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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: β-Cyfluthrin: requested review of data package

Tox.Chem No.: 266E
MRID No.: 412441 (01-17)
414057 (01-09;-14)
412678-01
DP Barcode: D148385
Submission No.: S278392
PC Code: 128831
HED Project No.: 0-065A

From: John C. Redden, Toxicologist
Section 3
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5/20/93

To: Adam Heyward
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Registration Division (H7505C)

Thru: Karen L. Hamernik, Ph.D.
Acting, Section Head Section 3
Toxicology Branch 1
Health Effects Division (H7509C)

5/24/93

ACTION:

Review the submitted data package for FCR 4545, β-cyfluthrin.

CONCLUSIONS:

1) GENERAL:

Beta-cyfluthrin (see Table 4), depending on the vehicle used, is, "up to 3-fold more acutely toxic than cyfluthrin by the oral route." The Registrant states that the increase in oral toxicity is due to the increased percentage of enantiomer pair II.

Beta-cyfluthrin and cyfluthrin have a low dermal toxicity. By the inhalation route beta-cyfluthrin is 5 times as toxic as cyfluthrin. Both products are slightly irritating to the eyes causing conjunctival redness reversible within seven days after exposure. Neither agent has dermal sensitization potential in

guinea pigs.

The Registrant requests the use of the Cyfluthrin database along with the acute studies for β-cyfluthrin to support the registration, "of end-use products containing beta-cyfluthrin for use in hygienic pest control." The Agency does not object to this if:

1) the Registrant conducts new studies (or satisfactorily answer the Agency's questions) for the data gaps in Cyfluthrin;

2) performs the requested bridging studies; and

3) conducts the acute battery for formulations where required.

2) DATA GAPS:

The following Data Gaps or bridging studies are required for the registration of FCR 4545, β-cyfluthrin:

• 81-6: Dermal Sensitization, Guinea Pig; Not a sensitizer by the Maximization Test; MRID No. 412441-07; This study is **Unacceptable.** This study may be upgraded with the requested information: individual data for the induction exposures in tabular form, and the presentation of the results;

• 81-7: Acute Neurotoxicity (mammal);

• 82-5: 90-Day Neurotoxicity (mammal); and

• 83-3 a or b: The Agency is requiring either a rat or rabbit Developmental Toxicity Study with β-cyfluthrin.

The following are data gaps in the Cyfluthrin data base:

• 82-1 Subchronic Oral; Dose levels: 0, 30, 100, 300 ppm in SPF Wistar (TNO W.74) strain. NOEL > 300 ppm (HDT). No definite test chemical effects noted. MRID No. 072008; Document No. 4285; downgraded to **Supplementary**; not tested to limit dose (1000 mg/kg/day). However, the Agency is not requiring the repeat of this study, as adequate chronic studies exist; and

• 82-2 21-Day Dermal rabbit; the NOEL > 250 mg/kg/day (HDT); MRID No. 00131527; Document No. 4285. No behavioral or clinical signs were noted. As the limit dose for a 21-day dermal is 1000 mg/kg/day, this study is down-graded to **Supplementary.** The Agency is requiring this study to be repeated. However, if an adequate explanation can be provided for the dose selection in MRID No. 00131527, the Agency may reconsider it's decision.

3) CONCERNS FOR BOTH THE CYFLUTHRIN AND BETA-CYFLUTHRIN DATA BASE:

A Rabbit Developmental Toxicity Study performed with Cyfluthrin; MRID 42675401 was submitted under 6 (a) (2) adverse effects. This study tentatively appears to fill the second species requirement for Cyfluthrin. Final determination on the status of this study will be determined after a detailed review.

4) ADDITIONAL STUDIES THAT MAY BE REQUIRED FOR THE REGISTRATION OF BETA-CYFLUTHRIN:

Depending on the results of the bridging studies the following studies may be required:

- 90-day inhalation toxicity study;
- second species developmental toxicity study;
- chronic/oncogenicity rodent toxicity study;
- chronic nonrodent toxicity study;
- oncogenicity/feeding second species toxicity study; and
- multi-generation reproduction study.

5) PERMANENT TOLERANCES FOR BETA-CYFLUTHRIN:

The Registrant suggests that the tolerance for β-cyfluthrin in all foods be 0.05 ppm (same as cyfluthrin). This is based on studies conducted with Cyfluthrin at twice the application rate of β-cyfluthrin, which revealed no detectable residues in foods (treatment for hygienic pest control). Toxicology Branch I has no objections to the granting of this tolerance under the following conditions:

- Residue Chemistry has no objection to the proposed tolerance; and
- the Registrant fulfill the data gaps.

6) TEMPO 1 (β-cyfluthrin) and TEMPO 10% Wettable Powder (β-cyfluthrin):

The Agency agrees to substitute the acute battery for TEMPO 2 (Cyfluthrin) for TEMPO 1 (β-cyfluthrin), as long as the Registrant agrees that for labeling purposes TEMPO 1 (β-cyfluthrin) will be Toxicity Category I, based on the fact that β-cyfluthrin is more irritating to eyes (β-cyfluthrin contains 11.5% more xylene than Cyfluthrin).

Although this could potentially place Tempo 1 into the restricted use category appropriate labeling of the hazard would probably be satisfactory instead. Product labeling must clearly state the potential eye irritation hazard and that goggles must be worn during product application to prevent contact of product with eyes.

The Agency will address the acute battery waiver request for TEMPO 10% Wettable (β-cyfluthrin) in a forthcoming memorandum.

BACKGROUND:

Technical Cyfluthrin contains in near equal proportions of four isomeric pairs. The Registrant has developed a process to partially isomerize two of the isomeric pairs into the other two pairs. The result is the proportion of isomeric pairs I and III has been reduced. The Registrant is calling this new isomeric mix Beta-cyfluthrin to distinguish it from Cyfluthrin.

SUMMARY:

Unless otherwise indicated all studies were reviewed by Clement International Corporation.

MRID No. 412441-01, "FCR 4525 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Xylene)." Fed and fasted male and female SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb) were orally dosed up to 5 mg/kg of the test material formulation. Vehicle control groups of 5 males and 5 females were administered 1 ml/kg of xylene. The following conclusions were extracted from the Clement review:

LD_{50} Male (fasted): 211 mg/kg (110-404 mg/kg*)
LD_{50} Female (fasted): 336 mg/kg (290-391 mg/kg*)
LD_{50} Male (fed): 307 mg/kg (260-364 mg/kg*)
LD_{50} Female (fed): 343 mg/kg (286-411 mg/kg*)

* = 95% Confidence Interval

Classification: **Acceptable.** This study satisfies the guideline requirement (81-1) for an acute oral toxicity study. The Toxicity Category is II.

MRID No. 412441-02, "FCR 4545 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Polyethylene Glycol E 400)." Male and female SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb) were orally dosed as follows: 1) fed males 10 to 2,500 mg/kg; 2) fed female 10 to 2,000 mg/kg; 3) fasted males 10 to 1,400 mg/kg; and 4) fasted females 10 to 2,000 mg/kg of the test material formulation. "A vehicle control group was not needed because historical data are available to determine the acute toxicity of the vehicle (polyethylene glycol E 400). The following

conclusions were extracted from the Clement review:

LD_{50} Male (fasted): 380 mg/kg (231-625 mg/kg*)
LD_{50} Female (fasted): 651 mg/kg (329-1,294 mg/kg*)
LD_{50} Male (fed): 655 mg/kg (395-1088 mg/kg*)
LD_{50} Female (fed): 1,369 mg/kg (1,137-1,651 mg/kg*)

* = 95% confidence interval

Classification: **Acceptable.** This study satisfies the guideline requirement (81-1) for an acute oral toxicity study. The Toxicity Category is II. Clinical signs in the > 10 mg/kg dose groups were as follows: lethargy, digging and preening movements, uncoordinated gait, splayed gait, salivation, piloerection, soft feces, rolling, increased activity, and difficult breathing. Clinical signs such as increased activity, digging and preening movements, uncoordinated gait, splayed gait, rolling, and salivation are characteristic of the Central Nervous System syndrome, which is known from pyrethroids with an α-cyano-phenoxybenzyl alcohol group.

MRID No. 412441-03, "FCR 4545 Technical Study of the Acute Oral Toxicity to Mice (Formulation in Polyethylene Glycol E 400)." The following conclusions were extracted from the Clement review:

LD_{50} (male) = 91 mg/kg
LD_{50} (female) = 165 mg/kg

Toxic signs: lethargy, digging and preening movements, uncoordinated gait, splayed gait, piloerection, rolling, increased activity, and difficult breathing. Dose levels were 10 to 500 mg/kg in Bor: WISW SPF-Han mice. The study is classified as **Acceptable.** The Toxicity Category is II. This study satisfies the guideline requirement (81-1) for an acute toxicity study in mice.

MRID No. 412441-04, "FCR 4545 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Acetone /Peanut Oil (1:9))." The following conclusions were extracted from the Clement review:

LD_{50} Male (fasted): 84 mg/kg (55-131 mg/kg)
LD_{50} Female (fasted): 77 mg/kg (65-93 mg/kg)
LD_{50} Male (fed): 141 mg/kg (113-177 mg/kg)
LD_{50} Female (fed): 108 mg/kg (78-152 mg/kg)

Toxic signs: lethargy, cramped posture, digging and preening movements, uncoordinated gait, splayed gait, soft feces, salivation, piloerection, rolling increased activity, and difficult breathing. Dose levels: 1 to 250 mg/kg. Classification: **Acceptable.** This study satisfies the guideline requirement (81-1) for an acute oral toxicity study. The Toxicity Category is II. Although, a vehicle control is not

required, it may have been useful considering the acetone used in the vehicle.

MRID No. 412441-05, "FCR 4545 Technical Study of the Acute Dermal Toxicity to Rats (Formulation in Xylene)." The following conclusions were extracted from the Clement review:

LD_{50} (male) ≥ 5000 mg/kg
LD_{50} (female) ≥ 5000 mg/kg

Toxic signs: Lethargy, uncoordinated gait, splayed gait, salivation, vocalization, jumping, digging and preening movements, difficult breathing and soft feces. Dose levels were 0 to 5000 mg/kg in the Bor: WISW (SPF-Cpb) rat. The study was classified as **Acceptable.** This study satisfies the guideline requirement (81-2) for an acute dermal toxicity study. The Toxicity Category is IV. The control group (5 males and 5 females) was treated with 0.4 ml of xylene.

MRID No. 412441-06, "FCR 4545 Technical Study of the Acute Dermal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)." The following conclusions were extracted from the Clement review:

LD_{50} (male) ≥ 5000 mg/kg
LD_{50} (female) ≥ 5000 mg/kg

Toxic signs were as follows: salivation, lethargy, uncoordinated gait, splayed gait, difficult breathing, and soft feces. Dose levels were 0 to 5000 mg/kg by the dermal route in Bor: WISW (SPF-Cpb) rats. The study is classified as **Acceptable.** The Toxicity Category is IV. A control group (5 males and 5 females) was treated with 0.6 ml of polyethylene glycol E 400.

MRID No. 412441-07, "FCR 4545 Technical: Study for Skin Sensitization Effect on Guinea Pigs." Under the conditions of the study FCR 4545 is not a skin sensitizer. The study is classified as **Unacceptable.** Guideline 81-6 requires the presentation of individual data for the induction exposures in tabular form. In addition no results were present. The study can be upgraded with the submission of the requested information.

MRID No. 412441-08, "FCR 4545 Subchronic Toxicological Study on Rats (Administration With Feed for 13 Weeks)," was reviewed by Melba S. Morrow, D.V.M. (HED, Toxicology I). Quoting Dr. Morrow:

> "Based on the results the NOEL is 125 ppm (9.5 mg/kg in males and 10.9 mg/kg in females) and the LEL is 500 ppm (37.0 mg/kg for males and 43.0 mg/kg in females) based on the presence of uncoordinated gait, impaired general condition (necrosis in the head and neck region), two deaths and delayed weight gain."

This study is classified as **Guideline**, and satisfies the Guideline requirement for a subchronic feeding study in rats.

MRID No. 412441-09, "FCR 4545 Range-Finding Toxicological Study to Establish Dosage for a Subchronic Study of Toxicity to Beagle Dogs," was reviewed by John Redden (HED, Toxicology Branch I). This was a 28-day dietary study. Dosing groups were from 10 to 640 ppm. After fourteen days the high dose group was reduced from 640 ppm to 320 ppm for the duration of the study. The dose was reduced due to, "the severity of the toxicity." A NOEL or LEL level could not be determined from this study. The study author suggested that dose levels for a subchronic feeding study should be 0, 10, 60, and 360 ppm of FCR 4545. This study is classified as **Supplementary** as range-finding studies are not used for regulatory purposes. In addition this study was not conducted in accordance with Good Laboratory Practices. This study can not be upgraded.

MRID No. 412441-10, "FCR 4545 Salmonella/Microsome Test for Point-Mutagenic Effect." Concentrations from 20 to 12,500 µg/plate were evaluated in the initial assay. However, a compound precipitation prevented the determination of revertant colonies at the high dose. Therefore, 500 to 8,000 µg/plate ± S9, which include one insoluble level (8,000 µg/plate ± S9) was tested. Results from both trials were in agreement and indicated that the test compound did not induce a cytotoxic or mutagenic response in S. typhimurium strains TA1535, TA1537, TA98, or TA100 either in the presence or absence of exogenous metabolic activation. Therefore, FCR 4545 was tested up to concentrations that exceeded the solubility limit with no evidence of a mutagenic effect. The study is classified as **Acceptable**. This study satisfies Guideline requirements (84-2) for genetic effects Category I, Gene Mutations.

MRID No. 412441-11, "FCR 4545 Micronucleus Test on the Mouse to Evaluate for Clastogenic Effects." Initial doses of 200 mg/kg, 120 mg/kg, and 100 mg/kg caused death. A single oral gavage dose of 80 mg/kg FCR 4545 to male and female mice did not cause a significant increase in the frequency of micronucleated polychromatic erythrocytes (MPEs) in bone marrow cells harvested 24, 48, or 72 hours post treatment. Clinical signs of compound toxicity observed in the treated animals were apathy, uncoordinated movement, staggering gait, rolling over, and salivation. It is unclear from these clinical signs if there was a cytotoxic effect on the target organ. FCR 4545 is nonclaustogenic in the mouse micronucleus assay. The study is classified as **Acceptable**, and satisfies Guideline requirements 84-2 for genetic effects Category II, Structural Chromosomal Aberrations.

MRID No. 412441-12, "FCR 4545 C.N. Cyfluthrin K+L (proposed Mutagenicity Study for the Detection of Induced Forward Mutations

in the CHO-HGPRT Assay In Vitro." Quoting from the Clement DER;

> "CONCLUSIONS -- EXECUTIVE SUMMARY: Insoluble (50-100 μg/ml) and soluble (20-40 μg/ml) doses of FCR 4545 with or without S9 activation were neither cytotoxic nor mutagenic in two independently performed Chinese hamster ovary (CHO) cells HGPRT assays. We conclude, therefore, that the test material was adequately investigated and found to be nonmutagenic in this mammalian cell gene mutation assay."

The study is classified as **Acceptable**, and the study satisfies Guideline requirements 84-2 for genetic effects, Category I, Gene Mutations.

MRID No. 412441-13, "FCR 4545 (Technical): Study of the Acute Intraperitoneal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)." The LD_{50} for males equals 8.5 mg/kg, and the LD_{50} for females equals 17 mg/kg. The following toxic signs were observed: lethargy, uncoordinated gait, splayed gait, salivation, difficulty breathing, reduced activity, digging and preening movements, and rolling. Dose levels: 1.0 to 25.0 mg/kg males and 1.0 to 50.0 mg/kg females. The dose was administered via abdominal intraperitoneal injection into Bor:WISW (SPF-Cpb) Wistar rats. The study is classified as **Supplementary** as the Agency does not regulate on acute intraperitoneal injection studies. This study cannot be upgraded.

MRID No. 412441-14, "FCR 4545, FCR 1272: Study of the Acute Intraperitoneal Toxicity to Mice (Formulation in Polyethylene Glycol E 400)." Results for FCR 4545: The LD_{50} equals 18.0 mg/kg; Toxic signs reported were reduced activity, lethargy, uncoordinated gait, dyspnea, splayed gait, and rolling; and Dose levels were 10.0 to 100.0 mg/kg and were administered by intraperitoneal injection into male Bor:NMRI (SPF-Han) mice. Results for FCR 1272: LD_{50} equals 63.0 mg/kg; Toxic signs reported were reduced activity, lethargy, uncoordinated gait, dyspnea, splayed gait, and rolling; and Dose levels were 1.0 to 100.0 mg/kg and were administered by intraperitoneal injection into male Bor:NMRI (SPF-Han) mice. The study is classified as **Supplementary** as the Agency does not regulate on acute intraperitoneal injection studies. This study cannot be upgraded.

MRID No. 412441-15, "FCR 4545 Range-Finding Test for Acute Toxicity to the Dog," was reviewed by John Redden (HED, Toxicology Branch I). The oral doses were 2500 and 5000 mg/kg body weight. The oral doses in this study were not lethal in dogs. However, the emetic effect of the compound make it difficult to determine the actual dose. The intravenous dose was approximately 0.9 ml/kg body weight males and approximately 1.3 ml/kg body weight females. A lethal dose value for intravenous administration, based on death in the one female tested, is 5.0

mg/kg body weight. This study is classified as **Supplementary** as this type of study is not used for regulatory purposes. In addition, this study was not conducted in compliance with the Good Laboratory Practice Standards of 40 CFR Part 160 (FIFRA).

MRID No. 412441-16, "FCR 4545: Study for Acute Oral Toxicity to the Chicken (Gallus domesticus)." FCR 4545 formulated with Cremphor EL in demineralized water (2% v/v). The LD_{50} in hens is > 5000 mg/kg. The study is classified as **Acceptable** for the Guideline requirement 81-1 acute oral toxicity study in chickens. The Toxicity Category is IV. Two minor deviation were noted: 1) hens were not fasted prior to oral administration of the test material; and 2) the homogeneity of the test material in the dosing solution was not determined.

MRID No. 412441-17, "FCR 4545 Subacute Study of Oral Toxicity to Rats." This was a 28-day repeated oral toxicity study in Bor: WISW (SPF-Cpb) rats. The NOEL for both sexes is 1 mg/kg and the LOEL for both sexes is 4 mg/kg. The following clinical signs were observed: Increased activity, salivation, and digging and grooming movements at 4 mg/kg; similar but more severe signs at 16 mg/kg as well as mortality, decreased body weight gain, spread gait, uncoordinated gait, dacryohemorrhea, soft stools, dyspnea, and rolling behavior. The study is classified as **Supplementary** as the Agency does not regulate on 28-day repeated oral toxicity studies. However, the study does supply information for establishing doses for a subchronic study, and pin points the nervous system as a target organ of toxicity.

MRID No. 412057-01, "FCR 4545 (c.n. cyfluthrin K+L proposed): Studies for Acute Inhalation Toxicity to Rats." The following conclusions were drawn from the Clement review:

> 1) LC_{50} = 0.081-0.082 mg/l (aerosol); Toxic signs: reduced motility, tonic extension spasms, bradypnea, reduced reflexes, piloerection, ungroomed coats, rolling movements; Concentration levels: 0.0534, 0.085, 0.0822, and 0.0967 mg/l by head and nose inhalation; Wistar (Bor:WISW (SPF-Cpb) rats.
>
> 2) LC_{50} = 0.532 mg/l (dust); Toxic signs: tonic extension spasm, rolling, dyspnea, slowed reflexes, reddened nose, nasal bleeding, and staggering gait; Concentration levels: 0.212, 0.417, 0.497, 0.640, and 867 mg/l by head and nose inhalation; Wistar (Bor:WISW (SPF-Cpb) rats.

The study is classified as **Acceptable** for the Guideline requirement 81-3 for acute inhalation study in rats. The Clement reviewer reports the following deficiencies: the percentage of oxygen in test atmosphere not reported, time of sampling for particle size not reported, not reported if the chamber concentration was equilibrated prior to the 4-hour exposures, and

the relative humidity was out of range. The Toxicity Category for Aerosol is II and for Dust the Toxicity Category is III. The overall Toxicity Category is II for FCR 4545.

MRID No. 412057-02, "FCR 4545 (Technical): Study for Irritant/Corrosive Effect on skin and Eye (Rabbit)." FCR 4545 is a slight primary dermal and ocular irritant in rabbits. The study is classified as **Acceptable** and satisfies the requirement 81-4 eye irritation study and 81-5 dermal irritation study. The Toxicity Categories are as follows: 81-4 III and 81-5 IV. Following deficiencies noted by Clement reviewer: no information provided for stability of the test substance; only 3 animals used for each experiment; and no quality assurance statement was included in the report. However, a Good Laboratory Practice compliance statement was present.

MRID No. 412057-03, "FCR 4545 In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects." Three nonactivated and three S9-activated doses of FCR 4545 were tested (500 to 500 μg/ml). The two highest doses were insoluble. There was no indication of a clastogenic response at any of the dose levels. Under the conditions of the test FCR 4545 is not clastogenic in this assay. The study is classified as **Acceptable**, and satisfies Guideline requirement 84-2 for genetic effects, Category II, Structural Chromosome Aberration. One minor deviation was noted; slides should have been coded to avoid bias.

MRID No. 412057-04, "Mutagenicity Test on FCR 4545 Technical in the Primary Hepatocyte Unscheduled DNA synthesis Assay." Cytotoxicity was observed at dose ≥ 25.2 μg/ml, and the test compound precipitated at levels ≥ 50.3 μg/ml. No evidence of UDS induction was observed for FCR 4545 in this assay. The study is classified as **Acceptable**, and satisfies Guideline requirement 84-2 for genetic effects Category III, Other Mutagenic Mechanisms.

MRID No. 412057-05, "FCR 1272; Diastereomers: Determination of the Acute Toxicity (LD_{50})." The compound was dissolved, emulsified, and suspended in warm Lutrol (polyethylene glycol 400). The following was extracted from the Clement review:

Chemical: FCR 1272 Diasteromers I, III, And IV
LD_{50} ≥ 5000 mg/kg
Toxic signs: not reported
Dose levels: 250, 500, 1000, 2500, and 5000 mg/kg
Route: oral
Strain: NMRI mice

Chemical: FCR 1272 Diasteromers II
LD_{50} = 31 mg/kg
Toxic signs: not reported
Dose levels: 15, 25, 35, 50, 75, 100, and 250 mg/kg

Route: oral
Strain: NMRI mice

Chemical: FCR 1272 Diasteromers I
LD_{50} = 99 mg/kg
Toxic signs: not reported
Dose levels: 50, 65, 100, 150, and 500 mg/kg
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diasteromers II
LD_{50} = 17 mg/kg
Toxic signs: not reported
Dose levels: 10, 12.5, 15, and 25 mg/kg
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diasteromers III
LD_{50} > 2500 mg/kg
Toxic signs: not reported
Dose levels: 50, 500, 1000, and 2500 mg/kg
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diasteromers IV
LD_{50} = 630 mg/kg
Toxic signs: not reported
Dose levels: 250, 500, and 1000 mg/kg
Route: intraperitoneal
Strain: NMRI mice

The study is classified as **Supplementary**, as the oral studies do not satisfy requirements for a Guideline 81-1 study, and there is no regulatory requirement for a intraperitoneal toxicity study.
Toxicity Category: FCR 1272 Diasteromer I: IV
FCR 1272 Diasteromer II: I
FCR 1272 Diasteromer III: IV
FCR 1272 Diasteromer IV: IV

The Clement reviewer noted the following deficiencies: 1) no information on the test material including purity, stability, or storage conditions; 2) information missing for the animals; 3) mice used, not rats; 4) no females; 5) no vehicle control; 6) not reported if route was actually gavage; 7) duration of fasting not reported; 8) no clinical observations; 9) no animal weight determinations; 10) time of death not reported; 11) necropsies not done on any animals; 12) tabulated data was not defined; 13) methods used for LD_{50} calculations and statistical analysis not reported; and no quality assurance statement was present.

MRID No. 412057-06, "FCR 4545 (C.N. Cyfluthrin K+L Proposed) Study for Sensory Irritant Potential in the Mouse (RD_{50}

Determination)." The following was extracted from the Clement report:

RD_{50} (sensory effect): 0.03724 mg/l
NOEL: ~ 0.002 mg/l
Route: inhalation
Species: mouse
Strain: OF4
Toxic signs: Extreme difficulty in breathing was noted in the mice exposed to a test vapor concentration of 0.0937 mg/l. No mice showed signs of clinical toxicity 4 hours after termination of treatment.

The study is classified as **Supplementary**. However, information from this study can be used to set limits on experiments involving inhalation exposure to FCR 4545.

MRID No. 412057-07, "FCR 4545 (C.N. Cyfluthrin K+L Proposed) Study for Sensory Irritant Potential in the Rat (RD_{50} Determination)." The following information was extracted from the Clement review:

RD_{50} (sensory irritation): ~ 0.038 mg/l for a 45 minute period
NOEL: ~ 0.0003 mg/l (extrapolated
Route: inhalation
Species: SPF-bred Wistar rats
Strain: Bor:WISW (SPF-Cpb)
Toxic signs: piloerection and decreased respiration at ≥ 0.0145 mg/l.
hypersalivation at ≥ 0.0585 mg/l.
nasal irritation at 0.0912 mg/l.

The study is classified as **Supplementary**. However, information from this study can be used to set limits on experiments involving inhalation exposure to FCR 4545.

MRID No. 412057-08, "FCR 4545 (Common Name: Cyfluthrin K+L, suggested) Study of the Range-Finding Subacute Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 403." The following conclusions were drawn from the Clement review:

NOEL = 0.00025 mg/l (no clinical signs)
LEL = 0.00378 mg/l in males and females based on the occurrence of treatment-related clinical signs of systemic toxicity (unpreened hair coat and piloerection) and the statistically significant occurrence of gross lesions (hepatoid foci in the lungs)
Dose Levels: 0.00025, 0.00378, and 0.02801 mg/l
Route/Duration: Inhalation/6 hours/day for 5 days

Strain: Wistar rats

The study is classified as **Supplementary.** The Agency does not regulate on range-finding studies. However, the study provides information for establishing dosage levels for a 4-week subacute inhalation study.

MRID No. 412678-01, "FCR 4545 Study of Subchronic Oral Toxicity to Dogs (13 - Week Feeding Study)," was reviewed by Melba S. Morrow, D.V.M. (HED, Toxicology I). Quoting Dr. Morrow:

> "Under the conditions of this study, the NOEL of FCR 4545 was 60 ppm (3.9 mg/kg) and the LEL was 360 ppm (13.9 mg/kg for males and 15.4 mg/kg for females) based on the occurrence of motor disturbances which include awkward, staggering gait and occasional buckling of the hind limbs in dogs treated at this level. A decrease in body weight gain in females was also reported at doses of 360 ppm."

This study is classified as **Minimum**, and satisfies the Guideline requirement for a subchronic toxicity study in non-rodents.

MRID No. 412057-14, "Overview of Studies which Support Registration of Two End-Use Products (Tempo™ 10% Wettable Powder and TEMPO™ 1) Containing Beta-Cyfluthrin as the Active Ingredient," is not a toxicology study, but rather an argument that:

> "The data, taken collectively, support regulation of end-use products containing beta-cyfluthrin as if they were simply formulations of cyfluthrin."

The Registrant requests the use of the Cyfluthrin database along with the acute studies for β-cyfluthrin to support the registration, "of end-use products containing beta-cyfluthrin for use in hygienic pest control." Table 1 Summarizes the Toxicity Data on Beta-Cyfluthrin and Cyfluthrin that Supports the Registration of Beta-Cyfluthrin, and identifies datagaps.

Table 2 is a Toxicology Profile of Cyfluthrin. Table 3 is a Toxicology Profile of β-cyfluthrin. Table 4 is a Comparison of the Acute Toxicity of Cyfluthrin and Beta-Cyfluthrin

Table 1: Summary of Toxicity Data on Beta-Cyfluthrin and Cyfluthrin for the Support of Registration of End-Use Products Containing Beta-Cyfluthrin.

Study Type	Test Article β-cyfluthrin	Cyfluthrin
81-1 Acute Oral Toxicity	Y	Y
81-2 Acute Dermal Toxicity	Y	Y
81-3 Acute Inhalation Toxicity	Y	Y
81-4 Primary Eye Irritation	Y	Y
81-5 Primary Dermal Irritation	Y	Y
81-6 Dermal Sensitization	N	Y
81-7 Acute Delayed Neurotoxicity (hen)	-	Y
82-1 Subchronic Oral Toxicity	Y	N
82-2 21-Day Dermal, Rabbit	-	N
82-4 21-Day Inhalation, Rat	-	Y
82-4 90-Day Inhalation, Rat	-	Y
82-5 90-Day Neurotoxicity, Rat	-	N
83-1 Chronic Feeding, Dog	-	Y
83-2 Oncogenicity/Feeding, Mouse	-	Y*
83-3 Developmental Toxicity, Rat	-	Y
83-3 Developmental Toxicity (Inhalation), Rat	-	Y
83-3 Developmental Toxicity, Rabbit	-	T
83-4 3-Generation Reproduction, Rat	-	Y
83-5 Chronic Oncogenicity/Feeding, Rat	-	Y
84-2 Gene Mutation	Y	Y
84-2 Structural Chromosome Aberration	Y	Y
84-2 Other Genotoxic Effects	Y	Y
85-1 Metabolism	-	Y

Y = Acceptable or graded at least Minimum
N = Unacceptable or graded Supplementary
T = Tentatively satisfied
- = No study available
* = Supplementary for chronic feeding

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Table 2: Toxicology Profile for Cyfluthrin Technical Registration No. 3125-356 (96.3% a.i.)

Study	Results
81-1: Acute Oral, Rat Minimum / I-III Document No. 4285 MRID Nos. 00131499 and 00131518	LD_{50}: 16.2 (13-19.5) mg/kg (♂ only) in cremophor/distilled water by gavage. 254 (220-294) mg/kg (♂ only) in acetone by gavage. 396 (317-494) mg/kg (♂ only) in DMSO by gavage. 500-1000 mg/kg in (♂ only) in N-methyl pyrollidon by gavage. 590 (509-695) mg/kg (♂), 1189 (1002-1443 mg/kg (♀) in PEG 400 by gavage. 869 (685-1051) mg/kg (♂), 1271 (1102-1456 mg/kg (♀) in PEG 400 by gavage.
81-2: Acute Dermal, Rat Minimum / III Document No. 4285 MRID No. 00131499 and 00131518	LD_{50} >5000 mg/kg (♂ & ♀) undiluted, and in cremophor/distilled water, PEG 400, and 0.9% NaCl.
81-3: Acute Inhalation, Rat Minimum / II Document No. 4285 MRID No. 00131509	4-Hour LC_{50}: >0.735 mg/l (♂), 0.200-0.735 mg/l (♀) in aqueous cremophor. 0.575 (0.458-0.722) mg/l (♂), 0.490 (0.412-0.582) mg/l (♀) in DMSO/PEG.
81-4: Primary Eye Irritation, Rabbit Minimum / III Document No. 4285 MRID No. 00131499	Transient irritation

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81-5: Primary Dermal Irritation, Rabbit Minimum / IV Document No. 4285 MRID No. 00131499	No irritation
81-6: Dermal Sensitization, Guinea Pig Guideline Document No. 4285 MRID No. 00131513	Not a sensitizer by the Maximization Test
81-7: Neurotoxicity, Hen Minimum Document No. 5649 MRID No. 00163040	1. <u>Delayed Neurotoxicity Study</u> - 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. Clinical signs - aggression, anorexia, somnolence, and cyanosis of the crest. There were no gross or microscopic lesions. 2. <u>Neurotoxic Esterase Activity</u> - NTE activity in hens dosed with 4300 mg/kg/day X1 of cyfluthrin resembled that of the vehicle controls.
82-1: 90-Day Oral Subchronic, Rat Minimum to Supplementary Document No. 4285 MRID No. 072008	Dose levels: 0, 30, 100, 300 ppm (0, 1.5, 5, 15 mg/kg/day) in SPF Wistar (TNO W.74) strain. NOEL > 300 ppm (15 mg/kg/day) HDT. No definite test chemical effects noted. Downgraded from Minimum to Supplementary (not tested to the limit dose 1000 mg/kg/day).

82-2: 21-Day Dermal, Rabbit Minimum to Supplementary Document No. 4285 MRID No. 00131527	NOEL >250 mg/kg/day (HDT); Minimum to Supplementary as not tested to the limit dose (1000 mg/kg/day).
82-4: 21-Day Inhalation, Rat Minimum Document No. 4285 MRID No. 00131528	NOEL = 0.0014 mg/l LEL = 0.0023 mg/l (decreased body weight gain)
82-4: 90-Day Inhalation, Rat Minimum Document No. 6426 MRID Nos. 00157793 and 00157882	NOEL = 0.00009 mg/l/day LEL = 0.00071 mg/l/day (unthriftiness, unkempt fur, lethargy, and increased urinary protein)
82-5: 90-Day Neurotoxicity, mammal Data Gap	Data Gap
83-1: Chronic Feeding, Dog Minimum Document No. 4285 MRID No. 00151358	NOEL = 4 mg/kg/day LEL = 16 mg/kg/day (slight ataxia, increased vomiting, diarrhea, and decreased male body weights)
83-2: Oncogenicity, Mouse Supplementary for chronic feeding Minimum for oncogenicity Document No. 4285 MRID No. 00137304	Systemic NOEL <7.5 mg/kg/day (LDT, increased alkaline phosphatase activity in males) Oncogenic NOEL >120 mg/kg/day (HDT)

83-3: Developmental Toxicity, Rat Guideline Document No. 5362 MRID No. 00157794	Maternal NOEL >10 mg/kg/day (HDT) Developmental NOEL >10 mg/kg/day (HDT). Dose ranging study MRID 00157794 showed some effects on maternal toxicity at 10 mg/kg: 1) transient decrease of body weight gain from day 6 to day 11 p.c.; 2) decrease in food consumption during the treatment period; and 3) "single females of the 3 and 10 mg/kg group exhibited slight dyspnea after administration on single days."
83-3: Developmental Toxicity (Inhalation), Rat Minimum Document No. 7628 MRID Nos. 40780401 and 40968501	Maternal NOEL = 0.0011 mg/l Maternal LEL = 0.0047 mg/l (reduced motility, dyspnea, piloerection, ungroomed coats, eye irritation). Developmental NOEL = 0.00059 mg/l Developmental LEL = 0.0011 mg/l (unspecified sternal anomalies, increased runt incidence) **NOTE: This study was lacking specifics on the skeletal and visceral anomalies found, so it was not possible to fully assess the teratogenic effect.**
83-3: Developmental Toxicity, Rabbit	Data Gap
83-4: 3-Generation Reproduction, Rat Minimum Document No. 4285 MRID No. 00131532	Systemic NOEL = 2.5 mg/kg/day Systemic LEL = 7.5 mg/kg/day (decreased pup body weights) Reproductive NOEL = 2.5 mg/kg/day Reproductive LEL = 7.5 mg/kg/day (decreased viability)

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83-5: Chronic Feeding/Oncogenicity, Rat Minimum Document No. 4285 MRID No. 00137303	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)
84-2: Gene Mutation: CHO/HGPRT Mutation Acceptable Document No. 5362 MRID Nos. 00157796 and 00157885	Negative
84-2: Structural Chromosome Aberration: Sister Chromatic Exchange Acceptable Document No. 5362 MRID Nos. 00157795 and 00157884	Negative
84-2: Other Genotoxic Effects: Unscheduled DNA Synthesis Acceptable Document No. 5362 MRID No. 00157798 and 00157886	Negative
85-1: Metabolism Minimum Document No. 4285 MRID No. 00131517	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.

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Table 3: Toxicology Profile for β-Cyfluthrin.

81-1: Acute Oral LD50, Rat, Mouse, and Hen All studies are Acceptable MRID No. 412441-01, -02, 03, 04 and 16	Formulation in Xylene MRID 412441-01 (Rat): LD_{50} Male (fasted): 211 mg/kg (110-404 mg/kg*) LD_{50} Female (fasted): 336 mg/kg (290-391 mg/kg*) LD_{50} Male (fed): 307 mg/kg (260-364 mg/kg*) LD_{50} Female (fed): 343 mg/kg (286-411 mg/kg*); Toxicity Category is II. Formulation in Polyethylene Glycol E 400 MRID 412441-02 (Rat): LD_{50} Male (fasted): 380 mg/kg (231-625 mg/kg*) LD_{50} Female (fasted): 651 mg/kg (329-1,294 mg/kg*) LD_{50} Male (fed): 655 mg/kg (395-1088 mg/kg*) LD_{50} Female (fed): 1,369 mg/kg (1,137-1,651 mg/kg*); Toxicity Category II. Formulation in Polyethylene Glycol E 400 MRID 412441-03 (Mouse): LD_{50} (male) = 91 mg/kg; LD_{50} (female) = 165 mg/kg; Toxicity Category II. Formulation in Acetone /Peanut Oil (1:9) MRID 412441-04 (Rat): LD_{50} Male (fasted): 84 mg/kg (55-131 mg/kg) LD_{50} Female (fasted): 77 mg/kg (65-93 mg/kg) LD_{50} Male (fed): 141 mg/kg (113-177 mg/kg) LD_{50} Female (fed): 108 mg/kg (78-152 mg/kg); Toxicity Category II. Formulation in Cremphor EL MRID No. 412441-16 (Gallus domesticus): LD_{50} > 5000 mg/kg.

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81-2: Acute Dermal LD50, Rat Acceptable MRID Nos. 412441-05, -06	Formulation in Xylene MRID 412441-05: LD_{50} (male) ≥ 5000 mg/kg LD_{50} (female) ≥ 5000 mg/kg Formulation in Polyethylene Glycol E 400 MRID 412441-066: LD_{50} (male) ≥ 5000 mg/kg LD_{50} (female) ≥ 5000 mg/kg
81-3: Acute Inhalation LD50, Rat Acceptable MRID No. 412057-01	Aerosol = 0.082 mg/l (males) and 0.081 mg/l (females); Dust = 0.532 mg/l (males and females); Toxicity Category II.
81-4: Primary Eye Irritation, Rabbit Acceptable MRID No. 4112057-02	Slight irritation; Toxicity Category III.
81-5: Primary Dermal Irritation, Rabbit Acceptable MRID No. 4112057-02	Very slight irritation; Toxicity Category IV.
81-6: Dermal Sensitization, Guinea Pig Unacceptable MRID No. 412441-07	Not a sensitizer by the Maximization Test; the study may be upgraded with the submission of the listed information: individual data for the induction exposures in tabular form, and the results.
82-1: Oral Subchronic, Dog Minimum MRID No. 412678-01	NOEL = 60 ppm (3.9 mg/kg) and the LEL = 360 ppm (13.9 mg/kg for males and 15.4 mg/kg for females) based on the occurrence of motor disturbances which include awkward, staggering gait and occasional buckling of the hind limbs in dogs treated at this level. A decrease in body weight gain in females was also reported at doses of 360 ppm.

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Missing 90-day Rat from this table

83-3 a or b: Developmental Toxicity Study with either rat or rabbit	The Agency is requiring a Developmental Toxicity Study (Rat or Rabbit) with β-Cyfluthrin (bridging study).
84-2: Mutagenicity, Salmonella/Microsome (Ames Assay) Category I Acceptable MRID No. 412441-10	Negative
84-2: Mutagenicity, CHO/Hgprt Mutation Test Category I Acceptable MRID No. 412441-12	Negative
84-2: Mutagenicity, In Vivo Micronucleus Test Category II Acceptable MRID No. 412441-11	Negative
84-2: Mutagenicity, In Vitro Cytogenetics Test Human Lymphocytes Category II Acceptable MRID No. 412057-03	Negative
84-1: Mutagenicity, In Vitro UDS Assay, Rat Hepatocyte Category III Acceptable MRID No. 412057-04	Negative

Note : The results of the bridging studies may required the following: 1) Second species Developmental Toxicity study; 2) 90-Day Inhalation Toxicity Study; and 3) Two Species Chronic/Oncogenicity Toxicity Studies.

