8-9-91

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

AUG 9 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Registration of Bayocide™ Pour-On Insecticide, and Review of a Domestic Animal Safety Study in Cattle.

EPA ID# 11556-RNT
Record No. 266749

Project No. 0-1677
Tox. Chem. No. 266E

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section 1, Toxicology Branch I
Health Effects Division (H7509C)

John E Whalan
7-31-91

TO: George LaRocca (PM Team # 15)
Registration Division (H7505C)

THRU: Roger L. Gardner, Section Head
Section 1, Toxicology Branch I
Health Effects Division (H7509C)

Roger L. Gardner
8-2-91

I. Background:

Mobay Corporation has requested registration of a new pesticide named Bayocide™ Pour-On Insecticide which contains Baythroid (cyfluthrin; cyano (4-fluoro-3-phenoxyphenyl) methyl 3-(2,2-dichloroetheny)-2,2-dimethylcyclopropanecarboxylate) to control horn flies, face flies, biting lice, and sucking lice on beef and dairy cattle (including lactating cattle). The formulation for this new product is as follows:

Baythroid	1.1%
[redacted]	

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Bayocide Pour-On Insecticide is a ready-to-use solution which is applied directly with a syringe or other calibrated device along the top of the back and top of the head of the animal. Cattle can be repeatedly treated for flies once every 3 weeks. Optimal treatment for lice calls for two applications, 3 weeks apart. Bayocide does not control cattle grubs. The label signal word is **WARNING**.

The Registrant submitted a Domestic Animal Safety Study in Cattle in support of this registration (attached). The test article was defined as "Cyfluthrin 1% Pour-On" which, according to Bill Wagner of Mobay, is identical to Bayocide Pour-On Insecticide. Male and

female cattle were dermally dosed with 1, 3, and 5 times the use rate. They were dosed twice, 2 weeks apart, rather than every three weeks as described on the product label. Scruffiness (slight epidermal loss) was seen at all three doses. At the highest dose, the cattle failed to gain weight. These findings are not clinically significant. There were no clinical pathology anomalies.

No other studies were submitted to support this end-use product. Dermal studies of technical cyfluthrin report an LD_{50} >5000 mg/kg (♂ & ♀) in rats, and a 21-Day NOEL >250 mg/kg/day (HDT) in rabbits. In animal studies, cyfluthrin caused transient irritation to the eye and no irritation to the skin. As a class, pyrethroids are irritants and have been reported by humans to cause a characteristic burning sensation on skin contact. This may explain Group IV's nervousness and failure to gain weight.

II. Conclusions:

Although no acute toxicity data were submitted to support this registration, the data base for technical cyfluthrin suggests that dermal absorption and systemic toxicity should not be a problem. Dermal irritation, typical of pyrethroids, should be expected from purposeful animal exposure and accidental human exposure. TB-I defers to DEB to assess the impact of residues on meat and milk.

The inert ingredient is not found in any other cyfluthrin-based product. TB-I thus defers to RD to determine whether this inert has been cleared for use.

III. 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 (first species)
83-3	Y	N	Developmental Toxicity (second species)
83-4	Y	Y	Reproduction
83-5	**	Y	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	N	-	Domestic Animal Safety

Formulation: Bayocide™ Pour-On Insecticide (1.1% a.i.)
Registration 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)

Y - Yes
N - No
W - Waived
P - Partially

* The requirement is satisfied if an acceptable chronic study is available.
** Not required if acceptable chronic and oncogenicity studies are available.

IV. 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 001-31518	LD_{50} >5000 mg/kg (♂ & ♀) undiluted, and in cremophor/distilled water, PEG 400, and 0.9% NaCl.

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81-3	Acute Inhalation, Rat Minimum / II Document No. 4285 MRID No. 00131509	4-Hour LC_{50}: >0.735 mg/l (♂), 0.200-0.735 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
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)
83-2	Oncogenicity, Mouse Supplementary for chronic feeding Minimum for oncogenicity Document No. 4285 MRID No. 00137304	Systemic NOEL <7.5 mg/kg/day (LDT, increased alkaline phosphatase activity in males) Oncogenic NOEL >120 mg/kg/day (HDT)

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 motility, 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 terato-genic effect.**
83-3	Developmental Toxicity, Rabbit	**DATA GAP. See Sections V, VI, and IX.**
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	Chronic Feeding/Oncogenicity, Rat Minimum Document No. 4285 MRID No. 00137303	Oncogenic NOEL >22.5 mg/kg/day (HDT) 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 001-57886	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 cremo-phor/-distilled water than when administered in polyethylene glycol.
	Neurotoxicity, Hen Minimum Document No. 5649 MRID No. 00163040	1. <u>Delayed Neurotoxicity Study</u> - Cyfluthrin was mildly neurotoxic at 4300 mg/kg/day X2, but did not cause the classic delayed neurotoxic signs seen in hens dosed with TOCP. Clinical signs - aggression, anorexia, somnolence, and cyanosis of the crest. There were no gross or microscopic lesions. 2. <u>Neurotoxic Esterase Activity</u> - NTE activity in hens dosed with 4300 mg/kg-/day X1 of cyfluthrin resembled that of the vehicle controls.
	Neurotoxicity, Rat Guideline Document Nos. 4461 and 5128 MRID No. 00157801	Wistar Bor:WISW rats given 14 oral doses of 50 or 60 mg/kg/day had non-specific disturbed behavior, rolling, tremors, stretched gait, uncoordinated gait, salivation, phonation, weight loss (♂), and death. Histopathologic lesions included slight brain hemorrhages and necrosis of the skeletal muscle fibers.
	Neurotoxicity, Rat Guideline Document Nos. 4461 and 5128 MRID No. 00157887	Male SD rats given oral doses of 80 mg/kg/day for 5 days, then 40 mg/kg/day for 9 days had straddled gait, slow leg movement, titubation, salivation, red tears, and reduced weight gain. Histopathologic lesions included axonal degeneration of the sciatic nerve (light microscopy); and microtubular dilatations with proliferation of neurofilaments and mitochondria degeneration in the sciatic and femoral nerves (electron microscopy).

