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

004285

FEB 15 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR. Cyfluthrin (Baythroid). Request for Tolerances for Residues of Cyfluthrin in/on Cottonseed, Cottonseed Oil, Cottonseed Hulls, Meat and Milk. Request for Registration of Baythroid 2 Formulated Product.

Tox Chem No. 266E

TO: Timothy A. Gardner, Product Manager #17
Registration Division (TS-767)

FROM: J. D. Doherty, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

and

Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 2/14/85

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber 2/14/85

Requested Action:

The Mobay Chemical Corporation (Kansas City, MO) requests registration of the formulated product Baythroid 2 (EPA #3125-GLR) for use on cotton together with the following tolerances (revised May 9, 1984).

Crop	Proposed Tolerances (ppm)
Cottonseed	1.0
Meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep	0.05
Milk	0.01
Cottonseed, refined, deodorized oil	2.00
Cottonseed, hulls	2.50

Cyfluthrin is a new synthetic pyrethroid insecticide. This is the first request for permanent tolerances for this chemical.

Conclusions:

1. All toxicology studies required to support the proposed registration of Baythroid 2 for use on cotton (only) and the requested tolerances have been submitted to and have been reviewed by Toxicology Branch.

   NOTE: Toxicology Branch was informed by Chris Dively (PM Team #17) on 1/31/85 that she had spoken with G.E. Brussell (Mobay Chemical Corporation) on 1/31/85 and that he had assured her that the formulated product described in this review as Baythroid 240 EC and the formulated product for which registration is proposed for use on cotton (i.e. Baythroid 2, EPA #3125-GLR) are identical and that only the "name" had been changed. Toxicology Branch requests that Mobay be asked by Registration Division to verify this statement in writing prior to registration of Baythroid 2 for use on cotton.

2. Toxicology Branch has no objection to the proposed registration and tolerances provided that the following requirements are adequately addressed and responses submitted to Toxicology Branch within a reasonable period ot time. It is not necessary that this be done prior to registration of Baythroid 2 for use on cotton or prior to establishment of the tolerances. In other words, the following are "conditional requirements."

   a. Many of the toxicology studies were not signed by the persons responsible for the work. Signed reports of these studies must be submitted to EPA. Failure to submit the signed reports will result in reclassification of the studies to INVALID status.

   b. Neurotoxicity studies in chickens. Cyfluthrin was tested in several studies for possible delayed type neurotoxicity. Evidence of nerve fiber degeneration was noted in some of these studies. The data generated thus far are not conclusive with respect to determining the potential for cyfluthrin to produce delayed type neurotoxicity in chickens.

The registrant is requested to conduct an additional study to assist in determining the potential of cyfluthrin to affect the nervous system. This study should be a "hen brain neurotoxic esterase" study. It is strongly suggested that the registrant, prior to performing this study, submit the proposed protocol to Toxicology Branch for comment.

Note - Toxicology Branch does not consider the inconclusive results of the acute delayed neurotoxicity tests in chickens to be of sufficient concern at this time to warrant delaying the registration of this product and the associated tolerances. Considerable toxicology data in mammalian species is presently available which does not suggest an unreasonable potential hazard to the nervous system of humans under conditions of use. Toxicology Branch considers the latter evidence to be more relevant to its determination of potential hazards to humans. Nevertheless, in order to assist in the resolution of this outstanding issue, the "hen brain neurotoxic esterase study" is required to be performed and submitted.

It is suggested that the registrant consider information presented in the following reference when designing the "hen brain neurotoxic esterase study."

Johnson, M. K., Structure-activity relationships for substrates and inhibitors of hen brain neurotoxic esterase, Biochem. Pharmacol., 24: 797-805, 1975.

This study should include a negative control group and a positive control group of hens. Toxicology Branch is aware that relatively few toxicology laboratories are prepared to perform this type of study. Nevertheless, a few do. If requested by the registrant, Toxicology Branch will supply the names of some laboratories that have the capability of performing this study. Toxicology Branch is also willing to discuss with the registrant, if requested, problems that may arise during the design and/or performance of this study.