Table 4

Comparison of Acute Toxicity Data for Beta-Cyfluthrin and Cyfluthrin

Vehicle	Species	Feeding Status	Sex	Beta-cyfluthrin	Cyfluthrin
				Acute Oral LD50 Values (mg/kg)	
Acetone/peanut oil (1:10)	Rat	Fasted	M	84	254
			F	77	-
		Fed	M	141	-
			F	108	-
Polyethylene Glycol E 400	Rat	Fasted	M	380	590
			F	651	1189
		Fed	M	655	869
			F	1369	1271
Xylene	Rat	Fasted	M	211	499
			F	336	-
		Fed	M	307	-
			F	343	-
Polyethylene Glycol E 400	Mice	Fasted	M	91	291
			F	165	609
				Acute Intraperitoneal LD50 Values (mg/l)	
Polyethylene Glycol E 400	Mice		M	18	63
				Acute Inhalation LC50 Values mg/l	
	Rat		M/F	81.5	405
				Acute Dermal LD50 Values (mg/kg)	
	Rat		M/F	>5000	>5000
				Eye Irritation	
	Rabbit		M/F	Slight irritant	Slight irritation
				Skin Irritation	
	Rabbit		M/F	Slight irritant	Not an irritant
				Dermal Sensitization	
	Guinea Pig		M	Not a sensitizer	Not a

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The Agency does not object to the use of the Cyfluthrin data base to support the registration of β-cyfluthrin if the below listed considerations are taken into account.

The June 29, 1992 draft document entitled, "Toxicology Data Requirements for Enriched Isomer Technical Chemicals," requires the below listed studies for registration of a Food Use Technical:

- acute toxicity battery (6 studies)
- 90 day repeated dose study
- developmental toxicity study (2 species)
- reproduction study
- mutagenicity test battery (3 studies)
- 2 chronic studies
- 2 cancer studies

This paper also states that, "the second species developmental, reproduction, two chronic studies and two cancer studies for the mixed isomer technical could be used to support the isomer enriched technical if side by side acute and 90 day studies for both the mixed isomer and enriched isomer technicals were available and the results were similar."

The Rabbit Developmental Toxicity Study is a data gap for Cyfluthrin. However, a Rabbit Developmental Toxicity Study; MRID 42675401 was submitted under 6 (a) (2) adverse effects. This study tentatively appears to fill the second species requirement. However, this is subject to change pending a detailed review of the study.

In addition the June 29, 1992 draft document entitled, "Toxicology Data Requirements for Enriched Isomer Technical Chemicals," recommends the first species (rat or rabbit) developmental study be performed with the enriched isomer. The Agency is requiring either a rat or rabbit Developmental Toxicity Study with β-cyfluthrin.

Data gaps in the Cyfluthrin data base:

- The 82-2: 21-Day Dermal (Cyfluthrin), Rabbit the NOEL > 250 mg/kg/day (HDT); MRID No. 00131527; Document No. 4285. No behavioral or clinical signs were noted. As the limit dose for a 21-day dermal is 1000 mg/kg/day, this study is down-graded to **Supplementary**. This is a data gap for Cyfluthrin, and the Registrant is required to repeat this study, or provide satisfactory information as to why this was the correct dosing regimen.

- In addition, 82-1: Subchronic Oral (Cyfluthrin), Rat Dose levels: 0, 30, 100, 300 ppm in SPF Wistar (TNO W.74) strain. NOEL > 300 ppm (HDT). No definite test chemical effects

noted. MRID No. 072008; Document No. 4285; Core graded **Minimum**, but downgraded to **Supplementary**, as not tested to limit dose (1000 mg/kg/day). However, the Registrant is not required to repeat this study, because acceptable chronic studies are available.

The following Data Gaps or bridging studies are required for the registration of FCR 4545, β-cyfluthrin:

- 81-6: Dermal Sensitization, Guinea Pig; Not a sensitizer by the Maximization Test; MRID No. 412441-07; This study is **Unacceptable**. This study may be upgraded with the requested information: individual data for the induction exposures in tabular form, and the presentation of the results.

- 83-3 a or b: The Agency is requiring either a rat or rabbit Developmental Toxicity Study with β-cyfluthrin.

Other considerations:

- A Rabbit Developmental Toxicity Study; MRID 42675401 was submitted under 6 (a) (2) adverse effects. This study tentatively appears to fill the second species requirement for Cyfluthrin. However, this is subject to change pending a detailed review of the study.

MRID No. 412057-09, "Acute Toxicity of TEMPO 1 Insecticide: Extrapolation from Studies Performed with TEMPO 2 Insecticide," was reviewed by John C. Redden, M.S. (HED, Toxicology I). Normally six acute studies are required for registration of a new pesticide formulation.

The registrant maintains that the results from the acute studies performed with TEMPO 2 (containing Cyfluthrin) can be used to extrapolate EPA/FIFRA toxicity category for TEMPO 1 (containing β-cyfluthrin). The Registrant's reasoning follows:

1) Cyfluthrin and β-cyfluthrin contain similar amounts of the two more active isomers (II and IV);

2) As TEMPO 1 (β-cyfluthrin) contains 11.5% more xylene than TEMPO 2 (Cyfluthrin). TEMPO 1 (β-cyfluthrin) would probably be more irritating to eyes;

3) TEMPO 1 (β-cyfluthrin) contains approximately half as much active ingredient as TEMPO 2 (Cyfluthrin);

4) The acute studies conducted with TEMPO 2 (Cyfluthrin) were used to extrapolated toxicity categories for TEMPO 1 (β-cyfluthrin). An overall Toxicity Category of I (DANGER) as appropriate for TEMPO 1 (β-cyfluthrin); and

5) The registrant maintains that the acute studies for TEMPO 2 (Cyfluthrin) can be used to estimate the toxicity of TEMPO 1 (β-cyfluthrin).

Table 4, extracted from MRID No. 412057-14, is a comparison of the acute toxicity, eye and skin irritation and dermal sensitization studies on beta-cyfluthrin and cyfluthrin. From this table it can be seen that beta-cyfluthrin, depending on the vehicle used, is, "up to 3-fold more acutely toxic than cyfluthrin by the oral route." The Registrant states that the increase in oral toxicity is due to the increased percentage of enantiomer pair II.

As can be seen from the table beta-cyfluthrin and cyfluthrin have a low dermal toxicity. However, by the inhalation route beta-cyfluthrin is 5 times as toxic as cyfluthrin. Both products are slightly irritating to the eyes causing conjunctival redness reversible within seven days after exposure. Neither agent has dermal sensitization potential in guinea pigs.

Based on the reasoning stated by the Registrant and the Acute Toxicity comparisons, the Agency agrees to substitute the acute battery for TEMPO 2 (Cyfluthrin) for TEMPO 1 (β-cyfluthrin), as long as the Registrant agrees that for labeling purposes TEMPO 1 (β-cyfluthrin) will be Toxicity Category I. However, the Registrant needs to supply the requested information to upgrade MRID No. 412441-07 Dermal Sensitization, Guinea Pig.

Quoting MRID No. 412057-14:

> "Dietary exposure to beta-cyfluthrin from use in food areas of food handling establishments would be negligible. Studies with cyfluthrin using twice the application rate that will be used for beta-cyfluthrin revealed no detectable residues in foods following treatment for hygienic pest control. The tolerance established for cyfluthrin in all foods, 0.05 ppm, was based on the sensitivity of the analytical residue method since no residues were found in food samples. Since beta-cyfluthrin will be used at one-half the rate, the tolerance for cyfluthrin in all foods covers beta-cyfluthrin as well. The data, taken collectively, support regulation of end-use products containing beta-cyfluthrin as if they were simply formulations of cyfluthrin."

Toxicology Branch I has no objections to the granting of this tolerance under the following conditions:

- Residue Chemistry has no objection to the proposed tolerance; and
- the Registrant fulfills the data gaps.

In addition:

"With the exception of the exposure estimates used, the risk assessments performed by the Agency for use of TEMPO 20% Wettable Powder and TEMPO 2 for hygienic pest control are applicable to the corresponding beta-cyfluthrin end-products, TEMPO 10% Wettable Powder and Tempo 1. One-half the exposure estimates used for the cyfluthrin products are appropriate for beta-cyfluthrin products because they will be applied at One-half the application rate used for cyfluthrin products. Beta-cyfluthrin is more efficacious than cyfluthrin due to the fact that it contains more of isomers II and IV. Huge margins of Safety (MOS) ranging from 381 to over 800,000 demonstrate that the health hazards to PCOs and residents from use of products containing beta-cyfluthrin are negligible."

DOC930115

FINAL

010293

DATA EVALUATION REPORT

FCR 4545

Study Type: Special Study

Study Title: FCR 4545 (C.N. Cyfluthrin K+L, Proposed) Study for Sensory Irritant Potential in the Rat (RD50 Determination)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	John Liccione, Ph.D.	8/26/92 Date
Independent Reviewer:	Eve Andersen, Ph.D.	8/26/92 Date
QA/QC Manager:	Sharon Segal, Ph.D.	8/26/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-287
Project Officer: James E. Scott

EPA Reviewer: William B. Greear, M.P.H., DABT
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature

9/3/92
Date

Acting Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karen D. Hamernik for
Signature

5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Special study: Sensory irritancy test

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412057-07
P.C. Number: 128831

TEST MATERIAL: FCR 4545

SYNONYM: Cyfluthrin K+L

SPONSOR: Agricultural Chemicals Division, Mobay Corporation

STUDY NUMBER: T1029604

TESTING FACILITY: Bayer AG Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (C.N. Cyfluthrin K+L Proposed) Study for Sensory Irritant Potential in the Rat (RD50 Determination)

AUTHOR: Dr. J. Pauluhn

STUDY COMPLETED: May 31, 1988

CONCLUSIONS:

RD_{50} (sensory irritation): ~38 (15-291) mg/m^3 for a 45 minute period.

NOEL: ~0.3 mg/m^3 (extrapolated)

Toxic signs:
- piloerection and decreased respiration at $\geq$ 14.5 mg/m^3.
- hypersalivation at $\geq$ 58.5 mg/m^3.
- nasal irritation at 91.2 mg/m^3.

Route: Inhalation

Species: SPF-bred Wistar Rats

Strain: Bor:WISW (SPF-Cpb)

CLASSIFICATION: Core Supplementary. Information in this study can be used to set limits on experiments involving inhalation exposure to FCR 4545.

A. MATERIALS

1. Test Material

Compound: FCR 4545
Chemical name: Cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2, dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Molecular formula: $C_{22}H_{18}Cl_2FNO_3$
Purity of material: 96.3% (Sponsor analysis)
Physical description: White powder
Receipt date: Not specified
Batch no.: 16001/87
Vehicle: 50% ethanol, 50% polyethylene glycol E 400
Storage conditions: The test material was stored at ambient temperature in darkness.
Stability: The test material was guaranteed to be stable by the study sponsor for the duration of the study (data not provided).
Physical properties: pH = 6.5 (2% in water)

2. Controls

Materials: Vehicle (50% ethanol, 50% polyethylene glycol E 400); Air
Animals: Rats (4 males/group)

3. Test Animals

Species: SPF-bred Wistar Rats
Strain: Bor:WISW (SPF-Cpb)
Source: Winkelmann, Borchen, Kreis Paderborn
Receipt date: Not specified
Sex: Male
Number: Total number received not specified
Housing: 5 Animals/cage
Temperature: 22 ± 2°C
Relative humidity: 50%
Lighting: 12-hour light/dark cycle
Air cycle: 10 times/hour
Age at exposure: 8-12 Weeks
Weight: Approximately 160-210 g
Feeding: Food (Altromin® 1324 diet for rats and mice) and tap water provided ad libitum.
Assignment: Random

B. TEST PERFORMANCE

Inhalation Chamber

Four animals per group were individually exposed in Plexiglass® exposure tubes (converted to whole-body flow plethysmograph) attached to a chamber (Figure 1). This was done to ensure that exposure to the test atmospheres was within the animal's respective breathing zones (head and nose exposure only). At the time of exposure, rats were placed in the plastic exposure tubes under the influence of a light halothane anaesthetic in order to minimize the stress involved in placing the animals in the exposure chambers. Rats were adapted for approximately 30 minutes to the exposure conditions; the animals were considered adapted when the respiration frequency exceeded ~ 120 respirations/minute. Following adaptation, basal lung parameters were measured for approximately 15 minutes, at which time the rats were exposed to air only. After determining individual control values, rats were exposed to the test material aerosol (5 concentrations), the vehicle control (50% ethanol, 50% polyethylene glycol E 400), or air only (air control) for 45 minutes. A 10-15 minute recovery period followed exposure to the test substance aerosol.

Dose Preparation/Generation of Test Atmosphere

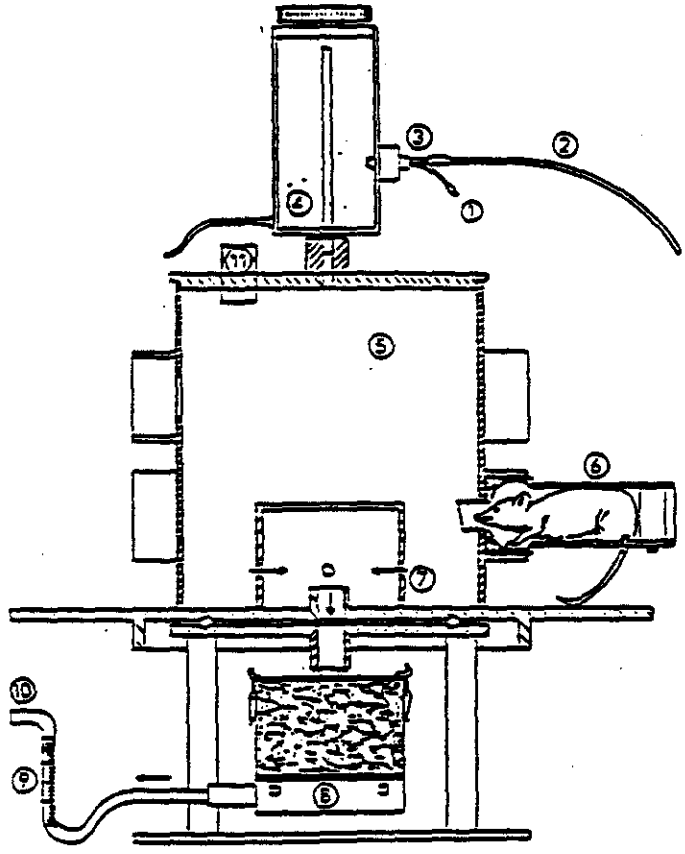
Prior to the initiation of the study, the purity of the test compound was determined to be 96.3%. The stability of the test substance was guaranteed by the sponsor for the duration of the study; however, stability data were not reported. The test aerosol was generated in a cylindrical inhalation chamber equipped with a baffle. The ratio of inlet to outlet air was selected so that 60-80% of the dynamic inlet air was extracted via an aerosol filter (a cotton wool cylinder). Inhalation chambers were operated under fume hoods. A nozzle and condensed compressed air (10 L/minute, dispersion pressure approximately 600 kPa) were used to nebulize a constant 200-µL/minute flow rate of spray solution, consisting of an appropriate amount of FCR 4545 dissolved in ethanol/polyethylene glycol E.

Analytical Determinations

Concentration of test spray in the test atmosphere was determined using gas chromatography (EC detector) from air samples taken from the breathing zone in the immediate vicinity of the test animals. Tubes filled with Florisil were used to collect air samples after a steady state concentration had been reached inside the exposure chamber. The mean analytical exposure concentrations were 0 (air control), 0 (vehicle control); and 0.4, 5.5, 14.5, 58.5, and 91.2 mg/m^3 for Groups 1, 2, 3, 4, 5, 6, and 7, respectively. Animals designated as air controls (Group 1) were exposed to air only. Animals designated as vehicle controls (Group 2) were exposed to ethanol/polyethylene glycol E. Nominal concentration of the test spray was calculated from the quotient of the test article (mg) nebulized into the baffle of the inhalation chamber and the total air throughout the inhalation chamber (m^3). The nominal concentrations of the test material were 0, 0, 10, 50, 160, 500, and 1000 mg/m^3 for Groups 1, 2, 3, 4, 5, 6, and 7, respectively. The study author noted that the lower analytical concentrations as compared to nominal concentrations were due to larger particles being eliminated in the baffle.

0.7

Figure 1: inhalation chamber for aerosol testing



1. Spray solution feed via a Braun infusion pump with 50 ml ground glass jet
2. Compressed air (10 l air/minute); pressure approx. 600 kPa
3. Two-component nozzle (Rhema Labortechnik Co.)
4. Baffle
5. Inhalation chamber
6. Rat in exposure tube (converted to whole-body flow plethysmograph)
7. Symmetrical radially-arranged air outlets
8. Cotton wool filter
9. Rotameter
10. Under-pressure system (vacuum pump)
11. Temperature and air humidity sensor (reference study)

Chamber Monitoring

Approximately 30 exchanges per hour of the inhalation chamber air volume were ensured as a result of the aerosol generation conditions. A humidity sensor with a hygroscopic polymer as a dielectric was used to record relative humidity in the inhalation chamber. Mean representative temperature for the exposure chamber was 22-25°C and mean relative humidity was approximately 30-40%. The mean intervals were a result of random sampling. The frequency of temperature and relative humidity recordings was not reported.

Particle Size Determinations

Particle size determinations were performed for all nominal concentrations with the exception of 10 mg/m^3. Particle size determinations were conducted with a TSI aerodynamic particle sizer with an APS 3300 laser velocimeter. The APS 3300 measuring apparatus was operated at two dilution levels in order to measure higher test aerosol concentrations. The specific distribution of parameters was calculated using a MacIntosh computer program. The frequency of particle size determinations was not reported. The mass median aerodynamic diameter (MMAD) was calculated to be between 1.22 and 1.27 µm and the geometric standard deviation of the particle size distribution was 1.34-1.38 µm. Approximately 99% of the particles were ≤2 µm.

Lung Function Tests

Lung function tests were conducted on all animals prior to exposure (15 minutes), during exposure (45 minutes), and following exposure (10-15 minutes). These tests were performed in a whole-body flow plesthysmograph under quasi-isobaric conditions. Air flows were measured from the pressure difference across a 4 x 400-mesh wire gauze using a differential pressure transducer mounted on the plesthysmograph wall. The functioning of the plethysmograph, differential pressure transducer, and flow integrator calibration were regularly monitored using a 2.0 mL calibration syringe. The following lung parameters were individually determined: peak expiratory flow, tidal volume, respiration rate, minute volume, inspiration time, and expiration time.

Body Weights/Clinical Observations/Gross Necropsies

The body weights of all rats were recorded manually prior to exposure and on days 1, 3, and 7 postexposure.

Animals that were observed for clinical signs of toxicity were observed before exposure, after exposure, but not during exposure unless there were clear signs of toxicity (e.g., abnormal movements, spasms, severe breathing distress). After exposure, animals were observed for clinical signs of toxicity at hourly intervals, if necessary, with particular attention to the following:

- gross appearance of eye and respiratory tract mucous membrane
- state of fur and grooming activity
- general state of exposed skin and pinna
- respiration
- cardiovascular parameters
- somato-motor system and behavior patterns
- central nervous system and autonomic signs

Seven days after treatment, all animals were sacrificed with Evipan-Natrium® (approximately 350 mg/rat, i.p. administration) and were subjected to a gross examination. The study report did not specify which tissures were evaluated for gross findings.

RD_{50} Determination

In order to determine the RD_{50}, the minimum for the smoothed measured respiratory rate (see Statistics section below) was calculated. Dose-response analysis of data (relative frequency decrease [y] as a function of concentration [x] = $\log_{10}$ (concentration)) was performed by the Least Square Method in order to determine the dose producing a 50% depression in the rate of respiration (RD_{50}). The 95% confidence interval (two-tailed) was also calculated.

Statistics and Dose-Response Curve Fitting

Body weight gain was evaluated using analysis of variance (ANOVA). If significant differences were reported in F-test values for ANOVA, a pairwise post hoc comparison using Games and Howell's modification of the Tukey-Kramer Significance Test was performed. Frequent gross pathology findings for the respiratory tract were evaluated using Fisher's pairwise test with a preceding RxC Chi square test. Evaluation of lung parameter values was performed utilizing an HP-ADVANCE-LINK program on an HP 3000 computer. Absolute data on lung parameters were smoothed using a polynomial of the 3rd degree regression model and then standardized to 100%.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Mortality

No mortalities were observed.

Clinical Signs

Groups 1, 2, 3, and 4, at respective concentrations of 0, 0, 0.7 and 5.5 mg/m^3 showed no treatment-related abnormal clinical signs. Rats exposed to 14.5 mg/m^3 of the test aerosol showed a slightly slower respiration rate and piloerection up to 2 hours following exposure. Rats exposed to 58.5 mg/m^3 also showed these clinical signs and, in addition, hypersalivation. Rats exposed to 91.2 mg/m^3 of the test substance aerosol showed signs of nasal irritation shortly after exposure termination, as

indicated by an abnormal burrowing in cage bedding and scratching in the area of the nose. Additional clinical signs reported for animals exposed to 91.2 mg/m^3 test aerosol included temporary hypersalivation, decreased respiration, and piloerection. All rats were free from clinical signs beyond the first day of treatment.

Body Weights

No statistically significant, treatment-related effects on body weight or body weight gain were observed in any of the treatment groups during the posttreatment observation period.

Lung Function Parameters

Increases in inspiration and/or expiration time were noted in rats following exposure to ≥14.5 mg/m^3. An abnormal increase in the inspiration time was noted in rats exposed to 91.2 mg/m^3 aerosol. Based on a cubic polynomial regression model, the percentage decrease in respiratory rate in rats exposed to 0.7, 5.5, 14.5, 58.5, and 91.2 mg/m^3 aerosol was 22, 30, 40, 50, and 63, respectively.

RD_{50} Calculation

The RD_{50} was estimated to be equal to 38 mg/m^3 air, with 95% confidence interval of 15-291 mg/m^3 air. A NOEL of ~0.3 mg/m^3 was estimated from the extrapolation of data; this value was also the RD0. The extrapolated NOEL is supported by the finding that animals exposed to 0.7 mg/m^3 aerosol displayed a similar response to that of control.

Gross Necropsy

The study report indicated that no gross lesions in any organs were noted in the test and control groups. However, the study author did not specify which organs were examined.

D. QUALITY ASSURANCE MEASURE

No quality assurance statement was presented.

A statement of data confidentiality, was signed and dated April 26, 1989.

A statement indicating that the study was not conducted in compliance with the Good Laboratory Practice Standards of 40 CFR Part 160, was attached and dated April 26, 1989.

E. REVIEWERS' DISCUSSION

Although there are no guidelines regarding irritancy testing of chemicals following inhalation exposure, the design and conduct of the sensory irritant test in rats, as well as the determination of the RD_{50}, were acceptable. However, a positive control (i.e., a chemical established as

a sensory irritant to the respiratory tract) was not included in the study design.

Based on the results, FCR 4545 tested positive as a sensory irritant in rats. The study author considered the sensory irritation of FCR 4545 to be relatively high; however, concentration-dependent data and an RD_{50} for an established positive control were not provided for comparative purposes. A maximum depression of respiratory rate of ~60% was achieved in this study. The RD_{50} was estimated to be ~38 (15-291) mg/m^3 test aerosol for a 45 minute period. Based on extrapolation of the data, an RD_0 of ~0.3 mg/m^3 was estimated; this value was also considered by the study author the NOEL. The decrease in respiratory rate was considered by the study author to be the result of overall slower breathing. Besides respiratory rate, changes in other lung function parameters, for example, increases in inspiration and/or expiration time, were noted in rats exposed to $\geq$14.5 mg/m^3 test material. Animals exposed to 91.2 mg/m^3 aerosol showed signs of an abnormally lengthened inspiration time.

In summary, FCR 4545 is a sensory irritant in rats following inhalation exposure.

Seven days after treatment, all animals were sacrificed with Evipan-Natrium® (approximately 350 mg/rat, i.p. administration) and were subjected to a gross examination. The study report did not specify which tissures were evaluated for gross findings.

RD_{50} Determination

In order to determine the RD_{50}, the minimum for the smoothed measured respiratory rate (see Statistics section below) was calculated. Dose-response analysis of data (relative frequency decrease [y] as a function of concentration [x] = $\log_{10}$ (concentration)) was performed by the Least Square Method in order to determine the dose producing a 50% depression in the rate of respiration (RD_{50}). The 95% confidence interval (two-tailed) was also calculated.

Statistics and Dose-Response Curve Fitting

Body weight gain was evaluated using analysis of variance (ANOVA). If significant differences were reported in F-test values for ANOVA, a pairwise post hoc comparison using Games and Howell's modification of the Tukey-Kramer Significance Test was performed. Frequent gross pathology findings for the respiratory tract were evaluated using Fisher's pairwise test with a preceding RxC Chi square test. Evaluation of lung parameter values was performed utilizing an HP-ADVANCE-LINK program on an HP 3000 computer. Absolute data on lung parameters were smoothed using a polynomial of the 3rd degree regression model and then standardized to 100%.

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Mortality

No mortalities were observed.

Clinical Signs

Groups 1, 2, 3, and 4, at respective concentrations of 0, 0, 0.7 and 5.5 mg/m^3 showed no treatment-related abnormal clinical signs. Rats exposed to 14.5 mg/m^3 of the test aerosol showed a slightly slower respiration rate and piloerection up to 2 hours following exposure. Rats exposed to 58.5 mg/m^3 also showed these clinical signs and, in addition, hypersalivation. Rats exposed to 91.2 mg/m^3 of the test substance aerosol showed signs of nasal irritation shortly after exposure termination, as indicated by an abnormal burrowing in cage bedding and scratching in the area of the nose. Additional clinical signs reported for animals exposed to 91.2 mg/m^3 test aerosol included temporary hypersalivation, decreased respiration, and piloerection. All rats were free from clinical signs beyond the first day of treatment.

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No statistically significant, treatment-related effects on body weight or body weight gain were observed in any of the treatment groups during the posttreatment observation period.

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Increases in inspiration and/or expiration time were noted in rats following exposure to ≥14.5 mg/m^3. An abnormal increase in the inspiration time was noted in rats exposed to 91.2 mg/m^3 aerosol. Based on a cubic polynomial regression model, the percentage decrease in respiratory rate in rats exposed to 0.7, 5.5, 14.5, 58.5, and 91.2 mg/m^3 aerosol was 22, 30, 40, 50, and 63, respectively.

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The study report indicated that no gross lesions in any organs were noted in the test and control groups. However, the study author did not specify which organs were examined.

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Based on the results, FCR 4545 tested positive as a sensory irritant in rats. The study author considered the sensory irritation of FCR 4545 to be relatively high; however, concentration-dependent data and an RD_{50} for an established positive control were not provided for comparative purposes. A maximum depression of respiratory rate of ~60% was achieved in this study. The RD_{50} was estimated to be ~38 mg/m^3 test aerosol.

6 (15 - 291) for a 45 min pose

Based on extrapolation of the data, an RD_0 of ~0.3 mg/m^3 was estimated; this value was also considered by the study author the NOEL. The decrease in respiratory rate was considered by the study author to be the result of overall slower breathing. Besides respiratory rate, changes in other lung function parameters, for example, increases in inspiration and/or expiration time, were noted in rats exposed to ≥14.5 mg/m^3 test material. Animals exposed to 91.2 mg/m^3 aerosol showed signs of an abnormally lengthened inspiration time.

In summary, FCR 4545 is a sensory irritant in rats following inhalation exposure.

DOC930104

FINAL

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DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Acute oral and intraperitoneal toxicity in mice

Study Title: FCR 1272; Diastereomers: Determination of the Acute Toxicity (LD50)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-293
Project Officer: James E. Scott

Guideline Series 81-1: Acute oral toxicity in mice
Guideline Series (N/A): Acute intraperitoneal toxicity in mice

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
Sept 4, 1992
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl D. Hoffele for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Acute oral and intraperitoneal toxicity in mice

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412057-05
PC Number: 128831

TEST MATERIAL: FCR 1272 (Diastereomers I, II, III, and IV)

SPONSOR: Mobay Corporation

STUDY NUMBER: Not reported

TESTING FACILITY: Bayer AG, Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany

TITLE OF REPORT: FCR 1272; Diastereomers: Determination of the Acute Toxicity (LD50)

AUTHOR: W. Flucke

STUDY COMPLETED: September 3, 1980

CONCLUSIONS: Chemical: FCR 1272 Diastereomers I, III, and IV
LD_{50} = >5000 mg/kg
Toxic signs: not reported
Dose levels: 250, 500, 1000, 2500, and 5000 mg/kg
Route: oral
Strain: NMRI mice

Chemical: FCR 1272 Diastereomer II
LD_{50} = 31 mg/kg
Toxic signs: not reported
Dose levels: 15, 25, 35, 50, 75, 100, and 250 mg/kg
Route: oral
Strain: NMRI mice

Guideline Series 81-1: Acute oral toxicity in mice
Guideline Series (N/A): Acute intraperitoneal toxicity in mice

Chemical: FCR 1272 Diastereomer I
LD_{50} = 99 mg/kg
Toxic signs: not reported
Dose levels: 50, 65, 100, 150, and 500 mg/kg
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diastereomer II
LD_{50} = 17 mg/kg
Toxic signs: not reported
Dose levels: 10, 12.5, 15, and 25 mg/kg
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diastereomer III
LD_{50} = >2500 mg/kg
Toxic signs: not reported
Dose levels: 50, 500, 1000, and 2500
Route: intraperitoneal
Strain: NMRI mice

Chemical: FCR 1272 Diastereomer IV
LD_{50} = 630 mg/kg
Toxic signs: not reported
Dose levels: 250, 500, and 1000 mg/kg
Route: intraperitoneal
Strain: NMRI mice

CLASSIFICATION: Supplementary Data. However, the oral studies do not satisfy requirements for a Guideline Series 81-1 study.

There are no Guideline Series available for acute intraperitoneal toxicity studies. However, the study provides supplemental information regarding the toxicity of the test material following oral and intraperitoneal exposures.

TOXICITY CATEGORY: FCR 1272 Diastereomer I: IV--Caution
FCR 1272 Diastereomer II: I--Danger
FCR 1272 Diastereomer III: IV--Caution
FCR 1272 Diastereomer IV: IV--Caution

A. MATERIALS

1. Test Material

Test material: FCR 1272 (Diastereomers I, II, III, and IV)
Purity: Not reported
Physical description: Not reported
Lot number: Not reported
Storage conditions: Not reported
Stability: Not reported

Guideline Series 81-1: Acute oral toxicity in mice
Guideline Series (N/A): Acute intraperitoneal toxicity in mice

2. Controls

Animals: None
Test substance: None

3. Test Animals

Species: Mouse
Strain: NMRI
Source: Not reported
Sex: Male
Numbers: 10/dose (also 5 and 20 were used for some dosage groups)
Housing: Not reported
Age: Not reported
Weight at exposure: Not reported
Feeding: Not reported except that animals were fasted prior to testing
Selection: Not reported

4. Exposure

Route of administration: Oral (not defined further) and intraperitoneal (i.p.) injection
Dose levels--Oral: 250, 500, 1000, 2500, and 5000 mg/kg (Diastereomers I, III, and IV)
15, 25, 35, 50, 75, 100, and 250 mg/kg (Diastereomer II)

Dose levels--i.p.: 50, 65, 100, 150, and 500 mg/kg (Diastereomer I)
10, 12.5, 15, and 25 mg/kg (Diastereomer II)
50, 500, 1000, 2500 (Diastereomer III)
250, 500, 1000 (Diastereomer IV)

B. TEST PERFORMANCE

The methods for calculating LD50 values or for statistical analyses were not reported. The Diastereomers were emulsified and suspended in warm Lutrol (polyethylene glycol 400). Animals were fasted prior to treatment. Oral and i.p. exposures were given in volumes of 5-10 ml/kg of body weight. There was a 14-day recovery period following exposure. No other details were provided.

C. RESULTS AND STUDY AUTHORS' CONCLUSIONS

Tables were presented for each of the FCR 1272 Diastereomers I, II, III, and IV for oral and i.p. exposures. A copy of these tables is shown in Appendix A of this report. The tables appear to present mortality incidence data for each exposure group; however, none of the parameters in the tables are defined. Also, undefined percentages are reported which appear to be the percent solution administered.

The author reported LD_{50} values for each of the diastereomers for both oral and i.p. exposures. For the oral exposures, Diastereomers I, III, and IV each had an LD_{50} value greater than 5000 mg/kg, the maximum dose tested. An LD_{50} of 31 mg/kg was reported for Diastereomer II. The reported LD_{50} values for Diastereomers I, II, III, and IV following i.p. injection are 99, 17, >2500, and 630 mg/kg, respectively. No other data were shown.

D. QUALITY ASSURANCE MEASURE

No Quality Assurance Statement was presented. A Good Laboratory Practice compliance statement was included.

E. REVIEWERS' COMMENTS

The study provided incidence of mortality data and LD_{50} values. However, data were not provided for time of death, clinical signs, and the purity and stability of the chemical. Also, it was not reported whether animals were observed for signs of toxicity and the methods of LD_{50} calculation and statistical analysis were not reported.

Due to the lack of definitions for the parameters in the mortality tables, it is difficult to draw any conclusions from the raw data. However, if it is assumed that the first column after the percentages represents incidence of mortality and the third column is the total number exposed, it can be concluded that the LD_{50} values that were reported by the study author are accurate. Based on these results, the Toxicity Category for the FCR 1272 Diastereomers I, III, and IV is IV--Caution. The Toxicity Category for FCR 1272 Diastereomers II is I--Danger.

The oral segment of this study was classified as Supplementary Data. The following limitations were noted: 1) no information was provided on the test material including purity, stability, or storage conditions; 2) very little information was provided for the animals and the treatment of the animals; 3) mice were used instead of rats, with no explanation; 4) no females were used; 5) a vehicle control was not included; 6) it was not reported whether the required route of gavage was used; 7) the duration of fasting was not reported; 8) no clinical observations were made, especially for Diastereomer II which was lethal at concentrations less than 5000 mg/kg; 9) animal weights were not determined; 10) time of death was not reported; 11) no autopsies were performed for any of the animals; 12) although the data were tabulated, no definition was given as to what the data represented; 13) the methods used for LD_{50} calculations and statistical analysis were not reported.

The intraperitoneal segment of this study is classified Supplementary Data. There are no guidelines for acute studies by this route of exposure. However, the study provides supplemental information.

The reviewers also note that no quality assurance statement was provided.

Guideline Series 81-1: Acute oral toxicity in mice
Guideline Series (N/A): Acute intraperitoneal toxicity in mice

APPENDIX A

Mortality Tables from the Report:
FCR 1272; Diastereomers: Determination of the Acute Toxicity (LD50)

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Bestimmung der akuten Toxizität (LD_{50}) / Determination of the Acute Toxicity (LD50)
Substanz: FCR 1272/Diastereomere / Substance: FCR 1272/Diastereomers

oral LD_{50}

FCR 1272/I, KRJ 200580/1
Diastereomer I

250 mg/kg	5 %	0/10/10
500 mg/kg	10 %	0/10/10
1000 mg/kg	20 %	0/10/10
2500 mg/kg	50 %	0/10/10
5000 mg/kg	50 %	0/10/10

LD_{50}: >5000 mg/kg

FCR 1272/II, KRJ 160879/2
Diastereomer II

15 mg/kg	0,3 %	2/10/10
25 mg/kg	0,5 %	4/10/10
35 mg/kg	0,7 %	7/10/10
50 mg/kg	1 %	8/10/10
75 mg/kg	1,5 %	8/10/10
100 mg/kg	2 %	9/10/10
250 mg/kg	5 %	10/10/10

LD_{50}: 31 mg/kg

FCR 1272/III, KRJ 200580/3
Diastereomer III

250 mg/kg	5 %	0/10/10
500 mg/kg	10 %	0/10/10
1000 mg/kg	20 %	0/10/10
2500 mg/kg	25 %	0/10/10
5000 mg/kg	25 %	0/10/10

LD_{50}: >5000 mg/kg

FCR 1272/IV, KRJ 200580/4
Diastereomer IV

250 mg/kg	5 %	0/10/10
500 mg/kg	10 %	0/10/10
1000 mg/kg	20 %	0/10/10
2500 mg/kg	25 %	0/10/10
5000 mg/kg	25 %	0/10/10

LD_{50}: >5000 mg/kg

intraperitoneal LD_{50}

FCR 1272/I, KRJ 200580/1
Diastereomer I

50 mg/kg	1 %	0/10/10
65 mg/kg	1,3 %	1/10/10
100 mg/kg	2 %	5/10/10
150 mg/kg	3 %	9/10/10
500 mg/kg	10 %	5/ 5/ 5

LD_{50}: 99 mg/kg

FCR 1272/II, KRJ 160879/2
Diastereomer II

10 mg/kg	0,2 %	0/10/10
12,5 mg/kg	0,25 %	5/20/20
15 mg/kg	0,3 %	4/10/10
25 mg/kg	0,5 %	8/10/10

LD_{50}: 17,0 mg/kg

FCR 1272/III, KRJ 200580/3
Diastereomer III

50 mg/kg	1 %	0/10/10
500 mg/kg	10 %	0/ 5/ 5
1000 mg/kg	20 %	0/10/10
2500 mg/kg	50 %	0/10/10

LD_{50}: >2500 mg/kg

FCR 1272/IV, KRJ 200580/4
Diastereomer IV

250 mg/kg	5 %	5/10/10
500 mg/kg	10 %	2/10/10
1000 mg/kg	20 %	9/10/10

LD_{50}: ca. 630 mg/kg

(Dr. W. Flucke)

Reviewed by: Melba S. Morrow, D.V.M. 7/2/91
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. 7/15/91
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic (90 Day) Oral Toxicity - Dogs.

GUIDELINE #: 82-1

TOX. CHEM. #: 266E

MRID #: 412678-01

TEST MATERIAL: FCR 4545

SYNONYMS: Beta Cyfluthrin, Tempo 1

STUDY NUMBERS: 98348

SPONSOR: Mobay

TESTING FACILITY: Bayer, AG
Germany

TITLE OF REPORT: FCR 4545 Study of Subchronic Oral Toxicity to Dogs (13 - Week Feeding Study)

AUTHORS: Dr. E. Von Keutz

REPORT ISSUED: 11/4/87

CONCLUSIONS: Under the conditions of this study, the NOEL of FCR 4545 was 60 ppm (3.9 mg/kg) and the LEL was 360 ppm (13.9 mg/kg for males and 15.4 mg/kg for females) based on the occurence of motor disturbances which included awkward, staggering gait and occasional buckling of the hind limbs in dogs treated at this level. A decrease in body weight gain in females was also reported at doses of 360 ppm.

CLASSIFICATION: Minimum

The study satisfies the requirements set forth in Subdivision F Guidelines for a subchronic toxicity study in non-rodents.

MATERIALS: The test material was FCR 4545 (beta cyfluthrin) which contained 99% active ingredient. The test animals were beagles which were 27 to 31 weeks of age and weighed between 7.6 and 9.7 kg and were obtained from Winkelmann, a breeder in Germany.

METHODS: Following an acclimation period during which time animals were vaccinated, dewormed, identified with tattoes and metal collars and given an ophthalmoscopic examination, four males and four females were randomly assigned to one of four groups. The groups received daily doses of the test material at the following levels:

Group	Dose (ppm)	Dose (mg/kg)
Group I	0	0
Group II	10 ppm	0.39
Group III	60 ppm	2.35(M), 2.5 (F)
Group IV	360 ppm	13.9 (M), 15.4 (F)

These doses were based on a two-week range finding study conducted in beagles. At the highest dose tested (640 ppm), motor disturbances were present in all dogs. Marked impairment in general physical condition, reduced feed consumption, weight loss, recumbency and death in one male dog were noted at this dose level. At 320 ppm, occasional vomiting, awkward gait involving the hind limbs and conjunctival irritation were reported.

Animals were individually housed and were subjected to a 12 hour light/dark cycle. The kennel temperature was maintained between 20 and 23° C and the relative humidity was between 30 - 50%.

The test compound was uniformly mixed with a dry ration and administered daily for thirteen weeks. Feed was made available to the dogs for a period of 20 to 22 hours. All unconsumed feed was weighed prior to the next feeding in order to determine the amount of test material that each individual consumed.

During the study period, animals were subjected to daily observations for clinical signs of toxicity. Body temperatures were measured and femoral pulse was taken. Feed consumption was measured daily, body weights were recorded weekly, and neurological exams were conducted which consisted of pupillary, corneal, patellar tendon and bending and righting reflexes. Neurological exams were conducted on one occasion prior to the start of the study and again on weeks 4, 7 and 13.

