2/14/85

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

004285

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: PP 4F3046/FAP 4H5427 and EPA Reg. No. 3125-GLR. Cyfluthrin (Baythroid). Request for Tolerances for Residues of Cyfluthrin in/on Cottonseed, Cottonseed Oil, Cottonseed Hulls, Meat and Milk. Request for Registration of Baythroid 2 Formulated Product.

Tox Chem No. 266E

TO: Timothy A. Gardner, Product Manager #17
Registration Division (TS-767)

FROM: J. D. Doherty, Ph.D.
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

and

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

Budd 2/14/85

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber 2/14/85

Requested Action:

The Mobay Chemical Corporation (Kansas City, MO) requests registration of the formulated product Baythroid 2 (EPA #3125-GLR) for use on cotton together with the following tolerances (revised May 9, 1984).

Crop	Proposed Tolerances (ppm)
Cottonseed	1.0
Meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep	0.05
Milk	0.01
Cottonseed, refined, deodorized oil	2.00
Cottonseed, hulls	2.50

✓ 1987

Cyfluthrin is a new synthetic pyrethroid insecticide. This is the first request for permanent tolerances for this chemical.

Conclusions:

1. All toxicology studies required to support the proposed registration of Baythroid 2 for use on cotton (only) and the requested tolerances have been submitted to and have been reviewed by Toxicology Branch.

   NOTE: Toxicology Branch was informed by Chris Dively (PM Team #17) on 1/31/85 that she had spoken with G.E. Brussell (Mobay Chemical Corporation) on 1/31/85 and that he had assured her that the formulated product described in this review as Baythroid 240 EC and the formulated product for which registration is proposed for use on cotton (i.e. Baythroid 2, EPA #3125-GLR) are identical and that only the "name" had been changed. Toxicology Branch requests that Mobay be asked by Registration Division to verify this statement in writing prior to registration of Baythroid 2 for use on cotton.

2. Toxicology Branch has no objection to the proposed registration and tolerances provided that the following requirements are adequately addressed and responses submitted to Toxicology Branch within a reasonable period ot time. It is not necessary that this be done prior to registration of Baythroid 2 for use on cotton or prior to establishment of the tolerances. In other words, the following are "conditional requirements."

   a. Many of the toxicology studies were not signed by the persons responsible for the work. Signed reports of these studies must be submitted to EPA. Failure to submit the signed reports will result in reclassification of the studies to INVALID status.

   b. Neurotoxicity studies in chickens. Cyfluthrin was tested in several studies for possible delayed type neurotoxicity. Evidence of nerve fiber degeneration was noted in some of these studies. The data generated thus far are not conclusive with respect to determining the potential for cyfluthrin to produce delayed type neurotoxicity in chickens.

The registrant is requested to conduct an additional study to assist in determining the potential of cyfluthrin to affect the nervous system. This study should be a "hen brain neurotoxic esterase" study. It is strongly suggested that the registrant, prior to performing this study, submit the proposed protocol to Toxicology Branch for comment.

Note - Toxicology Branch does not consider the inconclusive results of the acute delayed neurotoxicity tests in chickens to be of sufficient concern at this time to warrant delaying the registration of this product and the associated tolerances. Considerable toxicology data in mammalian species is presently available which does not suggest an unreasonable potential hazard to the nervous system of humans under conditions of use. Toxicology Branch considers the latter evidence to be more relevant to its determination of potential hazards to humans. Nevertheless, in order to assist in the resolution of this outstanding issue, the "hen brain neurotoxic esterase study" is required to be performed and submitted.

It is suggested that the registrant consider information presented in the following reference when designing the "hen brain neurotoxic esterase study."

Johnson, M. K., Structure-activity relationships for substrates and inhibitors of hen brain neurotoxic esterase, Biochem. Pharmacol., 24: 797-805, 1975.

This study should include a negative control group and a positive control group of hens. Toxicology Branch is aware that relatively few toxicology laboratories are prepared to perform this type of study. Nevertheless, a few do. If requested by the registrant, Toxicology Branch will supply the names of some laboratories that have the capability of performing this study. Toxicology Branch is also willing to discuss with the registrant, if requested, problems that may arise during the design and/or performance of this study.

The registrant is also requested to provide an explanation and/or rationale for the different results observed in the acute delayed neurotoxicity tests in chickens between the studies performed by Bayer AG Institute of Toxicology (in Germany) and those performed by Mobay Chemical Corporation (in the United States). Some points that should be addressed include:

- Possible differences in the test material

  ° Including a consideration of impurities, contaminants and/or manufacturing by-products in the test material.

  ° Including a consideration of possibly different ratios of active ingredient isomers in the test material.

- Possible differences in the test animals used

  ° Including a consideration of strain, source, etc.

  ° Including a consideration of normal background incidence of nervous system lesions in historical control animals of the same strain and source (if possible).

- Possible differences in investigational techniques employed.

- Other

c. Mutagenicity Studies:

The following additional mutagenicity studies are required:

- gene mutation in mammalian cells in culture

- cytogenetics assay in mammalian cells in culture

- DNA repair assay in mammalian cells in culture.

3. The inerts in the formulated product BAYTHROID 2 are cleared for the proposed use.

4. The following changes in the precautionary statements are recommended.

Add "May be fatal if inhaled." [Note: the product is Tox. Cat. II by inhalation exposure.]

Delete "No specific symptoms. Acute poisoning accompanied by general depression and illness."

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8-Point Review

1. Toxicity data with technical grade cyfluthrin considered in support of this tolerance (selected studies).

Acute Oral LD50, rats	LD50 = 590 mg/kg, males LD50 = 1,189 mg/kg, females
Acute Oral LD50, mice	LD50 = 291 mg/kg, males LD50 = 609 mg/kg, females
Acute Dermal LD50, rats	LD50 > 5,000 mg/kg, males and females
Acute Inhalation LC50, rats	LC50 > 1.089 mg/L, males and females
Dermal Sensitization, guinea pigs	Not a sensitizer
90-Day Feeding, rats	NOEL = 300 ppm (HDT)
6-Month Feeding, dogs	NOEL = 200 ppm LOEL = 600 ppm
12-Month Feeding, dogs	NOEL = 160 ppm LOEL = 640 ppm
2-Year Feeding/Oncogenicity, rats	Not oncogenic at dosage levels up to and including 450 ppm (HDT) NOEL = 50 ppm (or 2.5 mg/kg/day) LOEL = 150 ppm
23-Month Oncogenicity, mice	Not oncogenic at dosage levels up to and including 800 ppm (HDT)
3-Generation Reproduction, rats	NOEL = 50 ppm LOEL = 150 ppm
Teratology, rats	Not teratogenic at dosage levels up to and including 30 mg/kg/day (HDT)
Teratology, rabbits	Not teratogenic at dosage levels up to and including 45 mg/kg/day (HDT)
Delayed Neurotoxicity, hens (oral administration)	Inconclusive results.
Delayed Neurotoxicity, hens (dermal administration)	Negative for delayed effects on the nervous system

8-Point Review (contd.)

21-Day Inhalation, hens	Negative for delayed effects on the nervous system
5-Month Neurotoxicity, rats	Negative for delayed effects on the nervous system

Mutagenicity Studies:

Reverse Mutation Assays (with and without metabolic activation).

S. typhimurium	Negative
E. coli	Negative
S. cerevisiae	Negative

Recombination Assays

B. subtilis	Negative
S. cerevisiae	Negative

2. Additional toxicity data considered desirable ("conditional requirements" - see "Conclusions", above)

   a. "Hen brain neurotoxic esterase" study (see "Conclusions")
   b. Gene mutation in mammalian cells in culture
   c. Cytogenetic assay in mammalian cells in culture
   d. DNA repair assay in mammalian cells in culture

3. The above additional toxicity studies are requested in this review.

4. This is the first F petition for cyfluthrin.

5. Establishing these tolerances will result in 1.13% of the MPI being used up. (See computer printout, attached.)

6. The 2-year chronic feeding/oncogenicity study in rats with a NOEL of 50 ppm (equal to 2.5 mg/kg/day) and a safety factor of 100 were used to calculate the ADI (0.025 mg/kg/day). The MPI is 1.50 mg/day (60 kg).

7. There are no pending regulatory actions against the registration of cyfluthrin.

8. None.

NO CFR Number Baythroid 1/28/85

Unverified Printout

DRAFT

ACCEPTABLE DAILY INTAKE DATA

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NOEL change not rec ser

RAT, Other mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day (60kg)
2.500	50.00	100	0.0250	1.5000

Current Action 4F3046/4H5427

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Cottonseed (oil)(41)	2.000	0.15	0.00450
Meat, red(90)	0.050	10.81	0.00811
Milk&Dairy Products(93)	0.010	28.62	0.00429

MPI	TMRC	% ADI
1.5000 mg/day(60kg)	0.0169 mg/day(1.5kg)	1.13

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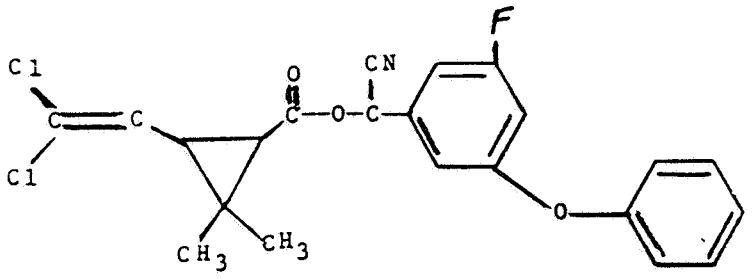
Substance Identification

1. Chemical name: cyano (4-fluoro-3-phenoxyphenyl) methyl 3-(2,2-dichloroethenyl) 2,2-dimethylcyclopropane-carboxylate.

2. Synonyms: Bay FCR 1272, cyfluthrin, BAYTHROID (trade name).

3. Structure:



4. Chemical class: synthetic pyrethroid.

Studies Reviewed

STUDIES WITH BAYTHROID TECHNICAL

Study	Results	Core Classification
Acute Toxicity		
Acute Oral LD_{50} - rats (fasted)	Males: 590 (509-695) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 1189 (1002-1443) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - rats (unfasted)	Males: 869 (685-1051) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 1271 (1102-1456) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - rats	16.2 (13.5-19.5) mg/kg males (in Cremophor EL/dist. H_2O)	Minimum
Acute Oral LD_{50} - rats	254 (220-294) mg/kg males (in acetone)	Minimum
Acute Oral LD_{50} - rats	396 (317-494) mg/kg males (in DMSO)	Minimum
Acute Oral LD_{50} - rats	500-1000 mg/kg males (in n-methyl-pyrollidon)	Minimum
Acute Oral LD_{50} - mice	Males: 291 (202-413) mg/kg (in polyethylene glycol 400)	Minimum
	Females: 609 (432-827) mg/kg (in polyethylene glycol 400)	Minimum
Acute Oral LD_{50} - mice	<100 mg/kg - females (in Cremophor EL/dist. H_2O)	Minimum
Acute Oral LD_{50} - rabbits	>1000 mg/kg - (males only) No rabbits died	Minimum
Acute Oral LD_{50} - dogs	>100 mg/kg (?) - (males only) No dogs died, but both dogs vomited at this level	Minimum
Acute Oral LD_{50} - dogs	Salivation and vomiting at 20 and 100 mg/kg. No deaths	Supplementary
Acute Oral LD_{50} - sheep	LD_{50} = 1000 mg/kg	Minimum

Studies Reviewed (contd.)

Study	Results	Core Classification
Acute Intraperitoneal (IP) LD_{50} - rats	Males: 66 (53-84) mg/kg Females: 104 (76-135) mg/kg	Acceptable
Acute IP - rats	20 (17-22) - males 24 (21-28) - females (in Cremophor EL/dist H_2O)	Acceptable
Acute IP - rats	34 (30-37) - males 96 (68-131) - females (in polyethylene glycol)	Acceptable
Acute Subcutaneous LD_{50} - mice	>2,500 mg/kg for both sexes (no deaths)	Acceptable
Acute Dermal LD_{50} - rats	>5,000 mg/kg for both sexes	Minimum
Acute Dermal LD_{50} - rats	>5,000 mg/kg in either Cremophor EL/dist. H_2O, 0.9% NaCl, or undiluted	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/lutrol) one hour exposure	LC_{50} >1,089 mg/m^3 (1.089 mg/L) (no deaths)	Minimum
Acute Inhalation LC_{50} - rats (in aqueous Cremophor) 4 hour exposure	LC_{50} Males - >735 mg/m^3 Females - 200-735 mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (DMSO/Lutrol) 4 hour exposure	LC_{50} Males - 575 (458-722) mg/m^3 Females - 490 (412-582) mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/ Lutrol) 4 hour exposure	LC_{50} = 469-592 mg/m^3	Minimum
Acute Inhalation LC_{50} - chickens (in ethanol/ Lutrol) 4 hour exposure	LC_{50} >596 mg/m^3 No hens died	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/ Lutrol) 4 hour exposure	LC_{50} < 596 mg/m^3	Minimum
Acute Inhalation LC_{50} - rats (in ethanol/Lutrol) 5 six hour exposures	LC_{50} = 47-196 mg/m^3	Minimum

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Studies Reviewed (contd.)

