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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

PC 128831

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EPA Reviewer: Pamela M. Hurley Pamela M Hurley Date 2/21/01
Registration Action Branch 2 (7509C)

EPA Secondary Reviewer: John Redden Date 2/28/2001
Antimicrobials Division (7510C)

DATA EVALUATION RECORD
Supplement to DER for MRID Nos.: 00157793, 40082901, 40239301 Cyfluthrin: [13-Week Inhalation Study in the Rat] **This supplement includes a revised executive summary and selected tables.**

STUDY TYPE: Subchronic (13-Week) Inhalation Study in the Rat
OPPTS Number: 870.3465 OPP Guideline Number § 82-4

DP BARCODE: N/A SUBMISSION CODE: N/A
P.C. CODE: 128831 TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Cyfluthrin Technical (94.9% a.i.)

SYNONYMS: FCR 1272; (R,S)-α-cyano-4-fluoro-3-phenoxybenzyl-(1R,S)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate; Baythroid

CITATIONS: Pauluhn, J. (1984) Study for Subchronic Inhalative Toxicity to the Rat for 13 Weeks: FCR 1272 (Cyfluthrin): Rept. No. 12436. Unpublished Mobay study no. 86443 prepared by Bayer AG Institute of Toxicology and Hanover Medical University. 170 p. MRID 00157793.

Pauluhn, J. (1987) Study of the Subchronic Inhalation Toxicity in Accordance with OECD Guidline No. 413: FCR 1272: Cyfluthrin: Addendum to Bayer Report No. 12436, Dated Feb. 1, 1984: Study No. T9015085. Unpublished Mobay Report No. 86443 prepared by Bayer AG. 157 p. MRID 40082901.

Pauluhn, J. (1983) Study of the Subchronic Inhalation Toxicity in Accordance with OECD Guideline No. 413: Baythroid: Supplemental Submission: Second Addendum to Bayer No. 12436. Unpublished study prepared by Bayer AG. 24 p. MRID 40239301.

SPONSOR: Mobay Chemical Corporation, Agricultural Chemicals Division

EXECUTIVE SUMMARY: In a subchronic inhalation toxicity study (MRIDs 00157793, 40082901, 40239301), Bor:WISW (SPF-Cpb) rats (10/sex/dose) were dynamically exposed by head-only inhalation to cyfluthrin (94.9% a.i.) in ethanol/polyethylene glycol 400 (1:1) at

concentrations of 0 (air control), 0 (vehicle control), 0.00009, 0.00071, or 0.00451 mg/L for 6 hours/day, 5 consecutive days/week for 13 weeks.

All animals survived the 13-week study, and no treatment-related changes were observed in organ weight, gross pathology, and histopathology.

At 0.00009 mg/L, by study termination, total decreases in mean body weight (6%, $p<0.05$) and mean body weight gain (21%) were observed in males when compared to the control group. Since there only appeared to be a slight effect on body weights in males and there were no other effects at this dose level, the apparent decrease in body weight gain is not considered to be toxicologically significant. At 0.00071 mg/L, total decreases in mean body weight (8%, $p<0.01$) and mean body weight gain (21%) were observed in males by study termination when compared to the control group. Ten of 10 females were observed to display unthriftiness/unkempt fur and lethargy following exposure on days 42 to 86. These signs were not present on days where no exposure took place. In addition, increased urinary protein was noted in mid- and high-dose males at 6 and 12 weeks. At 0.00451 mg/L, 10/10 of both sexes were observed to display the same clinical signs as the mid-dose group on days 13-88 for males and 9-86 for females. Agitation and "erect tails" were also observed in these animals, starting at week 5. On days when no exposure took place, these signs were still present, although only slightly. Mean body weights in males were decreased by 14% at study termination and mean body weight gain (weeks 0-13) was decreased by 46% when compared to the control group. Decreased urinary pH was also noted; however, no corresponding lesions were found to verify any possible nephritic damage.

The LOAEL is 0.0.00071 mg/L, based on decreases in body weight and body weight gain in males and clinical signs in females. The NOAEL is 0.00009 mg/L.

This study is classified as **acceptable guideline** and satisfies the guideline requirements for a 13-week inhalation study (**§82-4, 870.3465**) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Flagging statements were **not** provided in the original report. Stamped data confidentiality statements were provided. Quality assurance statements were provided in subsequent correspondence.