Ophthalmoscopic examinations were conducted on during the acclimation period and on weeks 7 and 13. Hematology, clinical chemistry and urinalysis were conducted prior to the administration of the test material and on weeks 4, 7 and 13.

The following parameters were measured:

x Hematocrit (HCT)
x Hemaglobin (HGB)
x Leucocyte count (WBC)
x Erythrocyte count (RBC)
x Platelet count
x Leucocyte differential
x Mean corpuscular hemaglobin
x Mean corpuscular hemaglobin concentration
x Mean corpuscular volume
x Reticulocytes

Blood clotting measurements:
Thromboplastin time
Sedimentation rate
Prothrombin time

Electrolytes:
x Calcium
x Chlorine
Magnesium
x Phosphorous
x Potassium
x Sodium

Enzymes:
x Creatinine phophokinase
x Alkaline phosphatase
x Lactic dehydrogenase
x SGPT
x SGOT
Gamma glutamyl transferase
x Glutamate dehydrogenase
Cholinesterase
x Inorganic phosphorus
x Cytochrome P450
x N- demethylase
x Triglyceride

Other Serum Chemistry Values:
x Albumen
x Blood creatinine
x BUN
x Cholesterol
x Globulin
x Glucose
x Total Bilirubin
x Total protein
x Triglycerides
Serum protein electrophoresis

Urinalysis:
x volume
x specific gravity
x pH
x protein
x glucose
x blood
x bilirubin
x ketone bodies

Animals were anesthetized and sacrificed by exsanguination. A full gross necropsy was performed on all animals. Brain, liver, heart, kidneys, spleen, pancreas, prostate, thyroid, adrenals and testes/ovaries were weighed.

Tissues were embedded in paraplast and sections were stained with hematoxylin and eosin. The kidneys were stained with PAS.

The following CHECKED (x) tissues were collected for histological examination. Weighed organs are designated by (xx)

Digestive system	Cardiovasc./Hemat.	Neurologic
x Tongue	x Aorta	xx Brain
x Salivary glands	xx Heart	xx Periph. nerves
Esophagus	x Bone marrow	x Spinal cord
x Stomach	x Lymph nodes	
x Duodenum	xx Spleen	
x Jejunum	x Thymus	Glandular
x Ileum	x Tonsils	x Parathyroids
x Cecum		xx Adrenals
x Colon	Urogenital	xx Thyroid
x Rectum	xx Kidneys	x Pituitary
	x Urinary bladder	
xx Liver	xx Testes	
xx Gall bladder	x Epididymides	Other
xx Pancreas	xx Prostate	x Bone
	x Seminal vesicle	x Skin
Respiratory	xx Ovaries	x Skel. muscle
x Trachea	x Uterus	x All gross lesions
x Lung	x Vagina	x Eyes/ Optic N.
Nose		
Pharynx		
Larynx		

At the end of the study, flouride levels were determined in the bones (femur) and teeth of all animals in the study.

Test Compound Analysis

The active ingredient was extracted from dog food with ethyl acetate. The quantitative determination of the test compound was made by using gas chromatographic detection. Peak areas of the analytical solutions were determined and compared to those of external standard solutions. Recoveries of the test compound were determined by recovery tests.

QUALITY ASSURANCE: A statement of Quality Assurance dated 10/30/87 was included in the submission.

STATISTICAL ANALYSIS: Descriptive statistical analysis was performed. Calculations included determination of the arithmetic mean and of the standard deviations. Levels of significance were not identified.

RESULTS: Clinical signs of toxicity were observed with the most frequency in the high dose group. Motor disturbances affecting 4 dogs in the 360 ppm group were observed on 41 occasions and consisted mainly of alterations in normal gait with occasional buckling of the hind limbs. These motor disturbances were

observed approximately 6 to 8 hours after feeding. Vomiting was reported for 4 dogs and pasty feces and diarrhea were reported in 2 and 5 dogs, respectively. Observations in the high dose group are considered compound related.

In the mid dose group (60 ppm), vomiting was reported on two occasions in one dog. Pasty feces were observed on two occasions and diarrhea was reported 5 times and affected four animals. No motor disturbances were observed in animals in this treatment group.

Motor disturbances and vomiting were not reported in the 10 ppm group. Diarrhea and pasty feces were reported in two dogs. Pasty feces were observed on two occasions and diarrhea was observed on three occasions.

In the control animals, one dog vomited and one dog had diarrhea on two occasions. (See Table I, extracted from the study report for information on the frequency of clinical signs).

In males feed intake was lowest in the 10 ppm group when compared to controls; however, in females the high dose group had the lowest feed consumption (9% lower than controls). When both sexes were combined, there did not appear to be a significant difference between groups.

Body weight was affected in females in the high dose group and was consistent with the decrease in feed intake. There was a 65% difference in body weight gain when these animals were compared to controls. An average weight gain of 0.35 kg was reported for females receiving 360 ppm and an average weight gain of 1.0 kg was reported for the control females at the end of the study. Decreased weight gain appeared to be associated with lower feed efficiency as calculated by the reviewer. Statistical significance was not determined in the report; however, the observed decrease in body weight gain appears to be biologically significant. No significant differences in average body weight gains were reported for males; treated males gained slightly more weight than controls. (See Table II for information on body weight gain and food intake in females).

FCR 4545 had no affect on hematology, serum chemistry or urinalysis. Positive tests for blood in the urine were reported for one dog in group I and for two dogs in group II. Repeat collections did not yield the same results; this finding was not considered to be treatment related and may have been the result of trauma.

No differences were observed in relative and absolute organ weights when treated animals were compared to controls. No compound related gross or microscopic lesions were observed and no significant differences were reported in the flouride content

of bones and teeth from treated and control animals.

With regard to the test compound analysis, the mean recovery of active ingredient was 104% of nominal with a standard deviation of 3.9%.

DISCUSSION: Based on the results of this study, the NOEL was 60 ppm and the LEL was 360 ppm based on the occurence of motor disturbances and a decrease in weight gain reported in high dose females. The observed motor disturbances are associated with pyrethrin intoxication and no gross or microscopic lesions were present that could be associated with these disturbances.

Feed efficiency was lower in the high dose females when compared to controls. This is indicative of the toxic effects of the compound and is reflected in the differences observed in the over all body weight gains for high dose females.

When the number of animals affected in the mid dose group is considered, the incidence of diarrhea appears to be dose related. However, it would be difficult to attribute this clinical observation to the test compound for the following reasons:

- Diarrhea occured on two occasions in one animal in the control group; one time in one animal and twice in another in the low dose group; one time in three animals and twice in one animal in the mid dose group. One or two episodes of diarrhea in individual animals over a three month period is not unusual in a laboratory setting.

- The time at which diarrhea was observed varied in each of the affected animals and with the exception of one animal in the mid dose group, diarrhea is followed by complete recovery.

- There are no additional clinical findings or pathological lesions that can be correlated to the occurence of diarrhea in these mid dose animals.

In the high dose group, the observed increase in incidence of diarrhea may be treatment related in that it occured on three or more occasions in two of the five animals that were affected. Additionally, the diarrhea occured in animals that had a high frequency of observed motor disturbances which indicates that compound related toxicity was present.

If doses between 60 and 360 were investigated a more accurate assessment of the LEL could be determined. The study is therefore classified as core minimum.

TABLE I - FREQUENCY OF CLINICAL SIGNS

Clinical signs (f/#)[a]	Dose Group (ppm)			
	0	10	60	360
Motor disturbance	0	0	0	41x/4
Vomiting	1x/1	0	2x/1	9x/4
Pasty feces	0	2x/2	2x/2	5x/2
Diarrhea	2x/1	3x/2	5x/4	14x/5

a = frequency of observation of symptoms / # of animals with symptoms

TABLE II - BODY WEIGHT GAINS, FOOD INTAKE and FEED EFFICIENCY for HIGH DOSE FEMALES[a]

	Dose Group (ppm)			
	0	10	60	360
Week		Body Weight Gain (kg)		
2	0.00	0.20	0.10	0.10
3	0.05	0.15	0.12	0.00
4	0.10	0.10	0.08	0.10
5	0.15	0.15	0.18	0.05
6	0.08	0.13	0.08	-0.10
7	0.18	0.18	0.08	0.08
8	0.13	0.05	0.08	0.05
9	-0.05	0.08	0.10	0.00
10	0.08	0.18	0.00	0.10
11	0.20	0.23	0.08	0.08
12	0.03	0.03	0.05	-0.02
13	0.05	0.15	0.18	-0.08
Total kg (% of control)	1.00	1.48(148)	1.13(113)	0.35(35)
		Food Intake (kg)		
1	2.45	2.45	2.45	2.27
2	2.45	2.45	2.45	2.41
3	2.45	2.45	2.45	2.45
4	2.66	2.66	2.66	2.45
5[b]	2.66	2.66	2.66	2.66
13	2.66	2.66	2.66	2.40

a = table derived from data provided by sponsor.
b = from weeks 6 thru 12, the food intake was the same as week 5.

C10293

DOC930114

FINAL

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Oral Toxicity in Rats

Study Title: FCR 4545 Technical: Study of the Acute Oral Toxicity to Rats (Formulation in Xylene)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel, M.P.H.	7-16-92 Date
Independent Reviewer:	John Liccione, Ph.D.	7-16-92 Date
QA/QC Manager:	Sharon Segal, Ph.D.	7-16-92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-295
Project Officer: James E. Scott

Approved by:
EPA Reviewer: John Redden, M.S.
Review Section III, Toxicology Branch I (HED)
Signature [signature]
Date 2/24/93

EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I (HED)
Signature [signature] for
Date 5/15/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-1: Acute oral toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-01
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in xylene

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 98349

STUDY NUMBER: T 1022142 (fasted animals); T 3022144 (fed animals)

TESTING FACILITY: BAYER AG, Institut fuer Toxicologie/Landwirtschaft, Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Xylene)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 4, 1987

CONCLUSION:

LD_{50} Male (fasted): 211 mg/kg (95% confidence interval = 110-404 mg/kg)
LD_{50} Female (fasted): 336 mg/kg (95% confidence interval = 290-391 mg/kg)

LD_{50} Male (fed): 307 mg/kg (95% confidence interval = 260-364 mg/kg)
LD_{50} Female (fed): 343 mg/kg (95% confidence interval = 286-411 mg/kg)

CLASSIFICATION: Acceptable. This study satisfies the guideline requirement (81-1) for an acute oral toxicity study. Neither summary nor individual

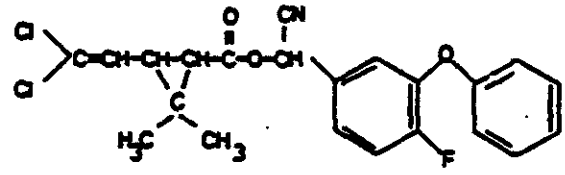
incidence data for clinical signs of toxicity in animals administered the test material were tabulated to show the number of animals displaying signs of toxicity. Therefore, the reviewers cannot assess if the effects were dose related.

TOXICITY CATEGORY: II

A. MATERIALS

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Xylene
Type of formulation: Suspension
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropance-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1% (Sponsor analysis)
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (21-22.5°C)
Odor: Odorless
Stability: When stored for 0 and 65 hours, stability of the 0.01 % nominal value was 112 and 115%, respectively, and stability of the 50% nominal value was 112 and 106%, respectively. Stability was determined before the study.
Homogeneity: Homogeneity of the test suspensions was maintained during administration by use of a magnetic stirrer. Homogeneity of three samples of the suspension (nominal value = 50%) was reported to be 99%, 104%, and 99%.

2. Controls

Animals: 5 Males; 5 females
Vehicle: Xylene

3. Test Animals

Species: Rat
Strain: SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb)

Source: Winkelmann, Borchen, Paderborn district, Federal Republic of Germany (FRG)
Sex and numbers: 100 Males; 85 females; includes vehicle control
Age: 7-12 Weeks
Initial body weight: Males, 162-192 g; females, 167-194 g
Housing: 5/Cage during the acclimation period; 1/cage during the study period. Animal room maintained at a temperature of 24±2°C and a relative humidity of approximately 50%. A 12-hour alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water in watering bottles were provided ad libitum.
Animal identification: Individual picric acid markings, and cage ID cards specifying the test compound, animal number, dose, sex and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to groups based on random number tables.
Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant.

B. TEST PERFORMANCE

FCR 4545 technical formulated in xylene was administered daily by oral gavage (0.1 mL/kg) to fed rats, and to rats that had been fasted for approximately 16 hours prior to treatment. Different doses were administered to male and female rats and to fed and fasted rats (see dosing schedule below). Vehicle control groups of 5 male and 5 female fed and fasted rats were administered 1 mL/kg of xylene. Fasted animals were provided feed 2 hours after dosing. Animals were observed for 14 days.

Dosing schedule:

Doses administered to 5 fed male rats: 1, 10, 100, 200, 250, 315, 355 or 500 mg/kg of the test material formulation. A dose of 400 mg/kg was administered to 10 fed male rats.

Doses administered to 5 fed female rats: 1, 10, 100, 250, 355, 400, 450 or 500 mg/kg of the test material formulation.

Doses administered to 5 fasted male rats: 1, 10, 50, 100, 250, 400 or 500 mg/kg of the test material formulation.

Doses administered to 5 fasted female rats: 1, 10, 100, 250, 315, 400 or 500 mg/kg of the test material formulation

The day of test material administration was referred to as day 0. Animals were frequently monitored for clinical signs of toxicity during test day

0, and at least once a day on test days 1-14. The duration of clinical observations was reported. Body weights were measured prior to dosing on test day 0 and daily thereafter. Rats that survived treatment were sacrificed at the end of the study using diethyl ether and necropsied. Rats that died during the study were also necropsied. Histopathological examinations were not performed on any of the animals.

Statistics

A computerized (HP 3000) program was used to calculate LD_{50}s by the method of A. P. Rosiello, M. M. Essigmann and G. N. Wogan (1977)[1] as modified by Pauluhn (1983)[2]. This method is based on the maximum likelihood method of Bliss (1938)[3]. The geometric mean was regarded as the "approximate LD_{50}" for data pairs with 0% and 100% mortality.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Table 1 summarizes the incidence of mortality and percent mortality in fed and fasted rats. No mortalities were reported for any of the vehicle control animals. The time of death for animals that died during the study ranged from a few hours following exposure up to 3 days.

Clinical signs of toxicity consisting of lethargy, reduced activity, and difficult breathing were observed in all vehicle control rats and all treated rats in the 1-mg/kg dose group. These signs had an onset time as early as 45 minutes following exposure and continued for a maximum of 1 day. At dose levels as low as 10 mg/kg, salivation and uncoordinated gait were observed in treated rats. At dose levels >10 mg/kg, additional clinical signs of toxicity consisted of cramped posture, splayed gait, piloerection, digging and preening movements, and rolling. The study report listed all treated animals as having clinical signs of toxicity but did not provide information on how many of the treated animals displayed clinical signs other than those observed in the vehicle control rats. For doses ≥10 mg/kg, the onset time of clinical signs was as early as 28 minutes and the maximum duration was 9 days. The study author stated

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[1]Rosiello, A. P., J. M. Essigmann and G. N. Wogan. 1977. Rapid and accurate determination of the median lethal dose (LD_{50}) and its error with small computer. J. Tox. and Environ. Health 3, 797-809 (1977).

[2]Pauluhn, J. 1983. Computer-Aided Estimation of the LD_{50}/LC_{50}. BAYER AG Report No.: 11835, 05/18/1983.

[3]Bliss, C.I. 1938. The determination of the dosage-mortality curve from small numbers. Q. J. Pharm. Pharmacol. 11, 192-216.

Table 1. Summary of the Incidence of Mortality and Percent Mortality in Fed and Fasted Rats Orally Administered FCR 4545 Technical (formulation in xylene)[a]

Dose (mg/kg)	Males		Females	
	Fasted	Fed	Fasted	Fed
0	0	0	0	0
1	0	0	0	0
10	0	0	0	0
50	1 (20)[b]	--	--	--
100	1 (20)	0	0	0
200	--	1 (20)	--	--
250	2 (40)	2 (40)	1 (20)	1 (20)
315	--	1 (20)	1 (20)	--
355	--	2 (40)	--	2 (40)
400	3 (60)	9 (90)	4 (80)	3 (60)
400	--	1* (20)	--	--
450	--	--	--	5 (100)
500	5 (100)	5 (100)	5 (100)	5* (100)

[a]Data extracted from Report number 98349, pp. 14, 16.
[b]Value in parentheses is the % mortality.
* Dose not used in calculating the LD_{50}.

that the observed clinical signs (i.e., increased activity, digging and preening movements, uncoordinated gait, splayed gait, rolling, and salivation) were in accordance with those of the CS syndrome (choreoathetosis and salivation) which is known from pyrethroids with an α-cyano-3-phenoxybenzyl alcohol group.

Data for individual absolute body weights throughout the observation period were provided. Absolute body weight means were calculated for each dosage group. For fasted rats administered the test material, there were slight decreases in absolute body weights observed in males at doses as low as 10 mg/kg and females at doses as low as 100 mg/kg for the first few days of the observation period when compared to their initial body weights. For fed rats administered the test material, there were slight decreases in absolute body weights observed in males and females at doses as low as 10 mg/kg for the first few days of the observation period when compared to their initial body weights. However, by the end of the first week body weights were higher than the initial body weights for fed and fasted rats in all dosage groups. Occasionally, vehicle control animals had very slight decreases in absolute body weights for fed or fasted animals for the first few days of the observation period as compared to their initial body weights.

Gross necropsy data for individual animals were presented by sex, dosage group, and fasting status. No gross findings were reported for vehicle control animals with the exception of 1 fasted male with lungs pervaded by numerous dark red zones. For animals that died during the observation period, gross findings were reported for the lungs (mottled to dark red, slightly distended), kidneys (occasionally mottled), liver (mottled, lobular pattern, occasionally pale and beige discoloration), spleen (mottled, somewhat pale), gastrointestinal tract (distended, empty, occasional dark mucous content), and forestomach (detachment of the mucosa). For animals that were sacrificed at the end of the study, no gross findings were reported. No microscopic examinations were performed on any of the animals.

LD_{50} Determination

All fed females (5/5) in the 500-mg/kg dosage group, and 5/10 fasted males in the 400-mg/kg dosage group were not included in the LD_{50} calculations. The estimated acute oral LD_{50} for FCR 4545 technical in fasted rats was 211 mg/kg for males (95% confidence interval 110-404 mg/kg) and 336 mg/kg for females (95% confidence interval 290-391 mg/kg). The estimated acute oral LD_{50} for FCR 4545 Technical in fed rats was 307 mg/kg for males (95% confidence interval 260-364 mg/kg) and 343 mg/kg for females (95% confidence interval 286-411 mg/kg).

Based on these mortality results, the study author classified the acute oral toxicity of CGA-169374 technical as "moderate."

E. REVIEWERS' COMMENTS

This study was classified as Acceptable. A deficiency of the study was that neither the summary nor individual incidence data for clinical signs of toxicity in animals administered the test material were tabulated to show the number of animals displaying signs of toxicity. Therefore, the reviewers cannot assess if the effects were dose related. However, LD_{50}'s could be calculated and the type of toxicity caused by the test material was characterized. The study authors did not mention their rationale for using both fed and fasted rats in this study. Generally, fasted rats are used to insure that there will be no food-related influence on the absorption of the test material from the intestinal tract.

Based on the mortality results, the estimated acute oral LD_{50} for FCR 4545 technical in fasted rats was 211 mg/kg for males (95% confidence interval 110-404 mg/kg) and 336 mg/kg for females (95% confidence interval 290-391 mg/kg). The estimated acute oral LD_{50} for FCR 4545 technical in fed rats was 307 mg/kg for males (95% confidence interval 260-364 mg/kg) and 343 mg/kg for females (95% confidence interval 286-411 mg/kg).

010293 DOC 930110

FINAL

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Dermal Toxicity in Rats

Study Title: FCR 4545 Technical: Study of the Acute Dermal Toxicity to Rats (Formulation with Xylene)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel Betty Shindel, M.P.H.	8/4/92 Date
Independent Reviewer:	John Liccione John Liccione, Ph.D.	8/4/92 Date
QA/QC Manager:	Sharon A. Segal Sharon Segal, Ph.D.	8/4/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-299
Project Officer: James E. Scott

Approved by:
EPA Reviewer: William B. Greear, M.P.H., D.A.B.T. Signature William B. Greear
Review Section IV, Toxicology Branch I (HED) Date 8/10/92

EPA Section Head: Karen Hamernik, Ph.D. Signature Karen Hamernik
Review Section III, Toxicology Branch I (HED) Date 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-2: Acute dermal toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-05
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in xylene

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 97488

STUDY NUMBER: T 9023329

TESTING FACILITY: BAYER AG, Institute of Toxicology/Agriculture of the Fachbereich Toxikologie of BAYER AG, Friedrech-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Dermal Toxicity to Rats (Formulation in Xylene)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 5, 1987

CONCLUSION:

LD_{50} (males) ≥5000 mg/kg
LD_{50} (female) ≥5000 mg/kg

Toxic signs: Lethargy, uncoordinated gait, splayed gait, salivation, vocalization, jumping, digging and preening movements, difficult breathing and soft feces
Dose levels: 0, 100, 1000, 2500 and 5000 mg/kg
Route: Dermal
Strain: Bor: WISW (SPF-Cpb)

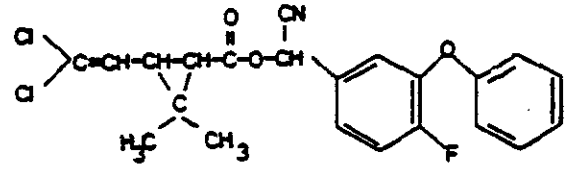
CLASSIFICATION: Acceptable. This study satisfies the guideline requirement (81-2) for an acute dermal toxicity study.

TOXICITY CATEGORY: ~~III~~ IV -Caution

A. MATERIALS --

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Xylene
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1%, 98.7% (two measurements); determined by sponsor before the study
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (23-27.5°C).
Odor: Odorless
Stability: Test material was stable for 24 hours. The active ingredient concentrations in percent of nominal value (3,125 mg/mL) were 96% and 93% for a storage period of 0 and 24 hours, respectively. Stability was determined by the sponsor before the study.

2. Controls

Animals: 5 males and 5 females
Vehicle: Xylene

3. Test Animals

Species: Rat
Strain: SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb)
Source: Winkelmann, Borchen, Paderborn district, FRG
Sex and numbers: 25 Males; 24 females (included control group)
Age: 8-16 Weeks
Initial body weight: Males, 200-220 g; females, 213-234 g
Housing: 5/Cage during the acclimation period; 1/cage during the study period. Animal room was maintained at a temperature of 23±2°C and a relative humidity of approximately 50%. A 12-hour alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water were provided ad libitum.
Animal identification: Individual picric acid markings; and cage ID cards specifying the test compound, animal number, dose, sex, and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to dose groups based on random number tables.

Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant

B. TEST PERFORMANCE

Fur was clipped from the dorsal area of each animal 1 day prior to application of the test. Five male and 5 female rats per dose were each dermally administered a single topical application of FCR 4545 technical made into a paste with xylene (0.008 mL for 100 mg/kg body weight; 0.08 mL for 1000 mg/kg body weight; 0.2 mL for 2500 mg/kg body weight; 0.4 mL for 5000 mg/kg body weight); the paste was made on the aluminum foil used for covering the test site. A control group of 5 males and 5 females were each treated with 0.4 mL of xylene. The doses of formulation administered to males and females were 100, 1,000, 2,500, and 5,000 mg/kg. The aluminum foil with the formulation paste was secured to an area of intact skin on the shaved dorsal area by use of a bandage wrapped around the animal's trunk. The dimensions of the test site were not specified. After a 24-hour exposure period, the bandages were removed and the test site was washed with soap and water to remove residual test material.

Animals were observed for 14 days. Clinical observations were recorded several times on the day of application and at least once a day thereafter. Clinical observations were omitted by error for 3 groups (Groups 2, 6 and 9; corresponding doses not specified) on 3 different days. Also, 2 animals (Group 2) were not evaluated for dermal irritation on 1 of the observation days. A standard method for scoring dermal irritation such as the Draize method was not used. Instead, the severity of dermal irritation was rated as minimal, moderate, or severe. Body weights were measured just prior to application on test day 0, and daily throughout the observation period. At the end of the study, animals were sacrificed with diethyl ether and necropsied. Histopathological examinations were not performed on any of the animals.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

No mortality was reported for any of the control animals or for any of the animals administered the test material formulation. One female from the 5,000-mg/kg group was sacrificed at 24 hours after exposure because of self-inflicted bite wounds. Based on these results, the acute dermal LD_{50} of FCR 4545 technical was >5,000 mg/kg for male and female rats.

The only clinical observation reported for vehicle control males was soft feces in all 5 males with an onset at day 3 after exposure and a duration of 1 day; no clinical observations were observed in the female vehicle control group. Clinical signs of toxicity were reported for all male rats at doses ≥1,000 mg/kg and for all female rats at doses ≥100 mg/kg. For males administered the test material, clinical signs were first observed in the 1,000-mg/kg dose group and were of minimal-to-moderate severity and consisted of lethargy, uncoordinated gait, splayed gait, salivation, vocalization and jumping. Additional signs observed at higher doses in

males consisted of digging and preening movements, and moderately difficult breathing. The time of onset for clinical signs in treated males ranged from 37 minutes to 3 days with a maximum duration of 11 days. For females administered the test material, clinical signs consisting of vocalization and jumping were first observed in the 100-mg/kg dose group. Additional signs observed at higher doses in females were of minimal-to-moderate severity and consisted of lethargy, uncoordinated gait, splayed gait, digging and preening movements, and salivation. The time of onset for clinical signs in treated females ranged from 25 minutes to 2 days with a maximum duration of 8 days. The study author stated that the signs observed were in accordance with the CS syndrome, known from pyrethroids containing a α-cyano-3-phenoxybenzyl alcohol group.

A slight decrease in body weight as compared to initial body weight was observed in all vehicle control animals and in all animals administered the test material; however, the decrease in body weight was reversed in all animals by day 11. The study author attributed the decrease in body weight gain to the effects of the vehicle because the decreases were observed in both vehicle control animals and animals administered the test material.

No gross findings were reported upon macroscopic examination for any of the animals with the exception of slightly reddened glandular stomach in 1 male and 1 female in the 2,500-mg/kg dose group, and several-to-many dark red zones on the lungs of 1 male from each of the 1,000- and 5,000-mg/kg dose groups.

Dermal irritation of the treated area in vehicle control animals consisted of peeling of the epidermal layer on the border of the treated area, reddening of moderate severity, scabs (moderate severity) and incrustation on the treated area or on the border of the treated area. The time of onset for dermal irritation in vehicle control animals was 2-5 days after exposure with a maximum duration of 7 days except for incrustation which had a duration of >14 days. Dermal irritation of the treated area in animals receiving the test material consisted of incrustation on the treated area or on the border of the treated area, reddening (minimal-to-severe), and peeling of the epidermal layer on the border of the treated area. The incidence of dermal irritation was not reported for individual animals or for dose groups. The study author did not consider the dermal irritation to be compound related because it was comparable for control animals and animals administered the test material.

E. REVIEWERS' COMMENTS

This study is classified as Acceptable. The incidence of dermal irritation as well as incidence of clinical signs were not reported. Clinical observations were omitted by error for 3 groups (Groups 2, 6 and 9) on 3 different days. The study report did not mention what dose levels corresponded to Groups 2, 6 and 9. Also, 2 animals (Group 2) were not evaluated for dermal irritation on 1 of the observation days.

The estimated acute dermal LD_{50} of FCR 4545 technical formulation in xylene for both male and female rats is >5,000 mg/kg. The highest dose administered in the study (5,000 mg/kg) exceeded the limit dose of 2,000 mg/kg specified in Guideline Series 81-2. Based on this LD_{50}, the Toxicity Category is ~~III~~ IV--Caution.

JCR

DOC 930101
FINAL

010293

DATA EVALUATION REPORT

FCR 4545

Study Type: Range-Finding Subacute Inhalation Toxicity Study in Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

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Principal Reviewer:	Jessica Kidwell Jessica Kidwell, M.S.	8/4/92 Date
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QA/QC Manager:	Sharon Segal Sharon Segal, Ph.D.	8/5/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-288
Project Officer: James E. Scott

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
August 9, 1992
Date

EPA Acting Section Head: Karen Hamernick, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl D. Hoffele for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Range-finding subacute inhalation toxicity study in rats

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412057-08
P.C. Number: 128831

TEST MATERIAL: FCR 4545

SYNONYM: Cyfluthrin K+L

SPONSOR: Agricultural Chemicals Division, Mobay Corporation

STUDY NUMBER: T8027171

TESTING FACILITY: BAYER AG, FACHBEREICH TOXIKOLOGIE, Freidrich-Ebert-Strasse 217-333, D 5600 Wuppertal 1, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (Common Name: Cyfluthrin K+L, suggested) Study of the Range-Finding Subacute Inhalation Toxicity to Rats in Accordance with OECD Guideline No. 403

AUTHOR: Dr. J. Pauluhn

STUDY COMPLETED: April 7, 1988

CONCLUSIONS:

NOEL = 0.25 mg/m^3 (no clinical signs)
LEL = 3.78 mg/m^3 in males and females (based on the occurrence of treatment-related clinical signs of systemic toxicity (unpreened hair coat and piloerection) and the statistically significant occurrence of gross lesions (hepatoid foci in the lungs)

Dose Levels: 0.25, 3.78, and 28.01 mg/m^3
Route/Duration: Inhalation/6 hours/day for 5 days
Strain: Wistar rats

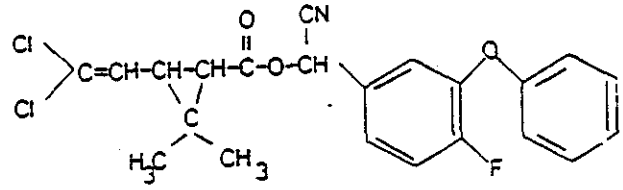
CLASSIFICATION: Supplementary Data. This study provides information for establishing dosage levels for a 4-week subacute inhalation study.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Compound: FCR 4545

Chemical formula: $C_{22}H_{18}Cl_2FNO_3$; Cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (MW = 434.3)



Purity: 98%
Physical property: White powder
pH: 6.5 (2% in water)
Batch no.: 16001/87
Storage conditions: Room temperature/exclusion of light
Stability of spray/stock solution: Stable during study period
Vehicle: Polyethylene glycol E 400/ethanol

2. Test Animals

Species: Rats
Strain: Wistar Bor:WISW (SPF-Cpb)
Source: WINKELMANN, in Borchen, Paderborn district, Federal Republic of Germany
Sex: Male and female
Number: 30 males and 30 females (10/sex/group)
Housing: Five/cage (during acclimation)
Temperature: 22±2°C
Relative humidity: 50-60%
Identification: Individual color markings and cage ID cards
Acclimation: One week
Age at exposure: Young adult
Weight: 190-200 g
Feeding: Feed (Altromin® 1324) and water were provided ad libitum, except during the exposure period.
Assignment: Randomization

3. Controls

Materials: Vehicle--Polyethylene glycol E 400/ethanol
Animals: 10 males and 10 females

4. Exposure Conditions

Inhalation Chamber/Generation of Test Atmosphere

Exposures (6 hours/day for 5 days, 2-week recovery period) to concentrations of 0.25, 3.78, and 28.01 mg/m^3 were conducted in a

head/nose only exposure system developed by RHEMA LABORTECHNIK, Federal Republic of Germany (Figure 1). Animals were individually housed in Plexiglass® exposure tubes which were adjusted to the size of the rat and placed in holders around the exposure system. To generate the test atmosphere, the test compound was nebulized under dynamic conditions in the vehicle, which was a 1:1 mixture of polyethylene glycol E 400/ethanol, and directed into the inhalation chamber with a preseparator (baffle). The preseparator increased the efficiency of the aerosol generation and removed larger particles.

Stability of the Test Atmosphere

Samples of the test atmosphere were collected from the breathing zone of the rats for 10-minute cycles every 40 minutes using a Ratfisch RS 55 total hydrocarbon analyzer with null gas and combustion gas generator (FI detector) which allows an overall test of all relevant inhalation chamber operating parameters. Results indicate relative stability of the exposure atmosphere.

Analytical Determinations

Analytical determinations of the breathing zone of the rats were conducted each day of exposure, with 3 air samples taken at the beginning (after equilibrium), middle, and toward the end of each 6-hour exposure. Ten or 20 liters of breathing zone air were collected in glass tubes packed with Florisil® and the active ingredient eluted with ethyl acetate. The mean analytical exposure concentrations (determined by gas chromatography with an EC detector) were 0.25, 3.78, and 28.01 mg/m^3 for Groups II, III, and IV, respectively. The nominal concentrations were calculated by dividing the amount of test material nebulized into the chamber by the total air flow through the chamber. The nominal concentrations were 2, 20, and 200 mg/m^3 for Groups II, III, and IV, respectively. The analytical concentrations were lower than the nominal concentrations due to the removal of the larger particles by the preseparator. Animals exposed to the vehicle control were designated as Group I.

Chamber Monitoring

The aerosol generation conditions sustained an air exchange of 30 times per hour. At this flow rate, steady-state conditions were reached in 6 minutes. Air flows were monitored continuously during exposure. Chamber temperature and humidity were monitored continuously at 10-minute intervals during exposure. The temperature in the exposure module averaged 23°C, while the relative humidity ranged from 20-40%. The study author reported that the lower humidity had no effect on the study.

Particle-Size Determinations

Particle-size distribution determinations were conducted using an Aerodynamic Particle Sizer with Laser Velocimeter (TSI-APS 3300). Samples were taken from the breathing zone of the animals 3 times during the study period. Mass median diameter averages for the three test groups ranged from 1.24 µm to 1.72 µm. For all three test

groups, 100% of the particles were ≤5 μm while an average of 50-70% of the particles were ≤1.0 μm. Particle-size results for the Group I (vehicle control) exposure were similar to those of the test group with 100% of the particles ≤5 μm and 50% ≤1 μm.

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5. Statistics

Body weights: A nonparametric rank test, the Mann-Whitney U test, was used to compare body weights of the control group with the test groups.

Gross pathological findings: The more frequently occurring findings pertaining to the respiratory tract were evaluated using the R x C Chi-Square Test and the Pairwise Fisher's test. The Fisher's test was used only when a difference between the groups was established using the R x C Chi-Square Test or when a frequency value of less than 5 was calculated.

6. Clinical Observations

The animals were observed for appearance and behavior at hourly intervals several times at the end of exposure, but not during exposure. The rats were evaluated for the following signs: appearance of the visible mucosae of eyes and respiratory tract; general condition of the nose, ear, and hair coat; preening activities; respiration, circulation, somatomotor activity and behavior pattern; central nervous and autonomic signs; and reflexes.

No clinical signs were reported for Groups I and II. All rats in Group III (males and females) showed an unpreened hair coat (behavioral sign) and piloerection (autonomic sign) on exposure days 3, 4, and 5. However, in each case for those 3 exposure days, the rats recovered after each exposure such that prior to the next exposure day all rats were normal. After each exposure, all rats in Group IV (males and females) showed reduced activity (neuromuscular), unpreened hair coat, and piloerection. These signs were seen in males and females from exposure day 1 through exposure day 5, and in females on the first day of the recovery period. The study author indicated that there were no indications of progressive severity. In each case, on the next exposure day, unpreened hair coats and piloerection were still observed, but the study author indicated that the signs were subsiding. No changes in reflexes were noted. Individual animal data were not provided.

7. Body Weights

Animals were weighed prior to treatment on day 0 (exposure day 1) and on days 4, 7, 14, and 21 (just prior to sacrifice).

There were statistically significant decreases ($p = 0.05$; $p = 0.01$) in mean absolute body weights for both males and females in the high-dose group (Group IV--28 mg/m^3), on day 4 (exposure day 5) compared to the control groups. A statistically significant decrease ($p = 0.05$) in mean body weight was also seen in male rats in Group IV on day 7 (third day of recovery) compared to the vehicle control (Group I)

(Table 1). No statistically significant effects were seen in males or females at 0.25 or 3.8 mg/m^3. By the end of the recovery period the body weights of all animals in each group exceeded their initial body weights.

Mean body weights were significantly decreased in males and females exposed to 28.01 mg/m^3. From days 0 to 4, weight gain was decreased 300% compared to the controls for males (4 g versus -8 g) and decreased 200% compared to the controls for females (-4 g versus -12 g). From days 0 to 7, weight gain was decreased 83% compared to the controls for males (12 g versus 2 g). Weight gain recovery was observed during the rest of the recovery period.

8. Gross Necropsies

Gross postmortem examinations were performed on all animals at the end of the 2-week recovery period. All abnormal findings were documented.

No gross lesions were seen in the vehicle control animals. In Group II, hollow kidney (1/20) and hepatoid foci in the lungs (1/20) were seen. Hepatoid foci in the lungs were seen in 4 of 20 rats (2/sex) in Group III and in 6 of 20 rats (3/sex) in Group IV. A statistically significant association between incidence of hepatoid foci in the lungs and dose levels was found for animals in Groups III and IV.

A Quality Assurance Statement, dated March 9, 1988, was presented, but was not signed. A Good Laboratory Practice compliance statement was included.

B. DISCUSSION

There are no EPA Guidelines for a range-finding subacute inhalation toxicity study. However, the study design was reasonable for OECD guidelines used in Europe.

No deaths occurred during the study.

The effects observed at each dose group are as follows:

Vehicle control -- No effects

0.25 mg/m^3 -- No clinical signs were observed. Hepatoid foci of the lung was seen in 5% of the animals, however, this finding was not statistically significant.

3.78 mg/m^3 -- Transitory treatment-related clinical signs seen during exposure only included unpreened hair coat and piloerection. Statistically significant incidence (20%) of detectable lung changes (hepatoid foci) was observed at this dose level.

28.01 mg/m^3 -- Clinical signs seen during exposure in the high-dose group included reduced activity, unpreened hair coat, and piloerection. During the exposure period, statistically significant decreases in body weight gain were seen in both males and females in the high-dose group only. A statistically significant decrease in body weight gain was also seen in males during the recovery period.

However, weight gain recovery was observed by the end of the recovery period. Statistically significant incidence (30%) of detectable lung changes (hepatoid foci) was also observed at this dose level.

Based on these results, inhalation exposure of FCR 4545 technical to rats 6 hours/day for 5 days at concentrations of 0.25, 3.78, and 28.01 mg/m^3 resulted in a NOEL of 0.25 mg/m^3 (no clinical signs) and a LOEL of 3.78 mg/m^3 in males and females based on the occurrence of treatment-related clinical signs of systemic toxicity (unpreened hair coat and piloerection) and the statistically significant occurrence of gross lesions (hepatoid foci in the lungs). The results of this study provide information for establishing dosage levels for a 4-week subacute inhalation study.

The reviewers note that, although a nonparametric statistical test (Mann-Whitney U) was used for comparing body weights, further analyses could be undertaken to determine if a parametric test would be more appropriate (i.e., more powerful) for body weight comparisons.