Study	Results	Core Classification
Dermal irritation - rabbits	PIS = 0	Minimum
Dermal irritation - rabbits	PIS = 0.25	Invalid
Eye irritation - rabbits	Transient irritation only	Minimum
Eye irritation - rabbits	Mildly irritating No corneal opacity	Invalid
Dermal sensitization - guinea pigs - (Draize type)	Not a sensitizer	Minimum
Dermal sensitization - guinea pigs - (Maximization Test)	Not a sensitizer	Guidelines
Dermal sensitization - guinea pigs -	Not a sensitizer	Invalid
Antidote study - rats	Musaril (a.i. tetrazepam, a benzodiazapine) was effective in changing the LD_{50} observed.	Minimum
Thiocyanate excretion - rats	Thiocyanate in urine could not be correlated with toxicity of cyfluthrin or deltamethrin.	Minimum
Absorption study - rats	Cyfluthrin is absorbed from the GI tract more rapidly when administered in Cremophor than when in polyethylene glycol - 400	Minimum
Short-Term Studies		
28-day subacute oral toxicity - rats (gavage) (with recovery phase)	NOEL = 20 mg/kg/day LEL = 40 mg/kg/day (Nerve stimulation, body weight loss, liver and adrenal weight changes)	Minimum
90-day feeding - rats	NOEL = 300 ppm (HDT). No definite test chemical effects noted	Minimum
28-day feeding - rats (with recovery phase)	NOEL = 100 ppm LEL = 300 ppm (minimal decrease in blood glucose)	Supplementary

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Studies Reviewed (contd.)

Study	Results	Core Classification
	AT 1000 ppm (HDT) behavioral changes, body weight loss, urobilinogen and ketone bodies in urine, decreased RBC, hematocrit and hemoglobin counts, increased weights of submaxillary glands (also had cytoplasmic swelling) liver weight change. Some evidence of single nerve fiber degeneration in the sciatic nerve which was not evident in the recovered rats.	
28-day feeding - mice (with recovery phase)	NOEL = 300 ppm LEL = 1000 ppm (behavioral changes, decreased body weight gain, increased liver weight, cytoplasmic swelling of the submaxillary glands). At 3000 ppm (HDT) - in addition to above, possible decrease in WBC, increase in "AIP" and BUN, increased weight of submaxillary glands, decreased spleen, adrenal and ovary weights.	Supplementary
21-day subacute dermal - rabbits	NOEL = 250 mg/kg/day (HDT)	Minimum
21-day subacute inhalation - rats	NOEL = 1.4 mg/m^3 LEL = 2.3 mg/m^3 (decreased body weight gain). At $\geq$ 10.5 mg/m^3, there were behavioral changes, body weight changes and organ weight changes in liver, spleen, and possibly other organs.	Minimum
21-day subacute inhalation - chickens	1 death at 614 mg/m^3 Nonspecific symptomology at this level.	Minimum
Long-Term Studies		
6-month feeding - dogs	NOEL = 200 ppm LEL = 600 ppm (stiff gait, uncoordination, arched backs late in study, vomiting, diarrhea, possibly decreased thymus weights	Minimum

Studies Reviewed (contd.)

Study	Results	Core Classification
12-month feeding - dogs	NOEL = 160 ppm LEL = 640 ppm (slight ataxia in 2 animals on 1 occasion each, increased vomiting and diarrhea, decreased body weights in males)	Minimum
3-generation reproduction - rats	NOEL = 50 ppm for reproductive effects LEL = 150 ppm (decreased viability index, some pup deaths) NOEL = 50 ppm for systemic effects in pups LEL = 150 ppm (body weight decrease in pups)	Minimum
5-month neurotoxicity - rats	Not neurotoxic (axonal degeneration or myelin effects) at 60/80 mg/kg/day orally by gavage for 5 months	Minimum
Teratology - rats	No teratogenic effects noted up to and including 30 mg/kg/day (HDT).	Minimum
Teratology - rabbits	No teratogenic effects noted up to and including 45 mg/kg/day (HDT)	Minimum
2-year chronic feeding/oncogenicity - rats	Not oncogenic at doses up to and including 450 ppm (HDT). NOEL = 50 ppm. LOEL = 150 ppm (decreased body weights in males, inflammatory foci in kidneys of females)	Minimum for chronic toxicity Minimum for oncogenicity
23-month chronic feeding/oncogenicity - mice	Not oncogenic at doses up to and including 800 ppm (HDT). NOEL < 50 ppm. LOEL = 50 ppm (increased alkaline phosphatase activity in males)	Supplementary for chronic toxicity Minimum for oncogenicity
Delayed type neurotoxicity - hens (oral) - single dose	LD_{50} about 5000 mg/kg (in polyethylene glycol 400). Behavorial changes in 2/10 hens and some signs of nerve fiber degeneration reported ("moderate" in degree).	Supplementary

Studies Reviewed (contd.)

Study	Results	Core Classification
Delayed type neurotoxicity - hens (oral) - multi dose (2 doses)	Behavorial changes in 4 hens. Nerve fiber degeneration in majority of treated hens.	Supplementary
Delayed type neurotoxicity - hens (oral) - multi dose (5 doses)	Behavorial changes in 3/6 surviving hens. Nerve fiber degeneration also observed.	Supplementary
Delayed type neurotoxicity - hens (oral) - single dose	No behavorial changes. No microscopy of nervous tissue performed. Dose was 5000 mg/kg.	Supplementary
Delayed type neurotoxicity - hens (oral) - multi dose (2 doses)	Negative for behavioral and microscopic changes in nervous tissue. Dose was 5000 mg/kg	Minimum
Delayed type neurotoxicity - hens (dermal)	No evidence of delayed neurotoxicity by the dermal route.	Minimum
Mutagenicity Studies:		
Mutagenic - Salmonella microsome	Negative for S. typhimurium TA-1535, 1537, 100, and 98 strains, with and without metabolic activation.	Unacceptable
Mutagenic - Micronucleus test: mice	Negative for hematopoietic effect in NMRI/ORIG Kisslegg mice.	Unacceptable
Mutagenic - Dominant lethal test; mice	Systemic NOEL > 60 mg/kg (X1) Embryotoxic NOEL > 60 mg/kg (X1) Reproductive NOEL > 60 mg/kg (X1)	Unacceptable
Mutagenic - Differential Bacterial Toxicity test	Negative for E. coli pol A_1^- and pol A^+ strains with and without metabolic activation.	Acceptable

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Studies Reviewed (contd.)

Study	Results	Core Classification
Mutagenic - Bacterial mutagenicity tests	Rec-Assay - Negative for NIG 45 and NIG 17 Bacillus subtilis strains.	Unacceptable
	Reversion Assay - Negative for S. typhimurium TA- 1535, 1537, 1538, 98, and 100 strains and E. coli B/r WP2 try⁻ her⁻ strain, with and without metabolic activation.	Acceptable
Mutagenic - Microbial mutagenicity	Rec-Assay - Negative for H17 and M45 Bacillus subtilis strains.	Acceptable
	Reversion Assay - Negative for S. typhimurium TA- 1535, 1537, 1538, 98, and 100 strains and E. coli WP2 her strain, with and without metabolic activation.	Acceptable
Mutagenic - Reverse mutation induction	Cytotoxicity Study - Not cytotoxic for S. cerevisiae S211	Acceptable
	Reverse Mutation Assay - Negative for S211 and S138 strains of Saccharomyces cerevisiae with and without metabolic activation.	Acceptable
Mutagenic - Recombination and conversion assays	Cytotoxicity Study - Not cytotoxic for D_7 strain of Saccharomyces cerevisiae	Acceptable
	Recombination and Conversion - negative for D_7 strain of Saccharomyces cerevisiae	Acceptable
	STUDIES WITH BAYTHROID 240 EC (Baythroid 2)	
Acute Oral LD_{50} - rats	LD_{50} = 1015 (651-1671) mg/kg - males. LD_{50} = 826 (598-1225) - females . Tox Cat III	Minimum
Acute Dermal LD_{50} - rabbits	LD_{50} >2000 mg/kg both sexes. Tox Cat III	Minimum
Acute Inhalation LC_{50} - rats	LC_{50} = 1323 (1138-1505)mg/m^3 - males. 1434 (1153-1877) mg/m^3 - females Tox Cat II	Guidelines
Primary Eye Irritation - rabbits	Corneal opacity >21 days. Tox Cat I	Guidelines
Primary Dermal Irritation - rabbits	PII = 0.8 (4 hour exposure). Tox Cat IV	Guidelines

FCR 1272 Acute Toxicity Studies (Several species)

Bayer AG Institut fur Toxikologie, Report No. 8800
(also study No. FCR 1272/013-021). Jan 7, 1980
EPA Acc. No. 072008, Tab 3.1.2a

Part I. Acute oral LD_{50}

The test material (FCR 1272, batch 1600/79 Lo-Nr 2151, said to be of 83.6% purity) was dissolved in Lutrol (polyethylene glycol-400) and was administered to rats (fasted and unfasted), mice (fasted), rabbits (fasted, males only) and beagle dogs. The following table summarizes the results:

Species	LD_{50} (mg/kg)	Symptoms
Rat (fasted) (7-9 dose levels with 15 rats/sex/ group)	Males: 590 (509-695) mg/kg Females: 1189 (1002-1443) mg/kg Tox. Category III	Onset 10-60 min Duration up to 10 days. restlessness, salivation, hypermotility (scratching, scraping, shaking head etc.) "slow wormlike movement." Reduced breathing rate followed by apathy, ataxia, straddled gait, reduced sensitivity. Symptoms suggested CNS extrapyramidal involvement.
Rat unfasted (same as above)	Males: 869 (685-1051) mg/kg Females: 1271 (1102-1456)mg/kg Tox. Category III	same as above
Mice (7 dose levels of 15 mice/sex/ group)	Males: 291 (202-413) mg/kg Females: 609 (432-927) mg/kg Tox. Category II	Onset 15-60 min. Duration up to 6 days. restlessness, hypermotility, dyspnea, ataxic movements, and apathy.

Species	LD_{50} (mg/kg)	Symptoms
Rabbits (4 dose levels, 3 males per group)	>1000 mg/kg (no rabbits died at this level) Tox. Category III	Onset - 1 hour Duration - 7 days (Max.) Apathy and reduced appetite.
Dogs (3 dose levels, 2 males per group)	>100 mg/kg (?) (no dogs died at this level, both dogs vomited at this level) Tox. Category - None	Vomiting and reduced appetite.

Necropsy of the rats and mice did not reveal definite lesions due to the test material. No necropsy comments were provided for the rabbits or dogs. CORE MINIMUM

Part 2. Acute intraperitoneal toxicity - rats.

Nine groups of males (15/group) and 7 groups of females (15/group) were dosed with FCR 1272 over the broad range of 0.5 to 500 mg/kg intraperitoneally. LD_{50}s of 66 (53-84) mg/kg for males and 104 (76-135) mg/kg for females were calculated.

The symptoms were said to be the same as for oral administration. The symptoms were reported as being cleared 2-3 days earlier. This study is ACCEPTABLE.

Part 3. Acute subcutaneous toxicity to mice.

Groups of male and female mice were dosed with up to 2500 mg/kg (15 mice/group/sex) of FCR 1272 in Lutrol subcutaneously. No mice died. This study is ACCEPTABLE.

Part 4. Acute dermal toxicity to rats

The test material in concentrated form was applied to the prepared backs of rats and kept in contact for 24 hours at dose levels of 2500 and 5000 mg/kg.

A single female rat died. The toxic symptoms of "apathy" and ataxia resulted and cleared 5-7 days after exposure. CORE MINIMUM. Tox. Category III.

Part 5. Inhalation toxicity to rats.

Rats were exposed to aerosols of FCR 1272 dissolved in ethanol and Lutrol. The aerosol was generated into a dynamic flow chamber and the atmospheric

concentrations of FCR 1272 determined by trapping the aerosol onto cotton-wool and subsequent chemical analysis. Three separate experiments were run. One hour exposure (5 groups of 10 rats, males and females, were exposed for one hour to either 24, 83, 310, 655 or 1089 mg/m^3). Four-hour exposure (7 groups of 10 males and 9 groups of 10 females were exposed to atmospheric concentrations ranging from 44 to 1067 mg/m^3 for four hours). Five six-hour exposures (three groups of 10 male and 10 females were exposed to either 12, 47, or 196 mg/m^3 for 6 hours at a time for a total of 5 exposures).

Part A. One-hour exposure

No rats died. Symptoms were noted in rats dosed with 83 mg/m^3 and above, but were more pronounced at the higher dose levels. The symptoms included stiff gait, staggering, irritation of the nasal mucosae. The acute inhalation LC_{50} (1 hour) > 1089 mg/m^3 (or 1.089 mg/l). Tox. Category II.

