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

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FEB 24 1987

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Acute Toxicology Data in Support of the Registration of Tempo™ 20% Wettable Powder for Use in Food Handling Establishments

EPA No. 3125-GTT, 6H-5515 Project No. 7-0205
Record No. 183991, 181433 Tox. Chem. No. 266E

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

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c)

John E Whalan 1-21-87

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

Budd 2/18/86

[redacted] 2/18/86

Mobay Chemical Corporation has requested the registration of Tempo™ 20% Wettable Powder, "for use by pest control operators and professional applicators for pest control in buildings and structures including food areas of food handling establishments." The proposed tolerance is 0.05 ppm for cyfluthrin (cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxylate) in or on all food items in food handling establishments where food or food products are held, processed, or prepared. It is to be applied as a general, spot, and crack and crevice treatment. Food should be removed or covered. The product should not be applied directly to food or food handling surfaces.

Tempo™ 20% Wettable Powder is reportedly [redacted]

Powder (from the study reports) are as follows:

[redacted]

CONFIDENTIAL INFORMATION WHICH MAY REVEAL INERT INGREDIENTS AND THE MANUFACTURING PROCESS IS NOT INCLUDED

In support of this action, the following studies were submitted:

1. Acute Oral Toxicity of ®Baythroid 20% Wettable Powder in Albino Rats
2. Acute Dermal Toxicity of ®Baythroid 20% Wettable Powder in Albino Rabbits
3. Acute Inhalation Toxicity Study with ®Baythroid 20% Wettable Powder Dust in Rats
4. Primary Eye Irritation of ®Baythroid 20% Wettable Powder in Albino Rabbits
5. Primary Dermal Irritation of ®Baythroid 20% Wettable Powder in Albino Rabbits
6. Dermal Sensitization of ®Baythroid 20% Wettable Powder in Male Guinea Pigs

These studies have been reviewed and found to be acceptable. Reviews of these studies follow.

The ADI was recently reevaluated and established as 0.025 mg/kg/day (based on a 2-year rat feeding study with a NOEL of 2.5 mg/kg/day). Using this ADI, the current commitment for Toxicology Branch approved tolerances is 34.38% of the ADI, with a TMRC of 0.0086 mg/kg/day (60 kg body weight, 1.5 kg diet). Granting these tolerances will increase the % ADI to 39.38%, and the TMRC to 0.0098 mg/kg/day (see attachment). The Toxicology Branch has no objection to granting these tolerances, RCB considerations permitting. The inert ingredients have been cleared. The submitted label is acceptable.

An 8-Point Summary is attached.

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ACUTE ORAL TOXICITY STUDY OF BAYTHROID 20% WP IN RATS

Mobay Corporation; Report No. 756; June 11, 1986; Accession No. 264524

PROTOCOL: Male (280-356 g) and female (190-222 g) Sprague-Dawley rats were randomly assigned to groups of 5 rats/sex. Baythroid 20% WP (20.8% cyfluthrin) was formulated in deionized water. The rats were fasted overnight, then dosed by gavage with the test article (dose volume of 10 ml/kg) as follows:

Doses (mg/kg)	
Male	Female
500	500
1000	1000
--	1500
2000	2000
3000	--
4000	--

The rats were observed at least once daily for clinical signs, and weighed weekly during the 14-day study. Food and water were available ad libitum. Terminal weights were measured for all animals which died or were sacrificed moribund. All rats were necropsied and examined grossly.

RESULTS: There were no deaths in males and females dosed at 500 and 1000 mg/kg. The females were nearly twice as sensitive to the test article as the males. The LD_{50} values were calculated to be 3084 (2160-4459) mg/kg for males, and 1733 (1491-2014) mg/kg for females. The slopes of the dose-response curves were 4.5 and 13.6, respectively. There were no clinical signs in the 500 mg/kg males. The occurrence of clinical signs in the other groups was as follows:

	Males (mg/kg)					Females (mg/kg)			
	500	1000	2000	3000	4000	500	1000	1500	2000
Salivation	X	X	X	X		X	X	X	X
Lacrimation		X		X				X	X
Red nasal discharge				X					
Diarrhea		X		X				X	X
Urine stained fur		X	X	X				X	X
Decreased activity		X	X	X		X	X	X	X
Tremors			X			X			
Ataxia		X	X	X		X		X	X
Writhing		X	X	X			X	X	X

Clinical signs (not otherwise specified) were observed immediately after dosing, and had reversed by day 5 in the survivors. There were no control animals against which to compare body weights, but there was clearly a dose-related decrease in male weight gain on day 7. Dose-related gross lesions seen in rats which died during the study included discharge and staining of the fur, reddened cervical lymph nodes, reddened lungs, salivation, fluid-filled stomach, and reduced amount of stomach ingesta. There were no compound-related gross lesions in rats sacrificed on day 14.

STUDY CLASSIFICATION: This study is CORE MINIMUM, Toxicity Category III. There was a great deal of disparity between the LD_{50} values, slopes, and clinical signs for the two sexes. It is very likely that some groups were dosed with improper or nonhomogeneous formulations. If in fact there was a genuine sex difference, it would probably be due to the inert ingredients used in the formulation in which case, there should have been vehicle controls. In the absence of analytical information, the data presented in this report are suspect. This study received Quality Assurance Review. It was submitted to the EPA although the Quality Assurance Officer declared it to be in violation of the Good Laboratory Practice requirements for analysis of test article homogeneity, stability, and concentration.

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ACUTE DERMAL TOXICITY STUDY OF BAYTHROID 20% WP IN RABBITS

Mobay Corporation; Report No. 743; April 23, 1986; Accession No. 264524

PROTOCOL: Five male (2.85-3.06 kg) and five female (3.02-23.42 kg) New Zealand White rabbits were given the limit dose (2000 mg/kg) of Baythroid 20% WP (20.8% cyfluthrin). The test article was formulated as a paste (using an unspecified vehicle) and applied to a 240 cm^2 area on the shaved backs of each rabbit. The doses were occluded with gauze, hypoallergenic tape, sheet plastic, and an elastic bandage. They were also fitted with plastic collars. The doses were removed after 24 hours by wiping the dosing sites with water moistened paper towels.

The rabbits were observed at least once daily for clinical signs, and weighed weekly during the 14-day study. Food and water were available ad libitum. All rabbits were necropsied and examined grossly.

RESULTS: There were no deaths or clinical signs during this study. Thus, the LD_{50} in both sexes was >2000 mg/kg (the limit dose). Body weight gain appeared normal for both sexes. The only compound-related gross lesion was a red zone on the back of one male, presumably due to local irritation.

STUDY CLASSIFICATION: This study is CORE MINIMUM, Toxicity Category III. There was no mention of the vehicle used to formulate a paste. This study received Quality Assurance Review, but the Quality Assurance Officer failed to note that it was in violation of the Good Laboratory Practice requirements to define the test article formulation, and analyze the test article for homogeneity, stability, and concentration.

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ACUTE INHALATION TOXICITY STUDY OF BAYTHROID 20% WP IN RATS

Mobay Corporation; Report No. 758; June 18, 1986; Accession No. 264524

PROTOCOL: Male (189-262 g) and female (180-216 g) Sprague-Dawley rats were randomly assigned to groups of 10 rats/sex. They were dynamically exposed "head-only" to either air (nontreated controls) or Baythroid 20% WP (20.8% cyfluthrin) aerosol in a 60-liter cylindrical chamber. The test article was generated with a Wright Dust Feed at a nominal chamber concentration of 12.052 mg/l (maximum attainable concentration). The aerosol was generated 30 minutes before introducing the rats into the chamber in order to reach a state of equilibrium. Exposure duration was 4 hours. Aerosol particle size distribution was assessed at four intervals with a TSI Aerodynamic Particle Sizer. Gravimetric concentration measurements were made at four intervals by passing the aerosol through 0.5 u Millipore PVC-5 filters placed near the rats' breathing zone.

The rats were observed for clinical signs during and after the exposure, and at least once daily during the 14-day study. They were weighed prior to exposure, and on days 3, 7, and 14. Food and water were available ad libitum, except during exposure. All rats were necropsied and examined grossly.