TABLE 1: MEAN BODY WEIGHTS

Dose Group	Day 0	Day 4	Day 7	Day 21
		Males		
Control	201	205	213	259
0.25 mg/m^3	201	205	213	266
3.78 mg/m^3	200	196	208	266
28.01 mg/m^3	198	190**	200*	256
		Females		
Control	194	190	190	200
0.25 mg/m^3	191	187	185	197
3.78 mg/m^3	192	185	189	201
28.01 mg/m^3	190	178**	189	197

**Statistically significant at p = 0.01
*Statistically significant at p = 0.05

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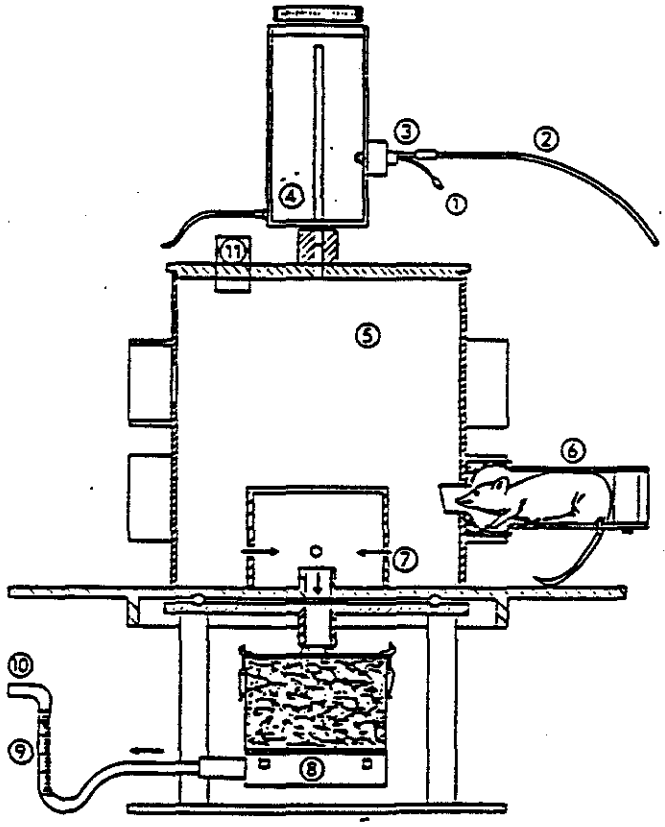
Figure 1: Inhalation Chamber for Aerosol Tests



1. Feed of spray solution with an infusion pump utilizing a 50-ml ground glass syringe (BRAUN-MELSUNGEN)
2. Compressed air (10 l air/min); pressure: approx. 500-600 kPa
3. Binary nozzle (RHEMA LABORTECHNIK);
4. Preseparator (baffle)
5. Inhalation chamber
6. Rat in exposure tube
7. Holes for exhaust air arranged symmetrically around the cylinder
8. Exhaust air purification (cotton wool filter)
9. Rotameter
10. Exhaust (negative pressure system)
11. Temperature and humidity sensor

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DATA EVALUATION REPORT

CYFLUTRIN (BETA)

Study Type: Mutagenicity: Mammalian Cells in Culture Cytogenetic Assay in Human Lymphocytes

Prepared for

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Nancy E. McCarroll, B.S Date 7/17/92

Independent Reviewer Lynne Haber, Ph.D. Date 7/17/92

QA/QC Manager Sharon Segal, Ph.D. Date 7/20/92

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-291
Project Officer: James Scott

GUIDELINE § 84: MUTAGENICITY
MAMMALIAN CELLS IN CULTURE CYTOGENETICS

EPA Reviewer: John Redden, Ph.D.
Review Section III,
Toxicology Branch I/HED (H-7509C)
Signature:
Date: 2/25/93

EPA Section Head: Henry Spencer, Ph.D.
Review Section III,
Toxicology Branch I/HED (H-7509C)
Signature:
Date: 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Mammalian cells in culture cytogenetic assay in human lymphocytes

EPA IDENTIFICATION Numbers:

Caswell Number: 266-E

MRID Number: 412057-03

TEST MATERIAL: FCR 4545

SYNONYMS/CAS Number: Cyflutrin (beta); cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethycyclopropanecarboxylate; $C_{22}H_{18}Cl_2FNO_3$/ 68359-37-5

SPONSOR: Mobay Corp., Kansas City, MO

STUDY NUMBER: 98361

TESTING FACILITY: Bayer AG, Wuppertal, Germany

TITLE OF REPORT: FCR 4545 In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects

AUTHOR: B. A. Herbold

REPORT ISSUED: September 6, 1988

CONCLUSIONS--EXECUTIVE SUMMARY: Human lymphocytes obtained from one male and one female donor were evaluated for clastogenic effects following exposure to three nonactivated and three S9-activated doses of FCR 4545 (500, 1000, or 5000 µg/mL). Results indicated that the two highest doses with and without S9-activation were insoluble. Cytotoxicity, as indicated by the slight-to-moderate reduction in the mitotic index (MI) was seen at 500 and 1000 µg/mL +/-S9. The lack of a clear cytotoxic effect at the high dose was probably related to test material insolubility. There was, however, no indication of a clastogenic response at any of the three evaluated concentrations. Based on the reduced MIs at 500 and 1000 µg/mL +/-S9, we conclude that the failure to induce a genotoxic effect was not associated with an inability of the test material to enter the cells. The study, therefore, provides acceptable evidence that FCR 4545 was assayed over an appropriate range of soluble and

insoluble concentrations and found to be not clastogenic in this in vitro human lymphocyte cytogenetic assay.

STUDY CLASSIFICATION: Acceptable. The study satisfies Guideline requirements (§84.2) for genetic effects, Category II, Structural Chromosome Aberration. However, it is recommended that for future studies, slides should be coded prior to analysis to reduce bias.

A. MATERIALS:

1. Test Material: FCR 4545

Description: White powder
Identification no.: Batch number: 16001/85
Purity: 98.8%
Receipt date: Not provided
Stability: Stable in the solvent (dimethyl sulfoxide, DMSO) at 50-500 mg/mL for at least 24 hours (see Appendix A).
Contaminants: None listed
Solvent used: DMSO
Other provided information: The test material was stored at refrigerator temperatures. It was assumed that the test material solutions were prepared on the day of use.

2. Control Materials:

Negative: None

Solvent/final concentration: DMSO/1%

Positive: Nonactivation (concentrations, solvent): Mitomycin C (MMC) was prepared in Hank's salt solution to yield a final concentration of 0.15 µg/mL.

Activation (concentrations, solvent): Cyclophosphamide (CP) was prepared in Hank's salt solution to yield a final concentration of 15 µg/mL.

3. Activation: S9 derived from adult male Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
____ phenobarbital	____ noninduced	____ mouse	____ lung
____ none		____ hamster	____ other
____ other		____ other	

The S9 liver homogenate was prepared by the performing laboratory and was reported to contain 26.9 mg protein/mL. The composition of the S9 mix per mL was as follows:

S9 mix composition:

Component	Concentration/mL
$MgCL_2$	2.71 mg
KCl	4.10 mg
Glucose 6-phosphate	2.98 mg
NADP	5.25 mg
Phosphate buffer (100.0 mM)	0.5 mL
S9	0.5 mL (50%)

NOTE: 0.1 mL of the S9 mix was added to 10-mL volumes of culture medium to yield a final concentration of 0.5% S9 fraction.

4. Test Compound Concentrations Used:

   (a) Preliminary cytotoxicity assay: Five doses (50, 100, 500, 1000, and 5000 µg/mL) were assayed with and without S9 activation for cytotoxic effects on the mitotic index (MI).

   (b) Cytogenetic assay:

      (1) Nonactivated conditions: The three concentrations evaluated without S9 activation were 500, 1000, and 5000 µg/mL.

      (2) S9-activated conditions: As above

5. Test Cells: Human lymphocytes were obtained from the blood of two healthy subjects (one male and one female); no further information on the donors was provided. Lymphocyte cultures were grown in chromosome medium B (Seromed) containing phytohemagglutinin (concentration not specified) for 48 hours at 37°C prior to treatment.

   Properly maintained? Yes.

   Cell line or strain periodically checked for mycoplasma contamination? Not applicable.

   Cell line or strain periodically checked for karyotype stability? Not applicable.

B. TEST PERFORMANCE:

1. Cell Treatments:

   (a) Cells exposed to test compound for:
   21 hours (nonactivated) 2.5 hours (activated)

   (b) Cells exposed to positive controls for:
   21 hours (nonactivated) 2.5 hours (activated)

   (c) Cells exposed to negative and/or solvent controls for:
   21 hours (nonactivated) 2.5 hours (activated)

2. Protocol:

(a) Preliminary assay: Details of the preliminary assay were not reported; effects on the MI were used to select doses for the cytogenetic assay.

(b) Cytogenetic assay:

(1) Treatment: Prepared cultures (two/sex), were exposed to the selected test material doses, the solvent control (DMSO), or the positive controls (MMC -S9 or CP +S9). One of the replicates from each treatment group was held in reserve.

In the nonactivated assay, cells were dosed for 21 hours. Colcemid (0.4 µg/mL) was added and incubation was continued for 3 hours. Under S9-activated conditions, cells were exposed for 2.5 hours, washed, refed culture medium and reincubated. Colcemid was added 3 hours before the cultures were harvested.

Metaphase cells were collected, treated with 0.56% KCl and fixed in ethanol + glacial acetic (3+1). Slides were stained with 5% Giemsa; the report did not indicate whether slides were coded prior to analysis.

(2) Metaphase analysis: One hundred metaphase cells per culture were scored for chromosome aberrations; damaged metaphases were photographed. The MI was determined for each group by counting 4000 cells.

(3) Statistical methods: The data were evaluated for statistical significance at p values of 0.05 and 0.01 using the one-sided Chi-square test.

(4) Evaluation criteria:

(a) Assay validity: The study was considered acceptable if (1) the aberration frequency in the solvent control group was within the unspecified historical range of the performing laboratory, and (2) the positive controls induced a biologically relevant increase in chromosome aberrations.

(b) Positive response: The test material was considered positive if it induced a dose-related and statistically significant ($p \leq 0.05$) increase in the number of metaphases with structural chromosome aberrations.

(5) Protocol: None provided

C. REPORTED RESULTS:

1. Preliminary Cytotoxicity Assay: The range-finding study was conducted with five test material doses ranging from 50 to 5000 µg/mL +/-S9. The report indicated that the test material was insoluble at the two highest doses (1000 and 5000 µg/mL). In the nonactivated phase of testing, relative MIs ranged from 91.2% at 50 µg/mL to 45.6% at 1000 µg/mL. At the highest nonactivated level (5000 µg/mL), the relative percent of recovered mitotic cells (76.5%) was higher than the percentages calculated for two of the intermediate doses (48.5 and 45.6% at 500 and 1000 µg/mL, respectively). Relative MIs were more consistently dose dependent in the presence of S9 activation and ranged from >100% at the low dose (50 µg/mL) to 41.4% at the highest dose (5000 µg/mL). Based on these results, 500, 1000, and 5000 µg/mL +/-S9 were selected for further study.

2. Cytogenetic Assay: Compound precipitation was reported for concentrations of FCR 4545 ≥1000 µg/mL +/-S9. MIs, combined for both donor cultures, were significantly reduced compared to the solvent control at all nonactivated and S9-activated levels (Table 1). As previously noted for the nonactivated phase of the preliminary test, cytotoxicity was less pronounced at the high dose with and without S9 activation than at the lower concentrations. This finding suggests that penetration of cellular membranes was limited by the solubility properties of the test material. Nevertheless, the reductions in mitotic cells at lower doses indicated that partially soluble (1000 µg/mL +/-S9) and soluble (500 µg/mL +/-S9) concentrations of the test material interacted with the lymphocytes and caused cellular damage. There was, however, no evidence that treatment with FCR 4545 increased the frequency of structural or numerical chromosome aberrations in male or female donor lymphocytes either in the presence or absence of S9 activation. By contrast, both the nonactivated (0.15 µg/mL MMC) and S9-activated (15 µg/mL CP) positive controls induced significant ($p \leq 0.01$) clastogenic responses in both donor cell cultures.

The study author concluded, therefore, that FCR 4545 was negative in this in vitro human lymphocyte cytogenetic assay.

D. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS: We assess that the study was properly conducted and that the study author's interpretation of the data was correct. FCR 4545 was assayed at insoluble doses (≥1000 µg/mL +/-S9) and at a single soluble level (5000 µg/mL +/-S9) but failed to induce a clastogenic effect in human lymphocyte cultures derived from a male and a female donor. The reduced MIs at 500 and 1000 µg/mL both with and without S9 activation further indicated that the test material entered the lymphocytes; therefore, the lack of a clastogenic response was not due to an inability of FCR 4545 to penetrate cellular membranes. Additionally, the sensitivity of the test system to detect a clastogenic effect was adequately demonstrated by the significant results obtained with both donor cell cultures exposed to the nonactivated and S9-activated positive controls. The study, therefore, provides acceptable evidence of a negative response in this test system. It is, however,

TABLE 1. Representative Results of the Human Lymphocyte In Vitro Cytogenetic Assay with FCR 4545

Substance	Dose	S9 Activation	No. of Cells Scored	Mitotic Index (% of control)[a,b]	Total No. of Structural Aberrations[c]	No. of Cells with Structural Aberrations[a,c]	Percent Cells with Structural Aberrations[a,c]	Biologically Significant Aberrations (No./Type)
Solvent Control								
Dimethyl sulfoxide	1%	-	100M	100.0	4	9	4.5	3TB; 1SF
	1%	-	100F		5			3TB; 2SF
	1%	+	100M	100.0	0	1	0.5	--
	1%	+	100F		1			1TB
Positive Control								
Mitomycin C	0.15 µg/mL	-	100M	112.3	37	51*	25.5	25TB; 2SF; 1TD; 9E
		-	100F		24			11TB; 2SF; 11E
Cyclophosphamide	15 µg/mL	+	100M	80.9	16	35*	17.5	14TB; 2SF
		+	100F		≥26			18TB; 1SF; 3E; 1M
Test Material								
FCR 4545	500 µg/mL	-	100M	67.1[d]	1	4	2.0	1TB
		-	100F		3			2TB; 1SF
	1000 µg/mL[e]	-	100M	45.2[d]	1	3	1.5	1TB
		-	100F		5			1TB; 3SF; 1TD
	5000 µg/mL[e]	-	100M	82.6[f]	5	5	2.5	4TB; 1SF
		-	100F		0			--
	500 µg/mL	+	100M	51.5[d]	0	2	1.0	--
		+	100F		2			2TB
	1000 µg/mL[e]	+	100M	45.6[d]	1	3	1.5	1SF
		+	100F		2			2TB
	5000 µg/mL[e]	+	100M	64.2[d]	0	0	0.0	--
		+	100F		0			--

[a]Only combined data for both donor cultures were presented.
[b]Based on the count of 4000 cells per experimental group
[c]Gaps excluded
[d]Absolute value was significantly ($p \leq 0.01$) lower than the solvent control by X^2-test.
[e]Compound precipitation reported at these levels.
[f]Absolute value was significantly ($p \leq 0.05$) lower than the solvent control by X^2-test.

*Significantly ($p \leq 0.01$) higher than the solvent control by X^2-test.

Abbreviations used:
TB = Chromatid break
TD = Chromatid deletion
SF = Chromosome fragment
E = Exchange
M = Multiple aberrations (i.e., four or more aberrations/cell)

recommended that for future studies, slides should be coded prior to analysis to avoid bias.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A quality assurance statement was signed and dated August 9, 1988.)

F. CBI APPENDIX: Appendix A, Test Material Stability in Dimethyl Sulfoxide, CBI p. 22; Appendix B, Materials and Methods, CBI pp. 8-15.

CORE CLASSIFICATION: Acceptable. The study satisfies Guideline requirements (§84.2) for genetic effects, Category II, Structural Chromosome Aberrations.

APPENDIX A

TEST MATERIAL STABILITY
CBI p. 22

Pages 86-95 - *Access to FIFRA health and safety data is restricted under FIFRA

DOC930103

FINAL

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DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Primary Dermal and Eye Irritation Study in Rabbits

Study Title: FCR 4545 (Technical): Study for Irritant/Corrosive Effect on Skin and Eye (Rabbit)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D.	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-290
Project Officer: James E. Scott

Guideline Series 81-4: Primary eye irritation study;
Guideline Series 81-5: Primary dermal irritation study

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
Sept 4, 1992
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl D. Hamernik for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal and eye irritation study in rabbits

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412057-02
PC Number: 128831

SYNONYM: Cyfluthrin

TEST MATERIAL: Technical FCR 4545

SPONSOR: Mobay Corporation

STUDY NUMBER: T 9019775

TESTING FACILITY: Bayer AG, Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (Technical): Study for Irritant/Corrosive Effect on Skin and Eye (Rabbit)

AUTHOR: J. Pauluhn

STUDY COMPLETED: August 9, 1985

CONCLUSIONS: Cyfluthrin is a slight primary dermal and ocular irritant in rabbits.

CLASSIFICATION: Acceptable. This study satisfies the requirements for a Guideline Series 81-4 eye irritation study and a Guideline Series 81-5 dermal irritation study.

TOXICITY CATEGORY: 81-4: III--Caution
81-5: IV--Caution

Guideline Series 81-4: Primary eye irritation study;
Guideline Series 81-5: Primary dermal irritation study

A. MATERIALS

1. Test Material

Test material: FCR 4545 (technical)
Chemical name: α-cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Purity: 98.5% (Sponsor analysis)
Physical description: Solid (color not reported)
Lot number: 16002/84
Storage conditions: Not reported
Stability: Not reported

2. Controls

Animals: Treated animal served as its own control
Test substance: Water

3. Test Animals

Species: Albino rabbit
Strain: HC:NZW
Sex: Male and female
Source: Hacking and Churchhill Ltd., Huntingdon, UK or Interfauna UK Ltd.
Receipt date: Not reported
Numbers: Two males and one female (dermal)
Three males (ocular)
Housing: Individual
Acclimation: At least 14 days
Age: Adult
Weight: 2.9-3.6 kg
Feeding: Feed (Ssniff K 4) and water provided ad libitum
Selection: Not specified

4. Exposure

Route of administration: Dermal; ocular
Dose level: 0.5 g (dermal); 0.1 ml (ocular)

B. TEST PERFORMANCE

1. Dermal

Twenty-four hours prior to study initiation, approximately 6x6 cm of the flanks of 3 albino rabbits were clipped free of fur. 500 mg of cyfluthrin was applied to a Hansamed "Hypoallergen" dressing which was then applied to one flank of each rabbit so that 6 cm^2 of skin was treated. It was not indicated whether the test material was moistened prior to application. The dressing was held in place with elastic adhesive tape (semi-occlusive dressing). When neccesary, Leukoplast-poroes were used for fastening. The opposite flank of each animal was treated similarly using dressing moistened with water and served as a control site. The dressings and tape were removed after 4 hours and the treated skin was washed with water to

remove any residual test substance. The application sites were graded, using the DRAIZE scale, for erythema and edema within 1, 24, 48, and 72 hours after patch removal. The study was terminated 7 days posttreatment.

2. Ocular

A single dose of 0.1 mL (65 mg) of the test article was placed in the conjunctival sac of one eye of each animal. The eyelids were held together for 1 second to prevent loss of the material. The other eye remained untreated and served as the control. The eyes of all animals remained unwashed for 24 hours. Using the Draize scoring system, the eyes were examined for corneal opacity, iritis, and conjunctivitis at 1, 24, 48, and 72 hours and 7 days after treatment. The eyes were further examined with fluorescein after a 24-hour observation period.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

1. Dermal

Tables were provided for individual rabbit data on scoring of irritation. No edema was seen in any animal posttreatment. No dermal irritation was noted in any of the animals within the first hour postexposure. Very slight erythema (Grade 1) was present at the application site of all three rabbits at 24 and 48 hours posttreatment; all signs of dermal irritation were resolved by 72 hours after application. Data were not reported for the untreated control sites. The study author concluded that, under the conditions of this test, cyfluthrin is not considered to be an irritant to the skin of the rabbit (see Appendix 1a, p. 10). The author calculated an irritation score of 0.7 for each animal; no FIFRA Primary Irritation Index (FIFRA-PII) was calculated by the author.

2. Ocular

Neither corneal opacity nor iritis were seen in any of the rabbits during the study. After the first hour of exposure, conjunctival redness (Grade 1 in 2/3 animals; Grade 2 in 1/3 animals), conjunctival chemosis (Grade 2 in 3/3 animals), and tearing (Grade 2 in 2/3 animals; Grade 3 in 1/3 animals) were seen in all rabbits. At 24 hours, conjunctival redness (Grade 2 in 2/3 animals; Grade 1 in 1/3 animals), conjunctival chemosis (Grade 2 in 1/3 animals; Grade 1 in 2/3 animals), and tearing (Grade 1 in 1/3 animals) were observed. At 48 hours, 2 animals exhibited chemosis (Grade 1); conjunctival redness (Grade 1) was present in 3/3 animals. At 72 hours, conjunctival redness (Grade 1) was seen in 2 rabbits. By 7 days, all irritation was resolved. The average Draize scores at 1, 24, 48, and 72 hours were 1.9, 1.4, 1.0, and 1.0, respectively. Based on these scores, the study author concluded that cyfluthrin was a slight ocular irritant to male rabbits.

D. QUALITY ASSURANCE MEASURE

There was no Quality Assurance Statement included in the report. A Good Laboratory Practice compliance statement was included.

010293

E. REVIEWERS' COMMENTS

There was no information provided for stability of the test substance. However, stability is not expected to be a problem for the 4-hour dermal and 24-hour ocular exposure periods used in this study. Only 3 animals were used for each experiment; however, the results were largely consistent among the test animals and performing the respective studies using more animals would not be expected to alter the conclusions. The reviewers note that no quality assurance statement was included in the report.

1. Dermal

Cyfluthrin induced slight irritation in all 3 rabbits which was resolved between 48 hours and 72 hours after exposure.

The reviewers calculated an irritation score of 0.5 (2/4; the sum of the erythema and edema scores for each animal for the 1-, 24-, 48-, and 72-hour intervals, divided by the total number of intervals) for each animal. This irritation score disagrees with the score of 0.7 that was reported by the author. The reviewers calculated a FIFRA Primary Irritation Index (FIFRA-PII) of 0.5 (1.5/3; the sum of the irritation scores for each animal divided by the total number of animals) for the test substance. Based on the results of this study, the Toxicity Category is IV--Caution.

2. Ocular

The reviewers agree with the study author's conclusion that cyfluthrin is a slight ocular irritant to the eyes of rabbits. Based on these results, the Toxicity Category is III--Caution.

The studies were classified as Acceptable according to Guideline Series 81-4 and 81-5. However, only 3 animals were tested in each of the dermal and ocular studies.

DOC930124

FINAL

010293

DATA EVALUATION REPORT

CYFLUTRIN (BETA)

Study Type: Mutagenicity: Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Lynne T. Haber Date 7/14/92
Lynne T. Haber, Ph.D.

Independent Reviewer Nancy E. McCarroll Date 7/14/92
Nancy E. McCarroll, B.S.

QA/QC Manager Sharon Segal Date 7/14/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-292
Project Officer: James Scott

MUTAGENICITY STUDIES

EPA Reviewer: John Redden, Ph.D. Signature: [signature]
Review Section III,
Toxicology Branch I/HED (H7509C) Date: 2/25/93
Acting EPA Section Head: Henry Spencer, Ph.D.
Review Section III, Signature: [signature]
Toxicology Branch I/HED (H7509C) Date: 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: In vitro unscheduled DNA synthesis assay in primary rat hepatocytes.

EPA IDENTIFICATION Numbers:

Caswell Number: 266-E

MRID Number: 412057-04

TEST MATERIAL: FCR 4545 technical

SYNONYMS/CAS NUMBER: Cyflutrin (beta); cyano (4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; $C_{22}H_{18}Cl_2FNO_3$/ 68359-37-5

SPONSOR: Bayer AG, Wuppertal, Germany/Mobay Corp., Kansas City, MO.

STUDY NUMBER: 98585; Sponsor's study number: T 9024869; HLA study number: 9778-0-447

TESTING FACILITY: Hazleton Laboratories America, Inc., Kensington, MD

TITLE OF REPORT: Mutagenicity Test on FCR 4545 Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay

AUTHOR: M. A. Cifone

REPORT ISSUED: September 8, 1987

CONCLUSIONS-EXECUTIVE SUMMARY: Under the conditions of the unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, FCR 4545 technical was tested to cytotoxic and insoluble levels. Cytotoxicity was observed at doses ≥25.2 µg/mL and the test compound precipitated at levels ≥50.3 µg/mL. However, concentrations ranging from 1.01 to 1010 µg/mL did not induce a genotoxic response. Based on these findings, it was concluded that FCR 4545 technical was tested over an appropriate range of concentrations with appropriate controls and showed no evidence of UDS induction.

STUDY CLASSIFICATION: Acceptable; the study satisfies Guideline requirements (§84-4) for genetic effects Category III, Other Mutagenic Mechanisms.

A. MATERIALS:

1. Test Material: FCR 4545 technical

Description: White powder
Identification no: Batch number 16001/85
Purity: 99.5%
Receipt date: February 26, 1987
Stability: Not reported.
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Dosing solutions were prepared immediately before use. The storage conditions were not reported.

2. Indicator Cells: Primary rat hepatocytes were obtained by the in situ perfusion of the liver of a male Fischer 344 rat (150-300 g) purchased from Charles River Breeding Laboratories, Inc.

3. Control Substances: DMSO at a final concentration of 1% was the solvent control; the positive control was 2-acetylaminofluorene (2-AAF) prepared at 0.10 µg/mL in DMSO.

4. Medium: WME: Williams' Medium E with 2 mM L-glutamine and antibiotics; WME+: WME supplemented with 5% fetal bovine serum (FBS) and 2.4 µM dexamethasone.

5. Test Compound Concentrations Used: Fifteen concentrations ranging from 0.025 to 1010 µg/mL were assayed; eight doses (1.01, 2.52, 5.03, 25.2, 50.3, 101, 252, and 1010 µg/mL) were scored.

B. STUDY DESIGN:

1. Cell Preparation:

(a) Perfusion techniques: The rat liver was perfused for ≈4 minutes with Hanks' balanced salt solution containing 0.5 mM EGTA and Hepes buffer, pH 7.2, and for ≈10 minutes with WME containing 50-100 units/mL collagenase. The liver was excised and placed in WME-collagenase solution; cells were detached by mechanical dispersion, filtered, centrifuged and resuspended in WME+.

(b) Hepatocyte harvest/culture preparation: Recovered cells were stained with trypan blue to determine viability, and ≈5 x 10^5 viable hepatocytes were inoculated into multi-well culture dishes containing coverslips. Parallel cultures were prepared in multi-well culture dishes without coverslips for cytotoxicity measurements. Hepatocytes were allowed to attach for 1.5-2 hours in a

37°C, 5% CO_2 incubator. Unattached cells were removed, and viable cells were fed WME. Within 3 hours, the medium was replaced by the treatment medium to start the UDS assay.

2. UDS Assay:

(a) Treatment: Five replicate cultures were exposed to each of the selected test material doses, the solvent control (DMSO), or the positive control (2-AAF) in treatment medium consisting of WME supplemented with 1% FBS and 1 µCi/mL [^{3}H] thymidine. After exposure for 18-19 hours, three of the cultures in each group were washed with WME containing 1 mM thymidine, exposed to 1% sodium citrate for 8-10 minutes, fixed in acetic acid:ethanol (1:3) and mounted. The remaining two cultures were reincubated for an additional 1-6 hours and stained with trypan blue to determine cell viability. A range of 15 test material levels were evaluated and slides were analyzed from at least the six highest levels that had a sufficient number of surviving cells with normal morphology.

(b) Preparation of autoradiographs/grain development: Slides were coated with Kodak NTB2 emulsion, exposed for 7-10 days at 4°C in light-tight boxes containing a dessicant, developed in D19, fixed, stained with Williams' modified hematoxylin and eosin procedure, coded and counted.

(c) Grain counting: Fifty randomly selected, morphologically normal cells on each of three coverslips were counted (150 cells/dose) for each test dose, as well as the solvent and positive controls. Cytoplasmic background counts were determined by counting three nuclear-sized areas adjacent to the nucleus. Net nuclear grain counts were determined by subtracting the mean cytoplasmic background count from the nuclear grain count. The percentage of cells in repair (≥6 net nuclear grains) and the percentage of cells with ≥20 net nuclear grains were also calculated.

3. Evaluation Criteria:

(a) Assay validity: The following conditions must be met in order for the assay to be considered acceptable: 1) hepatocyte viability following perfusion must be ≥50%; 2) viability of the monolayer cultures must be ≥70%; 3) the number of viable cells in the solvent control monolayer culture must not drop by >50% following treatment; 4) net nuclear grain counts in the solvent control must not be >2; 5) no more than 10% of the solvent control cells may have a net nuclear grain count ≥6; 6) no more than 1% of the solvent control cells may have a net nuclear grain count ≥20; and 7) the positive control must meet all three criteria listed below for a positive response.

(b) Positive response: The test material was considered positive if at any dose 1) the difference between the mean net nuclear grain count of the test material and the solvent control was ≥6; 2) the

percentage of nuclei with ≥6 net grains exceeded 10% of the analyzed population after subtraction of the concurrent negative control value; or 3) ≥2% of the analyzed cells had ≥20 net nuclear grains.

4. Protocol: A protocol was not provided.

C. REPORTED RESULTS:

1. UDS Assay: The study author reported that FCR 4545 technical at 100 mg/mL formed a clear, colorless solution in DMSO. The test material was soluble at concentrations up to 25.2 µg/mL in WME containing 1% FBS; however, a cloudy precipitate formed at ≥50.3 µg/mL. The assay was conducted with 15 concentrations of FCR 4545 technical ranging from 0.025 to 1010 µg/mL. The report indicated that cells treated with the high dose were obscured by test compound precipitate; however relative survival at this level was reduced to 50% (Table 1). Decreased relative survival and the presence of vacuoles in the cells were observed at doses ≥25.2 µg/mL. Based on these observations, cultures exposed to 1.01-1010 µg/mL FCR 4545 technical were analyzed for UDS. Results indicated that there was no evidence of genotoxicity at any scored dose. Slight increases in net nuclear grains and the percentage of cells with ≥6 net nuclear grains were scored at 2.52 and 5.03 µg/mL. These increases were confined to these levels and did not approach the reporting laboratory's minimum criteria for a positive response (i.e., >6.57 net nuclear grains, ≥11.3% of cells with ≥6 net grains, or ≥2% of cells with ≥20 net nuclear grains). By contrast, the positive control, 0.1 µg/mL 2-AAF, induced a marked increase in UDS. From the overall findings, the study author concluded that FCR 4545 technical was negative in the primary rat hepatocyte UDS assay.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that FCR 4545 technical was tested to cytotoxic and insoluble concentrations and exhibited no evidence of a genotoxic effect at any scored level. Results from the positive control, 0.1 µg/mL 2-AAF, indicated that the test system was sufficiently sensitive to detect a positive response. We, therefore, conclude that FCR 4545 technical was adequately tested and found to be not genotoxic in this test system.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? Yes. (A quality assurance statement was signed and dated September 11, 1987.)

F. CBI APPENDICES: Appendix A, Materials and Methods, CBI pp. 10-17.

CORE CLASSIFICATION: Acceptable; the study satisfies Guideline requirements (§84-4) for genetic effects Category III, Other Mutagenic Mechanisms.

TABLE 1. Representative Results of the Unscheduled DNA Synthesis (UDS) Rat Hepatocyte Assay with FCR 4545 Technical

Treatment	Dose/mL	Number of Cells Scored	Relative % Survival[a]	Net Nuclear Grains[b]	Percent Cells with ≥6 Net Nuclear Grains[b]	Percent Cells with ≥20 Net Nuclear Grains[b]
Solvent Control						
Dimethyl sulfoxide	1%	150	100.0	0.57	1.3	0.0
Positive Controls						
2-Acetylaminofluorene	0.1 µg	150	96.0	9.76[c]	75.3[c]	7.3[c]
Test Material						
FCR 4545 technical	2.52 µg[d]	150	95.9	0.83	2.0	0.0
	5.03 µg	150	96.5	1.04	3.3	0.0
	25.2 µg	150	84.4	0.75	0.0	0.0
	1010 µg[e]	150	50.0	0.67	0.7	0.0

[a]Relative survival at 21 hours
[b]Average results from triplicate slides (50 cells/slide)
[c]Fulfills reporting laboratory's criteria for a positive response (i.e., >6.57 net nuclear grains, ≥11.3% of cells with ≥6 net grains, or ≥2% of cells with ≥20 net nuclear grains).
[d]Results from a lower dose (1.01 µg/mL) did not suggest a genotoxic effect.
[e]Highest assayed dose; results from intermediate levels (50.3, 101, and 252 µg/mL) did not suggest a genotoxic effect. The test compound precipitated at concentration >25.2 µg/mL.

APPENDIX A

MATERIALS AND METHODS
CBI pp. 10-17

Pages 109-116 - *Access to FIFRA health and safety data is restricted under FIFRA

010293

DOC 930112

FINAL

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Oral Toxicity in Mice

Study Title: FCR 4545 Technical: Study of the Acute Oral Toxicity to Mice (Formulation in Polyethylene Glycol E 400)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel, M.P.H.	8/4/92 Date
Independent Reviewer:	John Liccione, Ph.D.	8/4/92 Date
QA/QC Manager:	Sharon Segal, Ph.D.	8/4/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-297
Project Officer: James E. Scott

Approved by:
EPA Reviewer: William B. Greear, M.P.H., D.A.B.T. Signature William B. Greear
Review Section IV, Toxicology Branch I (HED) Date 8/7/92

EPA Section Head: Karen Hamernik, Ph.D. Signature Karen B. Hamernik for
Review Section III, Toxicology Branch I (HED) Date 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-1: Acute oral toxicity in mice

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-03
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in polyethylene glycol E 400

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 98350

STUDY NUMBER: T 7022139

TESTING FACILITY: BAYER AG, Institute of Toxicology/Agriculture of the Fachbereich Toxikologie of BAYER AG, Friedrech-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Oral Toxicity to Mice (Formulation in Polyethylene Glycol E 400)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 4, 1987

CONCLUSION: ORAL LD_{50}s in mice were established as follows:

LD_{50} (Male) = 91 mg/kg (58-146 mg/kg)
LD_{50} (Female) = 165 mg/kg (137-200 mg/kg)

Toxic signs: lethargy, digging and preening movements, uncoordinated gait, splayed gait, salivation, piloerection, rolling, increased activity, and difficult breathing,
Dose levels: 10, 25, 50, 71, 100, 160, 200, 224, 250 and 500 mg/kg
Route: Oral gavage
Strain: Bor: WISW SPF-Han

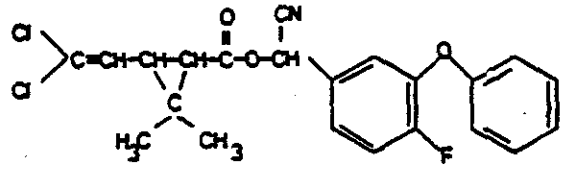
CLASSIFICATION: Acceptable. This study satisfies the guideline requirement (81-1) for an acute oral toxicity study in mice.

TOXICITY CATEGORY: II--Warning

A. MATERIALS

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Polyethylene glycol E 400
Type of formulation: Suspension
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1% (Sponsor analysis)
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (22-24°C)
Odor: Odorless
Date of receipt: March 10, 1986
Stability: When stored for 0 and 24 hours, stability of the 0.01 % nominal value was 91% and 87%, respectively; and stability of the 50% nominal value was 107 and 106%, respectively. Stability was determined before the study.
Homogeneity: Homogeneity of the test suspensions was maintained during administration by use of a magnetic stirrer. Homogeneity of three samples of the suspension (nominal value = 30%) was reported to be 115, 115, and 114%.

2. Controls

Animals: Not needed
Vehicle: Not needed

3. Test Animals

Species: Mice
Strain: SPF-bred NMRI rats, strain Bor: WISW (SPF-Han)
Source: Winkelmann, Borchen, Paderborn district, Federal Republic of Germany (FRG)
Sex and numbers: 40 Males; 45 females

Age: 4-5 Weeks
Initial body weight: Males, 20-23 g; females, 19-23 g
Housing: 20/Cage during the acclimation period; 1/cage during the study period. Animal room maintained at a temperature of 23±2°C and a relative humidity of approximately 50%. A 12-hour alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water were provided ad libitum.
Animal identification: Individual picric acid markings; and cage ID cards specifying the test compound, animal number, dose, sex, and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to groups based on random number tables.
Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant

B. TEST PERFORMANCE

FCR 4545 technical formulated in polyethylene glycol E (400) was administered in 5 mL/kg volumes by oral gavage to male and female mice that had been fasted for approximately 16 hours prior to treatment. Animals were observed for 14 days. Different doses were administered to male and female mice (see dosing schedule below). Fasted animals were provided feed 2 hours after dosing. There was no vehicle control group.

Dosing schedule:

Doses administered to groups of 5 fasted male mice: 10, 25, 50, 71, 100, 160, 250 or 500 mg/kg of the test material formulation.

Doses administered to groups of 5 fasted female rats: 10, 50, 71, 100, 160, 200, 224, 250 or 500 mg/kg of the test material formulation. An additional 5 females were administered 100 mg/kg for a total of 10 females in this dosage group.

The day of test material administration was referred to as day 0. Animals were frequently monitored for clinical signs of toxicity during test day 0, and at least once a day on test days 1-14. The duration of clinical observations was reported. Body weights were measured prior to dosing on test day 0 and daily thereafter. Mice that survived treatment were sacrificed at the end of the study using diethyl ether and necropsied. Mice that died during the study were also necropsied. Histopathological examinations were not performed on any of the animals.

Statistics

A computerized (HP 3000) program was used to calculate LD_{50}s by the method of A. P. Rosiello, M. M. Essigmann and G. N. Wogan (1977)[1] as modified by Pauluhn (1983)[2]. This method is based on the maximum likelihood method of Bliss (1938)[3]. The geometric mean was regarded as the "approximate LD_{50}" for data pairs with 0 and 100% mortality.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Table 1 summarizes the incidence of mortality and percent mortality. The time of death for animals that died during the study ranged from approximately 1 hour following exposure up to 2 days.

Clinical signs of toxicity of minimal-to-moderate severity were observed in all mice at each dose level except for the low-dose group (10-mg/kg dose level). Clinical signs consisted of lethargy, digging and preening movements, uncoordinated gait, splayed gait, salivation, piloerection, rolling, increased activity, and difficult breathing. These signs had an onset time ranging from 31 minutes to 3 hours and 34 minutes following exposure and continued for a maximum of 4 days. The study author stated that the observed clinical signs were in accordance with those of the CS syndrome which is known from pyrethroids with an α-cyano-3-phenoxybenzyl alcohol group.

Data for individual absolute body weights throughout the observation period were provided. Absolute body weight means were calculated for each dose group. The test material did not have an effect on body weight gain.

Gross necropsy data for individual animals were presented by sex, and dose group. For animals that died during the observation period, gross findings were reported for the lungs (slightly distended), liver (slight lobular pattern, mottled, pale), kidneys (mottled, slightly marbled, pale), stomach (distended, filled with dark mucous), and gastrointestinal tract (filled with dark mucous). No gross findings were

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[1]Rosiello, A. P., J. M. Essigmann and G. N. Wogan. 1977. Rapid and accurate determination of the median lethal dose (LD_{50}) and its error with small computer. J. Tox. and Environ. Health 3, 797-809 (1977).

[2]Pauluhn, J. 1983. Computer-aided estimation of the LD_{50}/LC_{50}. BAYER AG Report no. 11835, dated 05/18/1983.

[3]Bliss, C.I. 1938. The determination of the dosage-mortality curve from small numbers. Q. J. Pharm. Pharmacol. 11, 192-216.

Table 1. Summary of the Incidence of Mortality and Percent Mortality in Fasted Mice Orally Administered FCR 4545 Technical (formulation in polyethylene glycol E 400)[a]

Dose (mg/kg)	Males	Females
10	0	0
25	0	--
50	1 (20)[b]	1* (20)
71	3 (60)	0
100	3 (60)	1** (10)
160	4 (80)	3 (60)
200	--	2 (40)
224	--	4 (80)
250	3 (60)	5 (100)
500	5 (100)	3* (60)

[a]Data extracted from Report number 98350, p. 14.
[b]Value in parentheses is the % mortality.
*Dose not used in calculating the LD_{50}
**10 Animals in this group; all other groups have 5 animals.

reported for animals that were sacrificed at the end of the study. No microscopic examinations were performed on any of the animals.

Based on these results, the study author stated that FCR 4545 technical was moderately toxic to the mouse following acute oral administration.

LD_{50} Determination

The estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted mice was 91 mg/kg for males (95% confidence interval = 58-146 mg/kg) and 165 mg/kg for females (95% confidence interval = 137-200 mg/kg). Mortality results of female mice in the 50- and 500-mg/kg dose group were not included in the LD_{50} calculation for females.

E. REVIEWERS' COMMENTS

The title page of this study indicated that the data requirement for this study was "EPA Guideline n/a." The correct EPA Guideline series is 81-1.

Based on the mortality results, the estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted mice was 91 mg/kg for males (95% confidence interval 58-146 mg/kg) and 165 mg/kg for females (95% confidence interval 137-200 mg/kg).