Part B. Four-hour exposure

LC_{50}s of 469-592 mg/m^3 were determined for both males and females. Most of the females dosed with 592 mg/m^3 died. The symptoms included stiff gait, staggering, flinging of the legs, lateral recumbency, salivation, moist coat, cramps (said to be a CNS nicotine-like effect). Deaths occurred within 24 hours.

Part C. Five six-hour exposures.

LC_{50}s were estimated to be 47-196 mg/m^3. Nine of the 10 males and females in the group-receiving 196 mg/m^3 died. Behavioral disorders were noted in the rats dosed with 12-47 mg/m^3. Some signs of lesions in the lung were noted at autopsy. The rats at all exposure levels initially lost weight due to exposure.

The inhalation LC_{50} data are CORE MINIMUM.

Part 6. Dermal irritation.

The procedure recommended by the USDA (FR 38:187,2709, 1973) was said to have been followed. An unspecified amount of FCR-1272 was applied to the backs of 6 rabbits and kept in place for 24 hours.

No irritation developed. The PIS was 0. Tox. Category IV. CORE MINIMUM

Part 7. Eye Irritation.

The procedure recommended by the U.S. Dept. of Health, Education and Welfare (Fed. Reg. 37(83): p. 8535, 1972) was said to have been followed. The eyes were exposed for 5 min (5 rabbits) and 24 hours (3 rabbits).

No corneal opacity developed. Transient redness of the conjunctivae developed. Tox. Category III. CORE MINIMUM.

Acute Toxicity for Sheep after Oral Administration

Bayer AG Institute of Toxicology. Report No. 9750
Jan. 27, 1981, EPA Acc. No. 072008, Tab 3.1.2b

Four groups of sheep were dosed as follows: 250 mg/kg (1 male, 3 females), 500 mg/kg (1 male, 1 female), 1000 mg/kg (1 male, 1 female), 2000 mg/kg (1 male, 1 female). The test material (FCR 1272, batch 16003/79, the purity was not stated) was administered by gavage as a suspension in 0.5% tylose. The sheep were described as 3-10 months old and weighed between 41 and 47 kg.

An LD_{50} of 1000 mg/kg (approx.) was determined. Both of the sheep receiving 2000 mg/kg and one sheep receiving 1000 mg/kg died. The death in the 1000 mg/kg dose group was 13 days after treatment. Deaths in the 2000 mg/kg group occurred 3 and 11 days after treatment.

The symptoms of intoxication were loss in body weight, reduced food consumption, staggering, cramps and foamy discharge.

This study is CORE MINIMUM. Sheep are not an acceptable species for LD_{50} studies for regulatory purposes. Only 2 were used for some dose groups.

Acute Oral Toxicity to Dogs

Bayer AG Institut Fuer Toxikologie, October 19, 1981, Mobay Ag Chem No. 80325, No EPA accession number, Tab 3.1.2c (in Brochure No. 1238, dated December 15, 1983).

FCR 1272 (purity 95.0%) was suspended in an aqueous solution with Cremophor EL and administered by gavage to 1 male and 1 female pure-bred beagle dog (15.0 kg and 14.3 kg respectively) at a dosage level of 20 mg/kg. Salivation was exhibited immediately after dosing and both dogs vomited at < 2 hours after administration. Both dogs appeared normal on the day after treatment.

One week later, doses of 100 mg/kg were administered by gavage to the same dogs. Salivation was again observed and followed by vomiting at 20 minutes to 2 hours after administration. No clinical symptoms were observed in either dog on the day after treatment, although the female dog exhibited reduced feed consumption for about 1 week.

This study is Core Supplementary. No toxicity category was determined (due to vomiting).

FCR 1272 Baythroid active ingredient (common name cyfluthrin) study for acute and subacute inhalation toxicity of chickens

Bayer AG Institute of Toxicology, Report No. 11558
Feb. 14, 1983, EPA Acc. No. 072008, Tab. 3.1.4b

1.) The test material used for this study was FCR 1272. It was from batch 816 170 019 and was stated as being 95.0% pure.

2.) The test animals used were leghorn hens (1 to 2.5 kg and from 15-20 months old). For a comparative study Wistar rats (160-200 gm) were used. Rats and hens were exposed for a single 4-hour exposure. Hens were also exposed for 15 six-hour exposures over a 3-week period.

3). The rats and hens were exposed in a dynamic inhalation chamber and the test material was dissolved in a mixture of lutrol:ethanol.

4.) The atmospheric concentrations were said to be determined by gas chromatography. For these studies the rats and hens were exposed to 596 mg/m^3. Hens were also exposed to 285, 445, and 596 mg/m^3 in an acute LC_{50} study and to 614 mg/m^3 in a subacute inhalation study.

5.) The particle sizes of the atmosphere were determined by a cascade impactor and the mass distribution was determined by an Anderson impactor. These results showed that about 50% of the aerosol mass and about 90% to 95% of the aerosol count was respirable or less than 5 micrometers.

6.) Nine of the 10 rats exposed died and the LC_{50} was determined to be <596 mg/m^3. The symptions were similar to those reported in the previous study. None of the hens exposed to up to 596 mg/m^3 died. Only some nonspecific symptoms resulted (behavior disturbances, sedation, eye irritancy). These symptoms disappeared after 2 days. Some initial weight loss was also noted.

Fifteen six-hour exposures of hens over a period of 3 weeks resulted only in nonspecific symptoms. One of the hens died. Necropsy was reported as being unremarkable.

7.) These data are CORE MINIMUM. Hens are not a usual species for inhalation toxicity testing.

FCR 1272 Study for Acute Inhalation Toxicology (Effect of Formulating Agent on Inhalation).

Bayer AG Institute of Toxicology, Report No. 10965
June 28, 1982, EPA Acc. No. 072008, Tab. 3.1.4a

1.) The test material used for this study was FCR 1272 from batch 816170019 and was stated to be 95% pure.

2.) The test animals used were male and female Wistar rats from a German supplier. They were approximately 160-200 gm prior to exposure. The study consisted of exposure of 10 males and 10 females per dose level for a single four-hour exposure.

3.) The rats were exposed in a "dynamic inhalation apparatus" such that there was little dermal contact and obligatory breathing of the apparatus. Two different mists containing FCR 1272 were generated. The first was a mixture of FCR 1272 in aqueous aerosol to which cremophor was added. The second was a mixture of DMSO:lutrol (1:1). The various atmospheric concentrations were generated by using 0.1% to 5.0% formulations of FCR 1272 in the aqueous matrix and 5-50% formulations in the DMSO:lutrol matrix.

4.) The atmospheric concentrations were said to be determined by gas chromatography (EC detector) and were reported as "conc. theor. analyt." For the aqueous aerosol the levels were 17, 62, 179, 200 and 735 mg/m^3. For the DHSO:lutrol aerosol the levels were 120, 290, 307, 357, 408, 615 and 1214 mg/m^3. The mg refers to the level of FCR 1272 in the atmosphere.

5.) The particle sizes were determined by cascade impactor and it was noted that for the aqueous aerosol <76-87% were < 7 um aerodynamic equivalent diameter. For the lutiol:DMSO aerosol the aerodynamic equivalent diameter was reported to be <7 for 100% of the particles.

6.) The following LC_{50}s were determined (in mg/m^3).

Aerosol	Sex	
	Males	Females
Aqueous Cremophor	>735 (no deaths)	200-735
DMSO:Lutrol	575(458-722)	490(412-582)

7.) The symptoms were more pronounced in the group dosed with DMSO: lutrol aerosol. They included: apathy, debilitation, side and stomach posture, "rowing movements," dyspnoea, irritation of the eyes. During postexposure (first week) signs of muscular tremor, cramps, uncoordinated movements, CNS symptoms such as excitation, hyperkinesis and convulsions. Body weight gain also showed initial decreases. Autopsy of the rats that died as a result of exposure showed signs of lesions in their lungs (dark red spots, greyish distended, dark red and hepatoid discolored oedematous lungs). The kidney and spleen also showed some signs of effects. Some of the survivors also showed possible effects of irritation of the lungs.

8.) Conclusion. This study is CORE MINIMUM. The technical FCR 1272 is Tox Cat II by the inhalation route.

Eye and Skin Irritation

Lab. Not identified, No report No., date June 17, 1982
EPA Acc. No. 072008, Tab 3.1.5

This study is INVALID pending receipt and review of the study protocol, identification of the testing laboratory, and the individual test animal scores.

According to the study summary, 1.0 ml of test material (FCR 1272 of 95% a.i.) was instilled into the eye of each of 12 rabbits. The eyes of 6 of the rabbits were washed 30 seconds after instillation.

No corneal opacity developed. The testing laboratory concluded that the test substance was mildly irritating.

For the skin irritation study, 0.1 ml of test material was applied on a patch. The time that the patch was kept in contact with the skin was not provided.

The PIS was determined to be 0.25 for the lateral abdomen and 0.00 for the scapha of auricula.

FCR 1272 Intracutaneous sensitization test on guinea pigs (Draize Test)

Bayer AG Institut fur Toxikologie, Report No. 10222
Sept. 25, 1981. EPA Acc. No. 072008, Feb 3.1.7a

The test material used for this study was FCR 1272, batch 16001/79.

The test animals used were Pirbright white male guinea pigs supplied by a German Company (Lippische Versuchstierzucht [Hagemann]). They were prepared for the study by shaving. The induction phase of the study consisted of giving 0.05 ml of 0.1% test material dissolved in polyethylene glycol 400 followed by 0.1 ml/animal for the next nine treatments. The test doses were equivalent to 0.05 and 0.1 mg of FCR 1272 per guinea pig per application.

The guinea pigs were challenged by making an injection of 0.05 of the 0.1% solution 14 days after the last induction dose.

A control group received injections of the polyethylene glycol 400 only.

No signs of sensitization resulted. The challenge reactions were reported as not being stronger than the first 10 induction applications in the vehicle control.

This study is CORE MINIMUM (together with study described below). No positive control was included.

FCR 1272 Test for Sensitizing Effect on Guinea Pigs (Maximization Test according to Magnusson and Kligman)

Bayer AG Institute of Toxicology, Report No. 10267
October 19, 1981, EPA Acc. No. 072008 Tab 3.1.7b

The test material used for this study was FCR 1272 batch 16003/80. The purity of this product was not stated.

The test animals used were male guinea pigs of the Pirbright white strain bred by Winkelmann, Borchon. They had a body weight of 250-325 gm at the start of the study. Prior to application of the test material the guinea pigs were shorn at the application sites.

Induction: Each induction consisted of 0.1 ml injection of (a) either Freund's complete adjuvant, (b) 1% FCR 1272 formulated in polyethylene glycol 400, or (c) mixture of a and b. The injections made were intracutaneously.

One week after the intracutaneous induction topical applications were made. The applications were either 25% FCR 1272 in polyethylene glycol 400 or solvent alone. The patches were kept in place for 48 hours.

Challenge: The challenge for sensitization consisted of applying a filter paper soaked with 25% FCR 1272 on the guinea pigs' flesh for 24 hours.

Results: No signs of sensitization developed.

This study is CORE GUIDELINES.

Sensitization study - guinea pigs

Laboratory not identifed - no study number, dated March 17, 1983, EPA Acc. No. 072008, Tab 3.1.7c

10 guinea pigs (exact strain not stated) were sensitized (induction phase) by intracutaneous injections of 1% and 0.01% of the test material (FCR 1272). After two weeks, the inducted guinea pigs were challenged by making intracutaneous injections of the test material (.01, 0.005 or .001%) or by patch application (95% or 1%).

No signs of a sensitization reaction were noted.

This study is INVALID. The test laboratory was not identified.

Tests to determine antidote effect against FCR 1272 Toxicity in Rats.

Bayer AG Institut fur Toxikologie, Report No. 11854
(also Mobay No. 85880) June 1, 1983
EPA Acc. No. 072008, Tab 3.1.9

In this set of experiments, a series of 13 drugs of known pharmacological activity were tested for their effectiveness in changing the LD_{50} for FCR 1272 and reversing the observed symptoms due to this agent.

The LD_{50} for FCR 1272 was determined to be 19.6 (17.7-21.7) mg/kg based on a preliminary study. The symptoms observed were writhing, splayed gait, uncoordinated movements, increased activity, vocalization, salivation, difficult breathing, and lethargy. These symptoms were said to appear approximately 30-60 minutes after administration and persist for up to 5 days. Deaths were said to occur between 2 to 3 hours after administration.

The following agents were tested and did not change either the LD_{50} or the observed toxic signs.

Anti-inflammatory-analgesics-acetylsaliylic acid and Aspisol

Antiepileptic - Ergenyl

Sedatives - Myoscain

Neuromuscular transmission regulators - Rhex Hobein or Pancuronicum

Blood pressure regulators - Methyldopa and Niconacid

Cyanide antidotes - methylene blue, sodium thiosulfate-5-hydrate, Thionin

Ca^{++} agent - Calceno "-D"

The only agent which showed an effect was Musaril which contains tetrazepam a benzodiazapine type compound that is classified as a centrally-acting muscle relaxant.