RESULTS: The gravimetric analyses of the chamber atmosphere indicated a mean chamber concentration of 1.180 mg/l in the breathing zone of the rats. The chamber concentration was sufficiently consistent throughout the exposure. This was reportedly a maximum attainable concentration. The mass median aerodynamic diameter was calculated to be 3.8 u (particle size distribution was not reported).

There were no deaths in any group. Thus the LC_{50} was >1.180 mg/l. Because this was reportedly the maximum attainable concentration, the limit test was satisfied and no other dose groups were needed. Compound-related clinical signs included salivation, lacrimation, ocular and nasal irritation, dry crusty skin about the eyes and ears, decreased activity, and periorbital alopecia. All of these signs reversed within three days except for the skin lesions and alopecia, which had nearly reversed by day 14. Weight gain was similar in the dosed and control groups. Gross findings of dark red lungs were reported in 4/10 males and 2/10 females. These lesions could have been caused by either the test article or CO_2 euthanasia.

STUDY CLASSIFICATION: This study is CORE MINIMUM, Toxicity Category III. Particle size distribution was measured but was not reported, so it was impossible to assess the aerosol's dispersion, or what portion of the aerosol was respirable. Nevertheless, only mild toxicity was seen at this maximum attainable concentration. This study received Quality Assurance review. The Quality Assurance Officer stated that this study was in violation of the Good Laboratory Practice regulations since, "The mixture of the test substance with the carrier was not analyzed for homogeneity, stability, or concentration of the test substance." Since a carrier (vehicle) was not used by the laboratory, these analyses are not necessary and the study did not violate the Good Laboratory Practice regulations. The test article, a formulated powder, was used as prepared by the manufacturer. Thus, the stability of the powder was known, and homogeneity and concentration should not have varied appreciably.

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PRIMARY EYE IRRITATION STUDY OF BAYTHROID 20% WP IN RABBITS

Mobay Corporation; Report No. 735; April 14, 1986; Accession No. 264524

PROTOCOL: Six New Zealand White rabbits were dosed by placing 100 mg of Baythroid 20% WP (20.8% cyfluthrin) into the conjunctival sac of the left eye. The eyelids were then held together for 1 second. None of the eyes were rinsed. The right eyes served as controls. The eyes were evaluated for irritation at 1, 24, 48, and 72 hours, and at 7 days. No other observations were made. Food and water were available ad libitum.

RESULTS: No corneal lesions were seen in any of the rabbits. Sluggish irises were seen in two rabbits at 24 hours; these lesions had reversed by the 48 hour evaluation. Conjunctival lesions were seen after 1 hour in all rabbits and reversed by 72 hours in one rabbit, and by day 7 in the other rabbits. These lesions included injected to beefy red vessels, chemosis which ranged from slight to lids swollen half closed, and slight to considerable discharge.

STUDY CLASSIFICATION: This study is CORE MINIMUM, Toxicity Category III. There was no mention of the age, weight, or sex of the rabbits used. This study received Quality Assurance review.

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PRIMARY DERMAL IRRITATION STUDY OF BAYTHROID 20% WP IN RABBITS

Mobay Corporation; Report No. 742; April 14, 1986; Accession No. 264524

PROTOCOL: Six New Zealand White rabbits were each dosed with 500 mg of Baythroid 20% WP (20.8% cyfluthrin) applied to a 6 cm^2 area on their shaved backs and sides. The doses were occluded with gauze, hypoallergenic tape, sheet plastic, and an elastic bandage. They were also fitted with plastic collars. The doses were removed after 4 hours by wiping the dosing sites with water moistened paper towels.

The dosing sites were evaluated for irritation 0.5, 1, 24, 48, and 72 hours after dose removal. Food and water were available ad libitum.

RESULTS: One rabbit had very slight erythema 24 hours after dose removal. No other irritation was seen. Thus, the test article was a mild irritant.

STUDY CLASSIFICATION: This study is CORE MINIMUM, Toxicity Category IV. There was no mention of the age, weight, or sex of the rabbits used. This study received Quality Assurance review.