Doc930118

FINAL

010293

DATA EVALUATION REPORT

FCR 4545

Study Type: Special Study

Study Title: FCR 4545 (C.N. Cyfluthrin K+L, Proposed) Study for Sensory Irritant Potential in the Mouse (RD50 Determination)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: John Liccione, Ph.D. — 8/26/92 Date

Independent Reviewer: Eve Andersen, Ph.D. — 8/26/92 Date

QA/QC Manager: Sharon Segal, Ph.D. — 8/26/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-294
Project Officer: James E. Scott

EPA Reviewer: William Greear, M.P.H., DABT
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
Sept 4, 1992
Date

Acting Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl P. Hetzler for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Special study: Sensory irritancy test

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412057-06
P.C. Number: 128831

TEST MATERIAL: FCR 4545

SYNONYM: Cyfluthrin K+L

SPONSOR: Agricultural Chemicals Division; Mobay Corporation

STUDY NUMBER: T8027496

TESTING FACILITY: Bayer AG Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (C.N. Cyfluthrin K+L Proposed) Study for Sensory Irritant Potential in the Mouse (RD50 Determination)

AUTHOR: Dr. J. Pauluhn

STUDY COMPLETED: May 9, 1988

CONCLUSIONS:

RD_{50} (sensory effect): 37.24 mg/m^3

NOEL: ~2 mg/m^3

Route: inhalation

Species: mouse

Strain: OF4

Toxic Signs: Extreme difficulty in breathing was noted in the mice exposed to a test vapor concentration of 93.7 mg/m^3. However, no mice showed signs of clinical toxicity 4 hours after termination of treatment.

CLASSIFICATION: Supplementary Data. Information presented in this study can be used to set limits on experiments involving inhalation exposure to FCR 4545.

A. MATERIALS

1. Test Material

Compound: FCR 4545
Chemical name: Cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2,-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Molecular formula: $C_{22}H_{18}Cl_2FNO_3$
Purity of material: 98% (Sponsor analysis)
Physical description: White powder
Receipt date: Not specified
Batch no.: 16001/87
Vehicle: 50% ethanol, 50% polyethylene glycol E 400
Storage conditions: The test material was stored at ambient temperature in darkness.
Stability: The test material was guaranteed by the sponsor for the duration of the study.
Physical properties: pH = 6.5

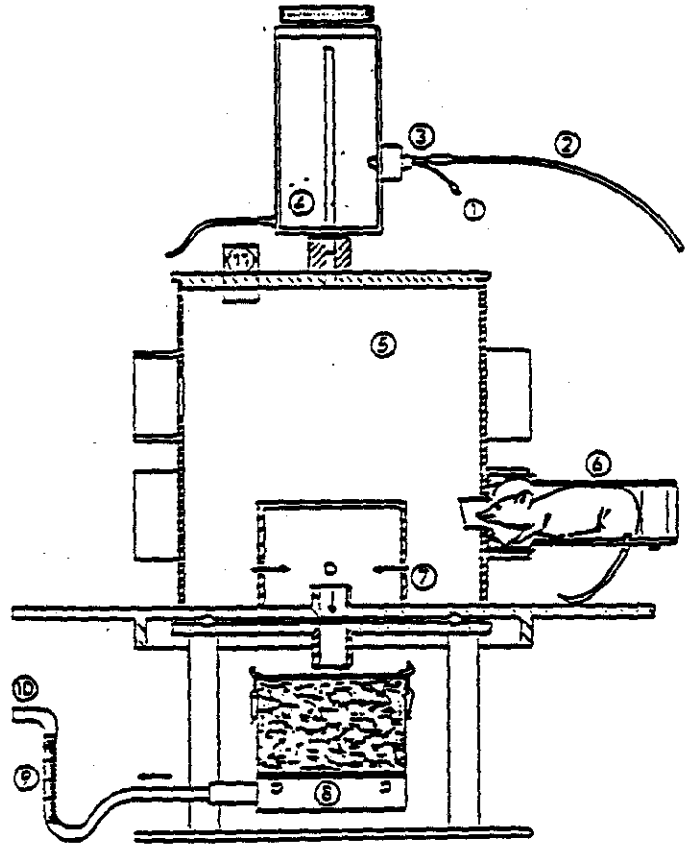
2. Controls

Materials: Vehicle (50% ethanol; 50% polyethylene glycol E 400)
Animals: Mice (4 males/group)

3. Test Animals

Species: SPF pure-bred mouse
Strain: OF4
Source: IFFA CREDO, L'Arbresle, France
Receipt date: Not specified
Sex: Male
Number: Total number received not specified
Housing: 5 Animals/cage
Temperature: 22 ± °C
Relative humidity: 50%
Lighting: 12-hour light/dark cycle
Air cycle: 10 times/hour
Age at exposure: 5-6 Weeks
Weight: Approximately 26-32 g (prior to exposure)
Feeding: Food (Altromin® 1324 diet for rats and mice) and tap water provided ad libitum.
Assignment: Random

Figure 1: inhalation chamber for aerosol testing



1. Spray solution feed via a Braun infusion pump with 50 ml ground glass jet
2. Compressed air (10 l air/minute); pressure approx. 600 kPa
3. Two-component nozzle (Rhema Labortechnik Co.)
4. Baffle
5. Inhalation chamber
6. Mouse in exposure tube (converted to whole-body flow plethysmograph)
7. Symmetrical radially-arranged air outlets
8. Cotton wool filter
9. Rotameter
10. Under-pressure system (vacuum pump)
11. Temperature and air humidity sensor (reference study)

B. TEST PERFORMANCE

Inhalation Chamber

Four animals per group were individually exposed in Plexiglass® exposure tubes (converted to whole-body flow plethysmograph) attached to a chamber (Figure 1). This was done to ensure that exposure to the test atmospheres was within the animal's respective breathing zones (head and nose exposure only). At the time of exposure, mice were placed in the plastic exposure tubes under the influence of a light halothane anaesthetic in order to minimize the stress involved in placing the animals in the exposure chambers. Mice were adapted for approximately 30 minutes to the exposure conditions; mice were considered adapted when the respiration frequency exceeded ~200 inspirations/minute. Following adaptation, basal lung parameters were measured for approximately 15 minutes, at which time the mice were exposed to air only. After determining individual control values, mice were exposed to the test material aerosol (7 concentrations) or the vehicle control (50% ethanol, 50% polyethylene glycol E 400) for 45 minutes. A 10-15-minute recovery period followed exposure to the test substance aerosol.

Dose Preparation/Generation of Test Atmosphere

Prior to the initiation of the study, the purity of the test compound was determined to be 98%. The stability of the test substance was guaranteed by the sponsor for the duration of the study; however, stability data were not reported. The test aerosol was generated in a cylindrical inhalation chamber equipped with a baffle. The ratio of inlet to outlet air was selected so that 60-80% of the dynamic inlet air was extracted via an aerosol filter (a cotton wool cylinder). A nozzle and condensed compressed air (10 L/minute, dispersion pressure approximately 600 kPa) were used to nebulize a constant 200-µL/minute flow rate of the test solution, consisting of an appropriate amount of FCR 4545 dissolved in 50% ethanol/50% polyethylene glycol E.

Analytical Determinations

Concentration of test spray in the test atmosphere was determined using gas chromatography (EC detector) from air samples taken from the breathing zone in the immediate vicinity of the test animals. Tubes filled with Florisil were used to collect air samples after a steady state concentration had been reached inside the exposure chamber. The mean analytical exposure concentrations were 0, 1.7, 5.0, 10.6, 22.8, 36.9, 49.7, and 93.8 mg/m^3 for Groups 1, 2, 3, 4, 5, 6, 7, and 8, respectively. Animals designated as controls (Group 1) were only exposed to the vehicle -- ethanol/polyethylene glycol E. Nominal concentration of the test spray was calculated from the quotient of the test article (mg) nebulized into the baffle of the inhalation chamber and the total air throughout the inhalation chamber (m^3). The nominal concentrations of the test material were 0, 10, 50, 100, 200, 350, 600, and 1000 mg/m^3 for Groups 1, 2, 3, 4, 5, 6, 7, and 8, respectively.

Chamber Monitoring

Approximately 30 exchanges per hour of the inhalation chamber air volume were ensured as a result of the aerosol generation conditions. A humidity sensor with a hygroscopic polymer as a dielectric was used to record relative humidity in the inhalation chamber. Mean representative temperature for the exposure chamber was 22-25°C and mean relative humidity was approximately 30%. The mean intervals were a result of random sampling. The frequency of temperature and relative humidity recordings was not reported.

Particle Size Determinations

Particle size determinations were conducted with a TSI aerodynamic particle sizer with an APS 3300 laser velocimeter. The APS 3300 measuring apparatus was operated at two dilution levels in order to measure higher test aerosol concentrations. Characterization of particle distribution was not conducted at the beginning of each test since each test concentration had the same vehicle concentration. Also, particle analyses were not performed for test substances at nominal concentrations of 10, 50, and 200 mg/m^3. The specific distribution of parameters was calculated using a MacIntosh computer program. The frequency of particle size determinations was not reported. The mass median aerodynamic diameter (MMAD) was calculated to be between 1.20 and 1.29 µm and the geometric standard deviation of the particle size distribution was 1.35-1.41 µm. Approximately 99% of the particles were ≤2 µm.

Lung Function Tests

Prior to exposure, lung function tests were conducted on all animals. These tests were performed in a whole-body flow plesthysmograph under quasi-isobaric conditions. Air flows were measured from the pressure difference across a 4 x 400-mesh wire gauze using a differential pressure transducer mounted on the plesthysmograph wall. The functioning of the plethysmograph, differential pressure transducer, and flow integrator calibration were monitored regularly using a 0.4-mL calibration syringe. The following lung parameters were individually determined: peak expiratory flow, tidal volume, respiration rate, minute volume, inspiration time, and expiration time.

Body Weights/Clinical Observations/Gross Necropsies

The body weights of all mice were recorded prior to exposure and on days 1, 3, and 7 postexposure.

Animals that were observed for clinical signs of toxicity were observed before exposure, after exposure, but not during exposure unless there were clear signs of toxicity (e.g., abnormal movements, spasms, severe breathing distress). After exposure, animals were observed for clinical signs of toxicity at hourly intervals, if necessary, with particular attention to the following:

- gross appearance of eye and respiratory tract mucous membrane
- state of fur and grooming activity
- general state of exposed skin and pinna
- respiration
- cardiovascular parameters
- somato-motor system and behavior pattern (tremors, convulsions, hypersalivation, dyspnea, diarrhea, lethargy, sedation, and coma)
- central nervous system and autonomic signs

Seven days after treatment, all animals were sacrificed with Evipan-Natrium® (approximately 30-50 mg/mouse, i.p. administration) and were subjected to a gross examination. The study report did not specify which tissues were evaluated for gross findings.

RD_{50} Determination

In order to determine the RD_{50}, the minimum for the smoothed measured respiratory rate (see Statistics section below) was calculated. Dose-response analysis of data (relative frequency decrease [y] as a function of concentration [x] = $\log_{10}$ (concentration)) was performed by the Least Square Method in order to determine the dose producing a 50% depression in the rate of respiration (RD_{50}). The calculation of the RD_{50} was based on the minimum value of the respiration frequency. The 95% confidence interval (two-tailed) was also calculated.

Statistics and Dose-Response Curve Fitting

Increases in body weight were evaluated using analysis of variance (ANOVA). A pairwise post hoc comparison was performed using Games and Howell's modification of the Tukey-Kramer Significance Test for significant differences in F-test values for ANOVA. Frequent gross findings were evaluated using Fisher's pairwise test with a preceding RxC Chi square test. Evaluation of lung parameter values was performed utilizing an HP-ADVANCE-LINK program on an HP 3000 computer. Absolute data on lung parameter values were smoothed using a polynomial of the 3rd degree regression model and then standardized to 100%.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Mortality

No mortalities were observed.

Clinical Signs

Groups 1, 2, and 3, at respective concentrations of 0, 1.7, and 5.0 mg/m^3, showed no treatment-related abnormal clinical signs. Mice exposed to 10.6 and 22.8 mg/m^3 of the test aerosol had a slightly slower respiration rate, but were free of any signs of clinical toxicity 1-2 hours postexposure. No clinical signs were reported for mice exposed to 36.9 mg/m^3 of the test

substance. Mice exposed to 49.7 mg/m^3 of the test substance aerosol, had a moderately slow respiration rate, and showed no signs of clinical toxicity approximately 3 hours after exposure. Extreme difficulty in breathing was noted in the mice exposed to a test vapor concentration of 93.7 mg/m^3. However, no mice showed signs of clinical toxicity 4 hours after termination of treatment. Individual animal data were not provided.

Body Weights

No statistically significant, treatment-related effects on body weight or body weight gain were observed in any of the treatment groups during the posttreatment observation period.

Lung Function Parameters

Based on a cubic polynomial regression model, the percentage decrease in respiratory rate in rats exposed to 1.7, 5.0, 10.6, 22.8, 36.9, 49.7, or 93.8 mg/m^3 aerosol was 9, 19, 28, 42, 40, 46, and 81, respectively.

RD_{50} Calculation

The RD_{50} was estimated to be equal to 37.24 mg/m^3 air, with 95% confidence interval of 19.78-114.69 mg/m^3 air.

Gross Necropsy

The study author indicated that no gross lesions in any organs were noted in the test and control groups. However, the study author did not indicate which organs were examined.

D. QUALITY ASSURANCE MEASURE

A signed quality assurance statement was not provided.

A signed statement of data confidentiality, was signed and dated April 26, 1989.

A statement indicating that the study was not conducted in compliance with the Good Laboratory Practice Standards of 40 CFR Part 160, was attached and dated April 26, 1989.

E. REVIEWERS' DISCUSSION

Although there are no guidelines concerning irritancy testing by respiratory exposure, the design and conduct of the sensory irritancy test

in mice, as well as determination of the RD_{50} value were acceptable. However, the study author did not discuss the clinical signs observed in animals exposed to 36.9 mg/m^3 aerosol. Also, the study author referred to the test animals as "rats" rather than as mice on several occasions in the study report. For comparative purposes, a graphic representation of reflex bradypnea in a chemical possessing a severe irritant potential (i.e., aliphatic isocyanate) was included in the study report. However, the concentration of the positive control was not specified. Graphic presentations showing flow/volume curves for mice exposed to the vehicle and to 93.8 mg test material/m^3 air were also provided.

Based on the results, FCR 4545 tested positive as a sensory irritant. The study author considered the sensory irritation of FCR 4545 to be relatively high; however, dose-response data and an RD_{50} for the positive control were not provided for comparative purposes. A maximum depression of respiratory rate of ~80% was achieved in this study. The study author indicated there were no changes in lung functioning in terms of reflex bradypnea; the decrease in respiratory rate was considered to be due to slower breathing overall. The RD_0 was estimated by the study author to be ~2 mg FCR 4545/m^3; this value was also considered by the study author to be the NOEL.

In summary, FCR 4545 is a sensory irritant in mice following inhalation exposure.

DOC930117

FINAL

010293

DATA EVALUATION REPORT

FCR 4545

Study Type: Acute Oral Toxicity Study in the Chicken

Study Title: FCR 4545: Study for Acute Oral Toxicity to the Chicken (Gallus domesticus)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer: John Liccione, Ph.D. — Date: 8/26/92

Independent Reviewer: Eve Andersen, Ph.D. — Date: 8/26/92

QA/QC Manager: Sharon Segal, Ph.D. — Date: 8/26/92

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-307
Project Officer: James E. Scott

EPA Reviewer: William B. Greear, M.P.H., DABT
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
Sept 4, 1992
Date

EPA Acting Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-1: Acute oral toxicity study in chickens

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412441-16
P.C. Number: 128831

TEST MATERIAL: FCR 4545 technical

SYNONYMS: Cyfluthrin

SPONSOR: Agricultural Chemicals Division; Mobay Corporation

STUDY NUMBER: 95609

TESTING FACILITY: Bayer AG Institute of Toxicology, Federal Republic of Germany

TITLE OF REPORT: FCR 4545: Study for Acute Oral Toxicity to the Chicken (Gallus domesticus)

AUTHOR: Dr. W. Flucke

STUDY COMPLETED: August 6, 1985

CONCLUSIONS: The acute oral LD_{50} in hens is >5000 mg/kg.

CLASSIFICATION: Acceptable for an acute oral toxicity study in hens. However, hens were not fasted prior to the oral administration of the test material. Toxicity Category IV

A. MATERIALS

1. Test Material

Test Material: FCR 4545 (technical grade) formulated with Cremophor EL in demineralized water (2% v/v)
Chemical name: Cyano-(4-fluoro-3-phenoxyphenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Purity of material: 98.5% (Sponsor analysis)
Physical description: Not reported.
Batch no.: 16002/84
Storage conditions: Not reported.
Vehicle: Cremophor EL in demineralized water
Stability: Not reported.

2. Controls

Materials: None used
Animals: None used

3. Test Animals

Species: Hen (Gallus domesticus)
Strain: White (laying) Leghorn
Source: Brinkschulte, Senden
Receipt date: Not specified
Sex: Female
Number: 5 Hens
Housing: Individual
Age at exposure: 7-10 months
Weight: 1.75 kg-1.98kg (prior to dosing)
Acclimation: For a minimum of 1 week.
Feeding: Feed (LA Eierblitz sole feed for laying hens) and tap water, provided ad libitum
Assignment: Random

B. TEST PERFORMANCE

Dose Procedure

Five hens were orally administered a single dose of 5000 mg/kg of FCR 4545 formulation by stomach tube. The volume administered was 20 mL/kg body weight. Hens were not fasted prior to dosing. Hens were observed 21 days following exposure.

Body Weights/Clinical Observations/Gross Necropsies

Body weights of all animals were recorded before administration of the test substance solution, and once weekly thereafter for the remainder of the study. The animals were observed for clinical signs of toxicity several times on the day of test material administration, and once daily thereafter for the remainder of the study. At the end of the observation

period, all animals were sacrificed with Evipan®, and were dissected and subjected to a gross necropsy. The study report did not indicate if the animals received a complete necropsy.

LD_{50} Determination

An LD_{50} was not calculated since there were no mortalities.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Mortality

No mortality was observed in the 5 chickens dosed with FCR 4545.

Clinical Signs

There were no clinical signs of toxicity.

Body Weights

There were no significant variations in body weight for any of the animals tested.

LD_{50} Determination

The LD_{50} was determined to be >5000 mg/kg, since no mortalities were observed at this dose level.

Gross Necropsy

No treatment-induced gross effects were noted.

D. QUALITY ASSURANCE MEASURE

A Good Laboratory Practice compliance statement was signed and dated August 28, 1989.

E. REVIEWERS' COMMENTS

This study was conducted according to OECD Guidelines, and is acceptable for an acute oral study in chickens. Based on the results presented, the acute oral LD_{50} in chickens is >5000 mg/kg body weight. There were no signs of toxicity. The homogeneity of the test material in the dosing solution was not determined.

DOC920102

FINAL

010293

DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Acute Inhalation Toxicity in Rats

Study Title: FCR 4545 (c.n. cyfluthrin K+L proposed): Studies for Acute Inhalation Toxicity to Rats

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D.	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-289
Project Officer: James E. Scott

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
9/9/92
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl V. Hatcher for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Guideline series 81-3: Acute inhalation toxicity in rats

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412057-01
PC Number: 128831

TEST MATERIAL: FCR 4545

SYNONYMS: Cyfluthrin; cyfluthrin K+L (proposed)

SPONSOR: Mobay Corporation

STUDY NUMBERS: T 6027719 (aerosol)
T 6027728 (dust)

TESTING FACILITY: Bayer AG, Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (c.n. cyfluthrin K+L proposed): Studies for Acute Inhalation Toxicity to Rats

AUTHOR: J. Pauluhn

STUDY COMPLETED: July 18, 1988

CONCLUSIONS: LC_{50} = 81-82 mg/m^3 (aerosol)
Toxic signs: reduced motility, tonic extension spasms, bradypnea, reduced reflexes, piloerection, ungroomed coats, rolling movements
Concentration levels: 53.4, 80.5, 82.2, and 96.7 mg/m^3
Route: head and nose inhalation
Strain: Wistar (Bor:WISW (SPF-Cpb)) rats

LC_{50} = 532 mg/m^3 (dust)
Toxic signs: tonic extension spasm, rolling, dyspnea, slowed reflexes, reddened nose, nasal bleeding, and staggering gait
Concentration levels: 212, 417, 497, 640, and 867 mg/m^3
Route: head and nose inhalation
Strain: Wistar (Bor:WISW (SPF-Cpb)) rats

CLASSIFICATION: Acceptable. This study did not satisfy the following Guideline Series 81-3 requirements for an acute inhalation study in rats: the percentage of oxygen in the test atmosphere during exposure was not reported; the time of sampling for measurement of particle size was not clearly reported; it was not reported whether the chamber concentration was equilibrated prior to the 4-hour exposures; and the relative humidity (10%) was out of range (40-60%). However, the study is acceptable and conclusions can be drawn from the data.

TOXICITY CATEGORY: Aerosol: ~~I-Danger~~ II
Dust: II-Warning III

A. MATERIALS

1. Test Material

Test material: FCR 4545 or β-Cyfluthrin
Chemical name: α-Cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Purity: 97.9% (Sponsor analysis; data not shown)
Physical description: Solid white powder
Lot number: 16001/87
Storage conditions: Room temperature; in darkness
Stability: Confirmed for the duration of the studies (Sponsor analysis; data not shown)
Vehicle: Polyethylene glycol E 400/ethanol mixture (1:1) (for aerosol only)

2. Controls

Animals: 1/Sex (aerosol studies only)
Test substance: Polyethylene glycol E 400/ethanol mixture (1:1) (vehicle)

3. Test Animals

Species: Rats
Strain: Wistar (Bor:WISW (SPF-Cpb))
Source: Versuchstierzucht Winkelmann, Borchen, Kreis Paderborn
Sex: Male and female
Numbers: 5/Dose/sex
Housing: 5/Cage
Climatic conditions: Temperature = 22±2°C; relative humidity = 50%; 12-hour light/dark cycle; air exchange rate = 10 times/hour

Acclimation: At least 5 days
Age: Young adult
Weight: 160-210 g
Feeding: Feed (Altromin^{R} 1324) and water provided ad libitum
Selection: Randomization

4. Exposure

Route of administration: Inhalation (head and nose only)
Concentrations: 53.4, 80.5, 82.2, and 96.7 mg/m^3 (aerosol)
212, 417, 497, 640, and 867 mg/m^3 (dust)

B. TEST PERFORMANCE

Inhalation Chamber

Inhalation studies were performed for the aerosol and dust forms of the test substance. The animals were confined separately in Plexiglass tubes that allowed maximum head and nose exposure and reduced whole body exposure. A commercially available exposure chamber was used (Rhema Labortechnik Co., D-6238 Hofheim, AM Stegskreuz 2) with the following dimensions: 30 cm (diameter) x 28 cm (height) and a volume of 20 liters. A diagram of the exposure chamber is shown on page 16 of the CBI study. Twenty rats, each in an exposure tube, can be simultaneously exposed in this chamber. It was not specified how many were exposed simultaneously for this study, but 5 animals/sex/dose were tested.

Generation of Test Atmosphere

A polyethylene glycol E 400/ethanol mixture (1:1) was used as a vehicle for aerosol exposures. No vehicle was needed for exposures to the dust form of the test substance. Compressed air was used to deliver 100 µl of the FCR 4545-vehicle solution to the baffle chamber at a rate of 10 L/minute. The aerosol was generated in the baffle chamber and was subsequently delivered to the inhalation chamber at a rate of 30 air exchanges per hour. Using a Bayer dust generator, the powder form of the test substance was delivered to the inhalation chamber as a uniform mixture of dust and air (20-30 L/minute) every 4-19 seconds. Exposure was continuous due to the slow rate in which the dust settles in the chamber.

Analytical Determinations

Concentrations of aerosol and dust were measured by gas chromatography (with an EC detector) from samples taken near the breathing zone of the animals prior to and twice during each exposure. The mean (2 samples) concentration of FCR 4545 (98% pure) aerosol in the test atmosphere was determined to be 53.4, 80.5, 82.2, and 96.7 mg/m^3 for the respective nominal concentrations of 500, 700, 850, and 1000 mg/m^3. Nominal concentrations were measured as the quotient of the test compound (mg) sprayed into the baffle chamber on the inhalation chamber and the total air throughput per inhalation chamber (m^3). The mean (3 samples) concentration of FCR 4545 (98% pure) dust in the test atmosphere was determined to be 212, 417, 497, 640, and 867 mg/m^3. Nominal concentrations could not be calculated for dust exposures because the

amount of test powder consumed during exposure could not be determined by weighing.

Air flows were continuously monitored using a rotameter. The temperature and humidity in the inhalation chamber were monitored every 10 minutes. The mean temperatures during aerosol and dust exposures were 23°C and 22°C, respectively. The mean relative humidity during aerosol exposure was 10% and the mean relative humidities during dust exposures varied from 34% to 46% for exposure groups 2-6. Oxygen availability to the animals during exposure was not reported.

Particle Size Determinations

Particle-size distribution for aerosol exposures was determined using an aerodynamic particle sizer with Laser Velocimeter (TSI-APS 3300). Particle-size distribution for dust exposures was determined using an Anderson cascade impactor. Particle-size distribution was measured for each concentration of FCR 4545 as either aerosol or dust. However, it is not clear whether air samples were taken to measure particle size during exposure or at some other time. The mean mass median aerodynamic diameter (MMAD) was reported to be 1.3 µm for aerosols (geometric standard deviation of 1.4), and ranged from 1.31 µm to 1.45 µm. The mean MMAD was reported to be 4.5 µm for dusts (geometric standard deviation of 1.7), and ranged from 4.16 µm to 4.69 µm. The percent of respirable particles (<5 µm) was reported to be 100% for aerosols and ranged from 55% to 64% for dusts. The graphical data (CBI Appendix 13, pp. 42-55) indicate that the percent of respirable particles that are <2 µm are 99-100% for aerosols and <10% for dusts.

Body Weights/Clinical Observations/Gross Necropsy

Animals were exposed to aerosol or dust for 4 hours, followed by a 14-day observation period. It was not reported whether the chamber was equilibrated to the appropriate concentration (a 6-minute process according to the study author) prior to the 4-hour exposure period. Animals were weighed prior to treatment and then on days 3, 7, and 14 of observation. Animals were observed for mortality and clinical signs several times on the day of exposure, but not during exposure (unless effects could be readily seen while the animals were confined to the tubes), on weekends, and on days 1, 2, 3, 7, and 14 of observation. Necropsies were performed on all animals. Abnormalities were described and reported.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Mortality data are summarized in Table 1. A concentration-response relationship for mortality was observed following exposures to FCR 4545 aerosol or dust for 4 hours or less. The mortality incidences were as follows: 1, 4, 4, and 10 of the 10 rats/dose died from exposures to 53.4, 80.5, 82.2, and 96.7 mg/m^3 aerosol, respectively; 2, 4, 7, and 10 of the 10 rats/dose died from exposures to 417, 497, 640, and 867 mg/m^3 dust, respectively. No deaths occurred following exposure to 212 mg/m^3 dust. Based on these results, the acute inhalation LC_{50} values of FCR 4545 in rats are 82 mg/m^3 for males exposed to aerosol; 81 mg/m^3 for females

Table 1. Mortality Data for Rats Exposed to FCR 4545 Aerosol and Dust by Inhalation.

Concentration (mg/m^3)	Males		Females	
	Incidence of Mortality/Total Number Exposed	Time of Death (hours)	Incidence of Mortality/Total Number Exposed	Time of Death (hours)
		Aerosol		
0.0	0/5	NA	0/5	NA
53.4	0/5	NA	1/5	< 4
80.5	1/5	< 4	3/5	< 4
82.2	2/5	< 4	2/5	< 4
96.7	5/5	< 4	5/5	< 4
		Dust		
0	0/10	NA	0/10	NA
212	0/5	NA	0/5	NA
417	0/5	NA	2/5	24
497	3/5	24	1/5	24
640	3/5	≤ 24	4/5	24-96
867	5/5	≤ 24	5/5	≤ 24

NA = Not applicable.

exposed to aerosol; and 532 mg/m^3 for male and females exposed to dust. Aerosol exposure induced death more rapidly than exposure to dust.

Symptoms were observed in all animals in each exposure group, following both aerosol and dust exposures, except for the high concentration-groups[1]; no symptoms occurred in any of the control animals. In general, symptoms were slight to moderate. However, in some animals, rolling and dyspnea were severe following aerosol or dust exposures; and slowed reflexes, reduced motility, and reddened noses were severe in some animals exposed to dust.

Animals exposed to 53.4, 80.5, and 82.2 mg/m^3 of FCR 4545 aerosol exhibited reduced motility, tonic extension spasms, bradypnea, reduced reflexes, piloerection, and ungroomed coats. In addition, rats exposed to 80.5 and 82.2 mg/m^3 aerosol exhibited rolling movements.

There are some discrepancies between symptoms reported by the study author (pp. 31 and 32) and those shown in the data summaries. Specifically, the data summaries show that slowed respiration, chromodacryorrhea, and nasal bleeding were only induced in the low-concentration group (CBI Appendix 13, pp. 59, 63, and 64). This is in disagreement with the study author's report that each of these effects occurred from exposures to 53.4-82.2 mg/m^3 (pp. 31-32). Chromodacryorrhea and nasal bleeding did not occur in males exposed to levels >53.4 mg/m^3, according to the summaries of male data; no summaries of female data were reported for these effects. The author's conclusions regarding chromodacryorrhea and nasal bleeding would be correct if these effects occurred only in the females of all three exposure groups and the female data were inadvertently omitted.

The study author also reported (p. 20) that no apparent effects were noted as a result of the low humidity level during aerosol exposures. Also, on page 61 of the study, (reduced) motility was incorrectly written as mortality.

There are also some discrepancies between the symptoms reported by the study author (pp. 33-34) and those shown in the data summaries (CBI Appendix 13, pp. 70-80)[2] for animals exposed to dust. First, the author reported that all animals exposed to 867 mg/m^3 (high-dose group) FCR 4545 dust, died during exposure, and therefore, no observations were made on these animals[1]. However, the data summaries indicate that 2 males and 3 females from the high-concentration group survived exposure and died by the following day. Tonic extension spasm, rolling, dyspnea, slowed reflexes, reddened nose, nasal bleeding, and staggering gait were reported in the data summaries to have occurred in animals of this group. Another discrepancy is that dyspnea was reported for animals exposed to 212 mg/m^3

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[1] It was not possible to assess symptoms in the animals exposed to 96.7 mg/m^3 aerosol or some animals exposed to 867 mg/m^3 dust since they died during exposure; assessments were difficult to make while animals were in the exposure tubes.

[2] For effects that were not translated in the study (bauchlage, atmung erschwert, and gang taumelnd) a German dictionary was used (Langenscheidt's German-English Dictionary; Pocket Books (Publ.), NY. 1970). From this source, it was concluded that bauchlage, which refers to the stomach, meant "prostration on the stomach" (p. 34 of the study); atmung erschwert, or "breathing aggravated", meant respiratory distress; and gang taumelnd, or "staggering movement" meant staggering gait.

dust; however, this is not evident in the data summaries (CBI Appendix 13, pp. 71 and 76). Ungroomed coats and staggering gait did not occur, according to the data summaries, in the animals exposed to 640 mg/m^3 dust (CBI Appendix 13, pp. 73, 74, 79, and 80), as was reported in the text. Also, respiratory distress occurred in animals exposed to 417 mg/m^3 dust (CBI Appendix 13, pp. 72 and 78), but this was not noted in the text.

The majority of the clinical effects, either from aerosol or dust exposures, subsided by 1 day following exposure; some effects were apparent in a few animals for 2-3 days after exposure.

Only male rats exposed to 212 and 640 mg/m^3 dust had slight decreases in mean body weights when compared to the controls. Also, females exposed to 640 mg/m^3 dust had a large decrease in body weight gain compared to the controls. This latter effect was considered to be clinically significant by the study author.

In animals that died from exposure to aerosol, several treatment-related lesions were detected: distended lung, with edema and a hepatoid appearance; pale liver with lobulation; pale kidneys, and reddened gastrointestinal tract. In animals that died from exposure to dust, treatment-related lesions were identical to those noted in the animals that died from aerosol exposure except that no kidney effects were detected and the gastrointestinal tract contained yellowish to bloody mucous in addition to its red appearance. No lesions were detected in the remaining animals exposed to either aerosol or dust that were sacrificed after the 14-day observation period.

D. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement dated April 7, 1988 was presented. A Good Laboratory Practice compliance statement was also included.

E. REVIEWERS' COMMENTS

This study was classified as Acceptable. According to Guideline Series 81-3, the study contains the following deficiencies: 1) the oxygen levels available to the animals during exposure were not reported; 2) it is not clear whether the particle sizes of the aerosol and dust were tested during exposure or at some other time; 3) it was not reported whether the chamber concentration was equilibrated prior to the 4-hour exposures; and 4) the relative humidity (10%) was out of range (40-60%). The reviewers also noted that there were some discrepancies between what the study author reported in the text and what was shown by the data summaries.

The reviewers agree with the study author that acute inhalation of the aerosol of FCR 4545 induces respiratory and nervous system effects at concentrations of 53.4-96.7 mg/m^3. Similar effects were noted in animals exposed to FCR 4545 dust at levels of 417-867 mg/m^3 and, to a lesser extent, at levels of 212 mg/m^3. In addition, the aerosol induced kidney lesions and both the dust and aerosol of FCR 4545 induced lung, liver, and gastrointestinal lesions in animals that died during or shortly after exposure. Based on the data in this study, acute 4-hour inhalation LC_{50}

values of 81-82 mg/m^3 and 532 mg/m^3, for FCR 4545 aerosol and dust, respectively, were calculated.

Despite its deviations from the guidelines and several discrepancies* in the reporting of the data, which may be the result of errors in translation, the conduct and design of the study is acceptable and the data clearly demonstrate neurotoxic and respiratory effects under the exposure conditions of the study. As the study author notes, cyfluthrin is and behaves typically of a pyrethroid; it induces rapidly reversible and non-specific central nervous effects (i.e., rolling movements, tonic extension spasms, reflex bradypnea).

* The discrepancies do not really exist. The author described the qualitative clinical signs of toxicity, not the quantitative clinical signs of toxicity in his discussion. Therefore, the study is acceptable.

F. APPENDIX

CBI Study: Figure 1, Schematic of Inhalation Exposure System, p. 16

010293

Reviewed by: John C. Redden, Toxicologist 2/21/92
Section III, Tox. Branch I
Secondary reviewer: Henry Spencer, Toxicologist 2/21/92
Section VI, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Range-Finding Test for Toxicity to Dog

GUIDELINE: N/A

TOX. CHEM NO: 266E

MRID NO.: 412441-15

TEST MATERIAL: Cyfluthrin

STUDY NUMBER: 95606

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer Ag
Institute of Toxicology
Federal Republic of Germany

TITLE OF REPORT: FCR 4545 Range-Finding Test for Acute Toxicity to the Dog.

AUTHOR(S): E. von Keutz

REPORT ISSUED: August 14, 1985

CONCLUSION:

The oral doses were 2500 mg/kg body weight and 5000 mg/kg body weight. Clinical signs, for 2500 mg FCR 4545 oral administration, included vomiting, foam on muzzles, loose faeces. Clinical signs, for 5000 mg FCR 4545 oral administration, included increased salivation, foam on muzzles, and vomiting. The oral doses in this study were not lethal in dogs. However, the emetic effect of the compound make it difficult to determine the actual dose. A Lethal Dose could not be determined for this reason.

The intravenous dose was approximately 0.9 ml/kg body weight males and approximately 1.3 ml/kg body weight females. Clinical signs, for intravenous injection, included laying on their sides, convulsions of the extremities, impaired respiration, foam on muzzles, and howling, which was attributed to pain. The female died after 40 minutes. A Lethal Dose in one female dog, for intravenous administration, is 5.0 mg/kg body weight.

Core Classification: supplementary. This type of study is not

addressed in 40 CFR.

QUALITY ASSURANCE: A statement signed and dated August 30, 1989 was present and stated: "This study was not conducted in compliance with the Good Laboratory Practice Standards of 40 CFR Part 160 (FIFRA) or with the ORCD Principles of Good Laboratory Practice, C(81) 30 (Final) Annex 2 (Paris, May, 1981)."

MATERIALS:

1. Test compound: α-cyano(4-fluro-3-phenoxy-phenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; FCR 4545 batch 16002/84; Purity=98.5% (sum of isomers).

2. Test animals: Species: Dog; Strain: Bor:Beagle; Age: 10 to 33 months; Weight: 7.9 to 14.5; Source: F. Winkelmann, D-4799 Borchen.

METHODS:

1. Animal Assignment: There was 1 male and 1 female in each group. Animals were housed individually. Animals were on a 12 hour light/dark cycle. Room temperature was between 20° and 23° C. Humidity was between 40% and 60%. The diet was Ssniff whole diet, Ssniff Versuchstierdiaeten GmbH, D-4770 Soest. Each dog received approximately 350 grams of feed. Tap water was available ad libitum.

2. Test Substance Administration: The compound was administered by the oral route and the intravenous route. The compound was suspended at 20% in 0.5% tylose solution. Volumes were 12.5 ml/kg body weight (2500 mg/kg body weight) and 25 ml/kg body weight (5000 mg/kg body weight). The solution was administered by stomach tube before the morning feeding. For intravenous administration the compound was dissolved at 0.4% in Lutrol. The dose was approximately 0.9 ml/kg body weight males and approximately 1.3 ml/kg body weight females. The injection site was the vena jugularis.

3. Observations: All animals were observed, for clinical signs, daily before compound administration and for up to fourteen days after administration. Food consumption was done daily, and body weights were determined at seven day intervals. All animals, rather moribund, found dead, or sacrificed were grossly dissected.

RESULTS:

Clinical signs, for 5000 mg FCR 4545 oral administration, included increased salivation, foam on muzzles, and vomiting. These signs persisted for up to five hours after oral administration. The female vomited one time during the fourteen day post observation period. The female did not finish the food

during the first three days post treatment, whereas the male ate all his food during the 14 day post observation period. Body weights (Table 1) remained constant during the post observation period.

Clinical signs, for 2500 mg FCR 4545 oral administration, included vomiting, foam on muzzles, loose faeces. Both dogs vomited on the day after administration of the compound, but were otherwise normal for the post observation period. The male consistently ate all his food. The female left food and lost weight during the first week (Table 1).

Table 1: Body Weights for Beagle Dogs Exposed by the Oral Route

Dose mg/kg	Dog Number/Sex		Body Weights (kg) 0 weeks	1 weeks	2 weeks	Amount administered ml/animal
5000	P451	Male	10.7	10.7	10.6	267.5
5000	P630	Female	9.7	9.7	9.7	242.5
2500	P373	Male	8.6	8.2	8.5	107.5
2500	P276	Female	7.9	7.5	7.5	98.7

The oral doses in this study is not lethal in dogs. However, the emetic effect of the compound make it difficult to determine the actual dose. A oral Lethal dose could not be determined for this reason.

Table 2: Summary of Results after Intravenous Administration of FCR 4545 to Beagle Dogs

Dose mg/kg	Dog Number/Sex		Body Weights (kg) 0 weeks	1 weeks	2 weeks	Amount administered ml/animal
3.6**	O 59	Male	14.5	13.8	13.7	13
5.1**	N 530	Female	11.7	+	+	15**

** Due to convulsions both doses had to be stopped early. The male received a dose of 3.6 mg/kg body weight, and the female received 5.1 mg/kg body weight.

+ Animal died.

Both animals began to have convulsions during the administration of this compound. Clinical signs included laying on their sides, convulsions of the extremities, impaired respiration, foam on muzzles, and howling, which was attributed to pain. The female died after 40 minutes. Necropsy did not reveal any unusual findings. In the male the convulsions continued for 1 hour and 45 minutes. The male appeared to be weak and to have swollen lips on the day following treatment. During the rest of the observation period the animal appeared normal. Although, the male ate all his food he lost 0.9 kg during the post treatment period.

A intravenous lethal dose in 1 female dog was 5.0 mg/kg body weight.

DISCUSSION

This study is not addressed by the 40 CFR. In addition this study was not performed in accordance with Good Laboratory Practices. It is Core graded as supplementary and cannot be upgraded.

The oral doses in this study ~~is~~ are not lethal in dogs. However, the emetic effect of the compound make it difficult to determine the actual dose. An oral lethal dose could not be determined for this reason.

A lethal dose value for intravenous administration, based on death in the one female tested, is 5.0 mg/kg body weight.