The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:

- Possible differences in the test material

  ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

  ° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

  ° Including a consideration of strain, source, etc.

  ° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed.

- Other

c. Mutagenicity Studies:

The following additional mutagenicity studies are required:

- gene mutation in mammalian cells in culture
- cytogenetics assay in mammalian cells in culture
- DNA repair assay in mammalian cells in culture.

3. The inerts in the formulated product BAYTHROID 2 are cleared for the proposed use.

4. The following changes in the precautionary statements are recommended.

Add "May be fatal if inhaled." [Note: the product is Tox. Cat. II by inhalation exposure.]

Delete "No specific symptoms. Acute poisoning accompanied by general depression and illness."

NO CFR Number Baythroid 1/28/85

Unverified Printout

DRAFT

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NOEL change not rec sa

ACCEPTABLE DAILY INTAKE DATA

FAT,Cleer NOEL mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
2.500	50.00	100	0.0250	1.5000

Current Action 4F3046/4H5427

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cottonseed (oil)(41)	2.000	0.15	0.00450
Meat, red(90)	0.050	10.81	0.00811
Milk&Dairy Products(93)	0.010	28.62	0.00429

MPI	TMRC	% ADI
1.5000 mg/day(60kg)	0.0169 mg/day(1.5kg)	1.13

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8-Point Review

1. Toxicity data with technical grade cyfluthrin considered in support of this tolerance (selected studies).

Acute Oral LD50, rats	LD50 = 590 mg/kg, males LD50 = 1,189 mg/kg, females
Acute Oral LD50, mice	LD50 = 291 mg/kg, males LD50 = 609 mg/kg, females
Acute Dermal LD50, rats	LD50 > 5,000 mg/kg, males and females
Acute Inhalation LC50, rats	LC50 > 1.089 mg/L, males and females
Dermal Sensitization, guinea pigs	Not a sensitizer
90-Day Feeding, rats	NOEL = 300 ppm (HDT)
6-Month Feeding, dogs	NOEL = 200 ppm LOEL = 600 ppm
12-Month Feeding, dogs	NOEL = 160 ppm LOEL = 640 ppm
2-Year Feeding/Oncogenicity, rats	Not oncogenic at dosage levels up to and including 450 ppm (HDT) NOEL = 50 ppm (or 2.5 mg/kg/day) LOEL = 150 ppm
23-Month Oncogenicity, mice	Not oncogenic at dosage levels up to and including 800 ppm (HDT)
3-Generation Reproduction, rats	NOEL = 50 ppm LOEL = 150 ppm
Teratology, rats	Not teratogenic at dosage levels up to and including 30 mg/kg/day (HDT)
Teratology, rabbits	Not teratogenic at dosage levels up to and including 45 mg/kg/day (HDT)
Delayed Neurotoxicity, hens (oral administration)	Inconclusive results.
Delayed Neurotoxicity, hens (dermal administration)	Negative for delayed effects on the nervous system

8-Point Review (contd.)

21-Day Inhalation, hens	Negative for delayed effects on the nervous system
5-Month Neurotoxicity, rats	Negative for delayed effects on the nervous system

Mutagenicity Studies:

Reverse Mutation Assays (with and without metabolic activation).

S. typhimurium	Negative
E. coli	Negative
S. cerevisiae	Negative

Recombination Assays

B. subtilis	Negative
S. cerevisiae	Negative

2. Additional toxicity data considered desirable ("conditional requirements" - see "Conclusions", above)

   a. "Hen brain neurotoxic esterase" study (see "Conclusions")
   b. Gene mutation in mammalian cells in culture
   c. Cytogenetic assay in mammalian cells in culture
   d. DNA repair assay in mammalian cells in culture

3. The above additional toxicity studies are requested in this review.

4. This is the first F petition for cyfluthrin.

5. Establishing these tolerances will result in 1.13% of the MPI being used up. (See computer printout, attached.)

6. The 2-year chronic feeding/oncogenicity study in rats with a NOEL of 50 ppm (equal to 2.5 mg/kg/day) and a safety factor of 100 were used to calculate the ADI (0.025 mg/kg/day). The MPI is 1.50 mg/day (60 kg).

