0	0	0	1	0	0
		47	1	0	0	0	0	0	3	2	0
		48	0	0	0	0	0	0	0	0	0

/ expressed as number of observations/4 weeks

Slight = Unsteady gait
Moderate = Incoordinated gait
Severe - Straddled gait/recumbency

There was no incidence of ataxia in control animals

* Killed in week 46

PP321: 1 YEAR ORAL DOSING STUDY IN DOGS

006004

TABLE 3 - continued

INCIDENCE AND SEVERITY OF ATAXIA (INDIVIDUAL ANIMALS)/

Treatment (mg PP321/kg/day	Sex	Animal No.	Duration (Weeks)		
			49-52(53)		
			SLIGHT	MODERATE	SEVERE
0.1	Male	14	0	0	0
0.5	Male	26	0	0	2
		27	0	0	1
		28	0	0	0
	Female	34	0	0	0
3.5	Male	37	3	1	0
		38	0	0	0
		39*	-	-	-
		40	9	1	6
		41	0	0	0
		42	7	0	3
	Female	43	2	0	2
		44	0	0	0
		45	0	0	0
		46	0	0	0
		47	0	0	0
		48	0	0	0

/ expressed as number of observations/4 weeks

Slight = Unsteady gait
Moderate = Incoordinated gait
Severe = Straddled gait/recumbency

There was no incidence of ataxia in control animals

* Killed in week 46

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