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	STUDY	RESULTS
81-1	Acute Oral	**DATA GAP**
81-2	Acute Dermal	**DATA GAP**
81-3	Acute Inhalation	**DATA GAP**
81-4	Primary Eye Irritation	**DATA GAP**
81-5	Primary Dermal Irritation	**DATA GAP**
81-6	Dermal Sensitization	**DATA GAP**
81-7	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.

V. Data Gaps:

A. An Oral Developmental Toxicology Study in Rabbits that had been used in regulatory decisions in the past was found to be inadequate. 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).

VI. 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.

VII. 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.

VIII. Pending Regulatory Actions:

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

IX. Toxicologic Issues Pertinent to Granting this Request:

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

B. 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 develop mental toxicity data was too poor to allow meaningful dialogue (John E. Whalan memorandum, June 8, 1990).

Compiled by John E. Whalan
Revised on July 30, 1991

Reviewed by: John E. Whalan 7-31-91 **GUIDELINE:** 86.1
Section I, Tox. Branch I (IRS) (H7509C)
Secondary reviewer: Roger L. Gardner 4-2-91
Section I, Tox. Branch I (IRS) (H7509C)

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DATA EVALUATION REPORT

STUDY TYPE: Domestic Animal Safety in Cattle - Dermal Exposure

MRID NO: 415557-04

TOX. CHEM. NO.: 266E

TEST MATERIAL: Cyfluthrin 1% Pour-On
Batch R86-303-136 (1.16% a.i.; vehicle not specified)

SYNONYMS: Bayocide™ Pour-On Insecticide

STUDY NUMBER(S): 74013

SUBMITTED BY: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Animal Health Division

TITLE OF REPORT: Domestic Animal Safety Cattle (Target Animal)

AUTHOR(S): M.L. Kohlenberg and J.A. Shmidl

REPORT ISSUED: February 15, 1990

CONCLUSIONS: 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 administered twice, 14 days apart), there was a failure to gain weight, and the animals were nervous. This may have been due to the burning sensation characteristic of all pyrethroids.

STUDY CLASSIFICATION: Core Guideline. This study received Quality Assurance review.

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PROTOCOL: This study was performed to assess the safety margin for dermally applied Cyfluthrin 1% Pour-On in cattle. Eight male (steers) and 8 female beef breeding cattle (a mix of Charolais, Angus X Hereford, Hereford, Hereford X, and Simmental) were placed on study after being examined for dermal irritation and general health, and evaluated for the following clinical pathology parameters:

Hematology:

Erythrocyte count	Erythrocyte morphology
Hemoglobin	Leukocyte count
Hematocrit	Differential count
MCV, MCH, MCHC	Platelet count

Clinical Chemistry:

Carbon dioxide	ALT (SGPT)
Glucose	AST (SGOT)
Blood urea nitrogen	Total protein
Uric acid	Albumin
Creatinine	Cholesterol
BUN/Creatinine ratio	Sodium
Total bilirubin	Potassium
Direct bilirubin	Chloride
Indirect bilirubin	Calcium
Alkaline phosphatase	Phosphorus
Lactate dehydrogenase	Ca/PO_4 ratio
γ-glutamyl transpeptidase	Na/K ratio

With the cattle held in chutes, the test article was dispensed with a syringe onto the dorsal midline from just posterior to the shoulders to the hips. Group I was a non-treated control; groups II, III, and IV were dosed twice, 14 days apart, according to the following regimen:

Group	Number of Cattle	Dose (ml/animal)	Use Rate
I	2♂, 2♀	0	--
II	2♂, 2♀	16	X1
III	2♂, 2♀	48	X3
IV	2♂, 2♀	80	X5

The cattle were observed daily for clinical signs. The dosing sites were examined closely on days 7 and 14 after each dosing for dermal irritation. Body weights were recorded prior to the first treatment, on the day of the second treatment, and then again 14 days later (i.e. every two weeks). The clinical pathology panel was repeated 14 days after the second dosing. The cattle were fed a 60/40 beef ration with grass hay and water ad libitum. The untreated cattle were separated from the treated cattle by an empty stall.

RESULTS: No clinical signs were observed in any group. One male and two female cattle in Group IV failed to gain weight. This was attributed to this being, "...a group of rather nervous animals." No dermal lesions were found in any of the Group I cattle. Fourteen days after the first treatment, slight epidermal loss along the dorsal midline was observed in one female in Group III. Fourteen days after the second treatment, the same lesion was observed in 1 female in Group II, 1 male and 2 females in Group

III; and in one male in Group IV. Although compound-related irritation was seen, it was not dose-related; the greatest response was, in fact, seen in Group III. There were no clinical pathology anomalies in any group.

DISCUSSION: In this study, the animals were dermally treated twice, 14 days apart. This differs from the product label instructions which call for doses to be applied 3 weeks apart. These data suggest that at the recommended dose, which corresponds to Group II, there may be slight dermal irritation. At three times the recommended dose, which corresponds to Group III, the incidence of this lesion was increased. The report described the slight epidermal loss as "scruffiness" which was not clinically significant. Thus, no signs of significant toxicity were observed at 1 and 3 times the use rate. At 5 times the use rate, there was a failure to gain weight, and the cattle were described as being nervous. This may be attributed to the characteristic burning sensation caused by all pyrethroids.

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Page_____ is not included in this copy.

Pages 13 through 16 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of 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.