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

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JUL 14 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: PP#IF03923: Petition to increase tolerances for residues of Cyfluthrin in the meat, fat and meat by-products of cattle.

Tox.Chem No.:	266E
MRID No.:	N/A
HED Project No.:	1-0267A
Submission No.:	S387270
PC No.:	128831
DP Barcode:	D159231

From: John C. Redden, Toxicologist 7/10/92
Section 3
Toxicology Branch 1
Health Effects Division (H7509C) WBG 7/10/92

To: John Hebert, PMT 15
Insecticide-Rodenticide Branch
Registration Division (H7505C)

Thru: Karen Hamernik, Ph.D. Marion Copley for KH. 7/10/92
Acting, Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

CONCLUSION:

Toxicology Branch 1 has no objection to the proposed increase in tolerances for Cyfluthrin in the milk, meat, fat and meat by-products of cattle provided the increase in the percent of the RfD utilized is small.

ACTION:

Review an IR-4 petition to increase the tolerance for cyfluthrin in the milk, meat, fat and meat by-products of cattle.

Bayocide Pour-On Insecticide is used for the control of horn flies, face flies, biting lice, and sucking lice on beef and dairy cattle (including lactating). It is ready to use and is applied, in measured amounts, directly along the top of the back of the head of the animal. Treatment for flies should be repeated no more than

once every three weeks, and for best lice control a second treatment should follow 3 weeks after the first treatment.

The proposed tolerance residues in are outlined in Table 1.

Table 1: Tolerance Proposal for residues of the insecticide cyfluthrin.

Commodity	Preslaughter Interval (Days)	Proposed Tolerance (ppm)
Milk	0	0.08
Meat, fat & meat by-products of cattle	0	0.40

I. Requirements (CFR §158.35):

Technical: Registration No. 3125-356 (96.3% a.i.)

	Required	Satisfied	
81-1	Y	Y	Acute Oral Toxicity
81-2	Y	Y	Acute Dermal Toxicity
81-3	Y	Y	Acute Inhalation Toxicity
81-4	Y	Y	Primary Eye Irritation
81-5	Y	Y	Primary Dermal Irritation
81-6	Y	Y	Dermal sensitization
81-7	N	-	Acute Delayed Neurotoxicity (hen)
82-1	Y	Y	Subchronic Oral (rodent)
82-1	Y	Y	Subchronic Oral (nonrodent)
82-2	Y	Y	21-Day Dermal
82-3	N	-	90-Day Dermal
82-4	Y	Y	21-Day Inhalation (tobacco use)
82-4	Y	Y	90-Day Inhalation
82-5	N	-	90-Day Neurotoxicity (hen)
82-5	N	-	90-Day Neurotoxicity (mammal)
83-1	Y	Y	Chronic Toxicity (rodent)
83-1	Y	Y	Chronic Toxicity (nonrodent)
83-2	Y	Y	Oncogenicity (two species)
83-3	Y	Y	Developmental Toxicity (rat)
83-3	Y	N	Developmental Toxicity (second species)
83-4	Y	Y	Reproduction
83-5	-	-	Chronic/Oncogenicity (see 83-1 & 83-2)
84-2	Y	Y	Mutagenicity - Gene Mutation
84-2	Y	Y	Mutagenicity - Structural Chrom. Aberr.
84-2	Y	Y	Mutagenicity - Other Genotoxic Effects
85-1	Y	Y	General Metabolism
85-2	N	-	Dermal Penetration
86-1	Y	Y	Domestic Animal Safety[1]

1 - A study was provided for Bayocide Pour-On Insecticide (1.1% a.i., EPA ID No. 11556-RNT).

Formulation: Bayocide Pour-On Insecticide (1.1% a.i.) EPA ID No. 11556-RNT

	Required	Satisfied	
81-1	Y	N	Acute Oral Toxicity
81-2	Y	N	Acute Dermal Toxicity
81-3	Y	N	Acute Inhalation Toxicity
81-4	Y	N	Primary Eye Irritation
81-5	Y	N	Primary Dermal Irritation
81-6	Y	N	Dermal Sensitization
81-7	N	-	Acute Delayed Neurotoxicity (hen)
86-1	Y	Y	Domestic Animal Safety

Y - Yes N - No

II. Toxicology Profile:

Technical: Registration No. 3125-356 (96.3% a.i.)

