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

DEC 13 1991

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum

Subject: PP#1F3923: Cyfluthrin (**Bayocide, Baythroid**) Dermal Application on Cattle. Evaluation of Analytical Method and Residue Data. MRID# 415557-02, -03; CBTS# 7414; DP Barcode D159229.

From: Robert Lascola, Chemist
Chemistry Branch, Tolerance Support
Tolerance Petition Section III
Health Effects Division (H7509C)

Through: R. S. Quick, Acting Branch Chief
Chemistry Branch, Tolerance Support
Health Effects Division (H7509C)

To: George Larocca / John Hebert (PM 15)
Insecticide/Rodenticide Branch
Registration Division (H7505C)

Mobay Corporation, Animal Health Division, Shawnee Mission, KS, requests increased tolerances for the pyrethroid, cyfluthrin [cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate], on cattle tissues (meat, fat, and meat by-products) at 0.4 ppm and milk at 0.08 ppm. This petition is connected with the proposed registration of **Bayocide** Pour-On Insecticide, (1% cyfluthrin) to control flies and lice on beef and dairy cattle (S. Hummel, EPA File Symbol 11556-RNT, 11/26/90). Cyfluthrin is already registered in cattle ear tags (Cutter Gold™ Insecticide Cattle Ear Tag, 11556-106) and for use on crops and ornamentals (Baythroid™, Baythroid 2™, and Tempo 2™).

Tolerances have been established (40 CFR §180.436) for residues of cyfluthrin in meat, fat, and meat byproducts of cattle, goats, hogs, horses, and sheep (0.05 ppm), milk (0.01 ppm), cottonseed (1.0 ppm), and fresh hops (4.0 ppm). A temporary tolerance has been established for tomatoes. Food additive tolerances have been established (40 CFR §185.1250) in processed foods (in food handling establishments) (0.05 ppm), cottonseed oil (2 ppm), and concentrated tomato products (temporary) (0.5 ppm). Feed additive tolerances have been established (40 CFR §186.1250) in cottonseed hulls (2 ppm), dried hops (20 ppm), and wet and dry tomato pomace (2 and 5 ppm, respectively; temporary). Numerous tolerances are pending, including higher

tolerances in animal products (1.5 ppm in meat, fat, and meat byproducts; 0.1 ppm in milk), livestock feed items and other racs and processed products (PP#9F3731/FAP#9H5574). There is an amended use registration pending for a premise application (DEB# 7744,7745,7746). Also, a Section 18 exemption (91-NM-01) is pending for use of cyfluthrin to control alfalfa weevil on alfalfa in New Mexico.

Conclusions

1. CBTS concludes that the manufacturing process of the active ingredient is adequately understood.

2. There is no dermal metabolism study available to support this proposed pour-on use. A dermal metabolism study is needed to evaluate the requested tolerances for cattle. Cyfluthrin, ^{14}C-labelled in the cyclopropane and fluoromethyl ring should be used in separate studies.

3. The analytical method used to generate all residue data provided in this petition has undergone a successful petition method validation and has been forwarded to the FDA for inclusion in PAM II. Additional analytical methodology and second laboratory validation may be needed if the requested dermal metabolism study determines that more metabolites require regulation.

4. Since there is evidence that cyfluthrin residues concentrate in fat, the petitioner should investigate the possible concentration of cyfluthrin into milkfat and submit the results of the study to the Agency. If the pesticide does concentrate in milkfat, the petitioner must also submit a revised Section F requesting an appropriate milkfat tolerance.

5. Additional animal treatment studies will be needed if the requested dermal metabolism study indicates that metabolites of cyfluthrin need to be regulated. CBTS will withhold our recommendations on these tolerance requests until after a dermal metabolism study has been submitted and reviewed.

6. The petitioner should submit a chemical name for cyfluthrin using the (RS) convention to identify the stereoisometry of each optically active site.