7. There are no pending regulatory actions against the registration of cyfluthrin.

8. None.

Studies Reviewed

STUDIES WITH BAYTHROID TECHNICAL

Study	Results	Core Classification
Acute Toxicity		
Acute Oral LD_{50} - rats (fasted)	Males: 590 (509-695) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 1189 (1002-1443) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - rats (unfasted)	Males: 869 (685-1051) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 1271 (1102-1456) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - rats	16.2 (13.5-19.5) mg/kg males (in Cremophor EL/dist. H_2O)	Minimum
Acute Oral LD_{50} - rats	254 (220-294) mg/kg males (in acetone)	Minimum
Acute Oral LD_{50} - rats	396 (317-494) mg/kg males (in DMSO)	Minimum
Acute Oral LD_{50} - rats	500-1000 mg/kg males (in n-methyl-pyrollidon)	Minimum
Acute Oral LD_{50} - mice	Males: 291 (202-413) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 609 (432-827) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - mice	<100 mg/kg - females (in Cremophor EL/dist. H_2O)	Minimum
Acute Oral LD_{50} - rabbits	>1000 mg/kg - (males only) No rabbits died	Minimum
Acute Oral LD_{50} - dogs	>100 mg/kg (?) - (males only) No dogs died, but both dogs vomited at this level	Minimum
Acute Oral LD_{50} - dogs	Salivation and vomiting at 20 and 100 mg/kg. No deaths	Supplementary
Acute Oral LD_{50} - sheep	LD_{50} = 1000 mg/kg	Minimum

Studies Reviewed (contd.)

Study	Results	Core Classification
Acute Intraperitoneal (IP) LD_{50} - rats	Males: 66 (53-84) mg/kg Females: 104 (76-135) mg/kg	Acceptable
Acute IP - rats	20 (17-22) - males 24 (21-28) - females (in Cremophor EL/dist H_2O)	Acceptable
Acute IP - rats	34 (30-37) - males 96 (68-131) - females (in polyethylene glycol)	Acceptable
Acute Subcutaneous LD_{50} - mice	>2,500 mg/kg for both sexes (no deaths)	Acceptable
Acute Dermal LD_{50} - rats	>5,000 mg/kg for both sexes	Minimum
Acute Dermal LD_{50} - rats	>5,000 mg/kg in either Cremophor EL/dist. H_2O, 0.9% NaCl, or undiluted	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/lutrol) one hour exposure	LC_{50} >1,089 mg/m^3 (1.089 mg/L) (no deaths)	Minimum
Acute Inhalation LC_{50} - rats (in aqueous Cremophor) 4 hour exposure	LC_{50} Males - >735 mg/m^3 Females - 200-735 mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (DMSO/Lutrol) 4 hour exposure	LC_{50} Males - 575 (458-722) mg/m^3 Females - 490 (412-582) mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/ Lutrol) 4 hour exposure	LC_{50} = 469-592 mg/m^3	Minimum
Acute Inhalation LC_{50} - chickens (in ethanol/ Lutrol) 4 hour exposure	LC_{50} >596 mg/m^3 No hens died	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/ Lutrol) 4 hour exposure	LC_{50} < 596 mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/Lutrol) 5 six hour exposures	LC_{50} = 47-196 mg/m^3	Minimum

Studies Reviewed (contd.)