This agent (at 100 mg/kg or higher) changed the LD_{50} from 20 to 30.5 mg/kg. The symptoms of vocalization and writhing were said to be reversed by the Musaril treatment. Mortality was delayed by the antidote treatment. For example, the rats treated with FCR 1272 died within 2-3 hours after administration. But the rats also treated with Murasil died up to 4 days later.

It should be noted that the dose level of Murasil used was based on the manufacturer's recommended daily dose for humans. Higher doses, mutiple doses did not change the effectiveness of the 100 mg/kg i.p. dose.

Conclusion:

This study is CORE MINIMUM.

TB notes that the product Murasil is somewhat effective as an antidote for FCR 1272 poisoning. TB cannot, however, recommended that the use of Murasil be included on the label as an antidote. Some of the problems regarding this are what route should be used (intravenous, oral, intramuscular) and are other benzodiazapines effective.

[Note: The LD_{50} for FCR 1272 was found to be only 19.6 mg/kg. This does not compare with the LD_{50} of 590 mg/kg from other studies. In the antidote study, the test material was dissolved in Cremophor EL distilled water. In the other studies it was dissolved in lutrol or polyethylene glycol.]

Thiocyanate excretion in rat's urine after intraperitoneal administration of FCR 1272 and decamethrin in comparable doses and after exposure to defined FCR 1272 concentrations in the inhalation air.

Bayer AG Institute of Toxicology. Report No. 10130
August 17, 1981, EPA Acc. No. 072008, Tab 3.1.10a

In this study, rats were dosed intraperitonealy with FCR 1272 (at 1, 5, 10 and 15 mg/kg) and with deltamethrin (at 5, 10, 15 and 20 mg/kg) or they were exposed to aerosols containing 59, 93 or 180 mg FCR 1272 in the atmosphere.

After exposure the urine was monitored for thiocyanate concentration. The purpose of this study was to attempt to evaluate the role which the nitrile group may play in the overall toxicity of the two synthetic pyrethroids (FCR 1272 and deltamethrin).

Following the intraperitoneal injections of FCR 1272. 23.6 to 42.4% of the available nitrile group was detected in the urine. The amount in the urine was roughly proportional to the administered dose. In contrast, only 6.3% to 9.7% of available nitrile group was detected in the urine for deltamethrin.

Following inhalation exposure, only from 1.6% to 6.3% of the available nitrile was recovered in the urine.

Discussion:

These observations of the nitrile content in the urine could not be related to the acute toxicity of the pyrethroids. Although the treatment with both of the pyrethroids resulted in exhibition of the expected toxic signs, there was no evidence that the cyano group was responsible for this observed toxicity.

[Note: In another study in this review, it was demonstrated that agents which are known to attenuate the effects of -CN poisoning had no effect on the LD_{50} of FCR 1272].

This study is CORE MINIMUM.

FCR 1272 Comparative tests for acute toxicity with various formulation aids

Bayer AG Institute of Toxicology. Report No. 10931
June 7, 1982, EPA Acc. No. 072008, Tab 3.1.10c

In this study rats (or in a few cases mice) were dosed either orally, dermally or intraperitoneally with FCR 1272 as a mixture in several different solvents to assess the influence of the solvent on toxicity. The FCR 1272 used for this study was said to be of 95.0% purity and from batch 816170019. The following table summarizes the results:

Route	Formulating Agent	Species	LD_{50} (mg/kg)
Oral	Cremophor EL/dist H_2O	Rat (males)	16.2 (13.5-19.5)
Oral	Acetone	Rat (males)	254 (220-294)
Oral	DMSO	Rat (males)	396 (317-494)
Oral	N-methyl pyrrolidon	Rat (males)	500-1000
Oral	Polyethylene Glycol	Rat (males)	590
Oral	Cremopher EL/Dist H_2O	Mouse (females)	<100
Oral	Polyethylene Glycol	Mouse (females)	609
Dermal	Cremophor El/dist H_2O	Rat (both sexes)	>5000
Dermal	0.9% NaCl	Rat (both sexes)	>5000
Dermal	Undiluted	Rat (females only)	>5000
IP	Cremophor El/dist H_2O	Rat (male)	20(17-22)
IP	Cremophor El/dist H_2O	Rat (female)	24(21-28)
IP	Polyethylene Glycol 400	Rat (male)	34(30-37)
IP	Polyethylene Glycol 400	Rat (female)	96(68-131)

The symptoms which developed were said to indicate an effect on the central nervous system and included tremors, rolling movements, disturbed motility and respiration. They were said to arise within 1 hour (following oral administration) and to last for 1-5 days.

Necropsy of the dead and sacrificed animals was said to have "conformed to the norm."

This study is CORE MINIMUM. Based on the data with Cremophor EL, the technical FCR 1272 should be classified as Tox. Cat. I.

Comparative study of rats on absorption of FCR 1272 after single oral administration in polyethylene glycol 400 or Cremophor EL/water as formulation vehicle.

Bayer AG Institute of Toxicology. Report No. 10715
March 10, 1982, EPA Acc. No. 072008, Tab 3.1.10b

In this study, two groups of 14 rats were dosed by stomach tube with FCR 1272 dissolved in either lutrol (polyethylene glycol 400) or Cremophor EL/distilled water at the dose level of 10 mg/kg. The rats were sacrificed at 0.5, 1, 2, 4, 6, 16 or 24 hours later (2 rats at each time interval) and the content of FCR 1272 in the blood and stomach was determined. The purpose of this study was an attempt to determine why FCR 1272 dissolved in Cremophor-distilled water emulsion was more toxic than that dissolved in polyethylene glycol 400.

The FCR-1272 used for this study was from batch 816170019 and had an isomer ratio of I 26.6%, II 19.1%, III 33.7%, IV 20.6%. When the blood and stomach contents were analyzed, the ratio of the different isomers was also determined in order to assess selective absorption of the isomers.

Analyses of the blood indicated that the concentration of FCR 1272 peaked after 1 hour and the rats showed signs of intoxication when FCR 1272 was administered with Cremophor. In contrast, when FCR 1272 was administered with polyethylene glycol the blood level peaked at 6 hours after dosing and the maximum blood level was about 1/5 of the level when the test substance was administered with Cremophor.

Consistent with the above, there was more FCR-1272 in the stomachs of the rats treated with polyethylene glycol than those treated with Cremophor.

Some differences were noted in the absorption of the cis and trans isomers but TB considers that there were an insufficient number of animals dosed to make meaningful comparisons at this time.

These data are CORE MINIMUM. The data provide an explanation as to why FCR 1272 dissolved in Cremophor and distilled water is more toxic than that dissolved in Lutrol (polyethylene glycol-400). The pyrethroid is absorbed from the GI tract quicker in the presence of Cremophor.

A. FCR 1272 28-Day Subacute Oral Toxicity Study in Rats

Bayer Ag Institut fur Toxikologie, Report No. 9039, March 28, 1980, EPA Acc. No. 072008, Tab 3.3.2a

B. The test material for this study was FCR 1272 from batch 16001/79 and lot No. 2151. It was stated as being of 85% purity.

C. The test animals used were SPF-Wistar albino rats provided by the German supplier, F. Winkelmann. At the start of dosing they were reported to be between 120-140 grams.

Four dose groups of 20 males and 20 females were dosed with either the control, 5, 20 or 80 (40) mg/kg/day. The high dose group received 80 mg/kg day the 1st and 3rd weeks of treatment and 40 mg/kg/day the 2nd and 4th weeks of treatment. This change in dose level was deemed necessary because of the toxic reactions noted in response to 80 mg/kg/day. The test material was administered by gavage as a mixture with Lutrol (polyethylene glycol 400). The control group was dosed with Lutrol only. The rats were dosed for 28 days (4 weeks) and after this period 10 rats of each sex/group or one half of the survivors/sex/ group were sacrificed and examined histologically. The remaining rats were allowed 6 weeks for recovery before they were sacrificed.

D. Survival. No rats died in the control or groups receiving 5 or 20 mg/kg/day. 6 males and 1 female in the high-dose test group died.

E. Clinical Signs. The symptoms that were consistently noted in the high-dose group were "apathy, ruffled coat, dyspnea, salivation, hyperkinesis, ataxia, and athetotic and choreiform movements." Only a single rat in in the mid dose group was reported as having any of these symptoms.

F. Body Weight. The only effect noted was retarded (decreased) body weight gain among the males in the high dose group (12-13%). The females were unaffected. The survivors in the male high dose group recovered from their body weight decreases during the recovery phase.

For sections G, H and I below, blood and urine samples were taken after day 28 of treatment and for the survivors after the 6-week observation period. Five rats of each sex per group were analyzed.

G. Hematology. There were no chemically related changes in erythrocyte counts, leukocyte counts, hemoglobin, hematocrit, mean hemoglobin content of erythrocytes, mean corpusculor volume, thrombocyte count, reticulocyte count, differential blood count.

H. Clinical Chemistry. Some slight differences were noted in phosphorous, K^+ and Ca^{++} levels in the male groups only. The laboratory report stated that these differences lacked a true dose response relationship and that the values obtained were within normal limits. Alanine amino transferase was elevated in high-dose group males, there were no differences noted with regard to aspartate transaminase, alkaline phosphatase, urea, blood sugar, creatinine, Mg^{++}, Na^+ or Cl^-.

I. Urinalyses. No differences were noted as a result of a comprehensive examination.

J. Organ Weights. The thyroid, heart, lungs, liver, spleen, kidney, adrenal, testes and ovary were weighted. The liver weights of high-dose females (increase + 24%), kidney weights of the high-dose males (decrease 12%), and adrenal weights of high-dose males (increase 15%) and females

(increase 19%) were affected after dosing for 28 days. The liver weights of the females were reduced (mid-dose group 32% and the high-dose group also 32%) after six weeks of recovery.

A NOEL for changes in organ weight is set at 20 mg/kg/day. At 40 (80) mg/kg/day there is a definite change in liver weight and a change in adrenal weight. [Note: it is of interest that the laboratory suggests that the change in adrenal weight is due to stress on the rat.]

K. No unusual or dose-related gross necropsy findings were noted.

L. No unusual or dose-related histopathological findings were noted. In particular, there were no lesions in the liver or adrenals which were found to be related to administration of the test material.

M. N/A.

N. 1.) This study is CORE MINIMUM. The 28-day dosing schedule does not qualify this study as a 90-day dosing study for regulatory purposes.

2.) The study provides useful information in that a NOEL of 20 mg/kg/day for 28 days is established. At 40/80 mg/kg/day toxic signs (nerve symptoms, body weight loss and liver and adrenal weight changes) were noted. The apparent biphasic liver weight changes noted at termination (an increase) and after recovery (a decrease) should be looked for in subchronic and chronic feeding studies with this chemical.

3.) N/A.

A. FCR 1272 Subchronic toxicity study on rats (three-month feeding experiment)

Bayer Ag Institut fur Toxikologie, Report No. 9386, June 4, 1980, EPA Acc. No. 072008, Tab 3.3.2b

B. The test material used for this study was technical grade FCR 1272 from batch 16003/79 and was stated to be of 84.2% purity.

C. The test animals used were SPF Wistar (TNO W.74 strain) bred and supplied by Winkelmann, Borchem. The rats weighed 72-73 (females) and 76-77 (males) grams and were 30-35 days old at the start of feeding. The rats were dosed for 3 months as either controls, 30, 100, or 300 ppm and each group consisted of 30 males and 30 females per dose group.

D. Survival. Only two rats died and their cause of death was said to result from an overdose of ether used in taking the blood sample.

E. Clinical reactions. No behavioral or physical reactions were reported. All rats were reported as being not different from the controls.

F. No consistent dose dependent effects on body weight gain were noted. All of the groups consumed about 19 (males) or 14-15 (females) gms/day of feed.

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Note: For sections G, H, and I below, hematology, clinical biochemistry and urinalysis were performed at one and three months using 5 males and 5 females from each dosage group.

G. No test chemical-related changes were noted in hematology after a comprehensive examination of the blood elements and thromboplastin time.

H. No test chemical-related changes were noted in chemical biochemistries after a comprehensive examination of blood levels of enzymes (4 types) and blood levels of electrolytes and substrates.

I. No test chemical-related changes in urinalyses were noted after a comprehensive examination of the urine for pH, substrates, bilirubin and deposits.

J. Organ weights. No test chemical-related changes in the thyroid, thymus, heart, lung, liver, spleen, kidney, adrenal, testes or ovaries were found.

K. Gross Pathology. No test chemical changes were noted.

L. Histopathology was conducted in two phases. The first included only 5 males and 5 females from the control and 300 ppm test group. The second consisted of supplementary (in order to meet FIFRA requirements) additional histopathology readings of 15 male and 15 female test rats from the control and 300 ppm test groups. Some 24 tissue types were evaluated for the control and high-dose group. The second phase of histopathology also evaluated the livers of 15 male and 15 female rats from the low (30 ppm) and mid (100 ppm) dose groups. No test chemical effects were noted.

M. Special Studies. The activity of the liver N-demethylase, O-demethylase and cytochrome P450 were determined at 7 and 28 days and at 3 months.