7. No Canadian or Mexican limits are established for residues of cyfluthrin in cattle tissues and milk, nor has a Codex limit been established for residues of cyfluthrin in cattle tissues. A Codex limit of 0.01 ppm has been established in cattle milk. As the current petition was submitted specifically for the purpose of proposing higher tolerances for cyfluthrin in cattle milk, we are unable to harmonize the residue limits with Codex.

Recommendation

CBTS recommends against the establishment of tolerances for cyfluthrin residues in the meat, fat, meat by-products, and milk of cattle for reasons delineated in Conclusions 2, 4, and 5.

Note to PM: The label warns that Bayocide is "[h]armful if swallowed, inhaled, or absorbed through the skin," yet does not explicitly require the user to wear appropriate gloves. Revision of this warning in Section B is not in the purview of CBTS, but this point should be brought to the attention of OREB.

Detailed Considerations

Manufacturing Process and Formulation

Bayocide is a pour-on insecticide containing 1.1% Baythroid technical (≡ 1% cyfluthrin).

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

[redacted]

For further discussion see R. Loranger's memo of 4/17/84, PP#4G2976. The petitioner should submit a chemical name for cyfluthrin using the (RS) convention to identify the stereoisometry of each optically active site.

The impurities in the technical product are not expected to cause a residue problem (PP#4F3046, K. Arne memo of 5/18/84). This specific pour-on formulation is not yet registered with the EPA. Clearance of the inert ingredients in the formulation is within the purview of RD. CBTS concludes that the manufacturing process of the active ingredient is adequately understood.

Proposed Use

Bayocide™ pour-on insecticide is proposed for use for the control of horn flies, face flies, biting lice, and sucking lice on beef and dairy cattle, including lactating cows. It is a ready-to-use solution that is applied directly to the animal with a syringe or other measuring device, from the top of the head along the back to the hips. (A dispenser appropriate for this use is supplied with the package.) The dosage used is dependent on the size of the animal, as summarized below.

Table 2. Dosage Rates for Bayocide on Cattle.

Animal Weight	Horn and Face Flies		Biting and Sucking Lice	
	mL	mg ai/kg bw	mL	mg ai/kg bw
< 400 lb	4	≥0.21	8	≥0.42
400 - 800 lb	8	0.42 - 0.21	16	0.84 - 0.42
> 800 lb	12	≤0.32	24	≤0.64

Treatment for flies can be repeated as often as needed but no more often than once every 3 weeks. For optimal lice control, an initial application followed by a second treatment 3 weeks later is recommended. **Bayocide** does not control cattle grubs. No pre-slaughter interval is specified (the petitioner is requesting a 0-day PSI).

CBTS concludes that the submitted labeling is adequate.

Nature of the Residue - Plants

Bayocide is to be applied directly to the animals. No residues of cyfluthrin are expected to occur in plants from the proposed use.

Nature of the Residue - Animals

No new animal metabolism studies have been submitted in support of this petition. Metabolism studies in dairy cows, poultry, and rats have previously been submitted with PP#4G2976 and PP#4F3046. As the proposed use of this product is restricted to cattle, only the dairy cow study

will be summarized here (the original review was made in R. Loranger's 2/23/84 memo, see PP#4G2976). That study entailed **oral** administration of 247 mg ^{14}C-phenyl labeled cyfluthrin (≡0.5 mg/kg body weight; 33 ppm in the diet) for 5 consecutive days. Milk was collected each morning and evening, and tissues (muscle, fat, heart, kidney, and liver) were collected the morning after the final dose (given in the evening).

Activity in milk peaked 72 hours after the initial dose and ranged from 0.01 - 0.08 ppm cyfluthrin equivalents. The activity was expressed almost entirely (> 98%) as the parent compound, cyfluthrin. Activity in tissues is summarized in Table 3.