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DERMAL SENSITIZATION [BUEHLER TOPICAL CLOSED-PATCH] STUDY OF BAYTHROID 20% WP IN GUINEA PIGS

Mobay Corporation; Report No. 755; June 9, 1986; Accession No. 264524

PROTOCOL: Twenty male Hartley guinea pigs were used in this study. Five of these served as noninduced controls, and the remaining fifteen were given induction treatments with aqueous solutions of Baythroid 20% WP. [NOTE: The report described using Baythroid 50% WP on page 8, but the report abstract mentioned the use of Baythroid 20% WP. Presumably, the page 8 reference was a typographical error which was overlooked by all editors.] The induced animals were given 0.5 ml topical doses of a 50% solution on day 0, and a 25% solution on days 7 and 14. The doses were applied onto the shaved skin of the left flank, and occluded for 6 hours with gauze, plastic sheeting, and an elastic bandage. These animals then had a 2-week rest period. Food and water were available ad libitum.

On day 28, the induced and noninduced control animals were challenged with the topical application of a 25% test article solution on the left flank. An equal volume of deionized water was applied to the right flank. The dosing sites were occluded for 24 hours. The animals were evaluated for skin irritation 24 and 48 hours after application of the induction doses, and 48 and 72 hours after application of the challenge doses.

RESULTS: None of the 15 guinea pigs had any skin irritation following the three induction doses. When these same animals were challenged, they also had no reaction. None of the noninduced controls had any reaction to the challenge doses. Thus, Baythroid 20% WP did not cause a sensitizing reaction in this study. Body weight gain in the induced and control animals was similar.

STUDY CLASSIFICATION: This study is CORE MINIMUM. This study received Quality Assurance Review. It was submitted to the EPA although the Quality Assurance Officer declared it to be in violation of the Good Laboratory Practice requirements for analysis of test article homogeneity, stability, and concentration.

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TOXICOLOGY BRANCH ADI PRINTOUT Date: 01/15/87

Cyfluthrin (Baythroid) 2yr feeding- rat ADI = 0.025000 mg/kg/day
Caswell #266E NOEL = 2.5000 mg/kg Safety Factor = 100
CFR No. 180. LEL = 7.5000 mg/kg
Status: TOX complete 3/14/86. ORD verified 4/8/86.

RESIDUE CONTRIBUTION OF PUBLISHED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY

No published tolerances listed in file.

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RESIDUE CONTRIBUTION OF TOX-APPROVED TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
2	Apples	2.000	6G3307	2.53	0.075900
19	Broccoli	3.000	5G3193	0.10	0.004500
20	Brussel sprouts	1.000	5G3193	0.03	0.000450
22	Cabbage, sauerkraut	1.000	5G3193	0.74	0.011100
27	Cauliflower	2.000	5G3193	0.07	0.002100
40	Corn, sweet	0.040	4G3126	1.43	0.000858
41	Cottonseed (oil)	2.000	4F3046	0.15	0.004500
68	Corn, grain (field corn)	0.040	4G3126	1.00	0.000600
90	Meat, red	0.050	4F3046	10.81	0.008108
90	Meat, red	1.950	4G3126	10.81	0.316192
90	Meat, red	0.000	6G3307	10.81	0.000000
93	Milk and dairy products	0.010	4F3046	28.62	0.004293
93	Milk and dairy products	0.190	4G3126	28.62	0.081567
93	Milk and dairy products	0.000	6G3307	28.62	0.000000
116	Pears	1.000	6G3307	0.26	0.003900
127	Potatoes	0.020	4G3126	5.43	0.001629

TMRC % ADI
0.008595 mg/kg/day (60kg BW, 1.5kg diet) 34.379800

RESIDUE CONTRIBUTION OF NEW (PENDING) TOLERANCES

	CROP	TOLERANCE (PPM)	PETITION NUMBER	FOOD FACTOR	MG/DAY
197	All foods	0.050	6H5515	100.00	0.075000000

TMRC % ADI
0.009845 mg/kg/day (60kg BW, 1.5kg diet) 39.379800

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SUMMARY OF CYFLUTHRIN TOXICITY DATA
and
EIGHT POINT FREE-STANDING SUMMARY