DOC930107

FINAL

010293

DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Acute Intraperitoneal Toxicity in Mice

Study Title: FCR 4545, FCR 1272: Study of the Acute Intraperitoneal Toxicity to Mice (Formulation in Polyethylene Glycol E 400)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D.	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-306
Project Officer: James E. Scott

Guideline Series N/A: Acute intraperitoneal toxicity study

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
5/8/92
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karen Hamernik for
Signature
5/18/92
Date

DATA EVALUATION REPORT

STUDY TYPE: Acute intraperitoneal toxicity in mice

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-14
PC Number: 128831

TEST MATERIAL: FCR 4545
FCR 1272

SYNONYMS: Cyfluthrin

SPONSOR: Mobay Corporation

STUDY NUMBER: FCR 4545 - T 3027130
FCR 1272 - T 1027129

TESTING FACILITY: Bayer AG, Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany

TITLE OF REPORT: FCR 4545, FCR 1272: Study of the Acute Intraperitoneal Toxicity to Mice (Formulation in Polyethylene Glycol E 400)

AUTHOR: F. Kroetlinger

STUDY COMPLETED: November 25, 1988

CONCLUSIONS:

Chemical: FCR 4545
LD_{50} = 18.0 mg/kg
Toxic signs: reduced activity, lethargy, uncoordinated gait, dyspnea, splayed gait, rolling
Dose levels: 10.0, 16.0, 17.0, 18.0, 20.0, 25.0, 100.0 mg/kg
Route: intraperitoneal injection
Strain: Bor:NMRI (SPF-Han) mice

Chemical: FCR 1272
LD_{50} = 63.0 mg/kg
Toxic signs: reduced activity, lethargy, uncoordinated gait, dyspnea, splayed gait, rolling

Dose levels: 1.0, 10.0, 25.0, 40.0, 50.0, 63.0, 71.0, and 100.0 mg/kg
Route: intraperitoneal injection
Strain: Bor:NMRI (SPF-Han) mice

CLASSIFICATION: Supplementary Data. The study provides supplemental information regarding the acute toxicity of the test material following intraperitoneal exposure.

TOXICITY CATEGORY: Not applicable.

A. MATERIALS

1. Test Materials

a) Test material: FCR 4545 (technical) or Cyfluthrin; (formulated in polyethylene glycol E 400)
Chemical name: Cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Enantiomer distribution: I 0.3%
II 35.8%
III 0.7%
IV 63.2%
Purity: 98.0% (Sponsor analysis)
Physical description: Solid white powder; odorless
Lot number: 16001/87
Storage conditions: Room temperature (24-28°C; without light)
Stability: Tested over a 24-hour period for 0.01% and 50% solutions. The content of the active ingredient in the 0.01% solution was reduced by 4% and in the 50% solution it was reduced by 1% over the 24-hour time period.
Homogeneity: Homogeneity was maintained for the 0.01% (range of 111-114% of nominal) and 2.038% (range of 92-102% of nominal) solutions.

b) Test material: FCR 1272 (technical)
(formulated in polyethylene glycol E 400)
Chemical name: Cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Enantiomer distribution: I 24.7%
II 19.4%
III 33.5%
IV 22.4%
Purity: 95.5% (Sponsor analysis)
Physical description: Brownish, syrup-like solid; odorless
Lot number: 233 690 489 - 3757
Storage conditions: Room temperature (24-28°C; without light)
Stability: Tested over a 24-hour period for 0.02% and 80% solutions. The content of the active ingredient in the 0.02% solution was not reduced over 24 hours; that of the 80% solution was reduced by 2% in this time period.
Homogeneity: Homogeneity was maintained for the 0.02% (range of

90-98% of nominal) and 75.64% (range of 104-106% of nominal) solutions.

2. Controls

Animals: Used for pathological examination (treatment of controls was not described); for body weight, baseline values were used as controls
Test substance: None used

3. Test Animals

Species: Mice
Strain: Bor:NMRI (SPF-Han)
Sex: Male
Source: Winkelmann, Borchen, Paderborn district, FRG
Receipt date: Not reported
Numbers: 5/dose
Housing: 20/cage during acclimation; individually during the study period
Climatic conditions: Temperature = 23±2°C; relative humidity = 50%; 12-hour light/dark cycle; air exchange rate = 10 times/hour
Acclimation: At least 7 days
Age: 6-8 Weeks (FCR 4545); 5-8 weeks (FCR 1272)
Weight: 33-39 g (FCR 4545); 31-39 g (FCR 1272)
Feeding: Feed (Altromin® 1324) and water provided ad libitum
Selection: Only healthy animals were chosen; random selection was used for dose group assignments; some assignments were based on body weights

4. Exposure

Route of administration: intraperitoneal (i.p.) injection
Dose level: 5 ml/kg of body weight;

FCR 4545: 10.0, 16.0, 17.0, 18.0, 20.0, 25.0, and 100.0 mg/kg

FCR 1272: 1.0, 10.0, 25.0, 40.0, 50.0, 63.0, 71.0, and 100.0 mg/kg (FCR 1272)

B. TEST PERFORMANCE

The test materials were formulated in polyethylene glycol E 400 immediately prior to administration (percent solution not specified). Animals were assigned to dose groups by tables of random numbers and/or on a body weight basis. Animals were fed prior to dosing with a single intraperitoneal injection of the test substance. LD50 values, based upon the median lethal dose, were calculated by computer (HP 3000) using the

method of Bliss[1,2]. For statistical analyses, the slope and confidence intervals for the mortality data were used when data were available for more than 2 dose groups. If there were only 2 dose groups with data (i.e., 0% and 100% mortalities), LD50 values were estimated.

Various doses were administered to determine the LD50 and establish the maximum tolerated dose at which no toxic signs occurred. Clinical observations (for appearance and behavior) were conducted several times on the day of exposure and once per day thereafter (excluding weekends and holidays). Body weights were measured prior to exposure and once per week postexposure. Following a 14-day observation period and sacrifice or death during the study, mice were examined for gross pathological effects.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

1. FCR 4545

Tabular individual body weight and pathological data were shown for male mice. Mortality data and clinical observations were tabulated for each dosage group. The LD50 was calculated to be 18.0 mg/kg for male mice based on exposures of 10.0-100.0 mg/kg FCR 4545 using 5 animals/dose. The mortality data are summarized in Table 1. The incidences of mortality were 1, 3, 5, 4, and 5 for the 5 animals/dose that were exposed to 17.0, 18.0, 20.0, 25.0, and 100.0, respectively. The time of death ranged from 0.9 to 1.7 hours. No mice died from exposure to 10.0 or 16.0 mg/kg.

Animals in each dose group showed clinical signs following exposures to FCR 4545. All of the effects were minimal to moderate in severity and subsided by day 2 postexposure. Clinical signs observed in all exposure groups were reduced activity and uncoordinated gait. Lethargy and dyspnea occurred in all groups except for the 18.0- and 16.0-mg/kg groups, respectively. Splayed gait appeared in all groups except for the 10.0-mg/kg group. Rolling was noted in groups exposed from 18.0 mg/kg to 100.0 mg/kg. Sporadic convulsions, spasmodic state, and tachypnea were each noted in only 1 group (10.0, 17.0, and 25.0 mg/kg, respectively) and therefore, may not be treatment related.

No treatment-related effects on body weight were noted in any of the animals.

In mice that died within 14 days following exposure, gross pathology examination revealed pale livers in 1-3 animals/dose exposed to 16.0 mg/kg to 25.0 mg/kg; and pale kidneys in 1-2 animals/dose exposed from 17.0 mg/kg to 100.0 mg/kg, with the exception of animals exposed to 20.0 mg/kg. Distended lungs, pale spleen, and reddened renal pelvis were only noted in 1 animal from the 17.0- or 25.0-mg/kg groups. In mice that were sacrificed after 14 days, no treatment-related effects were noted. In 1

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[1] Bliss, C.I. The calculation of the dosage-mortality curve. Am. Appl. Biol. 22:134, 1935.

[2] Bliss, C.I. The determination of the dosage-mortality curve from small numbers. Q.J. Pharm. Pharmacol. 11:192-216, 1938.

Table 1. Mortality Data for Mice Exposed to FCR 4545 and 1272 by Intraperitoneal Injection

Concentration (mg/kg)	Incidence of Mortality/ Total Number Exposed	Time of Death (hours)
	FCR 4545	
10.0	0/5	NA
16.0	0/5	NA
17.0	1/5	1.5
18.0	3/5	0.9-1.2
20.0	5/5	1.1-1.7
25.0	4/5	1.4-1.6
100.0	5/5	1.0-1.6
	FCR 1272	
1.0	0/5	NA
10.0	0/5	NA
25.0	0/5	NA
40.0	1/5	0.6
50.0	2/5	1.8
63.0	1/5	1.5
71.0	3/5	2.9
100.0	5/5	1.5-24

NA = Not applicable.

In 1 animal, dark red zones in the lung occurred which was not considered to be treatment related by the study author. No effects were noted in the untreated controls.

The observed clinical signs were considered to be treatment-related by the study author. Under the conditions of the study, FCR 4545 was identified to be mildly toxic, based upon an LD50 of 18.0 mg/kg in mice.

2. FCR 1272

Tabular individual body weight and pathological data were shown for male mice. Mortality data and clinical observations were tabulated for each dosage group. The LD50 was calculated to be 63.0 mg/kg for male mice based on exposures of 1.0-100.0 mg/kg FCR 1272 using 5 animals/dose. The mortality data are summarized in Table 1. Mortality incidences were 1, 2, 1, 3, and 5 in for the 5 mice/dose that were exposed to 40.0, 50.0, 63.0, 71.0, and 100.0 mg/kg, respectively. The time of death ranged from 0.6 to 24 hours. No mice died from exposure to 1.0, 10.0, or 25.0 mg/kg.

Animals in each dose group, except those exposed to 1.0 mg/kg, showed clinical signs following exposures to FCR 1272. All of the effects were minimal to moderate in severity and subsided by day 3 postexposure. All exposure groups exhibited reduced activity. Although present in the low-dose groups, lethargy did not occur in animals exposed to 71.0 or 100.0 mg/kg. All groups exhibited splayed gait except the 10.0 mg/kg and 63.0 mg/kg groups. Dyspnea occurred in all groups except for the 10.0- and 40.0-mg/kg groups. Rolling was noted only in groups exposed to 71.0 and 100.0 mg/kg. Spastic gait only occurred in mice exposed to 50.0 and 100.0 mg/kg. Sporadic convulsions was only noted in the group exposed to 10.0 mg/kg and therefore, may not be treatment related.

No treatment-related effects on body weight were noted in any of the animals.

In mice that died within 14 days following exposure, gross pathology examination revealed mottled to dark red lungs in 1 animal exposed to 40.0 mg/kg. Slightly distended lungs occurred in this animal and 1 animal from the 100.0-mg/kg group. In this same animal exposed to 100.0 mg/kg, mottled liver, a slight lobular pattern in the liver, and mottled spleen and kidneys were noted. Another animal from the high-dose group had pale kidneys. Pale livers were noted in 2 animals exposed to 50.0 mg/kg. In mice that were sacrificed after 14 days, no treatment-related effects were noted; in 1 animal exposed to 40.0 mg/kg, the lobes of the liver were adhered to the diaphragm, pancreas, peritoneum, glandular stomach and parts of the small intestinal tract. No lesions were noted following exposure to 1.0 mg/kg FCR 1272 nor in the untreated controls.

The observed clinical signs were considered to be treatment related by the study author. Under the conditions of the study, FCR 1272 was identified to be moderately toxic, based upon an LD50 of 63.0 mg/kg in mice.

D. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement dated November 22, 1988 was presented. A Good Laboratory Practice compliance statement was included.

E. REVIEWERS' COMMENTS

The reviewers agree with the study author's conclusions that FCR 4545 and FCR 1272 are mildly and moderately toxic to mice, respectively, via intraperitoneal injection. The acute LD50 values for FCR 4545 and FCR 1272 were found to be 18.0 mg/kg and 63.0 mg/kg, respectively. None of the pathological effects noted in the study were dose related; however, the data suggest that FCR 4545 may induce pale kidneys and livers in mice. Pale kidneys occurred animals that were exposed from 17.0 to 100.0 mg/kg FCR 4545, excluding exposure to 20.0 mg/kg. Pale liver occurred in animals that were exposed from 17.0 to 25.0 mg/kg FCR 4545, but not from exposure to 100.0 mg/kg.

This study cannot be classified since no Guideline Series are available for acute intraperitoneal toxicity studies. However, it provides supplemental information concerning the acute toxicity of the test material following intraperitoneal injection.

DOC930106

FINAL

DATA EVALUATION REPORT

010293

CYFLUTHRIN

Study Type: Acute Intraperitoneal Toxicity in Rats

Study Title: FCR 4545 (Technical): Study of the Acute Intraperitoneal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D.	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-305
Project Officer: James E. Scott

Guideline Series N/A: Acute intraperitoneal toxicity study

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B. Greear
Signature
9/8/92
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl D. Gerbec for
Signature
5/15/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Acute intraperitoneal toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-13
PC Number: 128831

TEST MATERIAL: FCR 4545 (Technical)

SYNONYMS: Cyfluthrin

SPONSOR: Mobay Corporation

STUDY NUMBER: T 6022138

TESTING FACILITY: Bayer AG, Institute of Toxicology, Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 (Technical): Study of the Acute Intraperitoneal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

AUTHOR: K.G. Heimann

STUDY COMPLETED: October 13, 1987

CONCLUSIONS: LD_{50} = 8.5 mg/kg (males)
17 mg/kg (females)
Toxic signs: lethargy, uncoordinated gait, splayed gait, salivation, difficulty breathing, reduced activity, digging and preening movements, and/or rolling
Dose levels: 1.0, 5.0, 7.1, 10.0, 11.2, 12.5, 25.0 mg/kg (male)
1.0, 10.0, 15.0, 16.0, 18.0, 20.0, 25.0, 50.0 mg/kg (female)
Route: abdominal intraperitoneal injection
Strain: Bor:WISW (SPF-Cpb) Wistar rats

CLASSIFICATION: Supplementary Data. There are no Guideline Series available for acute intraperitoneal toxicity studies. However, the study provides supplemental information regarding the acute toxicity of the test material following intraperitoneal injection.

TOXICITY CATEGORY: Not applicable

A. MATERIALS

1. Test Material

Test material: FCR 4545 (technical) or Cyfluthrin; (formulated in polyethylene glycol E 400)
Chemical name: α-Cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Purity: 99.1% (Sponsor analysis; data not shown)
Physical description: Solid white powder
Lot number: 16002/84
Storage conditions: Room temperature (21.5-24°C; without light)
Stability: Tested over a 24-hour period for 0.01% and 50% solutions. The content of the active ingredient in the 0.01% solution was reduced by 4% and in the 50% solution it was reduced by 1% over the 24-hour time period.
Homogeneity: Homogeneity was maintained (ranged from 114-115% of nominal) for the 30% solution and was achieved by a magnetic stirrer.

2. Controls

Animals: None (for body weight, baseline values were used as controls)
Test substance: None used

3. Test Animals

Species: Wistar rats
Strain: Bor:WISW (SPF-Cpb)
Sex: Male and female
Source: Winkelmann, Borchen, Paderborn district, FRG
Receipt date: Not reported
Numbers: 5/sex/dose for all doses except 20 mg/kg, at which 10 females were used (no explanation was given)
Housing: 5/cage during acclimation; individually during the study period
Climatic conditions: Temperature = 23±2°C; relative humidity = 50%; 12-hour light/dark cycle; air exchange rate = 10 times/hour
Acclimation: At least 7 days
Age: 7-12 weeks
Weight: 166-188 g (males); 173-194 g (females)
Feeding: Feed (Altromin® 1324) and water provided ad libitum
Selection: Only healthy animals were chosen; random selection was used for dose group assignments

4. Exposure

Route of administration: Abdominal intraperitoneal injection
Dose level: 5 ml/kg body weight
males: 1.0, 5.0, 7.1, 10.0, 11.2, 12.5, and 25.0 mg/kg
females: 1.0, 10.0, 15.0, 16.0, 18.0, 20.0, 25.0, and 50.0 mg/kg

B. TEST PERFORMANCE

The test materials were formulated in polyethylene glycol E 400 (percent solution not specified). Animals were assigned to dose groups by tables of random numbers. Animals were dosed with a single intraperitoneal injection of the test substance. LD50 values, based upon the median lethal dose, were calculated by computer (HP 3000) using the method of Bliss[1]. For statistical analyses, the slope and confidence intervals for the mortality data were used when data were available for more than 2 dose groups. If there were only 2 dose groups with data (i.e., 0% and 100% mortalities), LD50 values were estimated.

Various doses were administered to determine the LD50 and establish the maximum tolerated dose at which no toxic signs occurred. Clinical observations (for appearance and behavior) were conducted several times on the day of exposure and once per day thereafter. Body weights were measured prior to exposure and once per day postexposure. Following a 14-day observation period and sacrifice or death during the study, rats were examined for gross pathological effects.

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Tabular individual body weight and pathological data were provided for rats. Mortality data and clinical observations were tabulated for each dose group. The LD50 was calculated to be 8.5 mg/kg for males and 17 mg/kg for females based on exposures of 1.0 to 50.0 mg/kg with 5 rats/sex/dose.

The mortality data are summarized in Table 1. The mortality incidences were 1, 4, 5, 4, and 5 for 5 male rats/dose that were exposed to 7.1, 10.0, 11.2, 12.5, and 25.0 mg/kg, respectively. The time to death of males ranged from 1.6 to 3.3 hours. The mortality incidences were 1/5, 2/5, 8/10, 4/5, and 5/5 for female rats that were exposed to 15.0, 16.0, 20.0, 25.0, and 50.0 mg/kg, respectively. The time to death of females ranged from 2.5 to 4.7 hours. No rats died following exposure to 1.0 and 5.0 mg/kg (males) or 1.0, 10.0, and 18 mg/kg (females). In female rats, 15.0, 16.0, and 20.0 to 50.0 mg/kg were lethal in a dose-dependent manner; however, 18 mg/kg was not lethal to rats. No explanation was given for this discrepancy, but 18 mg/kg was not used in the LD50 calculation.

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[1] Bliss, C.I. The determination of the dosage-mortality curve from small numbers. Q.J. Pharm. Pharmacol. 11:192-216, 1938.

Table 1. Mortality Data for Rats Exposed to FCR 4545 Technical by Intraperitoneal Injection.

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Dose (mg/kg)	Incidence of mortality/total number exposed	Time of Death (hours)	Percent Mortality
		Males	
1.0	0/5	NA	0
5.0	0/5	NA	0
7.1	1/5	2.2	20
10.0	4/5	2.1-3.3	80
11.2	5/5	1.8-3.2	100
12.5	4/5	1.8-3.2	80
25.0	5/5	1.6-3.0	100
		Females	
1.0	0/5	NA	0
10.0	0/5	NA	0
15.0	1/5	3.2	20
16.0	2/5	3.1-4.7	40
18.0	0/5	NA	0
20.0	8/10	3.1-3.8	80
25.0	4/5	3.0	80
50.0	5/5	2.5-3.8	100

NA = Not applicable.

Clinical observations were negative for both sexes exposed to 1.0 mg/kg/day. All animals/sex/dose showed clinical signs following exposures to 10.0-55.0 mg/kg. In addition, all males exposed to 5.0 and 7.1 mg/kg (females were not exposed to these doses) and all females exposed to 50.0 mg/kg (males were not exposed to this dose) exhibited clinical signs. Males exposed to 7.1 mg/kg and animals of both sexes exposed to 10.0 mg/kg or more exhibited the following clinical signs: lethargy, uncoordinated gait, splayed gait, salivation, and difficulty breathing. Time to onset for these effects was 17 minutes to 2 hours. Exposure to 5.0 mg/kg (males) produced lethargy, reduced activity and splayed gait. Reduced activity occurred within 2.5 hours to 2 days of exposure. Exposure to 50.0 mg/kg (females) induced digging and preening movements, which was noted within 1.5 to 2 hours, and rolling in addition to the other effects noted above. All of the effects noted by clinical observation subsided after a maximum of 3 days and were generally minimal to moderate in severity. However, females exposed to 18 mg/kg were severely lethargic. No other severe effects were noted in any of the other exposure groups.

No treatment-related effects on body weight were noted in any of the animals. Some females in all dose groups exhibited body weight reductions but these effects were transient.

Gross pathology examination revealed distended lungs, lobular livers, and mottled kidneys in the majority of the rats that died from exposure. Mottled kidney was only noted in male rats. In most of the rats that were sacrificed after 14 days, swollen livers and livers with lobes grown together or with lobes that adhered to the diaphragm and mesentery were noted.

The clinical signs and pathological effects were considered to be treatment related by the author. The study author considered the pathological effects to result from "local irritant effects" of cyfluthrin and identified cyfluthrin to be of moderate toxicity to rats under the conditions of the study.

D. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated September 25, 1987, was presented. A Good Laboratory Practice compliance statement was included.

E. REVIEWERS' COMMENTS

The reviewers agree with the study author's conclusions that cyfluthrin is moderately toxic to rats via intraperitoneal injection. The acute LD50 for cyfluthrin in male and female rats was 8.5 mg/kg and 17 mg/kg, respectively. As the study author notes, cyfluthrin behaves typically of a pyrethroid that contains an α-cyano-3-phenoxy-benzyl alcohol group; it induces rapidly reversible and non-specific central nervous effects.

This study is classified as Supplementary Data. No Guideline Series are available for acute intraperitoneal toxicity studies. However, it

provides supplemental information concerning the acute toxicity of the test material following intraperitoneal injection.

010293

DOC930128

FINAL

DATA EVALUATION REPORT

CYFLUTRIN (BETA)

Study Type: Mutagenicity: Gene Mutation in Cultured Chinese Hamster Ovary Cells (CHO/HGPRT)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Nancy E. McCarroll, B.S Date 7/17/92

Independent Reviewer Lynne Haber, Ph.D. Date 7/17/92

QA/QC Manager Sharon Segal, Ph.D. Date 7/20/92

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-304
Project Officer: James Scott

GUIDELINE § 84: MUTAGENICITY
MAMMALIAN CELLS IN CULTURE GENE MUTATION

EPA Reviewer: John Redden, Ph.D.
Review Section III,
Toxicology Branch I/HED (H-7509C)
EPA Section Head: Henry Spencer, Ph.D.
Review Section III,
Toxicology Branch I/HED (H-7509C)

Signature: [signature]
Date: 2/25/93

Signature: [signature] for
Date: 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Gene mutation in cultured Chinese hamster ovary cells (CHO/HGPRT)

EPA IDENTIFICATION Numbers:

Tox Chem. Number: 266-E

MRID Number: 412441-12

TEST MATERIAL: FCR 4545

SYNONYMS/CAS Number: Cyflutrin (beta); cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethycyclopropanecarboxylate; $C_{22}H_{18}Cl_2FNO_3$/ 68359-37-5

SPONSOR: Mobay Corp., Kansas City, MO

STUDY NUMBER: 97481

TESTING FACILITY: Bayer AG, Wuppertal, Germany

TITLE OF REPORT: FCR 4545 C.N. Cyfluthrine K+L (proposed) Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay In Vitro.

AUTHOR: H. Lehn

REPORT ISSUED: June 27, 1988

CONCLUSIONS--EXECUTIVE SUMMARY: Insoluble (50-100 µg/mL) and soluble (20-40 µg/mL) doses of FCR 4545 with or without S9 activation were neither cytotoxic nor mutagenic in two independently performed Chinese hamster ovary (CHO) cells HGPRT assays. We conclude, therefore, that the test material was adequately investigated and found to be nonmutagenic in this mammalian cell gene mutation assay.

STUDY CLASSIFICATION: Acceptable. The study satisfies Guideline requirements (§84.2) for genetic effects, Category I, Gene Mutations.

A. MATERIALS:

1. Test Material: FCR 4545

Description: White powder
Identification no.: Batch number: 16001/85
Purity: 99.6%
Receipt date: Not provided
Stability: Reported to be stable in the solvent (dimethyl sulfoxide, DMSO) under the conditions used. The data from the stability analysis were not provided.
Contaminants: None listed
Solvent used: DMSO
Other provided information: The test material was stored at refrigerator temperatures and solutions of the test material were prepared immediately before use.

2. Control Materials:

Negative: Ham's F12 medium supplemented with 1 mM L-glutamine, 10% fetal calf serum (FCS), and antibiotics

Solvent/final concentration: DMSO/1%

Positive: Nonactivation (concentrations, solvent): Ethyl methanesulfonate (EMS) was prepared in an unspecified solvent to yield a final concentration of 1200 µg/mL.

Activation (concentrations, solvent): Dimethylbenzanthracene (DMBA) was prepared in an unspecified solvent to yield a final concentration of 20 µg/mL.

3. Activation: S9 derived from male Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
____ phenobarbital	____ noninduced	____ mouse	____ lung
____ none		____ hamster	____ other
____ other		____ other	

The S9 homogenate (lot number 07417) was purchased from Litton Bionetics, Inc., Kensington, MD. The protein content was listed as 41.6 mg/mL. The S9 fraction was checked for sterility and assayed for cytotoxicity as well as for the ability to convert DMBA or 3-methylcholanthrene to mutagenic forms prior to use.

S9 mix composition:

Component	Concentration
NADP	1 mM
Glucose 6-phosphate	5 mM
Potassium chloride	33 mM
Magnesium chloride	8 mM
Sodium phosphate buffer, pH 7.4	Not reported
S9 homogenate	40%

Final S9 concentration in treatment medium was 5%.

4. Test Cells: Mammalian cells in culture

_____ mouse lymphoma L5178Y cells
__x__ Chinese hamster ovary (CHO) cells
_____ V79 cells (Chinese hamster lung fibroblasts)
_____ other (list):

Properly maintained? Yes.
Periodically checked for mycoplasma contamination? Yes.
Periodically checked for karyotype stability? Yes.
Periodically "cleansed" against high spontaneous background? Yes.

5. Locus Examined:

_____ thymidine kinase (TK)
selection agent: _____ bromodeoxyuridine (BrdU)
(give concentration) _____ fluorodeoxyuridine (FdU)

__x__ hypoxanthine-guanine-phosphoribosyl transferase (HGPRT)
selection agent: _____ 8-azaguanine (8-AG)
(give concentration) 10 µg/mL 6-thioguanine (6-TG)

_____ Na^+/K^+ATPase
selection agent: _____ ouabain
(give concentration)

_____ other (locus and/or selection agent; give details):

6. Test Compound Concentrations Used:

(a) Preliminary cytotoxicity assay: Nine doses (0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25.0, 40.0, and 100.0 µg/mL) were evaluated without S9 activation. The nine doses evaluated with S9 activation were 0.19, 0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25.0, and 40.0 µg/mL.

(b) Mutation assay: Two nonactivated and two S9-activated assays were performed; doses tested were as follows:

(1) Nonactivated conditions:

Initial trial: 20.0, 25.0, 40.0, 50.0, 80.0, 90.0, and 100.0 µg/mL.

Repeat trial: 20.0, 25.0, 30.0, 35.0, 40.0, 50.0, and 100.0 µg/mL.

(2) S9-activated conditions:

Initial trial: 20.0, 25.0, 30.0, 35.0, 40.0, 50.0, and 100.0 µg/mL.

Repeat trial: As above for the initial S9-activated trial.

B. TEST PERFORMANCE:

1. Cell Treatments:

(a) Cells exposed to test compound for:
__5__ hours (nonactivated) __5__ hours (activated)

(b) Cells exposed to positive controls for:
__5__ hours (nonactivated) __5__ hours (activated)

(c) Cells exposed to negative and/or solvent controls for:
__5__ hours (nonactivated) __5__ hours (activated)

Note: The FCS concentration in the treatment medium (Ham's F12) was reduced to 5%.

(d) After washing, cells were cultured for __6__ days (expression period) before cell selection.

(e) After expression, $2x10^5$ cells/dish were cultured for __7__ days in selection medium to determine numbers of mutants; 200 cells/dish were cultured for __7__ days in nonselection medium to determine cloning efficiency.

2. Statistical Methods: The data were evaluated for statistical significance at p values of 0.05 and 0.01 using the tables of Kastenbaum and Bowman.

3. Evaluation Criteria:

(a) Assay validity: The assay was considered valid if the following criteria were met: (1) the absolute cloning efficiency of the negative control was ≥50%; (2) the spontaneous mutation frequency (MF) in the negative control did not exceed $25x10^{-6}$ cells; and (3) the positive controls induced MFs that were ≥3-fold higher than the negative control.

(b) Positive response: The test material was considered positive if a reproducible dose-related increase in the MF (≥2-fold) compared to the negative control was observed at three doses.

4. Protocol: None presented.

C. REPORTED RESULTS:

1. Solubility Determinations: The test material was reported to be soluble in DMSO at 50 mg/mL; however, concentrations >40 µg/mL prepared in DMSO precipitated in the treatment medium. Based on this information, 100.0 and 40.0 µg/mL were selected as the high concentrations for the nonactivated and S9-activated preliminary assessment of cytotoxicity, respectively.

2. Preliminary Cytotoxicity Test: In agreement with the earlier findings, the highest nonactivated dose (100.0 µg/mL) was insoluble. Results further indicated that FCR 4545 was not clearly cytotoxic at any level either with or without S9 activation. Accordingly, the dose range selected for the initial mutation assay was 20-100 µg/mL +/-S9.

3. Mutation Assays:

   (a) Nonactivated conditions: Representative results from the two nonactivated assays with FCR 4545 are shown in Table 1. Doses ≥50 µg/mL were insoluble, and there was no definitive evidence of a cytotoxic response at any level. Although significant increases ($p<0.01$) in the MF were observed for one of the two replicate platings of cultures treated with 40 and 50 µg/mL, the data did not suggest a dose-dependent response. Additionally, with the exception of the average MF calculated by our reviewers for the 50-µg/mL treatment group, all MFs were within the expected spontaneous range for CHO cells (0-20 mutants x 10^{-6}).[1] The repeat nonactivated assay was conducted with a narrow range of concentrations clustered around the "significant" levels. Results shown in Table 1 indicate that the significantly increased MFs recorded for single replicates in the first trial were not reproduced in the repeat trial.

   (b) S9-activated conditions: Results for the initial S9-activated assay were in good agreement with the nonactivated findings and indicated that FCR 4545 was neither cytotoxic nor mutagenic at soluble (20.0-40 µg/mL) or insoluble (50.0 and 100.0 µg/mL) doses (Table 2). In the repeat trial, the negative and solvent control MFs were beyond the acceptable range; however, the overall findings with FCR 4545 were comparable to the initial S9-activated test results. Although one of the replicate cultures treated with the lowest assayed level (20 µg/mL) induced a significantly increased MF ($p<0.01$), the lack of reproducibility and evidence of dose dependency suggest that this finding was anomalous.

The study author concluded, therefore, that FCR 4545 was not mutagenic in the CHO-HGPRT forward mutation assay.

D. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS: We assess that the study author's interpretation of the data was correct. In both the presence and absence of S9 activation, FCR 4545 was assayed beyond the solubility limit (≥50 µg/mL) but failed to induce a cytotoxic or reproducible mutagenic response in CHO cells. Although significant increases in the MF were noted in single replicate cultures under nonactivated (Trial 1) and S9-activated (Trial 2) conditions, we conclude that since the effect was

[1]Hsie, A. W., Casciano, D.A., Couch, D.B., Krahn, D.F., O'Neil, J.P., and Whittfield, B.L. (1981). The use of Chinese hamster ovary cells to quantify specific locus mutation and to determine mutagenicity of chemicals. Mutat. Res. 86:193-214.

TABLE 1. Representative Results of the Nonactivated Chinese Hamster Ovary (CHO) Cell Forward Gene Mutation Assays with FCR 4545

Substance	Dose/mL	Relative Percent Cloning Efficiency (After Treatment)[a]	Average Total Mutant Colonies per 8 Dishes[a]	Average Percent Relative Growth (at Selection)[a]	Average Absolute Percent Cloning Efficiency (at Selection)[a]	Average Mutation Frequency $x10^{-6}$[a,b]
Negative Control						
Culture medium	--	ND[c,d]	2	139.8	67.5	1.9
	--	ND[e]	3	99.1	77.9	2.4
Solvent Control						
Dimethyl sulfoxide	1%	100.0[c,d]	4	100.0	72.8	3.4
	1%	100.0[c,e]	6	100.0	72.3	5.2
Positive Control						
Ethylmethane sulfonate	1200 µg	ND[d]	91	16.0	12.8	443.3*
	1200 µg	ND[e]	244	19.0	29.5	516.9*
Test Material						
FCR 4545	25.0 µg/mL[f]	81.6[d]	4	185.1	56.9	4.4
	40.0 µg/mL	94.2	15	105.7	59.8	15.7[g]
	50.0 µg/mL	90.0	35	65.9	62.8	34.8[g]
	80.0 µg/mL[h]	81.1	5	79.0	59.0	5.3
	25.0 µg/mL[f]	ND[c,e]	1	64.8	86.4	0.7
	30.0 µg/mL	ND[c]	6	80.1	71.1	5.3
	35.0 µg/mL	ND[c]	4	107.9	69.7	3.6
	40.0 µg/mL	ND[c]	5	88.0	72.8	4.3
	50.0 µg/mL	ND[c]	3	84.6	80.6	2.6

[a]Based on the results from duplicate cultures; calculated by our reviewers.

[b]Mutation Frequency (MF) = $\frac{\text{Average Total Mutant Colonies}}{\text{No. of Dishes (8) x No. of Cells Plated } (2\text{x}10^5) \text{ x Cloning Efficiency}}$; calculated by our reviewers.

[c]ND = not done; culture(s) lost due to contamination.

[d]Results from the initial trial

[e]Results from the repeat trial

[f]Results for the lowest assayed level (20 µg/mL) did not suggest a mutagenic effect.

[g]One of the two replicate cultures produced a significant ($p<0.01$) increase in the MF.

[h]Compound precipitation occurred at levels ≥50 µg/mL. Findings for higher doses (80, 90, and 100 µg/mL) did not suggest a mutagenic effect.

*Significantly higher ($p<0.01$) than the corresponding solvent control by Kastenbaum and Bowman tables

TABLE 2. Representative Results of the S9-Activated Chinese Hamster Ovary (CHO) Cell Forward Gene Mutation Assays with FCR 4545

Substance	Dose/mL	Relative Percent Cloning Efficiency (After Treatment)[a]	Average Total Mutant Colonies per 8 Dishes[a,b]	Average Percent Relative Growth (at Selection)[a]	Average Absolute Percent Cloning Efficiency (at Selection)[a]	Average Mutation Frequency x10^{-6}[a,c]
Negative Cotnrol						
Culture medium	--	73.7[d]	5	106.5	80.9	3.9
	--	101.0[e]	33 (7)	85.6	69.6	34.0
Solvent Control						
Dimethyl sulfoxide	1%	100.0[d]	9	100.0	86.6	6.5
	1%	100.0[e]	27 (6)	100.0	74.1	30.4
Positive Control						
Dimethylbenzanthracene	20 µg	96.0[d]	52	74.8	68.3	47.7*
	20 µg	48.1[e]	208	49.8	70.0	185.7*
Test Material						
FCR 4545	20 µg[f]	107.1[d]	10	98.7	83.6	7.5
	40 µg	70.5	15	96.0	86.2	10.9
	100 µg[g]	87.7	10	117.5	74.6	8.4
	20 µg[f]	81.6[e]	43 (6)	70.6	69.4	51.6[h]
	40 µg	87.0	28 (6.5)	75.7	65.5	32.9
	100 µg[g]	75.9	33 (6.5)	87.5	64.5	39.4

[a]Based on the results from duplicate cultures; calculated by our reviewers.

[b]Average values for 8 dishes/culture unless otherwise indicated by the value in (). Selection medium plates in the specified experimental groups were lost due to contamination.

[c]Mutation Frequency (MF) = $\frac{\text{Average Total Mutant Colonies}}{\text{No. of Dishes (8) x No. of Cells Plated } (2\text{x}10^5) \text{ x Cloning Efficiency}}$; calculated by our reviewers.

[d]Results from the initial trial

[e]Results from the repeat trial

[f]Lowest assayed dose; findings for intermediate levels (25, 30, 35, and 50 µg/mL) did not suggest a positive response.

[g]Highest evaluated concentration; compound precipitation reported at this level and at 50 µg/mL.

[h]One of the two replicate cultures produced a significant ($p<0.01$) increase in the MF.

*Significantly higher ($p<0.01$) than the corresponding solvent control by Kastenbaum and Bowman tables

not reproducible or dose related, the increases probably represent isolated events that are not indicative of a positive response. We further assess that while background MFs in the second S9-activated trial were beyond acceptable ranges, there were sufficient valid data from both trials to support the study author's conclusion that S9-activated FCR 4545 was not a mutagen in the test system. In addition, the sensitivity of the assay to detect mutagenesis was adequately demonstrated by the significant results obtained with 1200 µg/mL EMS -S9 and 20 µg/mL DMBA +S9.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A quality assurance statement was signed and dated June 9, 1988).

F. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 10-19.

CORE CLASSIFICATION: Acceptable. The study satisfies Guideline requirements (§84.2) for genetic effects, Category I, Gene Mutations.

APPENDIX A

MATERIALS AND METHODS
CBI pp. 10-19

Pages 177-186 - *Access to FIFRA health and safety data is restricted under FIFRA

010293

Reviewed by: Melba S. Morrow, D.V.M. MSM 7/15/91
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Joycelyn E. Stewart, Ph.D. JES 7/17/91
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT 0-0065A

STUDY TYPE: Subacute Oral Toxicity - rat

GUIDELINE #: N/A

TOX. CHEM. #: 266E

MRID #: 412441-17

TEST MATERIAL: FCR 4545

SYNONYMS: Beta Cyfluthrin, Tempo I

STUDY NUMBERS: 98346

SPONSOR: Mobay

TESTING FACILITY: Bayer, AG
Federal Republic of Germany

TITLE OF REPORT: FCR 4545 Subacute Study of Oral Toxicity to Rats

AUTHORS: K.G. Heimann

REPORT ISSUED: 1/27/88

CONCLUSIONS: Based on the clinical signs observed at 4 and 16 mg/kg, the NOEL, under the conditions of this study, is 1 mg/kg. These clinical observations included increased digging and grooming and increased mobility at 4 mg/kg and increased activity, salivation, uncoordinated gait, spastic gait, dyspnea and dacryohemorrhagia and death at 16 mg/kg. Decreased body weight gain was also reported in high dose males.

TOX. CATEGORY: N/A
CLASSIFICATION: Supplementary. The study provided supplementary information on the target organs, cumulative effects and reversibility of effects for FCR 4545.

MATERIALS: FCR 4545, 98.5% purity batch # 16002/84 was the test material. SPF Wistar rats (150 males and 150 females) were the test animals. The males had mean body weights of 160 grams and females had mean body weights of 147 grams. The ages ranged from 7 to 9 weeks.

METHODS: Animals were acclimated for seven days and housed five animals per cage per sex. The environmental temperature was 22 ± 2° C and the relative humidity was 50%. Animals were exposed to a 12 hour light/dark cycle. Following the acclimation period, animals were randomly allocated to the following groups:

GROUP	DOSE	# ANIMALS	VOLUME
control	vehicle	30M, 30F	10 ml/kg
1	0.25 mg/kg	30M, 30F	10 ml/kg
2	1.0 mg/kg	30M 30F	10 ml/kg
3	4.0 mg/kg	30M, 30F	10 ml/kg
4	16.0 mg/kg	30M, 30F	10 ml/kg

Test material, which was prepared fresh daily, or the vehicle was administered by stomach tube for 28 days. The vehicle was cremophor EL in 10 ml of demineralized water. The groups were subdivided in such a manner that would provide 10 males and 10 females from each group for autopsy at the end of the treatment period, 10 males and 10 females for autopsy at the end of an additional 4 week observation and 10 males and 10 females for histopathology of the nervous system. Of the twenty animals designated for sacrifice and assessment of the nervous system, 5 per sex per group would be examined at the end of the treatment period and the remaining animals would be sacrificed at the end of the observation period.

Food and water were available to the animal ad lib.

During the study, animals were observed once daily for general appearance. Any clinical signs were recorded by noting the duration, intensity and type of symptoms. If death occurred, the time of death was recorded. Body weights were recorded prior to the start of the study,then weekly until study termination and finally at sacrifice.