Table 3. ^{14}C Activity in Cyfluthrin Oral Metabolism Study.†

Tissue	ppm ^{14}C	ID of Residue‡
Muscle	0.02 - 0.03	all parent
Fat	0.12 - 0.23	all parent
Heart	0.04	71% parent, 29% FPBalc
Kidney	0.19	56% parent, 43% FPBalc
Liver	0.62	86% parent, 14% FPBald

†For details, see PP#4G2976, R. Loranger memo of 2/23/84; also PP#4F3046, K. Arne memos 5/18/84, 2/14/85 and petitioner response dated 10/18/84.
‡FPBalc: 4-fluoro-3-phenoxy-benzenemethanol; FPBald: 4-fluoro-3-phenoxy-benzaldehyde.

No similar studies are available with the ^{14}C label in the cyclopropane moiety. From this oral metabolism study, the residue of concern has been determined to be the parent compound, cyfluthrin. The metabolites FPBalc and FPBald are not regulated, and neither is DCVA (dichloroethenyl-2,2-dimethylcyclopropanecarboxylic acid), an expected metabolite derived from the carboxylic acid moiety of cyfluthrin. DCVA is a major residue when ruminants are fed cyclopropyl-labeled ^{14}C-permethrin and cypermethrin.

Generally, we expect the metabolism of any compound to be different if it is adsorbed dermally compared to ingested orally, and thus require a separate dermal study involving radioactively labeled cyfluthrin. Thus, a dermal metabolism study is needed using cyfluthrin label in the cyclopropyl and phenyl rings. If the dermal metabolism study indicates that there are additional major residues requiring regulation, such as but not limited to DCVA, FPBalc, and FPBald, then proposed enforcement methodology, a second laboratory validation, and an Agency method validation of the proposed enforcement method will be needed.

Analytical Method

The analytical method used to generate all residue data provided in this petition is described in detail in Mobay Report No. 85883, "An Analytical Method of Baythroid Residues in Bovine and Poultry Tissues, Milk, and Eggs" (MRID# 403015-02, FAP#6H5515), with minor revisions. This method has undergone a successful petition method validation for cyfluthrin, **per se**, and has been forwarded to the FDA for inclusion in PAM II (PP#4F3046, M. Bradley memos of 1/2/88 and 3/18/88). The method proceeds as follows: Tissue samples are homogenized, and cyfluthrin is removed from the sample matrix by organic solvent extraction. The organosoluble extract is partitioned with various solvents to remove lipids and polar and non-polar interferences, and final purification is clean-up via silica gel or Florisil Sep-Pak chromatography. Analysis of the purified sample is achieved by GC/EC. The range of recovery for milk fortified at 0.02 ppm is 90-125%, and for bovine tissues, poultry tissues, and eggs fortified at 0.05 ppm are 67-100%, 74-94%, and 62-80%, respectively. The limit of detection is 0.01 ppm.

Cyfluthrin is recovered completely ($\geq$ 80%) by FDA Multiresidue Method 232.4, and partially (50-80%) by Method 212.1 (see PAM I).

CBTS concludes that there is an enforcement method available in PAM II for the parent compound cyfluthrin. If the dermal metabolism study confirms additional major metabolites, we will need analytical methodology for those metabolites, a second laboratory validation, and an Agency method validation.

Storage Stability

Storage stability studies were not submitted with this petition. Previously submitted short-term (30 and 90 days) studies have shown cyfluthrin to be stable in cattle tissues (PP#4F3046, K. Arne memo of 8/10/84). Samples from residue studies were frozen after collection and analyzed within 30 days. Therefore, the previously submitted storage stability studies are sufficient to determine the stability of the parent compound only for this period of time. The petitioner will need to provide storage stability studies for all major metabolites requiring regulation as determined by the requested dermal metabolism study.

Magnitude of the Residue in Meat and Milk

Two studies detailing the effects of dermal application of Bayocide™ have been submitted previously as part of an amended registration (PP#9F3731).