Mean Body Weights and Body Weight Gains in the 13-Week Inhalation Study in Rats (g)					
Dose (mg/L) Week	0 (air)	0 (vehicle)	0.00009	0.00071	0.00451
Males					
0	192	191	191	186	190
4	228	237	224	221*[a,b] (93)	205** (87)
8	255	263	243	243	223** (85)
12	277	276	258* (94)	253** (92)	236** (86)
Gain 0-12[c]	85	85	67 (79)	67 (79)	46 (54)
Females					
0	164	162	159	157	160
4	179	172	171	163	171
8	188	181	182	177	182
12	193	185	185	178	182
Gain 0-12	29	23	26	21	22 (96)

[a] * $p \leq 0.05$; ** $p \leq 0.01$
[b] (% vehicle control)
[c] Calculated by toxicology reviewer. No statistical analysis conducted.

13-Week Inhalation Study in Rats: Selected Urinalysis Data at 12 Weeks					
Dose (mg/L) Parameter	0 (air)	0 (vehicle)	0.00009	0.00071	0.00451
Males					
pH	7.25	7.25	6.55	6.6	6.15
Protein	2 (+)[a]	1 (+)	5 (+)	7 (+)	2 (+), 1 (++), 1 (+++)
Females					
pH	7.1	6.85	6.95	6.55	6.8
Protein	0	0	0	1 (++)	2 (+)

[a] Number of animals with protein in urine (the number of +'s indicates severity)

13-Week Inhalation Study in Rats - Microscopic Pathology					
Dose (mg/L)	0 (air)	0 (vehicle)	0.00009	0.00071	0.00451
Males					
Lungs					
Thickening of alveolar walls	9/10	10/10	7/10	9/10	10/10
Peribronchial round cell infiltration	10/10	8/10	9/10	10/10	9/10
Peripheral emphysema/lung periphery emphysema	4/10	7/10	6/10	3/10	4/10
Calcium deposit/calcification	4/10	1/10	2/10	3/10	3/10
Focal vascular	4/10	1/10	2/10	3/10	3/10
Females					
Lungs					
Thickening of alveolar walls	8/10	6/10	6/10	10/10	10/10
Peribronchial round cell infiltration	10/10	10/10	10/10	10/10	10/10
Peripheral emphysema/lung periphery emphysema	8/10	6/10	6/10	8/10	9/10
Calcium deposit/calcification	1/10	6/10	0/10	5/10	0/10
Focal vascular	1/10	6/10	0/10	5/10	0/10

REVIEWER

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

SEP 11 1987

Doc. # 6426

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Cyfluthrin. Review of a Subchronic Inhalation Study in Rats.

EPA No. 3125-GLE, 3125-GTE
Record No. 199665, 199666
Project No. 7-0946
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)

8-26-87

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
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9/2/87

9/10/87

Mobay Chemical Corporation submitted a Subchronic Inhalation Study in Rats and a Salmonella/Microsome test to the Toxicology Branch a year ago. These were two of many reports which had been submitted without the signatures of the performing scientists and Quality Assurance Officers. These studies were invalidated and returned (John Whalan memorandum, EPA No. 3125-GLE, July 11, 1986).

The Inhalation Toxicology report was lacking a summary of the histopathology data. The pathology tables were uninterpretable because they were encoded with German abbreviations. There was scant description of the inhalation chamber and aerosol generator; and no mention of chamber animal placement.

The Registrant submitted an addendum to the inhalation study, but many of the deficiencies were not addressed, chiefly the need for a summary of the histopathology data. The Toxicology Branch used the addendum and an archived copy of the original report to piece together a draft review of the study with the limited data. The study was classified Invalid, and the deficiencies were again listed (John Whalan memorandum, EPA No. 3125-GLE, May 18, 1987).

The Registrant submitted a second addendum (the impetus for this memorandum) which addressed most of the deficiencies, but still did not present lesion severities in the histopathology summary, or particle size distribution for all concentrations. Despite these inadequacies, the review was completed (attached), and the study was classified Core Minimum. The Toxicology Branch concurs with Bayer's defined doses which are as follows:

NOEL = 0.00009 mg/l/day
LEL = 0.00071 mg/l/day [unthriftiness, unkempt fur, and lethargy in females, and increased urinary protein in males].