	STUDY	RESULTS
81-1	Acute Oral, Rat Minimum / I-III Document No. 4285 MRID Nos. 00131499 and 00131518	LD_{50}: 16.2 (13-19.5) mg/kg (♂ only) in cremophor/distilled water by gavage. 254 (220-294) mg/kg (♂ only) in acetone by gavage. 396 (317-494) mg/kg (♂ only) in DMSO by gavage. 500-1000 mg/kg in (♂ only) in N-methyl pyrollidon by gavage. 590 (509-695) mg/kg (♂), 1189 (1002-1443 mg/kg (♀) in PEG 400 by gavage. 869 (685-1051) mg/kg (♂), 1271 (1102-1456 mg/kg (♀) in PEG 400 by gavage.
81-2	Acute Dermal, Rat Minimum / III Document No. 4285 MRID No. 00131499 and 00131518	LD_{50} >5000 mg/kg (♂ & ♀) undiluted, and in cremophor/distilled water, PEG 400, and 0.9% NaCl.

81-3	Acute Inhalation, Rat Minimum / II Document No. 4285 MRID No. 00131509	4-Hour LC_{50}: >0.735 mg/l (♂), 468 mg/l (♀) in aqueous cremophor. 0.575 (0.458-0.722) mg/l (♂), 0.490 (0.412-0.582) mg/l (♀) in DMSO/PEG.
81-4	Primary Eye Irritation, Rabbit Minimum / III Document No. 4285 MRID No. 00131499	Transient irritation
81-5	Primary Dermal Irritation, Rabbit Minimum / IV Document No. 4285 MRID No. 00131499	No irritation
81-6	Dermal Sensitization, Guinea Pig Guideline Document No. 4285 MRID No. 00131513	Not a sensitizer by the Maximization Test and Draize Test
82-2	21-Day Dermal, Rabbit Minimum Document No. 4285 MRID No. 00131527	NOEL >250 mg/kg/day (HDT)
82-4	21-Day Inhalation, Rat Minimum Document No. 4285 MRID No. 00131528	NOEL = 0.0014 mg/l LEL = 0.0023 mg/l (decreased body weight gain)
82-4	90-Day Inhalation, Rat Minimum Document No. 6426 MRID Nos. 00157793 and 00157882	NOEL = 0.00009 mg/l/day LEL = 0.00071 mg/l/day (unthriftiness, unkempt fur, lethargy, and increased urinary protein)
83-1	Chronic Feeding, Dog Minimum Document No. 4285 MRID No. 00151358	NOEL = 4 mg/kg/day LEL = 16 mg/kg/day (slight ataxia, increased vomiting, diarrhea, and decreased male body weights)
83-3	Developmental Toxicity, Rat Guideline Document No. 5362 MRID No. 00157794	Maternal NOEL >10 mg/kg/day (HDT) Developmental NOEL >10 mg/kg/day (HDT)

83-3	Developmental Toxicity (Inhalation), Rat Minimum Document No. 7628 MRID Nos. 40780401 and 40968501	Maternal NOEL = 0.0011 mg/l Maternal LEL = 0.0047 mg/l (reduced mobility, dyspnea, piloerection, ungroomed coats, eye irritation). Developmental NOEL = 0.00059 mg/l Developmental LEL = 0.0011 mg/l (unspecified sternal anomalies, increased runt incidence) **NOTE: This study was lacking specifics on the skeletal and visceral anomalies found, so it was not possible to fully assess the teratogenic effect.**
83-3	Developmental Toxicity, Rabbit Supplementary Document No. 008301 Acc. No. 072009	Maternal NOEL = 15 mg/kg/day Maternal LEL = 45 mg/kg/day (abortion & resorption) Develpmental NOEL 〉 45 mg/kg/day (HDT)
83-4	3-Generation Reproduction, Rat Minimum Document No. 4285 MRID No. 00131532	Systemic NOEL = 2.5 mg/kg/day Systemic LEL = 7.5 mg/kg/day (decreased pup body weights) Reproductive NOEL = 2.5 mg/kg/day Reproductive LEL = 7.5 mg/kg/day (decreased viability)
83-5	Carcinogenicity, Mouse Supplementary for chronic feeding Minimum for Carcinogenicity Document No. 4285 MRID No. 00137304	Systemic NOEL <7.5 mg/kg/day (LDT, increased alkaline phosphatase activity in males) No evidence of carcinogenicity
83-5	Chronic Feeding/Carcinogenicity, Rat Minimum Document No. 4285 MRID No. 00137303	No evidence of carcinogenicity Systemic NOEL = 2.5 mg/kg/day Systemic LEL = 7.5 mg/kg/day (decreased body weights in males, inflammatory foci in kidneys of females)
84-2	Gene Mutation: CHO/HGPRT Mutation Acceptable Document No. 5362 MRID Nos. 00157796 and 00157885	Negative