The first study is entitled "Depletion of Cyfluthrin Residues in Bovine Tissue and Milk From a Pour-On Formulation". (Mobay Report No. 74050; MRID# 415557-02) Milk, blood, and tissues from six Holstein lactating dairy cows were analyzed for residues of cyfluthrin after dermal application of Bayocide. Application was along the backside of the animal starting from

the shoulders to the base of the tail, using a calibrated syringe. There was no run-off of applied insecticide. Control animals were housed separately from treated animals. For each milking interval, untreated animals were milked prior to treated animals. Animals were monitored for general health, body weight, feed consumption, and milk production.

The following schedule was used for application of the pesticide and collection of samples. On Days 1, 2, and 3 of the study, 3 cows (hereafter designated as "Group A") were treated each day with 0.9 mg ai/kg body weight/application (≡ 42.8 mL/1000 lb body weight/appln), and 3 cows ("Group B") were not treated. Prior to the initial application, milk samples were taken from all cows and frozen immediately. Milk samples were taken from treated cows through Day 11. On Day 17, Group A received another 0.9 mg ai/kg bw dose, and Group B received a 0.63 mg ai/kg bw (≡ 30 mL/1000 lb bw/appln) dose. Milk samples were taken from Group A on Day 17, and from Group B on Days 17 through 28. Blood samples were also taken from Group B from Day 17 through Day 26. On Day 29, all cows received doses equivalent to the doses received on Day 17. On Day 31, all cows were sacrificed and muscle, fat, liver, and kidney samples were taken. All collected samples were frozen immediately at -10 to -20 °C until analysis. Samples were processed at the Mobay farm and shipped frozen to M.C. Bowman and Associates, Mt. Ida, AK for analysis for cyfluthrin. Analysis of liver and kidney occurred within 30 days of collection of the sample; all other analysis occurred within 2 weeks. Results are discussed below.

Milk: Cyfluthrin, **per se**, residue levels in milk from Group A (averaged over the members of the set) peaked approximately 2 days after the third daily dose of .9 mg/kg/day. The highest recorded residue level was 0.05 ppm. In Group B, average residue levels peaked 3 days after the application of the 0.63 mg/kg dose. The highest recorded residue level was 0.03 ppm. After 14 days, residue levels were <0.01 ppm.

Since pyrethroids are liposoluble, it is reasonable to presume that cyfluthrin residues will concentrate in milkfat. However, the petitioner has submitted no data addressing this issue. CBTS requests that the petitioner investigate the distribution of cyfluthrin residues into milk fat and skim milk components. If residues concentrate in milkfat, the petitioner should submit a revised Section F requesting appropriate tolerances in whole milk and milk fat.

Blood: Blood samples were taken in order to determine the appropriate time to take tissue samples (i.e. when the residue levels would be the highest). However, the samples analyzed showed no detectable levels of cyfluthrin residues. Thus tissue samples were taken after an interval corresponding to the peak observed in residues in milk, i.e. after 2 days.

Tissues: Tissue samples were taken two days after administration of the final dose. Observed residue levels are summarized in Table 4. Residue levels in control samples were non-detectable (<0.005 ppm for kidney, <0.002 ppm for all others).

The second study is entitled "Cyfluthrin - Magnitude of the Residue: Dermal Application to Beef Cattle." (Mobay Report No. 74051; MRID# 415557-03) Cyfluthrin 1% Pour-On formulation

Table 4. Cyfluthrin (per se) Residues (ppm) in Bovine Tissues.*		
Tissue	**Group A†**	**Group B‡**
Liver	<0.002, <0.002, <0.002	<0.002, <0.002, <0.002
Muscle	0.02, 0.01, 0.02	0.01, 0.01, 0.01
Kidney	0.02, 0.01, 0.01	0.01, 0.01, 0.01
Fat	0.17, 0.09, 0.24	0.09, 0.07, 0.11

*from MRID# 415557-02
†application rate 0.9 mg ai/kg bw/appln, group contained 3 cows
‡application rate 0.63 mg ai/kg bw/appln, group contained 3 cows

was applied dermally to 10 Hereford, Angus, or mixed breed cattle at a dose level of 0.44 mg ai/kg body weight. Three groups of three animals each received either one, two, or three applications, with 21 days between applications. One animal served as a control. Applied volumes were equivalent to 4.62 mL per 100 kg body weight (cattle ranged in weight from 178 - 238 kg) and were distributed with a calibrated syringe along the backline of the animal starting from the shoulders to the base of the tail. The entire dose remained on the animal without run-off. The control animal was housed apart from the treated cattle in such a manner as to prevent accidental pesticide uptake by grooming.

