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CASWELL FILE

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

FEB 4 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA #004001. Response to the Roussel Uclaf Proposal Concerning Testing One Allethrin Formulation as a Representative for Several Others

TO: Susan Lewis, PM Team #50 Tox. Chem. No. 25
Registration Division (TS-767c)

FROM: Pamela Hurley, Toxicologist Pamela M. Hurley
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THROUGH: Edwin Budd, Section Head
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I.D. No. 004001
Record Nos. 158,429; 159,037 and 160,241

W.D. 2-4-86

Action Requested and Background:

During the summer of 1985, the Toxicology Branch was requested to respond to a proposal submitted by Roussel Uclaf, dated June 11, 1985. The proposal concerned a data call-in notice on three allethrin formulations. The formulations contained identical chemical products except that the percentage of each product in each formulation was different. The data call-in notice required testing all three of the formulations for chronic, reproductive and oncogenic effects. Roussel Uclaf submitted a request, accompanied by a rationale, for testing one of the formulations as a representative for all three. At that time, in order to facilitate a decision concerning the proposal, the Toxicology Branch asked for the company to submit all the subchronic, chronic, reproductive, teratogenic and other relevant data already available on the three formulations. In addition, other relevant data and papers were obtained from the EPA files as well. All of the data collected on the three formulations have been reviewed.

Response:

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The Toxicology Branch has determined that the proposal to test Esbiothrin (EBT) in order to satisfy the data call-in requirements on the three formulations, Bioallethrin (BA), EBT and Esbiol (SBA) is acceptable.

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Discussion:

BA, EBT and SBA each contain almost exclusively the two isomers, d-trans chrysanthemate ester of d-allethrolone (d-isomer) and d-trans chrysanthemate ester of l-allethrolone (l-isomer). The relative ratios of these two isomers expressed as (d:l) are respectively:

50:50 for BA
77:23 for EBT
95:5 for SBA

An analysis of the existing data on the three formulations indicates that in oral studies, each affects the same target organs, particularly the liver. Although the acute oral studies indicate that the d-isomer appears to be more acutely toxic than the l-isomer, the subchronic studies indicate that the NOEL's and the LOEL's for BA and SBA are similar (no subchronic data were available for EBT). In addition, subchronic data were available for Pynamin and Pynamin Forte. These two formulations are similar to the other three except that the chrysanthemate portion of the molecules are cis/trans instead of only trans. The data on these two formulations also indicate similar NOEL's and LOEL's.

The rationale submitted by Roussel Uclaf also contains information concerning the chemistry and syntheses of the formulations and a list of inerts and impurities. This information also supports testing only EBT to satisfy the data call-in requirements for all three formulations.

Attachment

Comparison of Oral Studies Conducted on Several Allethrins

Chemical	Study	Dose Levels Tested	NOEL, LOEL, LD_{50}'s, etc.	Target Organs and Comments
Bioallethrin (50:50 d,l allethrolone d-trans chrysanthemic acid	Acute oral - Sprague-Dawley rat		LD_{50}: Male 709.0(397.9-1756.0) mg/kg; Female 1041.9(805.8-1348.7) mg/kg	Tremors, clonic convulsions epistaxis. Lung + stomach congestion; pale kidneys, heart - spots of hemorrhage.
	90-day subchronic oral - Wistar rat	0, 500, 1500, 5000, 10000 ppm	NOEL: 1500 ppm (135 mg/kg/day) LOEL: 5000 ppm	decr. bw gain 5000, 10000 ppm females-5000, 10000 ppm- sl. "liver dysfunction" in blood chem. Target organs: liver, kidneys (?)
	6-mo. dietary - Beagle dog	0, 200, 1000, 5000 ppm	NOEL: 200 ppm, LOEL: 1000 ppm	5000:gen. body trembling, sl. incr. ptyalism in males, decr bw gain (both sexes), decr. in food consump., sl. irreg. heart rhythms, decr. abs. wt. of heart, incr. liver blood chem., hepatocell. degen. 1000: decr. bw gain (males), hepatocell. degen.
	Teratology - Sprague-Dawley rats	0, 50, 125, 195 mg/kg/day (0, 1000, 2500, 3900 ppm)		NOEL's could not be determ. because report did not state cause of incr. in deaths for dams at 3900 ppm.
	Mutagenicity (Ames, Micronucleus), DNA damage + repair			TA100 + TA 1535 gave weak but positive results with S-9 in Ames. All other assays negative.