84-2	Structural Chromosome Aberration: Sister Chromatic Exchange Acceptable Document No. 5362 MRID Nos. 00157795 and 00157884	Negative
84-4	Other Genotoxic Effects: Unscheduled DNA Synthesis Acceptable Document No. 5362 MRID No. 00157798 and 00157886	Negative
85-1	Metabolism Minimum Document No. 4285 MRID No. 00131517	Blood levels of cyfluthrin isomers are higher and peak more quickly when cyfluthrin is administered in cremophor/distilled water than when administered in polyethylene glycol

Formulation: Bayocide® Pour-On Insecticide (1.1% a.i.)
Registration No. 11556-RNT

STUDY

86-1	Domestic Animal Safety	No signs of significant toxicity were observed at 1 and 3 times the use rate (16 and 48 ml/animal, respectively, administered twice, 14 days apart). At 5 times the use rate (80 ml/animal), there was a failure to gain weight, and the cattle appeared nervous.

(Note: Toxicology Branch 1 has not evaluated the 6 basic acute studies on the formulation and they are therefore considered to be data gaps. The studies may have been evaluated in the Registration Division (RD). If so RD should forward their evaluation of the six studies to Toxicology Branch 1.)

III. Data Gaps:

Technical

83-3 Developmental Toxicity (second species)

Formulation (Bayocide Pour-On Insecticide

81-1 Acute Oral Toxicity
81-2 Acute Dermal Toxicity

81-3	Acute Inhalation Toxicity
81-4	Primary Eye Irritation
81-5	Primary Dermal Irritation
81-6	Dermal Sensitization

IV. Action Taken to Obtain Additional Information or Clarification:

RD has been notified of the need for 1.) a new Oral Developmental Toxicology Study in Rabbits, and 2.) additional data to address the study deficiencies in the Inhalation Developmental Toxicology Study in Rats, and, herein, 3.) the need for the 6 basic acute toxicity studies on the formulation

V. Reference Dose (RfD):

The RfD was defined as 0.025 mg/kg/day. This value was calculated by using the 2-Year Rat Chronic Feeding/Oncogenicity study NOEL of 2.5 mg/kg/day (50 ppm) and a safety factor of 100. The RfD was verified by HED on March 14, 1986, and by EPA on April 8, 1986.

VI. Pending Regulatory Actions:

There are at this writing no pending regulatory actions against the Registration of this pesticide.

VII. Toxicologic Issues Pertinent to Granting this Request:

A. Currently, tolerances for residues of cyfluthrin exist on milk, meat, fat, and meat-byproducts of cattle under 40 CFR 180.436. This petition addresses proposed increases in the established tolerances. The toxicological data base for cyfluthrin is incomplete. However, the data base on cyfluthrin is substantial and only lacks one developmental toxicology study. Toxicology Branch 1 has no objection to the proposed increase in tolerances in the milk, meat, fat and meat by-products of cattle provided the increase in the percent of the RfD utilized is small.

B. The dietary impact of this new use with requested tolerances will be addressed by the Dietary Exposure Branch (DEB).

C. Cyfluthrin was recommended as a possible Special Review candidate because of positive findings in an Inhalation Developmental Toxicology Study in Rats. HED recommended against special review because the quality of the developmental toxicity data was too poor to allow meaningful dialogue (John E. Whalan memorandum, June 8, 1990).

D. Applicator exposure assessment should be addressed by the Occupational and Residential Exposure Branch (OREB).

E. The acute toxicity studies on Bayocide Pour-On Insecticide have not been

submitted to Toxicology Branch 1 and are therefore considered to be data gaps. Toxicology Branch 1 defers to RD with respect to whether the toxicology data requirements for this formulation have been satisfied.

VIII. Other:

A. 83-3 Developmental Toxicity (second species) Technical: An Oral Developmental Toxicology Study in Rabbits that had been used in regulatory decisions in the past was found to be inadequate, and was downgraded from Minimum to Supplementary. The Registrant has been asked to submit a new study (John Whalan memorandum; June 8, 1990).

B. An Inhalation Developmental Toxicology Study in Rats was found to be positive. The study report did not adequately describe the nature and extent of developmental effects. (John Whalan memorandum; June 8, 1990).

This memorandum should be forwarded to the sponsor in its entirety.