1. Summary of selected toxicology data considered for these actions:

STUDY	RESULTS	TOXICITY CATEGORY	CLASSIFICATION
Technical Cyfluthrin Data:			
Acute Oral LD_{50}, Rat	Depending on the vehicle used, LD_{50} values ranged from 16.2 mg/kg (cremophor/water) to 1271 mg/kg (PEG 400)	I-III	Minimum
Acute Dermal LD_{50}, Rat	LD_{50} >5,000 mg/kg, males and females	III	Minimum
Acute Inhalation LC_{50}, Rat	LC_{50} >0.735 mg/l, males (4-hour) LC_{50} 0.200-0.735 mg/l, females (4-hour)	II	Minimum
Primary Eye Irritation, Rabbit	Mild irritation	III	Minimum
Primary Dermal Irriatation, Rabbit	No irritation	IV	Minimum
Dermal Sensitization, Guinea Pig	Not a sensitizer by: the Draize Test the Maximization Test		Minimum Guideline
Teratology, Rat	Maternal NOEL = 3 mg/kg/day Maternal LEL = 10 mg/kg/day (behavioral changes in gait and coordination) Fetotoxic NOEL >30 mg/kg/day (HDT) Teratogenic NOEL >30 mg/kg/day (HDT)		Minimum
Teratology, Rabbit	Maternal NOEL = 15 mg/kg/day Maternal LEL = 45 mg/kg/day (abortion, resorption) Fetotoxic NOEL >45 mg/kg/day (HDT) Teratogenic NOEL >45 mg/kg/day (HDT)		Minimum

STUDY	RESULTS	TOXICITY CATEGORY	CLASSIFICATION
Mutagenicity Studies:			
A. Gene Mutation Test:			
CHO/HGPRT Mutation	Negative		Acceptable
B. Structural Chromosome Aberration Test:			
Sister Chromatic Exchange	Negative		Acceptable
C. Tests for Other Genotoxic Effects:			
Unscheduled DNA Synthesis	Negative		Acceptable
Metabolism	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 [sic].		Minimum
Chronic Feeding/Oncogenicity, Rat	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).		Minimum
Chronic Feeding, Dog	NOEL = 4 mg/kg/day LEL = 16 mg/kg/day (slight ataxia, increased vomiting, diarrhea, and decreased male body weights).		Minimum
Oncogenicity, Mouse	Oncogenic NOEL >120 mg/kg/day (HDT) Systemic NOEL <7.5 mg/kg/day (LDT, increased alkaline phosphatates activity in males) [sic].		Supplementary for chronic feeding Minimum for oncogenici

STUDY	RESULTS	TOXICITY CATEGORY	CLASSIFICATION
3-Generation Reproduction, Rat	Reproductive NOEL = 2.5 mg/kg/day Reproductive LEL = 7.5 mg/kg/day (decreased viability) Systemic NOEL = 2.5 mg/kg/day Systemic LEL = 7.5 mg/kg/day (decreased pup body weights)		Minimum
Neurotoxicity, Hen	1. Delayed Neurotoxicity Study 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. 2. Neurotoxic Esterase Activity NTE activity in hens dosed with 4300 mg/kg/day X1 of cyfluthrin resembled that of the vehicle controls.		Minimum
Neurotoxicity, Rat	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 (males), and death. Histopathologic lesions included slight brain hemorrhages and necrosis of the skeletal muscle fibers.		Guideline
Neurotoxicity, Rat	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).		Guideline

2. Summary of Data Considered Desirable but Lacking for This Action:

None

3. Action Being Taken to Obtain the Lacking Information or Other Additionally Needed Information:

Not applicable.

4. A Summary of Other Permanent Tolerances Granted for This Herbicide:

None

5. The current commitment for Toxicology Branch approved tolerances is 34.38% of the ADI with a TMRC of 0.0086 mg/kg/day (60 kg body weight, 1.5 kg diet). Granting these tolerances will increase the % ADI to 39.38%, and the TMRC to 0.0098 mg/kg/day.

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

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

8. Other Relevant Considerations in Setting These Tolerances:

None.