At 7 days, there were reported elevations in N-demethylase (all male groups, but not the female groups), O-demethylase (the mid and high dose female groups) and P-450 (the high-dose male group).

At 1 and 3 months, all three enzymes were equivalent to the control groups.

Toxicology Branch concludes that there may be at least a possible increase in liver enzyme activity to which the rat readily adapts. Toxicology Branch is not concerned that this be considered in setting a NOEL for this study.

Conclusion.

1.) This study is CORE MINIMUM.

2.) A NOEL is set at 300 ppm, the highest dose tested.

FCR 1272 Short-term toxicity tests on rats (4-week feeding and 4-week recovery tests).

Nihon Tokushu Noyaku Seizo K.K. (Japan), Report No. 215, March 15, 1982. EPA Acc. No. 072008, Tab. 3.2.2.c.

This study is assigned a CORE SUPPLEMENTARY classification for the following reasons.

- no protocol was presented
- the test material lot number and percentage purity were not provided
- the feeding phase of the study was for 4 weeks - an insufficient time interval for a 90 day feeding study for regulatory purposes.

The study consisted of dosing 4 groups of 18 male and female rats (strain and supplier were not identified) with FCR 1272 for 4 weeks. After 4 weeks 12 rats of each sex per dose were sacrificed and examined. The remaining were allowed 4 weeks to recover from any effect. The dose levels used were 0, 100, 300 and 1000 ppm. Based on the study report, the following effects were noted at 1000 ppm only unless otherwise indicated.

- behavioral reactions (straddle gait, salivation and/or nervousness) which disappeared in the later part of the dosing period.
- body weight, food consumption and water consumption decreases.
- urinalysis - urobilinogen and ketone bodies
- hematology - decrease in RBC count, hematocrit, and hemoglobin contents
- decreases in total protein and glucose in the blood. Glucose level was also decreased (-12%) in the mid-dose level.
- increased weight of the submaxillary glands, increased relative liver and kidney weight. These weight changes regressed after recovery.
- histologically there was noted cytoplasmic swelling of the glandular epithelium in the submaxillary glands.
- minimal degrees of single nerve fiber degeneration in the sciatic nerve were occasionally found. The number of incidences were not reported. This was said to have disappeared after 4 weeks of recovery.

The NOEL for this study is 100 ppm. The LEL is 300 ppm (minimal decrease in blood glucose).

FCR 1272 Short-term toxicity tests on mice (4-week feeding and 4-week recovery tests).

Nihon Tokushu Noyaku Seizo K.K., Report No. 221, April 14, 1982, EPA Acc. No. 072008, Tab. 3.2.2.d.

This study is assigned a CORE SUPPLEMENTARY classification for the following reasons.

- no protocol was presented
- the test material lot number and batch number and percentage purity were not provided
- the study used mice and this species is not usually acceptable for the subchronic feeding study for regulatory purposes.

[Note: The information generated may be useful in selecting the dose levels for the mouse oncogenicity study.]

The study consisted of dosing 4 groups of 18 male and female mice. (The strain and supplier were not identified), with FCR 1272 for 4 weeks. After 4 weeks, 12 males and 12 females from each group were sacrificed. The remaining mice were sacrificed after allowing 4 weeks for recovery. The dose levels used were 0, 300, 1000 and 3,000 ppm.

Based on the study report, the following effects were noted.

- behavioral signs (at both 1000 and 3000 ppm) included ataxia and/or emaciation. One high dose female died as a result of intoxication.
- depression in growth rate for males (3000 ppm group) and females (1000 and 3000 ppm groups).
- possible decrease in white blood cells (3000 ppm group).
- increased blood levels of "AIP" and BUN (males 3000 ppm). [Note "AIP" was not definitely defined.]
- dark red livers in some 3000 ppm dose group males and females
- increased weight for the submaxillary glands and kidneys (3000 ppm, males and females). Increased liver weight (1000 ppm and above), decreased spleen (males), adrenals and ovaries (females) in the 3000 ppm groups.
- histopathology revealed chromatic nuclei in males (1000 ppm and above) and in females (3000 ppm). Cytoplasmic swelling of the submaxillary glands was found in mice receiving 1000 ppm and above.
- Most of these findings disappeared after the four week recovery period.

A. FCR 1272 Subacute dermal toxicity study on rabbits

Bayer AG Institute fur Toxikologie, Report No. 8928, February 5, 1980. EPA Acc. No. 072009, Tab. 3.3.3.

B. The test material used for this study was FCR 1272 from batch 16001/79 and was of 83.5% purity. The test material was dissolved in Lutrol and applied to the backs of the test animals.

C. The test animals used for this study were New Zealand White rabbits. Three groups of 6 males and 6 females were dosed dermally at dose levels of 0, 50 or 250 mg/kg/day for 3 weeks or a total of 15 applications of 5 per week. The treated area was prepared by clipping or clipping plus abrading (for one half of the rabbits per sex per group). Abrading was done by using sandpaper. The test material was kept in contact for 6 hours. The treated areas were washed with acetone and then ethanol and then soap and water after the dosing period.

D. Survival. No rabbits died

E. Clinical reactions. No behavioral on clinical reactions were reported.

F. Body weight. No changes in body weight attributable to dosing were recognized. TB notes that the mid-dose groups for both males and females for both abraded and unabraded skin were lower than for the controls. The high-dose group was higher than the mid-dose group.

For sections G, H, and I below, blood and urine samples were taken from the rabbits prior to commencement and after three weeks of dosing. The blood was withdrawn from the ear vein.

G. Hematology. No changes in erythrocyte or leukocyte counts, hemoglobin, hemotocrit, thrombocyte count or differential blood count were noted.

H. Clinical biochemistry. No changes in aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatinine, plasma urea, or blood sugar were noted.

I. Urinalysis. No changes in urinalysis were noted.

J. Organ weights. The heart, lung, liver, spleen, kidneys, adrenals, testes, ovaries and thyroid were weighted but no effects of the test material were noted.

K. Gross pathology - No test chemical-related lesions were noted.

L. Histopathology - Tissues from the control and 250 mg/kg/day dose groups were examined. Only the testes from the 50 mg/kg/day group were examined. No test chemical-related effects were noted.

M. Special studies or aspects: Local reactions (dermal): Only reactions due to the abrasions caused by the sandpaper were noted. The test material did not appear to cause a local reaction at the site of application.

N. Conclusions

1) This study is CORE MINIMUM.

2) The NOEL is 250 mg/kg/day, the highest dose level tested.

A. FCR 1272 Subacute inhalational toxicity study on rats.

Bayer AG Institute fur Toxikologie, Report No. 9373, August 20, 1980. EPA Acc. No. 072009, Tab. 3.3.4

B. The test material used for this study was FCR 1272. It was from lot 16001/79 and was said to be of 85.3% purity.

The test material was generated into the atmosphere as a mixture with ethanol and lutrol (polyethylene glycol 400). The ethanol/lutrol mixture was 1:1. The aerosol was generated using a "dynamic flow inhalation apparatus" (i.e. see Kimmerle and Eben, Arch. Toxicol 30; 115, 1973).

For the first run of this experiment the apparatus was adjusted to generate aerosols with air concentrations of 10, 50 and 250 mg/m^3. Actual analysis of the atmosphere indicated that the concentrations were 2.3, 11.5 and 69.6 mg/m^3. Analysis for the particle size revealed that >90% were considered to be respireable (<3 u in diameter).

The control group received only the solvent at the rate of 20,000 ul solvent/m^3.

C. The test animals used for this study were male and female Wistar TNO/W 74 albino rats supplied by the Winkelmann, Borchen. At the start of the study they were nearly adult (180-220 gmes in weight). Each group consisted of 10 males and 10 females. They were exposed to the atmosphere containing CFR 1272 for 6 hours at a time, for 5 days per week for 3 weeks (15 exposures of 6 hours duration).

D. Survival. A single rat (male) receiving the high dose level died and its death was thought to be related to exposure.

E. Behavior reactions. The mid- and high-dose groups were reported as being effected and displayed ungroomed coat, a stiff, unsteady gait and eventually increased salivation.

A NOEL of 2.3 mg/m^3 is assigned for behavioral reactions.

F. Body weight. Weight gain was affected in all dosed groups. The low-dose groups did not gain weight. The mid- and high-dose groups had body weights lower after exposure than before. For example, the high-dose male group lost 4% of their body weight.

A NOEL for effects on body weight is <2.3 mg/m^3, the lowest dose level tested.

[Note for sections G, H, and I below blood and urine samples were performed on 5 male and 5 female rats from each group after the final exposure].

G. Hematology. No effects were noted on the blood elements (8 different parameters and the differential white blood cell counts were investigated).

H. Clinical chemistries. No effects were noted on aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, plasma urea, sugar or bilirubin. Serum electrolytes were not measured.

I. Urinalysis. There were no changes reported in the urine composition.

J. Organ weights. The thyroid, heart, lung, liver, spleen, kidneys, adrenals, testes, or ovaries were weighed. Of these, the following were indicated by the testing laboratory as being different from the control.

- heart - lower for all treated male groups, but higher for females
- liver - lower for male groups
- kidney - lower for male groups
- lung - lower for the high-dose males
- spleen - lower for the high-dose males
- thyroid - higher for the females
- adrenal - higher for females
- testes - higher for all male groups

Toxicology Branch notes the differences as above but considers that the magnitude and consistency of the effects do not require the conclusion that the differences noted were the result of the test material.

K. Gross pathology - The study report states that gross pathology performed on the rats sacrificed at the end of the experiment did not reveal any test compound-related tissue alterations.

L. Histopathology - Some 21 tissue types (including bone marrow smears) were reportedly evaluated for each of 5 rats of each sex per group. The only findings which the laboratory reported as related to the test material were inflammation of the trachea and emphysema of the lung.

M. Special Studies

1) Body temperature - The body temperature was measured rectally after the 1st, 5th, 10th and 15th exposure. The pre-exposure recordings were shown to be remarkably constant. However, there were several indications of the high-dose group (males and females) and sometimes the mid-dose group.

The testing laboratory dismissed the apparent differences as not being of sufficient consistency or magnitude to be of toxicological concern.

2) Liver enzyme levels - No effects were noted on N-demethylase, O-demethylase or cytochrone P-450.

Special Insert

Because the first experiment did not show a definite NOEL for "untoward effects" a second study was initiated. The second study utilized 4 groups exposed to either the solvent only (20,000 ul/m^3 of air), 2 mg/m^3, 10 mg/m^3 or 50 mg/m^3 of FCR 1272. By analytical concentration these levels were 0, 0.4, 1.4 and 10.5 mg/m^3 of FCR 1272. The mean particle size was determined and it was found that >96% were respirable for this study.

In the second study the rats dosed with 10.5 mg/m^3 only showed the behavioral reactions and their weight gain was said to be slightly less than the controls.

In the second study differences in the weights of the liver (high-dose group males) and spleen (high-dose group males) were lower. Other differences were noted for the relative weights of the adrenals (males and females) and heart (females).

There were no gross or histopathological changes noted.

N. Conclusions.

1) CORE classification of this study is MINIMUM. The pathology was done on only 5 rats of each sex per dose group.

2) The NOEL is 1.4 mg/m^3. At higher dose levels there are noted behavioral, body weight and organ weight changes.

A. FCR 1272 study for nerve damage effect on the rat after 5 months oral application.

Bayer, A.G., Institute of Toxicology, Report No. 10705, March 10, 1982. EPA Acc. No. 072009, Tab. 3.3.5

B. The test material used for this study was FCR 1272 and was from batch 16001/79 and was stated as being of 83.3% purity.

C. The test animals used were Wistar TNO/W74 albino rats bred by Winkelmann Borchem. They were young at the initiation of the study (140-150 gm). 15 male and 15 female rats were dosed orally with the test material in Lutrol. They were dosed 7 days a week for 5 months by stomach tube. The dose level used was 60-80 mg/kg bw. This dose range was chosen so that the rats always showed symptoms. A solvent control group of 15 rats of each sex was also run.

D. Survival. 4 control rats died. 10 treated rats died. This indicates that deaths were likely due to the test material.

E. Behavioral reactions. The treated rats reportedly showed "non-specific behavior disturbances" (apathy, out-of-condition coat, troubled respiration). Digging and grooming, tremors, gait abonormalities and salivation were also noted. No indications of paralysis were noted.

F. Body weights. The males showed signs of lower weight gain. The females were apparently not affected.

G. No hematology was conducted.

H. Liver tissue was assessed for N-demethylase, O-demethylase and cytochrome P-450 activity. Increases in these enzymes were not observed following 5 months of treatment with FCR 1272.

I. Urinalysis was not performed.

J. Organ weights. (Only the liver, kidney and brains were evaluated for weight changes.) The liver (-11%) and kidney (-19%) were depressed for the males. The liver (+16%) was increased for the females.

