CASWELL FILE 10

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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

EPA No. 3125-GLE
Record No. 190375

Project No. 7-0495
Tox. Chem. No. 266E

TO: George LaRocca (PM Team #15)
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John E Whalan 5-14-87

THRU: Edwin R. Budd, Section Head
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5/18/87

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. After several warnings that such reports would be classified Invalid and returned without review, 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 animal placement in the chamber.

The Registrant was told that histopathology summaries must include the number of each tissue type examined per group, lesion severities, a key defining the severities, and the incidence of each lesion. An example was supplied. The Registrant was informed that as with the lack of signatures, the lack of readily interpretable pathology data had been a persistent deficiency in the past and would be used as a criteria to invalidate future studies (John Whalan memorandum, EPA No. 3125-GLE, July 17, 1986).

In response to this invalidation, the Registrant submitted an addendum to the Subchronic Inhalation Study in Rats (the study report was not submitted, so a photocopy was obtained from the EPA archives for review). J.S. Thornton, Manager Registrations Research and Development at Mobay, stated in a cover letter (dated February 13, 1987) that the report deficiencies including the need for a histopathology summary had been addressed in the addendum.

The addendum did not contain a histopathology summary table as claimed, so the study was classified Invalid.

This study was evaluated to the extent possible (attached). In the course of the review, many deficiencies were discovered. The major ones are itemized below:

1. The Registrant failed to submit a summary histopathology table. This table must be presented as previously described.

2. The Quality Assurance Statement claims that the original report and the addendum received Quality Assurance reviews. The QA Officer's signature was illegible, and the Officer's name is unknown. The unknown QA Officer must be identified.

3. There was no justification offered for not observing animals during the exposures.

4. A major clinical sign was described as "non-specific disturbed behavior." This sign must be further defined.

All these deficiencies must be addressed before this study can be evaluated a third time. Only then will consideration be given to upgrading the Core Classification.

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/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 were collected in glass tubes filled with glass wool, which were then 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 were not observed during the exposures. 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 for 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)	Analytical Concentration (mg/l)	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 not reported, there was likely a significant proportion of respirable particles (<2 microns) in each exposure group.

There were no deaths in any group. The low-dose group had no clinical signs. The mid-dose rats had non-specific disturbed behavior following the exposures [no further details were provided regarding symptoms or weeks of occurrence]. The high-dose rats had non-specified disturbed behavior between weeks 2 and 5 following exposure. Between weeks 6 and the end of the study, the high-dose rats were agitated with "erect tails" following exposures, and had non-specified disturbed behavior on weekends between exposures. There is no way of knowing whether toxicity occurred during exposure since none of the rats were observed during this time. 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 mid and high-dose males had decreased urinary pH and increased urinary protein at the 6 and 12 week intervals. These findings suggest that there may have been nephritic damage. 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, but no other compound-related lesions were found. There were no compound-related effects on organ weights. The histopathology data were not evaluable.

This study is CORE INVALID. The Registrant did not comply with the Toxicology Branch request for a summary histopathology table. The Quality Assurance Statement claims that the original study report and the addendum received Quality Assurance reviews. The QA Officer's signature was illegible, and the Officer's name is unknown. These reports are in violation of the GLP regulations, since having an unknown QA Officer is tantamount to having unsigned reports. There was no justification offered for not observing animals during the exposures. A major clinical sign was described as "non-specific disturbed

behavior." This terminology is vague and must be defined. Particle size distribution data were not reported. Relative organ weight tables were not provided, and urinalysis data were not summarized.

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