Cattle were sacrificed 3 days after the final treatment. Muscle, fat, liver, and kidney sections were collected and frozen to -10 to -20 °C until analysis. Samples were homogenized while frozen and in the presence of dry ice. Homogenized samples were shipped in dry ice to M.C. Bowman Laboratories for analysis for the parent compound, cyfluthrin. All samples were analyzed within 2 weeks of collection.

Samples were analyzed via Mobay Method 85883 as outlined above. Recoveries of cyfluthrin from 0.05 ppm fortified samples ranged from 85-90% for all tissues. Only fat samples were analyzed after the first and second applications, while all three samples were analyzed after the third application. These results are summarized in Table 5.

The observed residues are within the proposed tolerances (milk: 0.08 ppm; meat, fat, and mbyp: 0.40 ppm). The use patterns and rates demonstrated in these studies are consistent with the proposed use. Residues in milk were shown to decrease to non-quantifiable levels (<0.01 ppm) 2 weeks after the last dose. The results also indicate that residues of the parent compound will accumulate in animal fat when the pesticide is applied every three weeks, as indicated on the label.

Since there is evidence that cyfluthrin residues concentrate in fat, the petitioner should investigate the possible concentration of cyfluthrin into milkfat and submit the results of the study to the Agency. If the pesticide does concentrate in milkfat, the petitioner must also submit

Table 5. Residue Levels of Cyfluthrin (per se) in Bovine Tissue†				
# Applications	ppm found			
	liver	muscle	kidney	fat
1	-	-	-	0.04, 0.03, 0.02
2	-	-	-	0.08, 0.08, 0.10
3	ND‡, ND, ND	0.006, 0.005, 0.004	0.006, 0.005, 0.006	0.15, 0.11, 0.10
Control	ND	ND	ND	ND
% recoveries of 0.05 ppm spikes	89.2 85.8	90.0 85.2	89.0 85.2	88.4 90.2

†from MRID# 415557-03. Application rate 0.44 mg ai/kg body weight.
‡Not Detectable (< 0.002 ppm in liver and kidney, < 0.001 ppm in muscle, < 0.003 ppm in fat).

a revised Section F requesting appropriate separate tolerances in whole milk and milk fat. This tolerance request should include the parent compound and all residues of concern as determined by the requested dermal metabolism study.

Additional animal treatment studies will be needed if the requested dermal metabolism study indicates that metabolites of cyfluthrin need to be regulated. CBTS will withhold our recommendations on these tolerance requests until after a dermal metabolism study has been submitted and reviewed.

Other Considerations

An International Residue Limit Sheet is appended to this review (Attachment 1). No Canadian or Mexican limits are established for residues of cyfluthrin in cattle tissues and milk, nor has a Codex limit been established for residues of cyfluthrin in cattle tissues. A Codex limit of 0.01 ppm has been established in cattle milk. As the current petition was submitted specifically for the purpose of proposing higher tolerances for cyfluthrin in cattle milk, we are unable to harmonize the residue limits with Codex.

Attachment 1: Codex Sheet (one page)
cc w/Attachment: R. Lascola, PP#1F3923, RF, **Baythroid**/Cyfluthrin SF, Circulation, C. Furlow (PIB/FOD).
RDI: P.V. Errico:12/13/91:R. Loranger:12/13/91
H7509C:CBTS/HED:CM#2:Rm803C:R. Lascola:305-7478:12/13/91 ◙:Disk1\3923a.txt