K. Gross necropsy. No gross necropsy lesions were noted which were definitely related to the test material.

L. Histopathology. The liver, kidneys, adrenals, brain, spinal marrow and nn ischiadici (sciatic nerve) of 5 females and 5 males were prepared for histopathology. The brain and spinal marrow were stained with Nissel's method and Luxol Fast Blue respectively.

No test chemical lesions were noted by histological examination. There were no lesions reported in either the brain or sciatic nerve.

N. Conclusions.

1. This study is CORE MINIMUM.

2. No effects on the structure of the nervous system were noted.

A. FCR 1272 chronic toxicity study in dogs (six-month feeding experiment)

Bayer, A.G., Institut fur Toxikologie, Report No. 9991, June 2, 1981. EPA Acc. No. 072009, Tab. 3.5.2a.

B. The test material for this study was FCR 1272 from batch 16003/79 which was stated to have a purity of 84.8%.

C. The test animals were beagle dogs. They were 24 and 31 weeks old at the start of the experiment. There were 4 test groups each with 6 male and 6 female dogs. The dose levels were 0, 65, 200 and 600 ppm of FCR 1272 and the dogs were fed their diets for 26 weeks (185-186 total dosing days).

D. Survival. One dog died as a result of fighting. This dog was in group II (600 ppm) and was replaced by another dog (which received the test diet for 165 days). There was no effect of the test material.

E. Clinical observations. There were no differences in the general appearance of the dogs. Behavioral reactions were noted only in the dogs receiving 600 ppm. These included hind limb abnormalities such as stiff gait, uncoordination, arching backs (these developed in the later weeks of the experiment). Other signs in the group receiving 600 ppm included vomiting and diarrhea. There were no differences noted in the several reflex tests conducted or in body temperature or pulse rate.

F. Body weight and food consumption. Apparent decreases in body weight were evident at the dose levels of 200 and 600 ppm, but statistical significance was not attained for the high dose group. TB considers that not enough dogs were available per group to conclude that small differences noted were related to the test material. There were no differences noted with regard to food or water consumption.

Note: For sections G, H, and I, blood and urine samples were obtained at weeks 0, 4, 7, 13 and 26. All dogs in each test group were used.

G. Hematology. The following parameters were measured: hematocrit, hemoglobin, erythrocyte count, thrombocyte count, reticulocyte count, MCV, MCHC, MCH, sedimentation rate and thromboplastin time, leucocyte count and differential blood cell count. There were no test chemical effects on these parameters.

H. Clinical chemistry. The following parameters were measured: glucose, urea, creatinine, total protein, glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT), alkaline phosphatase (AP), bilirubin, cholesterol, glutamate dehydrogenase (GLDH), Na^+, K^+ and Cl^-. Serum protein electrophoresis.

There was no test chemical effect on any of these parameters.

I. Urinalysis - No test chemical effects were noted on the various parameters investigated. The urinalyses were considered by this reviewer to be comprehensive.

J. Organ weights. The heart, lung, liver, kidneys, spleen, testes, ovaries, thyroid, adrenals, thymus, prostate, brain and pancreas were weighed.

Of these organs, only the thymus showed signs of depressed weight. For example, the male groups mid (-35%) and high (-34%) and female high dose group (-28%) were decreased in weight. The relative weights of these groups for the thymus were also similarly lower.

The liver weights were not affected.

K. Gross Pathology. There were no test chemical related lesions noted at gross necropsy. A possible exception may be that the female higher dose test group had 2 incidences of atrophied thymus.

L. Histopathology. Some 28 organs/tissues were examined for the control and high dose group dogs, but there were no test chemical related lesions noted.

M. Special studies.

1. Opthalmoscopic examination - (at weeks 0, 4, 7, 13 and 26). The examination included inspection of the outer parts, the transparent media and the ocular fundus. Opthalmoscopic examinations did not reveal test chemical effects.

2. Liver enzyme. No effects were noted on the activity of N-demethylase or cytochrome P-450 assayed in liver homogenates.

Conclusions

1. This study is CORE MINIMUM. Only the control and high dose group dogs were examined histologically.

2. A NOEL of 200 ppm is assigned. At 600 ppm there is evidence of neurological effects (hind limb effects) and gastrointestinal disturbance.

FCR 1272 (Proposed Common Name: Cyfluthrin) Multigeneration Study in Rats.

Bayer, A.G., Institute fur Toxikologie, Report No. 11870 (also Mobil No. 85881), June 8, 1983. EPA Acc. No. 072009, Tab. 3.6.2.

1. The test material used for this study was FCR 1272 and was from five batches designated as 2/80, 3/80, 5/80, 6/80 and 7/80. The purity of the material was not stated because the batches were as "pre-mix concentrates" at 50% with Wessalon S. The report stated that stability and homogeneity in the feed were checked before the start of the study but supporting data were not provided in the report.

2. The test animals used were SPF rats of the BOR:WISW strain and were bred by a German supplier. At the start of the study, the rats were 5-6 weeks old. There were 4 groups of 10 males and 20 females in each test group and they were dosed as either 0, 50, 150 or 450 ppm. Six sets of litters were bred. F_1a and F_1b from the F_0 parental groups; F_2a and F_2b from the F_1b parental groups and F_3a and F_3b from the F_2b parental groups. For each mating one male rat was mated with 2 female rats.

3. Survival, general appearance and behavioral reactions in adult rats. No test chemical related deaths were reported. Body weight gain for the adults was definitely depressed at 450 ppm for all groups.

4. Reproductive performance

   a. Fertility index (number of pregnant females/number of mated females.) No consistent change in the fertility index was noted. Usually 90-100% pregnancies resulted. The F_1b parents had occasions of 65-85% pregnancies and the F_2b generation high dose group resulted in the lowest rate (65%). This trend was not evident in the F_3a or b generations.

   b. Gestation index (number of females with live litters/number of pregnant females). No effects were noted and the gestation index was usually 90-100%.

   c. Viability index (number of live pups after 5 days/number of pups born). Indication of decreased viability was evident for the F_1a, F_2a, F_3a and F_3b generations. The F_3a and F_3b generations were most noticeably affected. For example, the F_3b generation had viability indexes of 99.0, 92.3, 89.0, and 77.4 for the control, low, mid and high dose groups.

      For the purpose of this study, the NOEL is set at 50 ppm because the decrease at 50 ppm is not consistent through the 6 litter sets and it is considered by this reviewer to be reasonably close to and within control range values.

   d. Lactation index (number of live pups after 4 weeks/no. of live pups at day 5, after reduction to 10): decreases in the lactation index were evident for the F_1a, F_1b, F_2a, F_2b and F_3b litter sets. The maximum difference was found for the F_2a and F_2b groups which were 75.8 and 72.4% for the mid and high dose levels versus 93.1% for the control group.

5. Condition of the pups

   a. Sex ratio - was not affected, there were approximately equal numbers of males and females.

b. Number of pups - For the F_1b and the F_3a groups there appeared to be few pups in the high dose group, but this trend was not evident in the other 4 litter sets.

c. Stillbirths - The F_1b group had 6 stillbirths in the high dose test group but the other litter sets did not show evidence of dose related stillbirths.

d. Body weight at birth - Body weight of the pups at birth was small for some occasions but this was not consistent for the high dose test group for all 6 of the litter sets.

e. Body weight gain of the pups - A NOEL for decrease or retarded weight gain is set at 50 ppm. At 150 and 450 ppm there was noted consistent effects and slower weight gain.

6. Gross necropsy and histopathology. The 4-week-old pups from the F_3b generation and their parents (the F_2b generation) were necropsied and subjected to histopathology. A single male and female from each of 10 dams from the control and high dose groups were examined histologically.

No dose related changes were noted by either gross necropsy or histopathology of the parents or pups examined.

The livers, kidneys and testes or ovaries of the parental rats were weighed but no test chemical effects were noted.

Conclusion: This study is Core Minimum. The NOEL for a decrease in the viability index is set at 50 ppm. There were noted occasions of pup deaths at 150 and 450 ppm. A NOEL for systemic effects is set at 50 ppm. Body weight decreases in the pups are noted at 150 and 450 ppm.

A. FCR 1272 [Study 007] Evaluation for embryotoxic and teratogenic effects on orally dosed rats.

Bayer, A.G., Institute fur Toxikologie, Report No. 10562, January 20, 1982. EPA Acc. No. 072009, Tab. 3.6.3a

B. The test material for this study was FCR 1272 and was from batch 16001/79 and was stated as being of 85% purity.

C. The test animals used for this study were male and female BAY: FB30 rats which were bred by the Bayer AG Institute. At the start of the study the females were between 181-247 gms (2-1/2 - 3-1/2 months of age), the males were between 350-500 gms (3-6 months of age). The males were allowed to inseminate the females such that ideally there would be about 25 pregnant females per dose group. Mating was allowed to take place overnight and the presence of a vaginal smear confirmed mating and the female was assumed to be pregnant. The pregnant females were dosed with either 0, 3, 10 or 30 mg/kg of test material (in lutrol or lutrol alone) on days 6 to 15 of gestation. On the 20th day of gestation the rats were sacrificed by CO_2 gas and the pups delivered by caesarean section.

D. Effects on the dams. None of the dams died. The dams in the mid and high dose group were described as exhibiting a "high stepping gait." Some of the dams in the high dose group were said to be ataxic and exhibited decreased motility. There was no adverse effect on weight gain throughout gestation.

There were 25, 23, 25 and 22 pregnant rats for the control, low, mid and high dose test groups.

There were no effects noted related to the in utero investigations made (number of implantations, litter size, number of resorptions, average placenta or weight).

E. Effects on the pups. There were 277, 261, 257 and 251 total number of fetuses for the control, low, mid and high dose test groups. Approximately 1/3 of these from each group were assessed for visceral deformities by a modified Wilsons technique. The remaining 2/3 were assessed for bone development.

No test chemical effects on either soft tissue or bone development were reported as resulting. There was a total of 14 deformed fetuses reported. 10 of these were in the control group.

F. Conclusion

1. Core classification of this study is MINIMUM.

   a. The report is unsigned.

2. Note - In a more recent submission from Mobay Chemical Corporation (January 14, 1985; EPA Accession No. 073255), historical control data for this strain of rat (FB30-Long Evans derived) was submitted. The data was for rats from the same breeding source and from the same laboratory (Bayer AG Institute of Toxicology, Germany) that performed this study on FCR 1272. The data covered 108 rat teratology studies conducted from 1971 to 1980 on 2,189 dams and 24,193 fetuses. The data is in Mobay report number 80211, dated August 20, 1980.

A. FCR 1272 [The active ingredient of Baythroid"] Study of embryotoxic (and teratogenic) effects on rabbits after oral administration.

Bayer, A.G., Institute fur Toxikologie, Report No. 11855, (also Mobay No. 85879), June 1, 1983. EPA Acc. No. 072009, Tab. 3.6.3b.

B. The test material used for this study was FCR 1272, from Batch No. 816170017 and was said to be of 95.0% purity.

C. The test animals used for this study were Himalayan rabbits (CHBB:HM strain, bred in Germany). Female rabbits were mated with males and copulation was verified by observation. Four groups of 15 inseminated rabbits were eventually dosed at either 0, 5, 15 or 45 mg/kg of the test material on days

6 through 18 (13 administrations). Of the 15 per group, there were 15, 15, 13 and 14 rabbits which proved to be actually pregnant for the control, low, mid and high dose groups. The rabbits were sacrificed on day 29 of gestation and the pups delivered by caesarean section.

D. Effects on the dams. There were no mortalities, body weight changes or behavioral reactions noted. Intrauterine effects were probably evident in the high dose group because two of the dams in this group aborted and a third had a complete resorption. Because of the abortions and resorption, there were 15, 15, 13 and 11 litters available after 28 days of gestation.

E. Effects on the pups. There were 100, 84, 92 and 70 pups available for the control, low, mid and high dose test groups. The low number in the high dose group is consistent with the two abortions and resorption. The pups from the dosed groups were stated as being equivalent to the controls with respect to size, weight, appearance, necropsy observations, bone and visceral development. The test laboratory asserted that there were no effects at all due to the test material.

"Arthrogryposis" (persistent flexure or contracture of a joint) was observed in FCR 1272 treated groups at a fetal incidence rate of 0, 2.4%, 2.2% and 4.3% and at a litter incidence rate of 0, 6.7%, 15.4% and 9.1% for the control, low, mid and high dosage levels respectively. See below for an assessment of this observation.

The only other noteworthy malformation reported was "asymmetrically positioned and deformed tailbone." There were 4 pups (from a single dam in the group receiving 15 mg/kg/day) with this lesion.

Note - In a more recent submission from Mobay Chemical Corporation (January 14, 1985; EPA Accession No. 073255), historical control data for this strain of rabbit (Himalayan) was submitted. The data was for rabbits from the same breeding sources and from the same laboratory (Bayer AG Institute of Toxicology, Germany) that performed this study on FCR 1272. One set of data (Mobay report No. 80210; dated January, 1981) covered 51 rabbit teratology studies conducted from 1971 until 1980 on 625 dams and 4,077 fetuses. A second set of data (Mobay report No. 88768, dated December 13, 1984) covered 27 studies conducted from 1980 until 1983 on 379 dams and 2,329 fetuses.