Study	Results	Core Classification
Dermal irritation - rabbits	PIS = 0	Minimum
Dermal irritation - rabbits	PIS = 0.25	Invalid
Eye irritation - rabbits	Transient irritation only	Minimum
Eye irritation - rabbits	Mildly irritating No corneal opacity	Invalid
Dermal sensitization - guinea pigs - (Draize type)	Not a sensitizer	Minimum
Dermal sensitization - guinea pigs - (Maximization Test)	Not a sensitizer	Guidelines
Dermal sensitization - guinea pigs -	Not a sensitizer	Invalid
Antidote study - rats	Musaril (a.i. tetrazepam, a benzodiazapine) was effective in changing the LD_{50} observed.	Minimum
Thiocyanate excretion - rats	Thiocyanate in urine could not be correlated with toxicity of cyfluthrin or deltamethrin.	Minimum
Absorption study - rats	Cyfluthrin is absorbed from the GI tract more rapidly when administered in Cremophor than when in polyethylene glycol - 400	Minimum
Short-Term Studies		
28-day subacute oral toxicity - rats (gavage) (with recovery phase)	NOEL = 20 mg/kg/day LEL = 40 mg/kg/day (Nerve stimulation, body weight loss, liver and adrenal weight changes)	Minimum
90-day feeding - rats	NOEL = 300 ppm (HDT). No definite test chemical effects noted	Minimum
28-day feeding - rats (with recovery phase)	NOEL = 100 ppm LEL = 300 ppm (minimal decrease in blood glucose)	Supplementary

Studies Reviewed (contd.)

Study	Results	Core Classification
	AT 1000 ppm (HDT) behavioral changes, body weight loss, urobilinogen and ketone bodies in urine, decreased RBC, hematocrit and hemoglobin counts, increased weights of submaxillary glands (also had cytoplasmic swelling) liver weight change. Some evidence of single nerve fiber degeneration in the sciatic nerve which was not evident in the recovered rats.	
28-day feeding - mice (with recovery phase)	NOEL = 300 ppm LEL = 1000 ppm (behavioral changes, decreased body weight gain, increased liver weight, cytoplasmic swelling of the submaxillary glands). At 3000 ppm (HDT) - in addition to above, possible decrease in WBC, increase in "AIP" and BUN, increased weight of submaxillary glands, decreased spleen, adrenal and ovary weights.	Supplementary
21-day subacute dermal - rabbits	NOEL = 250 mg/kg/day (HDT)	Minimum
21 day subacute - inhalation - rats	NOEL = 1.4 mg/m^3 LEL = 2.3 mg/m^3 (decreased body weight gain). At $\geq$ 10.5 mg/m^3, there were behavioral changes, body weight changes and organ weight changes in liver, spleen, and possibly other organs.	Minimum
21-day subacute inhalation - chickens	1 death at 614 mg/m^3 Nonspecific symptomology at this level.	Minimum
Long-Term Studies		
6-month feeding - dogs	NOEL = 200 ppm LEL = 600 ppm (stiff gait, uncoordination, arched backs late in study, vomiting, diarrhea, possibly decreased thymus weights)	Minimum

Studies Reviewed (contd.)

Study	Results	Core Classification
12-month feeding - dogs	NOEL = 160 ppm LEL = 640 ppm (slight ataxia in 2 animals on 1 occasion each, increased vomiting and diarrhea, decreased body weights in males)	Minimum
3-generation reproduction - rats	NOEL = 50 ppm for reproductive effects LEL = 150 ppm (decreased viability index, some pup deaths) NOEL = 50 ppm for systemic effects in pups LEL = 150 ppm (body weight decrease in pups)	Minimum
5-month neurotoxicity - rats	Not neurotoxic (axonal degeneration or myelin effects) at 60/80 mg/kg/day orally by gavage for 5 months	Minimum
Teratology - rats	No teratogenic effects noted up to and including 30 mg/kg/day (HDT).	Minimum
Teratology - rabbits	No teratogenic effects noted up to and including 45 mg/kg/day (HDT)	Minimum
2-year chronic feeding/oncogenicity - rats	Not oncogenic at doses up to and including 450 ppm (HDT). NOEL = 50 ppm. LOEL = 150 ppm (decreased body weights in males, inflammatory foci in kidneys of females)	Minimum for chronic toxicity Minimum for oncogenicity
23-month chronic feeding/oncogenicity - mice	Not oncogenic at doses up to and including 800 ppm (HDT). NOEL < 50 ppm. LOEL = 50 ppm (increased alkaline phosphatase activity in males)	Supplementary for chronic toxicity Minimum for oncogenicity
Delayed type neurotoxicity - hens (oral) - single dose	LD_{50} about 5000 mg/kg (in polyethylene glycol 400). Behavorial changes in 2/10 hens and some signs of nerve fiber degeneration reported ("moderate" in degree).	Supplementary

Studies Reviewed (contd.)