Laboratory examinations which consisted of hematology and serum chemistry were conducted at the end of the 28 day treatment period and at the end of the 28 day observation period. Five male and five female rats from each group were subjected to laboratory examinations of blood and urine. Liver tissue was also removed from 5 per sex per group to determine the microsomal enzyme activity. The following parameters were evaluated:

x Hematocrit (HCT)
x Hemaglobin (HGB)
x Leucocyte count (WBC)
x Erythrocyte count (RBC)
x Platelet count
x Leucocyte differential
x Mean corpuscular hemaglobin
x Mean corpuscular hemaglobin concentration
x Mean corpuscular volume
Reticulocytes

Blood clotting measurements:
Thromboplastin time
Clotting time
Prothrombin time

Electrolytes:
x Calcium
x Chlorine
Magnesium
Phosphorous
x Potassium
x Sodium

Enzymes:
Creatinine phophokinase
x Alkaline phosphatase
Lactic dehydrogenase
x SGPT
x SGOT
Gamma glutamyl transferase
Glutamate dehydrogenase
Cholinesterase

Other Serum Chemistry Values:
Albumen
x Blood creatinine
BUN
Cholesterol
Globulin
x Glucose
x Total Bilirubin
x Total protein
Triglycerides
Serum protein electrophoresis

Urinalysis
x pH
x urobilinogen
x blood
x protein
x glucose
x sediment

Animals were sacrificed by exsanguination while under deep diethyl ether anesthesia. A full gross necropsy was performed on all animals. Brain, liver, kidneys, adrenals and testes /ovaries were weighed. Tissue from these same organs along with tissues from the lung, spleen and skin were preserved in 10% aqueous formaldehyde and submitted for histopathological examination.

The following CHECKED (x) tissues were collected for histological examination. Weighed organs are designated by (xx)

Digestive system	Cardiovasc./Hemat.	Neurologic
Tongue	Aorta	x Brain
Salivary glands	xx Heart	x Periph. nerves
Esophagus	x Bone marrow	x Spinal cord
x Stomach	x Lymph nodes	
x Duodenum	xx Spleen	
x Jejunum	Thymus	Glandular
x Ileum		Parathyroids
x Cecum		xx Adrenals
x Colon	Urogenital	xx Thyroid
Rectum	xx Kidneys	Pituitary
	Urinary bladder	
xx Liver	xx Testes	
Gall bladder	x Epididymides	Other
Pancreas	Prostate	x Bone
	Seminal vesicle	x Skin
Respiratory	xx Ovaries	x Skel. muscle
Trachea	x Uterus	x All gross lesions
xx Lung	Vagina	x Eyes
Nose		
Pharynx		
Larynx		

Specimens were embedded in paraplast, cut and stained with hematoxylin and eosin. Kidneys were stained with positive acid schiff (PAS) and oil red O (ORO) was used to determine fat content of the liver. Bone was decalcified in EDTA.

Animals scheduled for sacrifice in order to examine the nervous system were also administered diethyl ether and were perfused with 100 ml of 10% formaldehyde. Brain, ischial nerve, total spinal cord, eyes and muscle were removed and fixed with 10% aqueous formaldehyde.

Any animals dying during the study were necropsied and specimens were collected providing post- mortem autolysis had not occured.

STATISTICAL ANALYSIS:
Arithmetic means, standard deviations and upper and lower confidence limits were calculated. Control and test groups were compared using Mann, Whitney and Wilcoxon's U test. The level of significance was 95%.

QUALITY ASSURANCE: A statement of quality assurance was provided in the submission. Additionally, a statement of compliance with GLPs was provided.

RESULTS:

Clinical Signs

No differences in appèarance or behavior were reported in the 0.25 and the 1.0 mg/kg groups. Animals in the 4.0 mg/kg group had increased digging and grooming and increased mobility when compared to controls. At 16 mg/kg, animals exhibited increased digging and grooming, salivation, apathy, uncoordinated gait, spastic gait, dyspnea and dacryohemorrhagia.

Mortality was observed in the high dose group (11M and 12F). No deaths were reported in the other dosage groups. In these animals, gross lesions were primarily in the lungs (distended, fluid filled, patchy), in the kidneys (mottled) and in the liver (slightly patchy, dark lobulation). Of the animals that died during the study, the earliest deaths (2M) were reported on day 2 of the study and the latest deaths were reported on day 28. No deaths occured during the observation period following dosage termination.

Hematology

No statistically significant differences were reported for most hematology parameters when treated animals were compared to controls. For values in which statistical significance was observed, no biological significance could be determined. These included elevations in the numbers of thrombocytes at 1 and 16 mg/kg, increased leukocytes at 16 mg/kg, increased hemoglobin at 1 and 16 mg/kg and increased MCHC at 1 and 16 mg/kg.

Clinical Chemistry

At the end of the treatment period, mean urea values were significantly decreased at 1 and 4 mg/kg in males. Mean creatinine values were also lower than controls in these animals. Bilirubin was lower at the 1, 4 and 16 mg/kg levels in males. High dose females had lower SGOT (AST) values and lower creatinine when compared to controls. No biological significance could be attached to these values and they are probably the result of individual variation.

At the end of the observation period, high dose males had GPT (ALT) levels that were statistically significantly higher than controls and creatinine levels that were significantly lower than controls. In females in the high dose group, significantly lower mean protein values were reported. All of these findings were considered incidental and were not attributed to the test compound.

Liver Enzymes

Treatment with FCR 4545 did not cause induction of the N or O demethylase activity. Cytochrome P 450 content was also unaffected by the compound.

Pathology

At the end of the treatment period, body weights were decreased at the 16 mg/kg level (9.4 %) in males. Splenic weights, both absolute and relative, were decreased and absolute and relative adrenal weights were increased at this same dose level in males. Relative testicular weights were also increased at at 16 mg/kg. In females, absolute lung and liver weights were increased at 4 and 16 mg/kg. Kidney weights were also significantly increased at 4 mg/kg but not at 16 mg/kg. In females, relative organ weights were significantly different (increased) from controls for the liver at 4 and 16 mg/kg and the lung at 16 mg/kg.

At the end of the observation period, mean absolute adrenal weights were increased in males in the 4 and 16 mg/kg groups and in females in the 16 mg/kg groups. In females mean absolute ovarian weights were also increased at 4 and 16 mg/kg when compared to controls.

No histopathological observations were made which could be correlated with the observed increases in organ weights in either the treatment or observation periods. With the exception of the liver, these findings were considered incidental.

DISCUSSION: The increases in liver weights may be the result of hypertrophy which is associated with the administration of the test compound. The other pathological changes in organ weights are not believed to be associated with treatment. Based on the clinical signs of toxicity observed at 4 and 16 mg/kg, the NOEL in this subacute study is 1 mg/kg.

At the end of the 4 week post- treatment observation period, none of the clinical observations made during the treatment phase were apparent. It was concluded that these clinical signs (increased activity, changes in gait, dyspnea, salivation and dacryohemorrhagia) were reversible.

The study is classified as supplementary. The study was conducted to identify target organs, to determine whether there was a potential for a cumulative effect to occur and to determine whether the observed effects of the compound were reversible. This supplementary information was provided with regard to the toxicity of the compound. Although inconsistencies were noted in the report, they are not of the magnitude that would alter the final outcome of the study. The study is acceptable and should be included in the data base.

DOC930125

FINAL

010293

DATA EVALUATION REPORT

CYFLUTRIN (BETA)

Study Type: Mutagenicity: Salmonella typhimurium/Mammalian Microsome Mutagenicity Assay

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer Lynne T. Haber Date 7/14/92
Lynne T. Haber, Ph.D.

Independent Reviewer Nancy E. McCarroll Date 7/14/92
Nancy E. McCarroll, B.S.

QA/QC Manager Sharon Segal Date 7/14/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-302
Project Officer: James Scott

MUTAGENICITY STUDIES

EPA Reviewer: John Redden, Ph.D. Signature:
Review Section III,
Toxicology Branch I/HED (H7509C) Date: 2/25/92
Acting EPA Section Head: Henry Spencer, Ph.D.
Review Section III, Signature:
Toxicology Branch I/HED (H7509C) Date: 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: Salmonella typhimurium/mammalian microsome mutagenicity assay

EPA IDENTIFICATION Numbers:

Caswell Number: 266-E

MRID Number: 412441-10

TEST MATERIAL: FCR 4545 technical

SYNONYMS/CAS NUMBER: Cyflutrin (beta); cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate; $C_{22}H_{18}Cl_2FNO_3$/ 68359-37-5

SPONSOR: Bayer AG, Wuppertal, Germany/Mobay Corp., Kansas City, MO.

STUDY NUMBER: 95605/T 7019737

TESTING FACILITY: Bayer AG, Wuppertal, Germany

TITLE OF REPORT: FCR 4545 Salmonella/Microsome Test for Point-Mutagenic Effect

AUTHOR: Herbold, B.

REPORT ISSUED: January 7, 1986

CONCLUSIONS--EXECUTIVE SUMMARY: Two independently performed Salmonella typhimurium/mammalian microsome plate incorporation assays were conducted with FCR 4545. Concentrations ranging from 20 to 12,500 µg/plate were evaluated in the initial assay; compound precipitation prevented the determination of the number of revertant colonies at the high dose. Accordingly, a narrower dose range was tested in the confirmatory assay (500-8000 µg/plate +/-S9), including one insoluble level (8000 µg/plate +/-S9). Results from both trials were in good agreement and indicated that the test compound did not induce a cytotoxic or mutagenic response in S. typhimurium strains TA1535, TA1537, TA98, or TA100 either in the absence or the presence of exogenous metabolic

activation. Based on these findings, it was concluded that FCR 4545 was adequately tested up to concentrations that exceeded the solubility limit with no evidence of a mutagenic effect.

STUDY CLASSIFICATION: Acceptable. The study satisfies Guideline requirements (§84-2) for genetic effects Category I, Gene Mutations.

A. MATERIALS:

1. Test Material: FCR 4545 technical

Description: White powder
Identification no: Batch number 16002/84
Purity: 98.5%
Receipt date: Not reported
Stability: Reported to be stable during the test period and stable in the solvent
Contaminants: None listed
Solvent used: Dimethyl sulfoxide (DMSO)
Other provided information: Neither the frequency of dosing solution preparation nor the storage conditions were reported.

2. Control Materials:

Solvent/final concentration: DMSO/not reported

Positive:

Nonactivation:		
Sodium azide	10	µg/plate TA1535
Nitrofurantoin	0.2	µg/plate TA100
4-Nitro-1,2-phenylenediamine	0.5	µg/plate TA98
4-Nitro-1,2-phenylenediamine	10	µg/plate TA1537
Activation:		
2-Aminoanthracene	3	µg/plate all strains

3. Activation: S9 derived from 200- to 300-g male Sprague-Dawley

x Aroclor 1254	x induced	x rat	x liver
____ phenobarbital	____ noninduced	____ mouse	____ lung
____ none		____ hamster	____ other
____ other		____ other	

The rat liver S9 homogenate was prepared by the testing laboratory on June 5, 1985.

S9 mix composition:

Component:	Amount/70 mL
Phosphate buffer (pH unspecified)	100 mM
Glucose 6-phosphate	179.1 mg
NADP	315.0 mg
$MgCl_2$	162.6 mg
KCl	246.0 mg
S9	30% (initial assay) or 10% (confirmatory assay)

4. Test Organism Used: S. typhimurium strains
_____ TA97 __x__ TA98 __x__ TA100 _____ TA102 _____ TA104
__x__ TA1535 __x__ TA1537 _____ TA1538
list any others:

Test organisms were properly maintained: Yes.
Checked for appropriate genetic markers (rfa mutation, R factor): Yes.

5. Test Compound Concentrations Used:

(a) Initial assay: Five doses (20, 100, 500, 2500, and 12,500 µg/plate) were evaluated in the presence and absence of 30% S9 in the S9-cofactor mix. Four plates were used per dose, per condition, per strain; all tester strains were used.

(b) Confirmatory assay: Five doses (500, 1000, 2000, 4000, and 8000 µg/plate) were evaluated in the presence and absence of 10% S9 in the S9-cofactor mix. Four plates were used per dose, per condition, per strain; all tester strains were used.

B. TEST PERFORMANCE:

1. Type of Salmonella Assay:
__x__ Standard plate test
_____ Pre-incubation (_____) minutes
_____ "Prival" modification
_____ Spot test
_____ Other (describe)

2. Protocol:

Mutation assays: The report stated that the mutation assay was conducted in accordance with the method of Ames et al.[1] Briefly, an aliquot of a 17-hour broth culture of the appropriate tester strain and the appropriate test material dose, solvent, or positive controls were added to tubes containing molten top agar. S9-cofactor mix was included in the S9-activated assays. The study author did not report the volume of any

[1]Ames, B.N., McCann, J., and Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

reagent, test material solution, or bacterial culture that was used. The contents of the tubes were mixed, poured over plates containing minimal medium and incubated at 37°C for 48 hours. Bacterial cultures were also diluted $1:10^{-6}$, plated and counted to determine viability; average titers were 1-5 x 10^9 cells/mL. Means and standard deviations for the mutation test were determined from the counts of four plates per strain, per dose, per condition.

3. Positive response: The test material was considered positive if it caused a reproducible, dose-related, approximately 2-fold increase in the mean number of revertants per plate of at least one strain.

C. REPORTED RESULTS:

In the initial mutation assay, revertant colonies could not be distinguished from compound precipitation on plates containing the highest evaluated dose (12,500 µg/plate +/-S9). Representative data presented in Table 1 indicated that no evidence of cytotoxicity or mutagenicity was observed at the remaining nonactivated or S9-activated doses of FCR 4545. The confirmatory assay was, therefore, conducted using a narrower concentration range (500-8000 µg/plate +/-S9). Compound precipitation was also observed at the high dose (8000 µg/plate +/-S9). In agreement with the initial results, the test material was neither cytotoxic nor mutagenic at any nonactivated or S9-activated dose in the confirmatory assay (Table 2). All strains responded to the appropriate nonactivated and S9-activated positive controls in both trials. Although the number of revertant colonies of strains TA1537 and TA98 induced by 4-NPA appeared low, this was the expected result. The concentrations of the positive control that were applied (10 µg/plate--strain TA1537; 0.5 µg/plate--TA98) approached the lowest detectable mutagenic level of 4-NPA with these strains.[2] The majority of strains in the S9-activated phase of the initial trial exhibited reduced sensitivity, which our reviewers attributed to the use of 30% S9 in the S9 mix. From the overall findings, the study author concluded that FCR 4545 was not mutagenic in this test system.

D. REVIEWERS' DISCUSSION/CONCLUSIONS: We assess that the study author's interpretation of the data was correct. The test material was assayed to insoluble levels (12,500 µg/plate in the initial assay and 8000 µg/plate in the confirmatory assay), but failed to induce a cytotoxic or mutagenic effect. In addition, all strains responded in the expected manner to the appropriate nonactivated and S9-activated controls in all trials, indicating that the assay had an adequate level of sensitivity to detect mutagenesis. It was concluded, therefore, that FCR 4545 was adequately tested and found to be negative in this microbial test system.

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[2]Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., and Zeiger, E. (1986) Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. vol 8 suppl. 7:1-119.

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLP? Yes. (A quality assurance statement was signed and dated December 19, 1985.)

TABLE 1: Representative Results of the Initial Salmonella typhimurium/Mammalian Microsome Mutation Assay with FCR 4545 Technical

Substance	Dose/Plate	S9 Activation[b]	Revertants per Plate of Bacterial Tester Strain[a] TA1535	TA1537	TA98	TA100
Solvent Control						
Dimethyl sulfoxide	NS	-	16±7	10±4	14±2	71±16
	NS	+	42±7	10±4	42±11	149±12
Positive Controls						
Sodium azide	10 µg	-	1024±145	--	--	--
Nitrofurantoin	0.2 µg	-	--	--	--	333±34
4-nitro-1,2-phenylene-diamine	10 µg	-	--	32±6	--	--
	0.5 µg	-	--	--	57±11	--
2-Aminoanthracene	3 µg	+	331±34	71±6	390±28	1631±80
Test Material						
FCR 4545	2500 µg[c]	-	20±7	7±3	14±4[d]	89±8
	2500 µg[c]	+	37±1	8±3	34±7	121±18

NS = Not stated

[a]Means and standard deviations of the counts from four plates

[b]The S9 mix contained 30% S9.

[c]Results for lower doses (20, 100, and 500 µg/plate +/-S9) did not suggest a mutagenic effect. The high dose (12,500 µg/plate +/-S9) could not be counted owing to compound precipitation.

[d]Mean and standard deviation of the count from triplicate plates; one of the four replicate plates was contaminated.

TABLE 2: Representative Results of the Confirmatory Salmonella typhimurium/Mammalian Microsome Mutation Assay with FCR 4545 Technical

Substance	Dose/Plate	S9 Activation[b]	Revertants per Plate of Bacterial Tester Strain[a] TA1535	TA1537	TA98	TA100
Solvent Control						
Dimethyl sulfoxide	NS	-	20±3	6±1	21±4	88±17
	NS	+	13±1	13±4	21±4	117±8
Positive Controls						
Sodium azide	10 µg	-	517±7	--	--	--
Nitrofurantoin	0.2 µg	-	--	--	--	244±5
4-nitro-1,2-phenylene-diamine	10 µg	-	--	57±9	--	--
	0.5 µg	-	--	--	52±14	--
2-Aminoanthracene	3 µg	+	223±46	454±51	1116±57	2629±186
Test Material						
FCR 4545	4000 µg[c]	-	19±5	9±2	13±4	70±10
	8000 µg[d]	-	16±3	8±4	15±2	71±14
	4000 µg[c]	-	12±4	8±2	21±6	85±7
	8000 µg[b]	+	10±3[e]	5±2	12±3	99±21

NS = Not stated

[a]Means and standard deviations of the counts from four plates

[b]The S9 mix contained 10% S9.

[c]Highest nonprecipitating level; results for lower doses (500, 1000, and 2000 µg/plate +/-S9) did not suggest a mutagenic effect.

[d]Highest evaluated dose; compound precipitation reported at this concentration.

[e]Mean and standard deviation of the count from triplicate plates; one of the four replicate plates was contaminated.

F. CBI APPENDICES: Appendix A, Materials and Methods, CBI pp. 7-13.

CORE CLASSIFICATION: Acceptable; the study satisfies the data Guideline requirement (§84-2) for genetic effects Category I, Gene Mutations.

APPENDIX A

MATERIALS AND METHODS
CBI pp. 7-13

Pages 203-209 - *Access to FIFRA health and safety data is restricted under FIFRA

010293

Reviewed by: John C. Redden, Toxicologist J.R.C. Redden 3/25/92
Section III, Tox. Branch I
Secondary reviewer: Henry Spencer, Toxicologist H.S. 3/25/92
Section VI, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: Range-Finding Toxicological Study to Determine Doses for a Subchronic Study.

GUIDELINE: N/A

TOX. CHEM NO: 266E

MRID NO.: 412441-09

TEST MATERIAL: β-Cyfluthrin (FCR 4545 Technical)

STUDY NUMBER: 95607

SPONSOR: Mobay Corporation

TESTING FACILITY: Bayer Ag
Institute of Toxicology - Pharma
Federal Republic of Germany

TITLE OF REPORT: FCR 4545 Range-Finding Toxicological Study to Establish Dosage for a Subchronic Study of Toxicity to Beagle Dogs.

AUTHOR(S): E. von Keutz

REPORT ISSUED: November 27, 1986

CONCLUSION:

One animal in the control group vomited food paste and had a pasty stool. In group I (10 ppm) two animals were observed to have diarrhoea. One of these animals, also, had pasty stool. In group III 640 ppm (first to fourteenth day) the following observations were made:

- impaired movement (26 times)
- vomiting of food paste (1 times)
- conjunctival irritation (12 times)
- one animal prone with spasms
- one animal found dead on the 15th day

It was reported that the animal died due to ~~the~~ , "the severity of the toxicity," of the compound. A necropsy was not done on this animal to determine the cause of death.

When the dose was reduced to 320 ppm in group III the following observations were made:

- impaired movement (13 times)
- vomiting of food paste (13 times)
- conjunctival irritation (5 times)

Food consumption was reported as, "no. left food weighed/week." The weight of the amount left was not reported. Food was left by 3 of the four dogs in the Group III (640 ppm) during the first fourteen days. After the dose was reduced to 320 ppm food was left only twice. The information given in the report does not allow food consumption to be determined, nor is it possible to determine mg/kg/day.

Males demonstrated weight loss in all the groups, however, Group III weight losses were greater.

The 640 ppm dose level resulted in a reduction in potassium concentration (one dog) and phosphorus concentration (three dogs) in the serum. After reduction of the dose to 320 ppm FCR 4545, these parameters returned to normal.

"Increase in specific gravity of the urine and a reduction in urine volume (two dogs each) after 640 ppm FCR 4545. One of these dogs died." No significant findings after reduction of the test material to 320 ppm was noted.

A NOEL or LEL level could not be determined from this study.

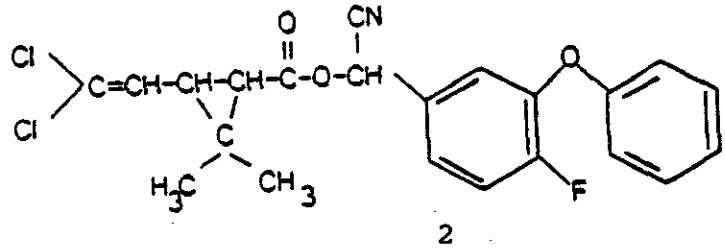
Core Classification: Supplementary as this type of study is not addressed in the 40 CFR. In addition this study was not conducted in accordance with Good Laboratory Practices. This study can not be upgraded.

QUALITY ASSURANCE:

A statement signed and dated August 30, 1989 stated: "This study was not conducted in compliance with the Good Laboratory Practice Standards of 40 CFR Part 160 (FIFRA) or with the OECD Principles of Good Laboratory Practice, C(81)30 (Final) Annex 2 (Paris, May, 1981)."

MATERIALS:

1. Test compound: α-cyano(4-fluro-3-phenoxy-phenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylate; FCR 4545 batch 16002/85; Purity=99.2% (sum of isomers); Appearance = white powder; Structural formula:



2

2. Test animals: Species: Dog; Strain: Bor: Beagle; Age: 44 to 65 weeks; Weight: 8.2 to 13.6 kg; Source: F. Winkelmann, D-4799 Borchen.

METHODS:

1. Animal Assignment: Animals were identified by ear tattoo and metal collar. Eight males and eight females were selected from a group of ten males and ten females. Animals were sorted by weight and assign to four groups of two males and two females. Animal Q 337 died during the third week and was replaced by animal # P 755. Animals were housed individually. Animals were on a 12 hour light/dark cycle. Room temperature was between 20° and 23° C. Humidity was between 30% and 60%. The diet was Ssniff Sole Diet for Dogs, Ssniff Versuchstierdiaeten GmbH, D-4770 Soest. The diet was routinely analyzed for composition and contaminants. Each dog received 400 grams of feed daily. Tap water was available ad libitum.

Results:

It was reported that animal Q 337 died due to the, "severity of the toxicity" of the compound. Necropsy was not done on this animal to determine the cause of death.

2. Test Substance Administration: The test compound was mixed into the diet to achieve the following concentrations:

Control:	0 ppm (1st to 28th day)
Group I:	10 ppm (1st to 28th day)
Group II:	80 ppm (1st to 28th day)
Group III:	640 ppm (1st to 14th day)
	320 ppm (15th to 28th day)

The diet was mixed in a "mixer granulator type MGT." The diet was analyzed for homogeneity and stability.

3. Observations: All animals were examined several times daily for appearance and behavior.

Results:

One animal in the control group vomited food paste and had a pasty stool. In group I (10 ppm) two animals were observed to have diarrhoea. One of these animals, also, had pasty stool. In group III 640 ppm (first to fourteenth day) the following observations were made:

- impaired movement (26 times)
- vomiting of food paste (1 times)
- conjunctival irritation (12 times)
- one animal prone with spasms

- one animal found dead on the 15th day

When the treatment was reduced to 320 ppm in group III the following observations were made:

- impaired movement (13x)
- vomiting of food paste (13x)
- conjunctival irritation (5x)

4. Food and Water Consumption: Food and water consumption was measured daily. Body weights were determined weekly.

Results:

Food consumption was reported as, "no. left food weighed/week." The weight of the food left was not reported. Food was left by 3 of the four dogs in Group III (640 ppm) during the first fourteen days. After the dose was reduced to 320 ppm, food was left only twice. The information given in the report does not allow food consumption or mg/kg/day of chemical.

Water consumption was not affected by the administration of the compound in the feed.

5. Body Weights: Animals were weighed weekly starting at week - one.

Results:

Males demonstrated weight loss in all the groups (Table 1).

Table 1 Mean Body Weights in Kilograms

		Week				
Group	Sex	-1	1	2	3	4
Control	Male	11.4	11.0	11.0	11.0	10.9
Group I	Male	10.2	9.7	9.5	9.6	9.6
Group II	Male	11.0	10.0	9.9	10.2	10.3
Group III	Male	11.0	10.1	9.6	10.6	10.6
Control	Female	9.4	9.3	9.5	9.3	9.5
Group I	Female	9.1	9.0	9.0	9.0	9.3
Group II	Female	9.4	9.1	9.1	9.2	9.3
Group III	Female	10.5	9.9	10.0	10.0	10.3

Note: Extracted from the Final Report.

4. Hematological Examination: Blood for these examinations was drawn from the vena jugularis into an EDTA (dipotassium ethylene diamine tetra-acetate) coated tubes. The following parameters were examined and included: hematocrit, haemoglobin, erythrocyte counts, leucocyte counts, mean corpuscular volume of single erythrocytes (MCV), mean haemoglobin content (MCH), mean cell haemoglobin concentration (MCHC); thrombocyte counts,

reticulocyte counts, thromboplastin time (TPT), blood sedimentation rate, and differential WBC counts.

Results:

No significant toxicity-related findings were found in the above parameters. Individual values were reported only.

5. Clinical Chemistry Examinations: These determinations were done with blood plasma. Electrolytes were measured in the serum. It is unclear which of these procedures used heparin. The following clinical chemistry parameters were examined; blood sugar, urea, creatinine, total protein, aspartate aminotransferase (AST/GOT), alanine aminotransferase (ALT/GPT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), bilirubin, cholesterol, sodium, potassium, calcium, and chloride.

Results:

The following was reported: "The level of 640 ppm test substance resulted in a reduction in potassium concentration (one dog) and phosphorus concentration (three dogs) in the serum. After reduction of the dose to 320 ppm FCR 4545, the laboratory parameters described returned to normal. All the other clinical chemical parameters were normal at the examination times."

6. Urinalyses: Animals were placed in metabolism cages for a period of 8 to 14 hours. During this period food and water were not available. Each animal received 250 ml of water by stomach tube before being placed in the metabolism cage. Animals which did not produce urine during a six hour period were kept in the cages for 14 hours. These animals were allowed food and water. The volume and specific gravity of the urine were measured. The urine was examined for the following parameters; protein, glucose, blood, bilirubin, ketone bodies, and pH.

Results:

"Increase in specific gravity of the urine and a reduction in urine volume (two dogs each) after 640 ppm FCR 4545. One of these dogs died." No significant findings after reduction of the test material to 320 ppm was noted.

7. Statistics: Statistics were not done in this study.

Study Author's Conclusions:

After 640 ppm FCR 4545 for fourteen days the following conclusions were made by the study author.

"The impaired movement, vomiting and reduced food

consumption are most likely to be substance-induced effects. It may be that FCR 4545 was also the cause of the spasms observed in one animal, and responsible for the conjunctival irritation noted in two dogs.

The reduced food consumption and vomiting led to impaired electrolyte levels and metabolism, with weight losses, impaired general well-being, increased urine specific gravity, reduction of potassium and phosphorus levels in the serum, and reduction of the urine volume. These toxic signs led to the death of one animal."

Once the dose was reduced to 320 ppm the following conclusions were made by the study author.

"The hematological(sic) parameters did not provide any indication of damaged to the red or white blood cells. Blood coagulation was also unimpaired." No damage to the kidneys or other organ groups was seen at this time. All other clinical chemistry parameters were normal at the end of the study, as were urinalyses.

It was concluded that 640 ppm was to high a dose to be administered to beagle dogs. This was justified by the toxic signs noted above, and the death of one animal at 640 ppm dose level. The signs observed at 320 ppm which were of less intensity.

The suggested dose levels for a subchronic feeding study are; 0, 10, 60 and 360 ppm of FCR 4545.

010293

Reviewed by: Melba S. Morrow, D.V.M. MSMorrow 9/1/91
Section II, Tox. Branch I (H7509C)
Secondary Reviewer: Marion P. Copley, D.V.M. MPC 7/15/91
Section II, Tox. Branch I (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Subchronic Toxicity - Rat

GUIDELINE #: 82-1

TOX. CHEM. #: 266D

MRID #: 412441-08

TEST MATERIAL: FCR 4545

SYNONYMS: Beta Cyfluthrin, Tempo I

STUDY NUMBERS: T8023085, 97492

SPONSOR: Mobay

TESTING FACILITY: Bayer, AG
Federal Republic of Germany

TITLE OF REPORT: FCR 4545 Subchronic Toxicological Study in Rats

AUTHORS: Dr. H. Suberg

REPORT ISSUED: November 1986

CONCLUSIONS: Based on the results the NOEL is 125 ppm (9.5 mg/kg in males and 10.9 mg/kg in females) and the LEL is 500 ppm (37.0 mg/kg for males and 43.0 mg/kg in females) based on the presence of uncoordinated gait, impaired general condition (necrosis in the head and neck region), two deaths and delayed weight gain.

CLASSIFICATION: Guideline
TOX. CATERGORY: N/A

MATERIALS: FCR 4545, a white odorless solid, having a purity of 99.7% was the test material. One hundred eighty Wistar rats (strain BOR:WISW), 4 to 5 weeks of age and ranging in weight from 56 to 73 grams (males) and from 49 to 68 grams (females) were the test animals. Test animals were obtained from Winkelmann Experimental Breeding Plant in Germany.

METHODS: Dose groups for this study were selected based on the results from two preliminary studies. In the first preliminary study which lasted for three weeks, the highest dose tested was 1,000 ppm. All animals in this group died after the first week of treatment. In another study, doses of 0 and 600 ppm were fed for two weeks, with only weight loss being reported in the treated animals.

Animals were randomly assigned to the following groups:

GROUP	DOSE (ppm)	DOSE (mg/kg)
1 & 2	control (0)	0
3 & 4	30	2.3 (M), 2.5 (F)
5 & 6	125	9.5 (M), 10.9 (F)
7 & 8	500	38.9 (M), 42.4 (F)
9 & 10	control *	0
11 & 12	500 *	37.0 (M), 43.0 (F)

Odd numbered groups were comprised of male animals. Groups 9 thru 12 were designated as recovery groups that underwent a four week observation period. The test substance was mixed in powdered animal feed. Control animals received feed without FCR 4545. During the observation period, the 500 ppm recovery group received the control substance.

Animals were individually housed in rooms with average temperatures of 22 $\pm$ 2° C and the relative humidity of approximately 50%, a 12 hour light/dark cycle and 10 air exchanges per hour.

Animals were observed twice daily for clinical signs of toxicity. Body weights were determined prior to treatment and at weekly intervals thereafter. Body weights were also recorded prior to necropsy. Feed consumption was also determined and provided information on the amount of test compound consumed by the test animals.

The stability of the test compound in the feed was analysed prior to the beginning of the study. Concentration and homogeneity were also assessed. Nominal concentrations were determined at 4 monthly intervals for the 500 ppm sample and at three intervals (July, August and October) for the 30 and 125 ppm samples. The homogeneity was determined for 3 of 5 samples obtained from different points in a rectangular tray. These samples were taken from the left and right front and rear locations and from a center location.

Clinical laboratory examinations were conducted in 10 animals in each group after one and three months on the study. Blood was collected from the caudal vein for glucose determination and from the retroorbital sinus for other blood parameters. After 13 weeks on the study, a tooth and a femur were removed from 5

animals per group for the determination of flouride content. These same animals were subjected to the measurement of liver microsomal enzyme activity. Urine was collected under fasting conditions. (See Table I for a checklist of hematology, serum chemistry and urinalysis parameters).

Necropsies were performed on all animals dying during the study and those which were sacrificed while moribund. Gross examinations were performed on organs and tissues from these animals. Animals completing the designated 13 weeks on the study were sacrificed by exsanguination while under diethyl ether anesthesia. Organs were subjected to gross and microscopic examination and all changes from normal were described. (See Table II for a checklist of the examined organs). Tissue sections were stained with hematoxylin and eosin; the kidneys were also stained with positive acid Schiff (PAS) and the liver was stained with oil red O (ORO) for the determination of fat content.

QUALITY ASSURANCE: A statement of quality assurance and compliance with Good Laboratory Practices were provided in the submission.

STATISTICAL ANALYSIS: Arithmetic means, standard deviations and upper and lower confidence limits were determined for body weights, organ weights and for food and water consumption. For comparison of treated and controls, Mann Whitney and Wilcoxon Tests were used. Determinations were made for $p \leq 0.05$ and for $p \leq 0.01$.

RESULTS:

Clinical Observations

Three deaths were reported at the 30 ppm level; one at the 125 ppm level and one each in the 500 ppm dose group and in the 500 ppm recovery group. Animals dying at the 30 and 125 ppm doses were believed to have expired as a result of improper blood collection techniques; however, at 500 ppm, the cause of death was not determined and may have been related to the compound.

Clinically, lack of coordination and poor general condition were observed during the first week of treatment in the high dose animals. At 500 ppm, necrosis in the head and neck regions was observed in six males and one female. Two males also had a "sore". These findings were attributed to treatment with FCR 4545. No treatment related findings were reported in the lower dose groups.

Body weights and weight gains were lower than controls in males in the 500 ppm group throughout the study. In females in the 500 ppm group, body weight gains were lower on weeks 1, 6 and 10 of the study. (See Table III). Food consumption was similar

between groups; however, water consumption was reduced by 18.8% in the 500 ppm dose group when compared to controls.

Hematology

Blood samples were collected at 1 and 3 months during the study. In 500 ppm males, hematology parameters after one month of FCR 4545 were statistically different from controls for hemaglobin, MCV, hematocrit, and MCH. In females, statistically significant decreases in hemoglobin and MCHC were reported at 30 ppm; decreases in hematocrit, hemaglobin and MCHC were reported at 125 ppm and decreases in erythrocytes, hemaglobin, hematocrit and MCHC were reported at 500 ppm. None of the reported changes were biologically significant since they were within the reference range for normal values.

After three months of FCR 4545 treatment, the parameters affected at one month were corrected. In males a decrease in leucocytes was reported at 30 ppm and in females at 125 ppm, statistically significant differences reported for the same parameter. Mean corpuscular hemoglobin concentration (MCHC) was increased in the 125 ppm and in the 500 ppm females when compared to controls. Again, no biological significance could be attached to these findings. In the recovery animals, no biologically significant alterations in hematology parameters were present.

Clinical Chemistry

After one month of receiving FCR 4545, males in the 30 ppm dose group had statistically significant decreases in SGOT and SGPT; males in the 125 ppm group had significantly lower triglyceride levels and males in the 500 ppm group had increased bilirubin and decreased protein, urea and creatinine levels. Additionally, males in the 500 ppm recovery group had elevated levels of SGPT and urea. These findings were not considered biologically significant as the values were within normal range.

Females receiving the test compound for one month had decreased alkaline phosphatase and triglycerides at 30 ppm; at 125 ppm decreased SGPT and triglycerides were reported and at 500 ppm, decreased triglycerides were reported. Recovery 500 ppm females had elevated alkaline phosphatase, SGPT and bilirubin levels when compared to controls and decreased creatinine. Again, the reported differences between treated and control animals were not biologically significant.

Three months into the study, most of the parameters affected after one month of treatment were comparable to values in controls for males. In the 500 ppm dose group triglycerides, protein and cholesterol were elevated but not to a level of biological significance.

In females, decreases in alkaline phosphatase were reported at 30 and 500 ppm; triglycerides remained lower in the high dose group when compared to controls and protein levels were significantly lower than controls at 30 and 500 ppm. Decreases in urea levels were reported for females in the 125 ppm group and increases in the same parameter were reported for the 500 ppm recovery females when compared to recovery controls. None of these findings are considered biologically significant because the values reported for these parameters are within the reference range for normal values, based on the investigators historical control data which appeared on pages 68 - 70 of the report.

Enzymes/ Flouride Levels

With the exception of a slight increase in cytochrome P 450 activity at 125 ppm, there were no other differences in liver enzymes. Results from tests to determine the flouride concentrations in bones and teeth did not reveal any significant differences between dose groups.

Urinalysis
After one month of receiving FCR 4545, urinary pH was lower in males receiving 30 and 125 ppm and higher in females receiving 30 ppm. Urinary calcium was higher at 30 ppm in males and at 500 ppm in both sexes. By the third month of treatment, these changes were no longer apparent indicating that the earlier increases were probably incidental findings.

Pathology
In males receiving FCR 4545 at 500 ppm, lower absolute organ (heart, liver and kidney) and body weights were reported. In females, absolute lung weights were elevated at 125 ppm and body weights were decreased at 500 ppm when compared to controls. Additionally, at 500 ppm, relative body weights were decreased and relative heart, lung, liver and kidney weights were increased. No significant differences were observed when recovery high dose animals were compared to recovery controls.

Fatty livers were present in all groups with approximately the same frequency in occurence. In the livers of 125 and 500 ppm females, perivascular lymphocytes were present at a greater frequency than in controls (3/15 at 125, 5/15 at 500 and 0/15 in controls). The presence of perivascular lymphocytes is indicative of a non-phagocytic process and is probably related to the detoxification of the test compound.

With regard to the stability of the test compound, the active ingredient was found to be stable over a 14 day storage period. The nominal concentration of the test compound ranged from 100 to 114% of the theoretical values. The distribution of the test material in the feed was also found to be homogeneous based on the analysis of three samples.

DISCUSSION: Based on the findings in this study the NOEL is 125 ppm. The LEL is 500 ppm based on decrease in weight gain at week one in males and females, and at weeks 5 and 7 in males, the occurence of two deaths and the observation of poor general condition with the presence of sores in the head region in animals in this group. The presence of perivascular lymphocytes in the livers of rats receiving the compound is indicative of a detoxification process and should not be considered an endpoint for toxicity.

In recovery animals which were allowed a four week period without receiving the test compound, no abnormalties were detected in hematology, clinical chemistry, urinalysis or pathology. Since these parameters were not affected to a level of biological significance, reversibility of symptoms can not be determined.

The study is classified as guideline and satisfies the requirements set forth in the Subdivision F Guidelines.

TABLE I
HEMATOLOGY, SERUM CHEMISTRY and URINALYSIS MEASUREMENTS

Hematology	Clinical Chemistry
+ Erythrocytes	Alkaline phosphatase
+ WBC and Differential Counts	+ SGOT
Thrombocytes	+ SGPT
Reticulocytes	+ Glucose
+ Hematocrit	+ Total bilirubin
+ Hemoglobin	Cholesterol
Mean corpuscular hemaglobin	+ Creatinine
Mean corpuscular hemaglobin conc.	+ Total protein
Mean corpuscular volume	+ Urea
+ Clotting time	Triglycerides
	+ Albumin
	+ Sodium
* Urinalysis	+ Potassium
pH	+ Calcium
volume	Inorganic phosphate
Specific gravity	+ Chloride
Glucose	Flouride
Blood	N- Demethylase
Protein	O- Demethylase
Ketones	Cytochrome P-450
Bilirubin	
Urobilinogen	
sediment	
Sodium	
Potassium	
Calcium	
Chloride	
Inorganic phosphate	

+ = required for subchronic studies under Subdivision F Guidelines

* = Urinalysis not routinely required under Guidelines for subchronic testing.