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Comparison of Studies on Allethrins (cont.)

Chemical	Study	Dose Levels Tested	NOEL, LOEL, LD_{50}'s etc.	Target Organs and Comments
Esbiothrine (77:23 d,l allethrolone d-trans chrysanthemic acid	Acute oral - rat Sprague-Dawley		LD_{50}: male 432.3(270.5-728.3) mg/kg; female 378.0(219.3-555.6) mg/kg	Tremors, clonic convulsions epistaxis; nasal discharge, stomach filled with fluid, congestion - lungs + stomach
	Mutagenicity - Ames, Micronucl. mouse lymphoma			All negative.
Esbiol (95:5 d,l allethrolone;d-trans chrysanthemic acid	Acute oral - Wistar rats, ddY mice		LD_{50}'s: rats: male 470 mg/kg females 340 mg/kg; mice: male 350 mg/kg, female 340 mg/kg	Convulsions, tremors, irritability, excitability, lung congestion, vacuolar degeneration of liver
	Acute oral - Wistar rats, ddY mice		LD_{50}'s: rats: male 373 mg/kg, female 170 mg/kg; mice: male 133 mg/kg, female 124 mg/kg	Same as above + acute inflammation of bile duct, giant cells in spleen
	Acute oral - Sprague-Dawley rats		LD_{50}'s: male 574.5(399.6-742.1) mg/kg; female 412.9(219.4-537.0) mg/kg	Same as above
	Subchronic oral rat;3 mo.+ 6 mo. Wistar	0, 100, 300, 1000, 3000 ppm - males; 0, 50, 100, 300, 1500 ppm - females	NOEL 1000 ppm, LOEL 3000 ppm (males); NOEL 300 ppm, LOEL 1500 ppm (females). NOEL close to 3000 ppm for males and 1500 ppm for females	Decr. wt gain highest dose but not stat. sig. Urea N incr. but still within normal limits (high dose both sexes, 300 ppm females) Incr. GPT 3000 ppm males but not sig.
	Teratogenicity - Wistar rats	Could not be determined - write-up confusing		Doses made no sense. Animals died at too low doses when compared to other studies (i.e.2 ppm). Target organs on dams appeared to be liver, lungs, congestion of brain and heart.

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Comparison of Studies on Allethrins (cont.)

Chemical	Study	Dose Levels Tested	NOEL, LOEL, LD_{50}'s etc.	Target Organs and Comments
Allethrin (d,l allethrolone (ratio unknown); cis/trans chrysanthemic acid (ratio unknown)	Chromosomal Aberration - Chinese Hamster Cells with S-9 mix			Highly positive at very low dose (0.019 mg/ml) Neg. without S-9. Unaccept. study in ref. to Guidelines because only one dose level
Also called Pynamin	90-day feeding Wistar rats	0, 1500, 4000 ppm	NOEL 1500 ppm LOEL 4000 ppm	Incr. GOT both levels (stat. sig. ?). Incr. GPT 4000 ppm females. Liver wts. incr. 4000 ppm males.
Pynamin Forte (d,l allethrolone (ratio unknown);cis/trans chrysanthemic acid (20/80)	90-day feeding Wistar rats	0, 750, 2000, 4000 ppm	NOEL 750 ppm (49.6 mg/kg/day males, 59.2 mg/kg/day females) LOEL 2000 ppm	Decr. bw. gain (females) at 4000 ppm. Incr. GOT, GPT at 4000 ppm (both). Incr. liver wt. 2000, 4000 ppm (both)