With respect to "arthrogryposis", the first set of data presented an overall incidence of 37/4077 (0.91%) for fetuses and 32/625 (5.1%) for litters. 25/51 of the studies had some incidence of "arthrogryposis" in the control fetuses. In 8 studies, the incidence in fetuses was > 2.0%; in 3 of these studies, it was >3.0%; and in 2 of these, it was $\geq$ 5.0%. The highest incidence for fetuses in a single study was 5.4% and for litters was 20-33%. In terms of litter incidence, 5 studies had a litter incidence of $\geq$ 14%. The second set of data presented an overall incidence of 33/2329 (1.4%) for fetuses and a maximum of 33/379 (8.7%) for litters.

A consideration of the results in this FCR 1272 study (with respect to "arthrogryposis") in relation to the historical control data presented above for the same lesion, has led Toxicology Branch to conclude that "arthrogyposis" observed in this study is most likely not related to the administration of test material.

F. Conclusion

This study is classified as CORE MINIMUM. The report is not signed.

FCR 1272 Neurotoxicity study in hens

Bayer, A.G., Institut fur Toxikologie, Report No. 9753. January 27, 1981, EPA Acc. No. 072009, Tab. 3.6.6a.

[Note: This study consists of four parts: acute single dose oral LD_{50} in hens determination; single dose oral neurotoxicity study; two oral doses at a three week interval study; and five oral doses within one week study.]

The test material used for these studies was technical grade FCR 1272. Three individual batches were used: batch 16001/79 of 85.3% purity; batch 16003/79 of 84.8% purity; and batch 16003/80 of 94.3% purity.

The test animals used for these studies were White Leghorn hens (layers) bred and supplied by Mechow, Wappertal and Brinkschulte, Senden. Apparently they were obtained from separate and independent suppliers. They were said to be between 15 to 20 months old and weighed between 1 and 2 kg.

Part 1 and Part 2. Acute oral LD_{50} and single oral dosing.

3 groups of 10 hens were dosed with either 1000, 2500 or 5000 mg/kg of test material that was suspended in polyethylene glycol 400 and observed for up to 42 days after treatment.

5 of the 10 hens dosed with 5000 mg/kg died. Thus, the LD_{50} in hens was considered to be 5000 mg/kg.

6 of the 10 hens receiving 2500 mg/kg were said to show signs of intoxication ("excitation") during the first 3 days following treatment. The hens dosed with 1000 mg/kg were said to be symptom free.

Two of the hens dosed with 5000 mg/kg showed signs of neurotoxic response. One of these developed symptoms (after first apparently recovering) on the 14th day and eventually died on day 19. The other developed symptoms on days 27 and 28. Histology of the brain, spinal marrow and left and right Nervi ischiadici (sciatic nerve) revealed "moderate" fiber alterations in the sciatic nerve. These alterations included axon fragmentation, occasional swelling and eosinophilia of the axon fragments and vacuolation of the myelin sheaths.

Part 3: Two oral applications at 3 week intervals.

30 hens were dosed with 5000 mg/kg (the maximum practical dose) by gavage on two occasions 21 days apart. After a second 21 days, any hens showing symptoms were perfused with 10% Formalin to fix the nerve tissue. In addition, several birds not showing symptoms were fixed in situ. The brain, spinal marrow and Nervi ischiadici were excised, processed and histologically examined. A separate group of 5 hens were dosed with 375 mg/kg of the positive control TOCP. These birds were fixed and excised after 21 days following treatment.

The hens dosed with TOCP showed both behavioral (within 7-8 days) and histological evidence of a positive response.

The birds dosed with FCR 1272 were said to show initial signs of intoxication (first 3 days) but were said to be normal thereafter until the second dose was administered. Following the second treatment, 4 hens died. There was a series of symptoms which most hens showed which regressed in a few days post-treatment and a second set of symptoms which developed in 4 birds. The latter symptoms resembled delayed type neurotoxicity. Histopathology of these birds indicated that nerve fiber degeneration was present in the majority of the birds dosed with FCR 1272. The myelin sheath was distended and the myelin sheath was described as being optically void or granularly disintegrated. The axons were described as swollen or fragmented and in some areas activated or proliferated Schwann's cells were noted. The nerves also contained macrophages in which cytoplasm contained granular material.

Part 3 confirms a positive response that was noted in Part 2. It should be noted that there was no negative control group (solvent only) for either Parts 1, 2 or 3.

Part 4. Five oral applications within one week. In this part of the study, 10 hens were dosed with 5000 mg/kg of FCR 1272 from batch 16003/80 for five consecutive days and observed for 43 days.

6 of these hens were eventually perfused and the nervous system removed for histological examination. 4 of the hens died due to the initial effects of the toxicant. All hens showed initial toxic responses that disappeared eventually. Behavioral disorders accompanied by drowsiness and a cramped gait developed in 3 of the six survivors. The 3 hens which showed symptoms were perfused when found in a moribund state. The other 3 hens were perfused on day 43 of the study.

Necropsy and histology of the heart, liver, lungs, spleen, kidneys, ovaries, crop, esophagus, stomach, intestine, leg and pectoral muscle were also done.

Mottled kidneys and brittle livers were noted at necropsy. No treatment related lesions were noted in non-nervous system tissue by histopathological analysis.

Treatment-related fiber degeneration, i.e., distension or granular disintegration of the medullary sheath, swollen or fragmented axis cylinders and proliferated Schwann's cell in the sciatic nerve were reported. One hen had similar lesions in the spinal marrow.

This positive result confirms the results of the previous studies.

These studies show that under the conditions of these assays FCR 1272 induces a delayed type neuropathy.

These studies are SUPPLEMENTARY. They do not utilize a proper negative control group (solvent only) or properly attempt to study a dose response.

Investigative Neurotoxicity Studies in Hens

Mobay, Study No. 165, March 9, 1981, EPA Acc. No. 0972009, Tab. 3.6.6b.

In this study three synthetic pyrethroids were tested for their potential to cause neurotoxicity in hens. The three chemicals were FCR 1272 (cyfluthrin), NAK 1472 ((+)-trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropanecarboxylic acid-pentafluorobenzyl ester and NAK 1654 (the (-) pure form of NAK 1472).

Groups of 10 hens (17 months of age) were dosed with either FCR 1272 (5000 mg/kg), NAK 1472 (1000 mg/kg), NAK 1654 (2500 mg/kg) or TOCP (500 mg/kg) and were observed for 56 days before being sacrificed. The test materials were dissolved in Carbowax prior to dosing.

In a second experiment, FCR 1272 was administered (in carbowax) at 5000 mg/kg to a group of 20 hens on two occasions 7 days apart. A positive control group of 5 hens were dosed with 500 mg/kg of TOCP. An untreated control group of 4 hens were also included. The hens were observed for 49 days.

The results of the single dosing experiment indicated that no hens dosed with the three pyrethroids showed signs of neurotoxicity (behavioral, no microscopy). The hens dosed with FCR 1272 showed initial weight loss but recovered. The positive control group (TOCP treated) developed the delayed type neurotoxicity.

In the second experiment, only a single hen showed some signs of neurotoxic response but this was evident by the behavioral response only and on day 30. Necropsy and histopathology failed to confirm the presence of lesions in the nervous system. The condition of this hen was determined (by the laboratory) to be due to "egg-yolk peritonitis."

[Note: The data table indicates that 2 hens died (or were sacrificed) but the text refers to only one hen which was sacrificed.]

The positive control (TOCP treated hens) and the untreated hens responded as expected.

The first experiment is is CORE SUPPLEMENTARY (no microscopy). The second experiment is CORE MINIMUM. Under the conditions of this assay, no evidence that FCR 1272 induced neurotoxicity in hens developed.

FCR 1272 (cyfluthrin, baythroid active ingredient) neurotoxicity study on chickens after cutaneous administration (cumulation tests).

Bayer, A.G., Institute of Toxicology, Report No. 10768, March 29, 1982, EPA Acc. No. 072009, Tab. 3.6.6c.

The test material used for this study was FCR 1272 and was from two lots (batch 16003/80, 91.4% pure and from batch 816170019, 95.0% pure).

It should be noted that the dermal route is not the usual method of application for a hen neurotoxicity study. Hens were treated dermally (cutaneously) with the test material (made into a paste with cellulose powder) at a dose level of 5000 mg/kg. In the first study (called the pilot study), ten hens were exposed for 5 days for 23 hours each day. For the second study, 10 adult hens were treated for 3 weeks each workday for 6 hours at 5000 mg/kg. The hens were dosed at the axillae following preparation by removing any feathers. The test material was kept in place by a dressing wrap. Prior to sacrifice, the nervous tissue was fixed in situ by formalin infusion. The brain, segments of the cervical, thoracic and lumbar regions of the spinal cord and proximal and distal areas of the right and left ischiadici (sciatic nerve) were examined.

Exposure to 5000 mg/kg/day for 23 hours (5 times) resulted in 2 deaths that occurred on the 3rd and 10th day after cessation of treatment. All of the other hens were said to have recovered from the major symptoms (apathy and disturbed behavior). Other signs included local irritation and weight loss. Histopatholoy of the hens revealed that 2 had a "minimal segment-like nerve fiber degeneration" (sciatic nerve) but this type is often found in untreated hens.

Exposure to 5000 mg/kg/day for six hours for 15 exposures resulted in hens that appeared "apathetic." For most of the hens this symptom was reversed after the first week but for 2 hens, this symptom persisted until the 38th and 51st day after the start of treatment. Other signs included local irritation and body weight loss. There were no signs, either behavioral or microscopic, that indicated a neurotoxic (delayed type) response to treatment with FCR 1272.

This study is CORE MINIMUM. No evidence of delayed type neurotoxicity was evident under the conditions of this study. It should be noted that the dermal route is not the usual method of application for studying delayed type neurotoxicity.

Acute Oral Toxicity of Baythroid 240 EC in Rats

Mobay, Study No. 83-011-03, August 11, 1983, EPA Acc. No. 072008, Tab. 3.2A.2.

8 groups of male and female fasted Sprague-Dawley rats were dosed with either 46 (females only), 74, 118, 188, 300, 480, 768, 1229, or 1966 (males only) mg/kg of Baythroid 240 EC (25.2% cyfluthrin) and observed for 14 days. The test material was dissolved in Carbowax and administered by gavage.

4

LD_{50}'s (with 95% confidence limits) were determined.

1015 (651-1671) mg/kg for males
826 (598-1225) mg/kg for females

Signs of toxicity were reported in all dose levels and included "lacrimation, salivation, urine staining, writhing, kyphosis, ataxia and decreased activity." Necropsy of the rats which died as a result of the poisoning revealed "pale kidneys, dark red and/or firm lungs, gas- and fluid-filled gastrointestinal tract, blood around the mouth, urine or diarrhea stain and freed blood in the thoracic cavity." Necropsy of the survivors was reported as unremarkable.

This study is Core Minimum. Tox Cat III. The behavioral signs and necropsy findings were summary statements only. No data were presented to qualify those statements or show intensity of response with increasing dose levels.

Acute Dermal Toxicity of Baythroid 240 EC in Rabbits

Mobay, Study No. 83-023-02, August 11, 1983, EPA Acc. No. 072008, Tab. 3.2A.2.

10 (5 male and 5 female) adult rabbits (New Zealand white) were prepared (clipped) and dosed with 2000 mg/kg of test material (Baythroid® 240 EC, 25.2% cyfluthrin). The test material was kept in place for 24 hours by means of an occlusive bandage. The rabbits were observed for 14 days.

No rabbits died and no signs of systemic intoxication were reported. Local irritation at the site of application resulted. Necropsy did not reveal test chemical effects.

This study is Core Minimum. The LD_{50} is >2000 mg/kg and the product may be assigned to Tox Cat III. Only a single dose level was tested.

Acute Inhalation Toxicity Study with Baythroid 240 Emulsifiable Concentrate in Rats

Mobay, Study No. 83-041-07, Sept. 9, 1983, EPA Acc. No. 072008, Tab. 3.2A.4.

1. Sample generation: The test material (Baythroid 240 EC) was generated into an exposure chamber by pumping the solution through a nozzle where it mixed with pressurized air. The mixture of air was blown into the top of the exposure chamber and a constant flow of air carried the aerosol to the rats. In this manner various atmospheric concentrations of Baythroid EC were generated by changing the airflow and flow rate of the liquid into the chamber. The rats were situated in individual tubes such that only their heads were exposed to the test material.

2. Atmospheric concentrations: Both nominal and analytical atmospheric concentrations were determined. The analytical concentration was said to be determined by taking samples near the rats breathing zone 4 times during the 4-hour exposure period. The concentration of cyfluthrin was determined analytically and converted to quantity of formulation. The chamber concentrations were thus shown to be 57, 90, 465, 510, 883, 1021, 1421, 1775 and 2437 mg/m^3. Note: only females were exposed at the 2437 mg/m^3 level.