TABLE II

ORGANS and TISSUE EXAMINED GROSSLY and MICROSCOPICALLY

Cardiovascular
+ Aorta
+ Heart

Gastrointestinal
Tongue
+ Esophagus
+ Stomach
+ Small intestines (all sections)
+ Cecum
+ Colon
+ Rectum
+ Liver xx
+ Pancreas

Urogenital
+ Kidney xx
Ureter
Urethra
+ Urinary bladder
+ Testes xx
Epididymides
Seminal vesicles
Prostate
Vagina
+ Uterus
Oviduct
Ovaries

Glandular
+ Pituitary
+ Mammary
Harderian
Extraorbital
+ Thyroid
+ Salivary
+ Adrenals xx

Respiratory
+ Trachea
+ Lungs xx

Lymphoreticular
+ Mesenteric l.n.
+ Cervical l.n.
+ Bone marrow
+ Spleen
+ Thymus

Nervous
+ Brain xx
Spinal cord
Optic nerve
+ Sciatic nerve

Other
Skin
Eyes
Eyelids
Bone
+ Gross lesions

+ = Required under Subdivision F Guidelines.

xx = organs that were weighed

TABLE III

MEAN BODY WEIGHT GAINS (g)[a]

Males **DOSE (ppm)**[b] Week	**0**	**500**	**% of control**
0 - 1	37	3	8
1 - 2	39	28	71
4 - 5	30	24	80
6 - 7	26	15	58
7 - 8	18	13	72
10 - 11	13	9	69

Females **DOSE (ppm)** Week	**0**	**500**	**% of control**
0 - 1	30	4	16
6 - 7	8	6	75
10 - 11	3	2	67

a = table derived from data provided by the sponsor

b = Only control and high dose groups compared for intervals where weight gain in the high dose group was $\leq$ 80% of the control value.. Weight gains in other groups comparable to control.

* = weight gains not comparable to controls (statistical significance not provided in the study report).

DOC930109

FINAL

010293

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Dermal Toxicity in Rats

Study Title: FCR 4545 Technical: Study of the Acute Dermal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel, M.P.H.	8/4/92 Date
Independent Reviewer:	John Liccione, Ph.D.	8/4/92 Date
QA/QC Manager:	Sharon Segal, Ph.D.	8/4/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-300
Project Officer: James E. Scott

Approved by:
EPA Reviewer: William B.Greear, M.P.H., D.A.B.T. Signature William B. Greear
Review Section IV, Toxicology Branch I (HED) Date 8/9/92

EPA Section Head: Karen Hamernik, Ph.D. Signature Karen V. Hamernik for
Review Section III, Toxicology Branch I (HED) Date 5/19/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-2: Acute dermal toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-06
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in polyethylene glycol E 400

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 98286

STUDY NUMBER: T 8023328

TESTING FACILITY: BAYER AG, Institute of Toxicology/Agriculture of the Fachbereich Toxikologie of BAYER AG, Friedrech-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Dermal Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 4, 1987

CONCLUSION:

LD_{50} (male) ≥5000 mg/kg
LD_{50} (female) ≥5000 mg/kg
Toxic signs: salivation, lethargy, uncoordinated gait, splayed gait, difficult breathing, soft feces
Dose levels: 0, 100, 1000, 2500, and 5000 mg/kg
Route: Dermal
Strain: Bor: WISW (SPF-Cpb)

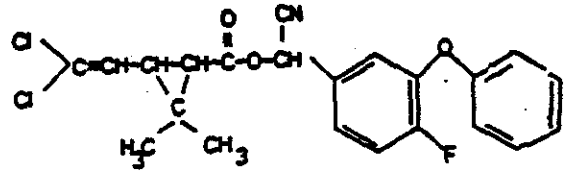
CLASSIFICATION: Acceptable. This study satisfies the guideline requirement (81-2) for an acute dermal toxicity study in rats.

TOXICITY CATEGORY: ~~III~~ IV --Caution JCR

A. MATERIALS

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Polyethylene glycol E 400
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1%, 98.7% (two measurements); determined by sponsor before the study
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (23-27.5°C)
Odor: Odorless
Stability: Test material formulation was stable for 24 hours. The active ingredient concentration in percent of nominal value for a 2,083-mg/mL solution was 99 and 98% for a storage period of 0 and 24 hours, respectively. Stability was determined before the study.

2. Controls

Animals: 5 Males and 5 females
Vehicle: 0.6 mL/kg polyethylene glycol E 400

3. Test Animals

Species: Rat
Strain: SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb)
Source: Winkelmann, Borchen, Paderborn district, FRG
Sex and numbers: 25 Males and 25 females (included control group)
Age: 8-18 Weeks
Initial body weight: Males, 202-222 g; females, 201-232 g
Housing: 5/Cage during the acclimation period; 1/cage during the study period. Animal room was maintained at a temperature of 23±2°C and a relative humidity of approximately 50%. A 12-hour alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water were provided ad libitum.
Animal identification: Individual picric acid markings; and cage ID cards specifying the test compound, animal number, dose, sex, and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to dosage groups based on random number tables.

Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant.

B. TEST PERFORMANCE

Fur was clipped from the dorsal area of each animal 1 day prior to application of the test material. Five male and 5 female rats per dose were each dermally administered a single topical application of FCR 4545 technical made into a paste with polyethylene glycol E 400 (0.012 mL for 100-mg/kg body weight dose group; 0.12 mL for 1,000-mg/kg body weight dose group; 0.3 mL for 2,500-mg/kg body weight dose group; 0.6 mL for 5,000-mg/kg body weight dose group). The paste was made on aluminum foil which was used to cover the test site. A control group of 5 males and 5 females was treated with 0.6 mL of polyethylene glycol E 400. The aluminum foil with the formulation paste was secured to an area of intact skin on the shaved dorsal area by use of a bandage wrapped around the animal's trunk. The dimensions of the test site were 5 cm x 6 cm. After a 24-hour exposure period, the bandage was removed and the test site was washed with soap and water to remove residual test material.

Animals were observed for 14 days. Clinical observations were recorded several times on the day of application and at least once a day thereafter. Body weights were measured just prior to application on test day 0, and daily throughout the observation period. At the end of the study, animals were sacrificed with diethyl ether and necropsied. Rats that died during the study were also necropsied. Histopathological examinations were not performed on any of the animals.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

No mortalities were reported for males. Mortality was reported for 1 female from the 5,000-mg/kg group resulting in a 20% mortality rate for this group. Based on these mortality results, the acute dermal LD_{50} of FCR 4545 technical was >5,000 mg/kg for male and female rats.

No clinical observations were reported for vehicle control animals, or for any of the treated animals from the 100-mg/kg dosage group. Clinical signs of toxicity were reported for all animals in the 1,000-, 2,500-, and 5,000-mg/kg dose groups. Clinical signs were of minimal-to-moderate severity and consisted of lethargy, uncoordinated gait, splayed gait, and salivation for males and females. The time of onset for clinical signs in males and females was 2 days following exposure; at 8 days the signs were no longer observed. Additional signs observed in the high-dose group (female) consisted of difficult breathing (moderate severity) and soft feces (moderate severity) which had an onset time of 3 days; at 4 days the signs were no longer observed. The study author stated that the observed clinical signs (starting at 1,000 mg/kg) were in accordance with the CS syndrome known from pyrethroids containing a α-cyano-3-phenoxybenzyl alcohol group.

A slight decrease in body weight as compared to initial body weight was observed in vehicle control animals and in animals administered the test material; however, body weights at the end of the observation period were greater than or equal to initial body weights. The study author attributed the decrease in body weight gain to the bandaging of the animals for a 24-hour period because the decreases in body weight were observed in both vehicle control animals and animals administered the test material.

No gross findings were reported upon macroscopic examination for any of the females that were sacrificed at the end of the study. For the 1 female from the 5,000-mg/kg dose group that died during the study, gross findings were reported for the lungs (mottled, severely distended), and gastrointestinal tract (severely distended, almost empty). No gross findings were reported for vehicle control males and males from the 100-mg/kg dosage group. For the 1,000-mg/kg dosage group, 1/5 males was reported to have a hollow left kidney, and 3/5 males were reported to have few-to-several dark red zones on the lung surface. For the 2,500-mg/kg dosage group, pinpoint zones on the lungs were reported in 1/5 males, and 4/5 males had no gross findings. For the male 5,000-mg/kg dosage group, no gross lesions were reported in 4/5 males, and a missing left kidney and an enlarged right kidney were reported.

No dermal irritation was reported for any of the vehicle control animals. For males administered the test material formulation, incrustation on the treated area was observed in some males from the 100- and 5,000-mg/kg dosage group with an onset time from 4 days to 8 days after exposure and a maximum duration of 14 days. For females administered the test material formulation, incrustation on the treated area and on the border of the treated area was observed in some females from the 100-, 1,000-, 5,000-mg/kg dosage group with an onset time ranging from 2-8 days with a maximum duration of >14 days. Individual animal data were not provided for the incidence of dermal irritation. The incidence of dermal irritation was also not reported for dose groups.

E. REVIEWERS' COMMENTS

The study is classified as Acceptable. However, the incidence of dermal irritation was not reported.

The estimated acute dermal LD_{50} of FCR 4545 technical formulation in polyethylene glycol E 400 for male and female rats is >5,000 mg/kg. The highest dose administered in the study (5,000 mg/kg) exceeded the limit dose of 2,000 mg/kg specified in Guideline Series 81-2. Based on this LD_{50}, the Toxicity Category is III--Caution.

DOC930105

FINAL

010293

DATA EVALUATION REPORT

CYFLUTHRIN

Study Type: Guinea Pig Skin Sensitization Test
(The Guinea Pig Maximization Test)

Study Title: FCR 4545 Technical: Study for Skin Sensitization Effect on Guinea Pigs

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
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Principal Reviewer	Regina Mastrangelo, M.S.	8/20/92 Date
Independent Reviewer	John Liccione, Ph.D.	8/20/92 Date
QA/QC Manager	Sharon Segal, Ph.D.	8/20/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-301
Project Officer: James E. Scott

EPA Reviewer: William B. Greear, M.P.H., D.A.B.T.
Review Section IV, Toxicology Branch I/HED

William B Greear
Signature
7/28/92
Date

Acting EPA Section Head: Karen Hamernik, Ph.D.
Review Section III, Toxicology Branch I/HED

Karl B. Hoffman for
Signature
5/18/93
Date

DATA EVALUATION REPORT

STUDY TYPE: Guideline series 81-6: Guinea pig skin sensitization test (Maximization Test)

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 266E
MRID Number: 412441-07
PC Number: 128831

TEST MATERIAL: FCR 4545 (Technical)

SYNONYMS: Cyfluthrin

SPONSOR: Mobay Corporation

STUDY NUMBER: T 2019822

TESTING FACILITY: Bayer AG, Institute of Toxicology, Wuppertal, Federal Republic of Germany

TITLE OF REPORT: FCR 4545 Technical: Study for Skin Sensitization Effect on Guinea Pigs

AUTHOR: K.G. Heimann

STUDY COMPLETED: March 4, 1986

CONCLUSIONS: Cyfluthrin is not a skin sensitizer.

CLASSIFICATION: Unacceptable. This study was classified as Unacceptable, according to Guideline series 81-6 because the study did not include a tabular presentation of individual data for the induction exposures and no results were reported for these experiments.

TOXICITY CATEGORY: Not applicable

A. MATERIALS

1. Test Material

Test material: FCR 4545 (technical) or Cyfluthrin
Chemical name: Cyano-(4-fluoro-3-phenoxy-phenyl)-methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate
Purity: 98.5% (Sponsor analysis; no data shown)
Physical description: Not reported
Lot number: 16002/84
Storage conditions: Stored in the dark at 23-26°C
Stability: Tested over a 44-hour period for 0.01% and 50% solutions: the content of the active ingredient in the 0.01% solution was reduced by 1% over 44-hours; that of the 50% solution was increased by 1% in this time period.
Homogeneity: Ranged from 71-76% of the nominal value as a 1% suspension and from 109-116% of the nominal value as a 30% suspension.

2. Test Animals

Species: Guinea pigs
Strain: Bor: DHPW/SPF
Sex: Male
Source: Winkelmann, Borchen
Receipt date: Not reported
Numbers: 20 (treated group); 10 (control group)
Housing: 5/cage
Age: Not reported
Weight: 318-375 g
Feeding: Feed (Altromin 3022 Diet) and water provided ad libitum.
Acclimation: Eight days
Selection: By weight and randomization

3. Exposure Conditions

a. Control Group

Induction phase

(a) Initial induction (day 0)

- Route of administration: Intradermal injection (0.1 ml)
- Solutions used: Freund's adjuvant diluted 1:1 with sterile physiological saline; Cremophor EL in sterile physiological saline solution (2% v/v); Cremophor EL in sterile physiological saline solution (2% v/v) with Freund's adjuvant in equal parts

(b) Second induction (day 7)

- Route of administration: Topical dermal application
- Solution used: Cremophor EL in sterile physiological saline solution (2% v/v) on skin pre-irritated with 10% sodium lauryl sulfate (SLS)

Challenge phase (day 21)

- Route of administration: Topical dermal application
- Solution used: 25% FCR 4545 formulated with Cremophor EL in sterile physiological saline solution (2% v/v)

b. Treated Group

Induction phase

(a) Initial induction (day 0)

- Route of administration: Intradermal injection (0.1 ml)
- Solutions used: Freund's adjuvant diluted 1:1 with sterile physiological saline; FCR 4545 (1%) formulated with Cremophor EL in sterile physiological saline solution (2% v/v); FCR 4545 (1%) formulated with Cremophor EL in sterile physiological saline solution (2% v/v) and with Freund's adjuvant in equal parts

(b) Second induction (day 7)

- Route of administration: Topical dermal application
- Solution used: 25% FCR 4545 formulated with Cremophor EL in sterile physiological saline solution (2% v/v) on skin previously irritated with 10% sodium lauryl sulfate (SLS)

Challenge phase (day 21)

- Route of administration: Topical dermal application
- Solution used: 25% FCR 4545 formulated with Cremophor EL in sterile physiological saline solution (2% v/v)

B. TEST PERFORMANCE

Data from a previously conducted range-finding study were shown but the methodologies for the study were not described. Based upon the range-finding study, in which guinea pigs were exposed to solutions of 0, 1, 2.5, and 5.0% FCR 4545, a 1% solution was identified as the initial induction dose for the current study. From second induction and challenge

doses of 3, 6, 12, and 25% that were used in the same range-finding study, a 25% solution was identified as the second induction and challenge doses for the current study. No irritation effects were noted in any of the animals exposed to these doses during second induction or challenge phase in this range-finding study; irritation information was not reported for the initial induction tests. The study report indicated that 10% sodium lauryl sulfate was used in the second induction, but no details were provided on the concentration administered or the results obtained.

Body weights and examinations

Individual body weights were recorded weekly and on day 24.

Throughout the study, animals were inspected for clinical signs twice daily, and once/day on weekends and holidays. Gross pathological examinations were conducted on all animals that died or were moribund during the study.

Initial induction--intradermal injection (day 0)

Hair was removed from the exposure sites by shearing 24 hours prior to exposure. Paired (parallel on each flank) intradermal injections on the back of each animal were administered at the following sites: cranial (site 1), medial (site 2), and caudal (site 3). Exposures by site were as follows:

> Site 1: 0.1 ml Freund's complete adjuvant diluted 1:1 with sterile physiological saline solution
>
> Site 2: 0.1 ml FCR 4545 (1%) formulated with Cremophor EL in sterile physiological saline solution (2% v/v)
>
> Site 3: 0.1 ml FCR 4545 (1%) formulated with Cremophor EL in sterile physiological saline solution (2% v/v) and with Freund's complete adjuvant in equal parts

Controls were likewise exposed except that FCR 4545 was not present in the formulations.

Second induction--topical application (day 7)

The same skin site which was previously injected was treated by topical patch administration. The test material was applied with hypoallergenic dressings on or near previously injected sites, covered with aluminum foil, and was secured with adhesive tape for 48 hours. Twenty-four hours prior to topical application, the skin was shaved and pre-irritated with 10% SLS. Controls were likewise exposed except that FCR 4545 was not present in the formulations.

Challenge test--topical application (day 21)

On day 21, the test material (25%, formulated as above) was topically applied to the previously unused left flank of guinea pigs in the treatment group and one control group. The test material was administered under an occlusive patch for 24 hours. The skin site was not irritated

intentionally by SLS treatment but was shaved and depilated with Pilca cream 24 hours prior to treatment. The vehicle controls from the induction studies were also exposed to 25% FCR 4545 using this same procedure; these animals served as a positive challenge control group. In addition, an identically treated vehicle control was used on the right flank of each animal. After 24 hours of contact, the skin was evaluated for gross lesions at 24 and 48 hours.

Assessment Scores

The following Assessment Scores were used to appraise the treated skin:

0 = no finding
1 = slight redness in places
2 = confluent, moderate redness
3 = severe redness and/or swelling

C. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Body Weights and Examinations

All animals gained weight during study days 0-21. However, 8 out of 10 of the control animals lost body weight within days 21-24 of the study period when compared to body weights on previous days. Similarly, 9 of the 20 treated animals that had gained weight throughout the study also lost weight within the last 3 days of the study, but to a lesser extent than the controls. The study author concluded that there were no treatment-related effects on body weight.

Although no data were shown, it was reported that the treated animals did not exhibit signs of toxicity, as detected by clinical observation. None of the animals died from treatment with FCR 4545.

Sensitization

No data for the induction phases were shown or described in the study. Following a challenge dose of 25% FCR 4545, 2/20 of the treated animals and 1/10 of the control animals exhibited slight redness. This effect was of the same intensity in both groups and subsided by 48 hours. The incidences of these effects were reported to be comparable between both groups by the study author and FCR 4545 was not considered to induce sensitization in male guinea pigs under the exposure conditions used in this study.

D. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement, dated 10/2/86, was presented. A Good Laboratory Practice compliance statement was included.

E. REVIEWERS' COMMENTS

This study was classified as Unacceptable, according to Guideline Series 81-6, because the study did not include a tabular presentation of individual data for the induction exposures and no results were reported for these experiments.

The reviewers agree with the study author's conclusion that FCR 4545 was not considered to be a skin sensitizing agent in guinea pigs under the exposure conditions of this study. Although the ages of the animals were not provided, the body weights were in the normal range for use in maximization studies.

F. CBI APPENDIX

CBI Appendices I, II, and III, pp. 10-12

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FINAL

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Oral Toxicity in Rats

Study Title: FCR 4545 Technical: Study of the Acute Oral Toxicity to Rats (Formulation in Acetone/Peanut Oil)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel, M.P.H.	8/4/92 Date
Independent Reviewer:	John Liccione, Ph.D.	8/4/92 Date
QA/QC Manager:	Sharon Segal, Ph.D.	8/4/92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-298
Project Officer: James E. Scott

Approved by:
EPA Reviewer: William B. Greear, M.P.H., D.A.B.T Signature William B. Greear
Review Section IV, Toxicology Branch I (HED) Date 8/10/92

EPA Section Head: Karen Hamernik, Ph.D. Signature Karen Hamernik
Review Section III, Toxicology Branch I (HED) Date 5/18/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline Series 81-1: Acute oral toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-04
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in acetone/peanut oil

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 98588

STUDY NUMBER: T 4022145 / T 5022146

TESTING FACILITY: BAYER AG, Institute of Toxicology/Agriculture of the Fachbereich Toxikologie of BAYER AG, Friedrech-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Acetone/Peanut Oil)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 5, 1987

CONCLUSION:

LD_{50} Male (fasted) = 84 mg/kg (55-131 mg/kg)
LD_{50} Female (fasted) = 77 mg/kg (65-93 mg/kg)

LD_{50} Male (fed) = 141 mg/kg (113-177 mg/kg)
LD_{50} Female (fed) = 108 mg/kg (78-152 mg/kg)

Toxic signs: lethargy, cramped posture, digging and preening movements, uncoordinated gait, splayed gait, soft feces, salivation, piloerection, rolling, increased activity, and difficult breathing
Dose levels: 1, 10, 63, 71, 80, 100, 160, 180, 200 and 250 mg/kg

Route: Oral gavage
Strain: Bor: WISW (SPF-Cpb)

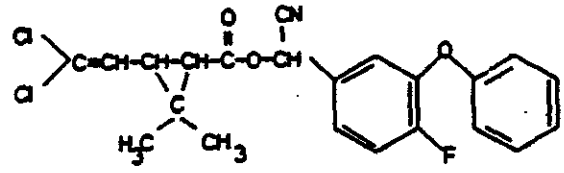
CLASSIFICATION: Acceptable. This study satisfies the guideline requirement (81-1) for an acute oral toxicity study in rats.

TOXICITY CATEGORY: II--Warning

A. MATERIALS

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Acetone/peanut oil (1:9)
Type of formulation: Suspension
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1% (Sponsor analysis)
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (21-25°C)
Odor: Odorless
Date of receipt: March 10, 1986
Stability: When stored for 0 and 18 hours, the stability results for the 0.01% nominal value were 100% and 101% of the nominal value, respectively; and stability of the 50% nominal value was 107 and 106%, respectively. Stability was determined before the study.
Homogeneity: Not performed.

2. Controls

Animals: Not needed
Vehicle: Not needed

3. Test Animals

Species: Rat
Strain: SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb)
Source: Winkelmann, Borchen, Paderborn district, FRG
Sex and numbers: 60 Males; 70 females
Age: 7-12 Weeks

Initial body weight: Males, 163-193 g; females, 169-193 g
Housing: 5/Cage during the acclimation period; 1/cage during the study period. Animal room was maintained at a temperature of 23±2°C and a relative humidity of approximately 50%. A 12-hour alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water were provided ad libitum.
Animal identification: Individual picric acid markings; and cage ID cards specifying the test compound, animal number, dose, sex, and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to dose groups based on random number tables.
Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant.

B. TEST PERFORMANCE

FCR 4545 technical formulated in acetone/peanut oil (1:9) was administered in 5-mL/kg volumes by oral gavage to fed rats and to rats that had been fasted for approximately 16 hours prior to treatment. Animals were observed for 14 days. Different doses were administered for male and female rats and for fed and fasted rats (see dosing schedule below). Fasted animals were provided feed 2 hours after dosing. There was no vehicle control group.

Dosing schedule:

Doses administered to 5 fed male rats: 1, 10, 100, 160, 180, or 200 mg/kg of the test material formulation.

Doses administered to 5 fed female rats: 1, 10, 71, 100, 160, 200 or 250 mg/kg of the test material formulation. The 71-mg/kg dose was administered to an additional 5 animals for a total of 10 animals.

Doses administered to 5 fasted male rats: 1, 10, 71, 100, 160 or 250 mg/kg of the test material formulation.

Doses administered to 5 fasted female rats: 1, 10, 63, 80, 100, or 160 mg/kg of the test material formulation

The day of test material administration was referred to as day 0. Animals were frequently monitored for clinical signs of toxicity during test day 0, and at least once a day on test days 1-14. The duration of clinical observations was reported. Body weights were measured prior to dosing on test day 0 and daily thereafter. Rats that survived treatment were sacrificed at the end of the study using diethyl ether and necropsied.

Rats that died during the study were also necropsied. Histopathological examinations were not performed on any of the animals.

Statistics

A computerized (HP 3000) program was used to calculate LD_{50}s by the method of A. P. Rosiello, M. M. Essigmann, and G. N. Wogan (1977)[1] as modified by Pauluhn (1983)[2]. This method is based on the maximum likelihood method of Bliss (1938)[3]. The geometric mean was regarded as the "approximate LD_{50}" for data pairs with 0 and 100% mortality.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Table 1 summarizes the incidence of mortality and percent mortality in fed and fasted rats. The time of death for animals that died during the study ranged from within a few hours following exposure up to 3 days.

Clinical signs of toxicity of minimal-to-moderate severity were observed in all rats at each dose level except for the 1-mg/kg dose level for which none of the animals exhibited clinical signs. For the 10-mg/kg dose group, lethargy and cramped posture were observed in both sexes of fasted rats as early as 1 hour after exposure with a maximum duration of 3 days. For fed rats in the 10-mg/kg dose group, the same clinical signs were observed as for fasted rats, and in addition, digging and preening movements were observed 2 hours after exposure (duration 3 hours). Clinical signs at dose levels higher than 10 mg/kg consisted of lethargy, cramped posture, digging and preening movements, uncoordinated gait, splayed gait, soft feces, salivation, piloerection, rolling, increased activity, and difficult breathing. These signs had an onset time as early as 33 minutes following exposure and continued for a maximum of 10 days; none of the signs were delayed. The study author stated that the observed clinical signs (i.e., increased activity, digging and preening movements, uncoordinated gait, splayed gait, rolling, and salivation) were in accordance with those of the CS syndrome which is known from pyrethroids with an α-cyano-3-phenoxybenzyl alcohol group.

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[1]Rosiello, A. P., J. M. Essigmann, and G. N. Wogan. 1977. Rapid and accurate determination of the median lethal dose (LD_{50}) and its error with small computer. J. Tox. and Environ. Health 3, 797-809.

[2]Pauluhn, J. 1983. Computer-aided estimation of the LD_{50}/LC_{50}. BAYER AG Report no. 11835, dated 05/18/1983.

[3]Bliss, C.I. 1938. The determination of the dosage-mortality curve from small numbers. Q. J. Pharm. Pharmacol. 11, 192-216.

Table 1. Summary of the Incidence of Mortality and Percent Mortality in Fed and Fasted Rats Orally Administered FCR 4545 Technical (formulation in acetone/peanut oil)[a]

Dose (mg/kg)	Males		Females	
	Fasted	Fed	Fasted	Fed
1	0	0	0	0
10	0	0	0	0
63	--	--	1 (20)[b]	--
71	2 (40)	--	--	3* (30)
80	--	--	3 (60)	--
100	3 (60)	1 (20)	4 (80)	2 (40)
160	4 (80)	3 (60)	5 (100)	3 (60)
180	--	3 (60)	--	--
200	--	5 (100)	--	4 (80)
250	5 (100)	--	--	5 (100)

[a]Data extracted from Report number 98588, pp. 14, 16.
[b]Value in parentheses is the % mortality.
* Only group with 10 animals; all other groups had 5 animals.

Data for individual absolute body weights throughout the observation period were provided. Absolute body weight means were calculated for each dose group. Slight decreases in absolute body weights were observed in males and females at doses as low as 71-80 mg/kg within the first few days of the observation period when compared to their initial body weights. However, by the end of the 14-day observation period, mean body weights were higher than initial body weights for all groups of rats with the exception of the 10-mg/kg dose group for fed female rats in which the body weights were still slightly lower.

Gross necropsy data for individual animals were presented by sex, dose group, and fasting status. For animals that died during the observation period, gross findings were reported for the lungs (slightly-to-severely distended, mottled, dark red), spleen (mottled), stomach (distended, detachment of the mucosa in the forestomach, filled with mucous and shavings), liver (lobular pattern, mottled, pale), kidneys (mottled, slightly marbled), and small intestinal tract (distended, filled with yellow mucous). The only gross finding reported for animals that were sacrificed at the end of the study was numerous small dark red zones on the lungs. No microscopic examinations were performed on any of the animals.

Based on these results, the study author stated that FCR 4545 technical formulation was moderately toxic to the rat after acute oral administration, and that it had a prolonged effect based on the duration of the clinical signs (10 day maximum) which were reversible by the end of the 14-day observation period.

LD_{50} Determination

The estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted rats was 84 mg/kg for males (95% confidence interval = 55-131 mg/kg) and 77 mg/kg for females (95% confidence interval = 65-93 mg/kg). The estimated acute oral LD_{50} for FCR 4545 technical in fed rats was 141 mg/kg for males (95% confidence interval = 113-177 mg/kg) and 108 mg/kg for females (95% confidence interval = 78-152 mg/kg).

E. REVIEWERS' COMMENTS

This study was in conformity with Guideline Series 81-1 and is classified as Acceptable. The study authors did not mention their rationale for using both fed and fasted rats in this study. Generally, fasted rats are used to insure that there will be no food-related influence on the absorption of the test material from the intestinal tract.

Based on the mortality results, the estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted rats was 84 mg/kg for males (95% confidence interval 55-131 mg/kg) and 77 mg/kg for females (95% confidence interval 65-93 mg/kg). The estimated acute oral LD_{50} for FCR 4545 Technical in fed rats was 141 mg/kg for males (95% confidence

interval 113-177 mg/kg) and 108 mg/kg for females (95% confidence interval 78-152 mg/kg).

DATA EVALUATION REPORT

Cyfluthrin

Study Type: Acute Oral Toxicity in Rats

Study Title: FCR 4545 Technical: Study of the Acute Oral Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

Prepared for:

Health Effects Division
Office of Pesticide Programs
Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

Principal Reviewer:	Betty Shindel Betty Shindel, M.P.H.	7-16-92 Date
Independent Reviewer:	John Liccione John Liccione, Ph.D.	7-16-92 Date
QA/QC Manager:	Sharon Segal Sharon Segal, Ph.D.	7-16-92 Date

Contract Number: 68D10075
Work Assignment Number: 1-84
Clement Number: 91-296
Project Officer: James E. Scott

Approved by:
EPA Reviewer: John Redden, M.S.
Review Section III, Toxicology Branch I (HED)
Signature
Date 8/24/93

EPA Section Head: Henry Spencer, Ph.D.
Review Section III, Toxicology Branch I (HED)
Signature
Date 8/18/93

DATA EVALUATION REPORT

STUDY TYPE: Guideline 81-1: Acute oral toxicity in rats

EPA IDENTIFICATION NUMBERS:

Tox. Chem. Number: 266E
MRID Number: 412441-02
PC Number: 128831

TEST MATERIAL: FCR 4545 technical, formulation in polyethylene glycol E 400

SYNONYM: Cyfluthrin

SPONSOR: Agricultural Chemical Division, Mobay Corporation

REPORT NUMBER: 98351

STUDY NUMBER: T 9022140 / T 0022141

TESTING FACILITY: BAYER AG, Institut fuer Toxicologie/Landwirtschaft Friedrich-Ebert-Strasse 217-333, D-5600 Wuppertal 1, Federal Republic of Germany (FRG)

TITLE OF REPORT: FCR 4545 Technical Study of the Acute Oral Toxicity to Rats (Formulation in Polyethylene Glycol E 400)

AUTHOR: Dr. K. G. Heimann

STUDY COMPLETED: November 5, 1987

CONCLUSION:

LD_{50} Male (fasted): 380 mg/kg (95% confidence interval = 231-625 mg/kg)
LD_{50} Female (fasted): 651 mg/kg (95% confidence interval = 329-1,294 mg/kg)

LD_{50} Male (fed): 655 mg/kg (95% confidence interval = 395-1088 mg/kg)
LD_{50} Female (fed): 1,369 mg/kg (95% confidence interval = 1,137-1,651 mg/kg)

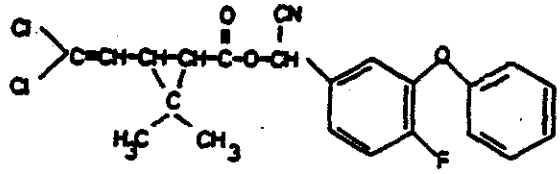
CLASSIFICATION: Acceptable. The study satisfies the guideline requirements (81-1) for an acute oral toxicity study.

TOXICITY CATEGORY: II (males), III (females)

A. MATERIALS

1. Test Material

Test material: FCR 4545 technical, formulation
Formulation vehicle: Polyethylene glycol E 400
Type of formulation: Suspension
Chemical name: α-cyano(4-fluoro-3-phenoxyphenyl)methyl-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate
Empirical formula: $C_{22}H_{18}Cl_2FNO_3$
Structural formula:



Molecular weight: 434.3 g/mole
Batch number: 16002/84
Purity: 99.1% (Sponsor analysis)
Physical description: White powder
Storage conditions: Stored in the dark at room temperature (21-24°C)
Odor: Odorless
Date of receipt: March 10, 1986
Stability: When stored for 0 and 24 hours, stability of the 0.01% nominal value was 91% and 87%, respectively, and stability of the 50% nominal value was 107 and 106%, respectively. Stability was determined before the study.
Homogeneity: Homogeneity of the test suspensions was maintained during administration by use of a magnetic stirrer. Homogeneity of three samples of the suspension (nominal value = 30%) was reported to be 115, 115, and 114%.

2. Controls

Animals: Not needed
Vehicle: A vehicle control group is not needed because historical data are available to determine the acute toxicity of the vehicle (polyethylene glycol E 400).

3. Test Animals

Species: Rat
Strain: SPF-bred Wistar rats, strain Bor: WISW (SPF-Cpb)
Source: Winkelmann, Borchen, Paderborn district, FRG
Sex and numbers: 80 Males; 75 females
Age: 7-12 Weeks
Initial body weight: Males, 160-190 g; females, 172-192 g
Housing: 5/Cage during the acclimation period; 1/cage during the study period. Animal room maintained at a temperature of 23±2°C and a relative humidity of approximately 50%. A 12-hour

alternating light/dark cycle was maintained in the animal room. There were approximately 10 air changes/hour in the animal room.
Feeding: Feed (Altromin® 1324 -- Haltungsdiaet, manufactured by Altromin GmbH, Lage, FRG) and tap water were provided ad libitum.
Animal identification: Individual picric acid markings; and cage ID cards specifying the test compound, animal number, dose, sex, and study number.
Acclimation period: At least 7 days prior to study initiation
Randomization: Animals assigned to groups based on random number tables.
Health status: Animals were examined for health status during the acclimation period. Study only used animals that were judged healthy. Females were nulliparous and not pregnant

B. TEST PERFORMANCE

FCR 4545 technical formulated in polyethylene glycol E (400) was administered daily in 5- or 10-mL/kg volumes by oral gavage to fed rats and to rats that had been fasted for approximately 16 hours prior to treatment. Animals were observed for 14 days. Different doses were administered for male and female rats and for fed and fasted rats (see dosing schedule below). Fasted animals were provided feed 2 hours after dosing. There was no vehicle control group.

Dosing schedule:

Doses administered to 5 fed male rats: 10, 100, 630, 800, 1,000, 1,400, or 2,500 mg/kg of the test material formulation.

Doses administered to 5 fed female rats: 10, 100, 1,000, 1,400, 1,800, or 2,000 mg/kg of the test material formulation.

Doses administered to 5 fasted male rats: 10, 50, 100, 250, 500, 710, 1,000 or 1,400 mg/kg of the test material formulation.

Doses administered to 5 fasted female rats: 10, 50, 100, 800, 1,000, 1,400, 1,500, 1,600 or 2,000 mg/kg of the test material formulation

The day of test material administration was referred to as day 0. Animals were frequently monitored for clinical signs of toxicity during test day 0, and at least once a day on test days 1-14. The duration of clinical observations was reported. Body weights were measured prior to dosing on test day 0 and daily thereafter. Rats that survived treatment were sacrificed at the end of the study using diethyl ether and necropsied. Rats that died during the study were also necropsied. Histopathological examinations were not performed on any of the animals.

Statistics

A computerized (HP 3000) program was used to calculate LD_{50}s by the method of A. P. Rosiello, M. M. Essigmann, and G. N. Wogan (1977)[1] as modified by Pauluhn (1983)[2]. This method is based on the maximum likelihood method of Bliss (1938)[3]. The geometric mean was regarded as the "approximate LD_{50}" for data pairs with 0 and 100% mortality.

C. QUALITY ASSURANCE MEASURE

A signed Quality Assurance Statement and a signed Good Laboratory Practice statement were included in the study report.

D. RESULTS AND STUDY AUTHOR'S CONCLUSIONS

Table 1 summarizes the incidence of mortality and percent mortality in fed and fasted rats. The time of death for animals that died during the study ranged from within a few hours following exposure up to 7 days.

Clinical signs of toxicity of minimal-to-moderate severity were observed in all rats at each dose level except for the 10-mg/kg dose level in which none of the animals exhibited clinical signs. Clinical signs consisted of lethargy, digging and preening movements, uncoordinated gait, splayed gait, salivation, piloerection, soft feces, rolling, increased activity, and difficult breathing. These signs had an onset time as early as 28 minutes following exposure and continued for a maximum of 12 days. The study author stated that the observed clinical signs (increased activity, digging and preening movements, uncoordinated gait, splayed gait, rolling, and salivation) were in accordance with those of the CS syndrome which is known from pyrethroids with an α-cyano-3-phenoxybenzyl alcohol group.

Data for individual absolute body weights throughout the observation period were provided. Absolute body weight means were calculated for each dosage group. Slight decreases in absolute body weights were observed in males and females at doses as low as 100 mg/kg within the first few days of the observation period when compared to their initial body weights.

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[1]Rosiello, A. P., J. M. Essigmann, and G. N. Wogan. 1977. Rapid and accurate determination of the median lethal dose (LD_{50}) and its error with small computer. J. Tox. and Environ. Health 3, 797-809.

[2]Pauluhn, J. 1983. Computer-aided estimation of the LD_{50}/LC_{50}. BAYER AG Report no. 11835, dated 05/18/1983.

[3]Bliss, C.I. 1938. The determination of the dosage-mortality curve from small numbers. Q. J. Pharm. Pharmacol. 11, 192-216.

Table 1. Summary of the Incidence of Mortality and % Mortality in Fed and Fasted Rats Orally Administered FCR 4545 Technical (formulation in polyethylene glycol E 400)[a]

Dose (mg/kg)	Males		Females	
	Fasted	Fed	Fasted	Fed
10	0	0	0	0
50	0	--	0	--
100	1 (20)[b]	0	1 (20)	0
250	1 (20)	--	--	--
500	2 (40)	--	--	--
630	--	2 (40)	--	--
630	--	4* (80)	--	--
710	4 (80)	--	--	--
800	--	3 (60)	2 (40)	--
1000	5 (100)	4 (80)	2 (40)	1 (20)
1400	5* (100)	3 (60)	3 (60)	2 (40)
1500	--	--	4 (80)	--
1600	--	--	5 (100)	--
1800	--	--	--	4 (80)
2000	--	--	5* (100)	5 (100)
2500	--	5 (100)		

[a]Data extracted from Report number 98351, pp. 14, 16.
[b]Value in parentheses is the % mortality.
*Doses not used in calculating the LD_{50}

However, by the end of the 14-day observation period body weights were higher than initial body weights for all rats.

Gross necropsy data for individual animals were presented by sex, dose group, and fasting status. For animals that died during the observation period, gross findings were reported for the lungs (slightly-to-severely distended, mottled), spleen (mottled, small), glandular stomach (distended, slightly reddened, dark mucus, foci), liver (lobular pattern, mottled), renal medulla and renal pelvis (slightly reddened), kidneys (mottled), and gastrointestinal tract (slightly-to-severely distended). No gross findings were reported for animals that were sacrificed at the end of the study. Animals sacrificed at the end of the study included fasted rats in the 10- and 50-mg/kg dose groups, and fed rats in the 10- and 100-mg/kg dosage group. No microscopic examinations were performed on any of the animals.

Based on these results, the study author stated that FCR 4545 technical was mildly toxic to the rat after acute oral administration, and that it had a prolonged effect based on duration of the clinical signs (12 days maximum) and the period during which death occurred (7 days maximum). Both fasted and fed males showed greater sensitivity than the females, and fasted rats were more sensitive than fed rats.

LD_{50} Determination

The estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted rats was 380 mg/kg for males (95% confidence interval = 231-625 mg/kg) and 651 mg/kg for females (95% confidence interval = 329-1294 mg/kg). The estimated acute oral LD_{50} for FCR 4545 technical in fed rats was 655 mg/kg for males (95% confidence interval = 395-1088 mg/kg) and 1369 mg/kg for females (95% confidence interval = 1137-1651 mg/kg). LD_{50} calculations did not include mortality results of male fasted rats in the 1400-mg/kg dose group, female fasted rats in the 2,000-mg/kg dose group, and male fed rats in the 630-mg/kg dose group.

E. REVIEWERS' COMMENTS

This study met the requirements for an acute oral toxicity study as stated in Guideline Series 81-1 and is classified as Acceptable.

The study report did not indicate the purpose of administering 630 mg/kg of the test material formulation to an additional 5 fed male rats, or indicate why the percent mortality in these additional animals was 40% higher than in the other 5 fed male rats at this dose, or why these animals were excluded from the LD_{50} calculations. The study author did not mention the rationale for using both fed and fasted rats in this study. Generally, fasted rats are used to insure that there will be no food-related influence on the absorption of the test material from the intestinal tract.

Based on the mortality results, the estimated acute oral LD_{50} for FCR 4545 technical formulation in fasted rats was 380 mg/kg for males

(95% confidence interval 231-625 mg/kg) and 651 mg/kg for females (95% confidence interval 329-1294 mg/kg). The estimated acute oral LD_{50} for FCR 4545 technical in fed rats was 655 mg/kg for males (95% confidence interval 395-1088 mg/kg) and 1369 mg/kg for females (95% confidence interval 1137-1651 mg/kg).

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Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/27/93**
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