Study	Results	Core Classification
Delayed type neurotoxicity - hens (oral) - multi dose (2 doses)	Behavorial changes in 4 hens. Nerve fiber degeneration in majority of treated hens.	Supplementary
Delayed type neurotoxicity - hens (oral) - multi dose (5 doses)	Behavorial changes in 3/6 surviving hens. Nerve fiber degeneration also observed.	Supplementary
Delayed type neurotoxicity - hens (oral) - single dose	No behavorial changes. No microscopy of nervous tissue performed. Dose was 5000 mg/kg.	Supplementary
Delayed type neurotoxicity - hens (oral) - multi dose (2 doses)	Negative for behavioral and microscopic changes in nervous tissue. Dose was 5000 mg/kg	Minimum
Delayed type neurotoxicity - hens (dermal)	No evidence of delayed neurotoxicity by the dermal route.	Minimum
Mutagenicity Studies:		
Mutagenic - Salmonella microsome	Negative for S. typhimurium TA-1535, 1537, 100, and 98 strains, with and without metabolic activation.	Unacceptable
Mutagenic - Micronucleus test: mice	Negative for hematopoietic effect in NMRI/ORIG Kisslegg mice.	Unacceptable
Mutagenic - Dominant lethal test; mice	Systemic NOEL > 60 mg/kg (Xl) Embryotoxic NOEL > 60 mg/kg (Xl) Reproductive NOEL > 60 mg/kg (Xl)	Unacceptable
Mutagenic - Differential Bacterial Toxicity test	Negative for E. coli pol A_1^- and pol A^+ strains with and without metabolic activation.	Acceptable

Studies Reviewed (contd.)

Study	Results	Core Classification
Mutagenic - Bacterial mutagenicity tests	Rec-Assay - Negative for NIG 45 and NIG 17 Bacillus subtilis strains.	Unacceptable
	Reversion Assay - Negative for S. typhimurium TA- 1535, 1537, 1538, 98, and 100 strains and E. coli B/r WP2 try⁻ her⁻ strain, with and without metabolic activation.	Acceptable
Mutagenic - Microbial mutagenicity	Rec-Assay - Negative for H17 and M45 Bacillus subtilis strains.	Acceptable
	Reversion Assay - Negative for S. typhimurium TA- 1535, 1537, 1538, 98, and 100 strains and E. coli WP2 hcr strain, with and without metabolic activation.	Acceptable
Mutagenic - Reverse mutation induction	Cytotoxicity Study - Not cytotoxic for S. cerevisiae S211	Acceptable
	Reverse Mutation Assay - Negative for S211 and S138 strains of Saccharomyces cerevisiae with and without metabolic activation.	Acceptable
Mutagenic - Recombination and conversion assays	Cytotoxicity Study - Not cytotoxic for D_7 strain of Saccharomyces cerevisiae	Acceptable
	Recombination and Conversion - negative for D_7 strain of Saccharomyces cerevisiae	Acceptable
STUDIES WITH BAYTHROID 240 EC (Baythroid 2)		
Acute Oral LD_{50} - rats	LD_{50} = 1015 (651-1671) mg/kg - males. LD_{50} = 826 (598-1225) - females . Tox Cat III	Minimum
Acute Dermal LD_{50} - rabbits	LD_{50} >2000 mg/kg both sexes. Tox Cat III	Minimum
Acute Inhalation LC_{50} - rats	LC_{50} = 1323 (1138-1505)mg/m^3 - males. 1434 (1153-1877) mg/m^3 - females Tox Cat II	Guidelines
Primary Eye Irritation - rabbits	Corneal opacity >21 days. Tox Cat I	Guidelines
Primary Dermal Irritation - rabbits	PII = 0.8 (4 hour exposure). Tox Cat IV	Guidelines