SUBCHRONIC INHALATION TOXICITY STUDY OF FCR 1272 IN RATS

Bayer AG Institute of Toxicology; Report No. 12436; February 1, 1984; Accession No. 261771

PROTOCOL: Male and female Bor: WISW (SPF-Cpb) rats (160-200 g; 6-12 weeks old) were randomly assigned to groups of 10 rats/sex. They were dynamically exposed "head-only" for 6 hours/day, 5 days/week, for 13 weeks in a 40 liter plastic inhalation chamber to nominal concentrations of 0 (air control), 0 (vehicle control), 0.0005, 0.003, and 0.020 mg/l. The test article (94.9% pure) was dissolved in a 1:1 mixture of ethanol and Lutrol (PEG 400), and generated as an aerosol with a spray nozzle. Formulations were prepared daily.

Aerosol concentrations were measured 2-3 times per exposure on 27 exposure days. Chamber aerosol samples, collected in glass tubes filled with glass wool, were analyzed for chamber concentration. Particle size distributions were measured with Bayer® cascade impactors. All rats were observed several times on the days of dosing, but they could not be observed during the exposures because of the chamber design. Body weights were measured prior to dosing and weekly throughout the study. Blood samples were drawn from the retroorbital venous plexus, and individual urine was collected from 10 rats/sex/group at weeks 6 and 12. The following parameters were assessed:

Hematology

Hematocrit	MCHC
Hemoglobin	MCH
Erythrocytes	Leukocytes, total
Reticulocytes	Leukocytes, differential
MCV	Thrombocytes

Clinical Chemistry

Glucose	Alkaline phosphatase
Blood urea nitrogen	*Cytochrome P-450
Bilirubin	*N-demethylase
SGOT	*O-demethylase
SGPT	

*Examined in liver specimens at the end of the study.

Urinalysis

Blood	pH
Protein	Urobilinogen
Glucose	Bilirubin
Sediment	

Food and water were available ad libitum (except during dosing). The rats were all necropsied at the end of the 13th week and examined grossly. The following tissues were fixed and examined histopathologically (the asterisked organs were weighed at necropsy):

* Heart	Cervical lymph nodes	Skin
Esophagus	*Testicles	Skeletal muscle
Stomach	*Ovaries	Brain
Duodenum	*Liver	Sciatic nerve
Jejunum	*Lung	Trachea
Ileum	*Spleen	Larynx
Colon	*Thyroids	Pharynx
Pancreas	Parathyroids	Head (with eyes, nasal
Salivary glands	*Adrenals	cavities, and scalp)

RESULTS: The mean chamber concentrations and mass median aerodynamic diameters for each group were as follows:

Nominal Concentration (mg/l/d)	Analytical Concentration (mg/l/d)	MMAD (um)
0 (air control)	—	—
0 (vehicle control)	0.02 ml vehicle/l of air	2.7
0.0005	0.00009	2.6
0.003	0.00071	2.5
0.020	0.00451	2.5

Although particle size distribution was reported only for the mid-dose group, there was likely a significant portion of respirable particles (<1 microns) in each exposure group.

There were no deaths in any group. The low-dose group had no clinical signs. The mid-dose females had non-specific disturbed behavior [defined as "unthriftiness/unkempt fur and lethargy] following the exposures on unspecified days, but they were normal on weekends. The high-dose rats had non-specific disturbed behavior following exposure between weeks 2 and 5. Between weeks 6 and the end of the study, the high-dose rats were agitated with "erect tails" following exposures, and had non-specific disturbed behavior on weekends between exposures. There is no way of knowing whether toxicity occurred during exposure since none of the rats could be observed. The high-dose males had dose-related decreases (10-15%) in body weight gain between week 2 and termination. All female groups gained weight at comparable rates.

The only clinical pathology anomalies were seen in the urinalyses of male rats. The high-dose males had decreased urinary pH (at 6 and 12 weeks), and the mid and high-dose males had increased urinary protein (at 6 and 12 weeks). These findings suggest that there may have been nephritic damage, but there were no corresponding lesions found. The vehicle controls had gross findings of distended foci and reddish mottling of the lungs. These vehicle-related lesions were also seen in the rats dosed with cyfluthrin. There were no compound-related gross or histopathologic lesions, and no effects on organ weights.

The defined analytical doses are as follows:

NOEL = 0.00009 mg/l/day
LEL = 0.00071 mg/l/day [unthriftiness, unkempt fur, and lethargy in females, and increased urinary protein in males].

STUDY CLASSIFICATION: This study is CORE MINIMUM. The summary histopathology table was lacking lesion severities. The original study report and the two addenda received Quality Assurance reviews. Particle size distribution data were reported only for the mid-dose chamber on one day; the other chambers were said to have similar particle size distribution, although no data were provided to support that claim.

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R058540

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PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/28/2001 12:00:00 AM**
File ID:	**00000000**
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