3. Particle size determinations: Samples were taken twice during the exposure periods for each of the test levels. A seven-stage Mercer (Lovelace) Cascade impactor was used. The average mass median diameter was determined to be 1.2 um. 96% of the particle mass sampled was said to be <10 um.

4. The following table indicates the deaths resulting at each dose level.

Dose level mg/m^3	Males	Females
99	0/10	1/10
465	0/10	1/10
510	0/10	1/10
883	7/10	4/10
1021	2/10	2/10
1421	5/10	4/10
1775	10/10	4/10
2437	Not assayed	10/10

Clear dose responses for deaths were not obtained. Using these data the following acute LC_{50} concentrations were determined.

For males 1323 (1138 to 1505) mg formulation/m^3.

For females 1434 (1153 to 1877) mg formulation/m^3.

The deaths occurred either during exposure or shortly afterward.

5. Signs of toxicity were noted at the lowest test dose level. The signs noted at the lower doses included salivation, decreased activity, and ocular and nasal irritation. At higher concentrations (883 mg/m^3) signs of writhing, ataxia and gasping were noted. Some of these signs persisted up to 14 days. Other signs included decreased body weight gain, alopecia and scabs behind the ears.

6. Gross necropsy of the rats which died revealed the presence of "reddened lumps, turbinates and cervical lymph nodes" and other systemic signs. No specific compound related lesions were noted by histopathology (although the dead animals had pulmonary congestion.)

Conclusion: This study is Core Guidelines. Baythroid 240 EC is toxicity category II by the inhalation route (for example <2.0 mg/l).

Eye and Dermal Irritation of Baythroid 240 EC in Rabbits

Mobay, Study No. 83-323-05 and 83-333-03, August 11, 1983. EPA Acc. No. 072008, Tab. 3.2A.5.

For both of these studies the test material was Baythroid 240 EC (25.2% cyfluthrin).

Part I: Eye Irritation

The eyes of 9 rabbits were instilled with 0.1 ml of the test material. Prior to treatment the eyes were treated with 0.5% proparacaine. The eyes of 3 of the treated rabbits were washed 45 seconds after test material instillation. The eyes were observed for 21 days afterward.

Corneal opacity which did not reverse in 21 days developed in 4/6 of the rabbits in the unwashed group. Corneal opacity which reversed by 14 days developed in the washed group.

This study is Core Guidelines. The product is Tox Cat I by eye irritation.

Part II: Dermal Irritation

The backs of 6 rabbits were prepared by clipping and abrading and dosed with 0.5 ml of the test material which was kept in place for 4 hours. The rabbits were observed for reactions for up to 14 days.

A PII of 0.8 was reported as resulting. Only "very slight to moderate erythema" was observed.

This study is Core Guidelines (1982). Tox Cat. IV.

OPP:HED:TOX:J.DOHERTY:E.BUDD:sb 1/29/85 x77395 #jd#1

"The following mutagenicity studies were reviewed by John Whalan of 004285 Toxicology Branch"

SALMONELLA/MICROSOME Test for Detection of Point-Mutagenic Effects Induced by FCR-1272

Bayer AG Institut Fur Toxikologie; Report No. 9273; June 27, 1980

Protocol: The histidine-requiring mutants of Salmonella typhimurium used in this study included TA 1535, TA 1537, TA 100, and TA 98. The tests were conducted by the method of Ames et al. Four agar plates were used per substance and dose. Four agar plates were treated with solvent and used as negative controls. The positive control materials were Endoxan® (cyclophosphamide, an alkylating agent and known promutagen) and trypoflavin (a frameshift promutagen). All groups were tested with and without S-9 mix in order to assess any detoxification due to metabolism. Two plates/group were used to score the total number of bacteria. DMSO was used as the solvent for FCR-1272 and trypoflavin, and demineralized water was used as the solvent for Endoxan®. Multiple tests were performed as needed to confirm mutagenicity.

Results: Doses of FCR-1272 as high as 24 mg/plate were not bacteriotoxic to the strains used in this study. FCR-1272 precipitated out of solution at doses of 2.5 mg/plate and greater. Instances of increased numbers of mutants were observed in some of the activated TA 1535 and TA 1537 tests only, but these results were not reproducible. Therefore, FCR-1272 could not be confirmed to be mutagenic in the strains tested. The positive controls elicited responses with each strain, particularly in the presence of S-9 activation, thus demonstrating the sensitivity of the activated test systems and the activity of the S-9 mixture.

This study is UNACCEPTABLE. The positive controls, Endoxan (cyclophosphamide) and trypoflavin, are not typically used in these tests, and they failed to demonstrate the sensitivity of the systems. Both controls required S-9 activation to elicit a clear mutagenic effect. Other positive controls should have been used that could demonstrate a mutagenic effect on activated and nonactivated systems. Means of the raw data were presented, but standard deviations were not included.

MICRONUCLEUS TEST for Detection of the Mutagenic Potential of FCR-1272 in Mice

Bayer AG Institut Fur Toxikologie; Report No. 9435; September 22, 1980

Protocol: Male and female NMRI/ORIG Kisslegg mice (26-37 g; 8-12 weeks old) were given two oral doses (separated by 24 hours) at 0 (Lutrol vehicle control) 7.5, and 15.0 mg/kg/day. A positive control group received two I.P. doses of 0.125 mg/kg/day of Trenimon®. FCR-1272 was dissolved in Lutrol, and Trenimon® was dissolved in demineralized water. Six hours after the second dose, the mice were decapitated and the femoral bone marrow prepared by the method of Schmid for evaluation. A total of 1000 polychromatic erythrocytes per mouse were counted.

Results: Two high dose females died of unknown causes at an unspecified time. No other toxic signs were observed. The ratios of normochromatic to polychromatic erythrocytes, and micronucleated cells to normochromatic and polychromatic erythrocytes were similar for the dosed and vehicle control groups. A signif-

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icant increase in micronucleated cells was seen in the polychromatic erythrocytes of those mice dosed with the positive control, Trenimon®. The ratio of polychromatic to normochromatic erythrocyes in the positive control resembled that in the vehicle control.

This study is UNACCEPTABLE. It is unlikely that a toxic dose of FCR-1272 was given to any mice since no toxic signs were seen. Although two mice died, the time and nature of those deaths were not given. The deaths may indeed have been accidental. Only two dose levels were used rather than the recommended five doses, and there was no attempt to dose any mice at the MTD. Ideally, single doses should have been given and samples of marrow taken at three different time intervals. The positive control substance, which was given by a different route (intraperitoneally v orally), elicited a definite reaction. There was, however, no evidence that a sufficient quantity of FCR-1272 reached the bone marrow to elicit hematopoietic toxicity.

DOMINANT LETHAL STUDY of FCR-1272 in the Male Mouse

Bayer AG Institut Fur Toxikologie; Report No. 9678; January 7, 1981

Protocol: NMRI/ORIG Kisslegg mice (28-39 g; 8-12 weeks old) were used in this study. Males only were given single oral doses of 30 mg/kg of FCR-1272 in Lutrol. Control males were dosed with the vehicle only. One treated male and one untreated female were housed together for four days. Each male was mated in this manner with 12 different females over a 48-day period to assess mutagenic effects during different phases of spermatogenesis. The dams were examined for pre- and post-implantation loss 16 days after mating commenced. The study was repeated for 3 mating intervals at doses of 30 and 60 mg/kg to confirm the findings in the initial experiment (specifically, an increased incidence of post-implantation deaths during the first mating interval).

Results: In the initial study, the dosed males showed no signs of toxicity or reduced fertility. Pre-implantation losses in the dams mated with dosed males was similar to the controls. Post-implantation loss was also similar except for those dams mated during the first mating interval (2.6 fold increase in dead implants). Since four of the 50 dams accounted for the majority of the dead implants, this occurrence was probably not compound-related. The repeat study was performed to verify the significance of this finding.

In the repeat study, a low-dose and a high-dose male each were grossly emaciated and had ruffled hair coats during the third mating period. Four high-dose mice died of "acute toxic effects" before they could be mated. The significance of these findings is doubtful since the other mice had no toxic signs. There was no effect on fertility. Pre- and post-implantation losses were not significantly greater in the dams mated with the dosed males at either dose level, compared to the controls.

This study is UNACCEPTABLE. The rationale for using a single dose regimen was not given. Three or four dose levels should be used, and the highest dose should cause frank toxicity (possibly including death) while not interferring with reproduction (although deaths were seen in this study, they did not appear to be compound-related). The study was written in a confusing manner. It was

difficult to determine the study designs for the two portions of this study, and the discussion of the results and presentation of the data were mixed and improperly labelled. In the absence of toxicity, it is doubtful whether a potentially mutagenic dose was administered in this study.

DIFFERENTIAL BACTERIAL TOXICITY TEST of FCR-1272 To Assess DNA Damage Repair

Bayer AG Institut Fur Toxikologie; Report No. 10450; December 23, 1981

Protocol: The procedures of Rosenkranz and Leifer (1980) were followed. Doses of FCR-1272 were placed on sheets of round filter paper, which were placed on a nutrient broth plate containing E. Coli infected soft agar and, in some cases, S-9 mixture. The E. Coli strains used were the repair deficient pol A_1^-, and the repair proficient pol A^+. The doses ranged from 62.5 to 1000 ug/plate. Additional tests were performed with a negative reference - chloramphenicol (a protein synthesis inhibitor) at a dose of 30 ug/plate, a positive reference - methyl methane sulphonate (an alkylaing mutagen) at a dose of 10 ul/plate, and the solvent - DMSO. The plates were incubated for 24 hours and the inhibiting zone diameters measured.

Results: Plates dosed with FCR-1272, both with and without S-9 mixture, showe no evidence of inhibition in either strain. The DMSO solvent control plates also showed no inhibition. Definite inhibition was seen in the negative reference plates and was similar in both strains with or without activation. An even greater degree of inhibition was seen in the positive reference with the pol A_1^- strain being the most affected, thus demonstrating the sensitivity of the system.

This study is ACCEPTABLE.

BACTERIAL MUTAGENICITY TESTS of FCR-1272

Nihon Tokushu Noyaku Seizo K. K.; Report No. 213; January 19, 1982

Protocol: A rec-assay was performed by the method of Kada et al (1972, 1974) using the recombinant repair deficient NIG 45 strain (rec^-), and the wild NIG 17 strain (rec^+) of Bacillus subtilis. Streaked solid agar plates were overlaid with paper disks that had been soaked with FCR-1272 dissolved in DMSO. These plates were incubated overnight, then measured for the length of growth inhibition. AF-2 served as a positive control.

A reversion assay was performed by the method of Ames et al (1973, 1975) using the TA 1535, TA 1537, TA 1538, TA 98, and TA 100 Salmonella typhimurium strains, and also the E. coli B/r WP2 try^- her^- strain. Plates were dosed at 5-5000 ug/plate. Vehicle control plates were dosed with DMSO. Half of the tests were activated with S-9 mixture and the other half were nonactivated. Revertant colonies were counted after 48 hours of incubation. The positive controls were ıta] -propiolactone (TA 1535), 9-aminoacridine (TA 1537), 2-nitrofluorene (TA 1538), and AF-2 (TA 98, TA 100, and E. coli). Each reversion assay was performed twice.

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Results:

Rec-assay - No inhibition was seen in the NIG 45 and NIG 17 strains of Bacillus subtilis when dosed with 200 ug/disk of FCR-1272. The positive control, AF-2, elicited significant inhibition in the NIG 45 strain, and virtually no inhibition in the NIG 17 strain. Thus, at the dose tested, no DNA damage occurred in these strains.

This study is UNACCEPTABLE. The Rec-assay should have been repeated to verify the findings. Justification was not given for the dose used in the rec-assay. Additional doses should have been used to establish a toxic dose or a solubility limit.

Reversion assay - No effect was seen in the activated and nonactivated plates at doses as high as 5000 ug FCR-1272/plate, relative to the vehicle controls. A significant effect was seen in the positive controls.

This study is ACCEPTABLE.

MICROBIAL MUTAGENICITY Study of FCR-1272

Toshihiro Ota Masaaki Moriya; May 17, 1982

Protocol: A rec-assay was performed using B. subtilis strains H17 (recombination-wild) and M45 (recombination-deficient). Streaked agar plates were overlaid by a filter paper disk soaked with FCR-1272 in DMSO at doses of 100-10,000 ug/disk. The inhibitory zones were measured after overnight incubation. Kanamycin was used as the negative control, and mitomycin C was used as the positive control. A reverse mutation test was performed using histidine requiring Salmonella typhimurium strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, and tryptophan-requiring E. Coli WP2 hcr. Infected agar plates were incubated for 2 days, then revertant colonies counted. All tests were made with and without S-9 mix to assess any detoxification. The positive controls were AF-2 (2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide - TA 100, TA 98, and WP2 hcr strains), ENNG (N-ethyl-N'-nitro-N-nitrosoguanidine - TA 1535 strain), 9-AA (9-aminoacridine - TA 1537 strain), and 2-NF (2-nitrofluorene - TA 1538 strain) in the absence of S-9 mix, and 2-AA (2-aminoanthracene) for all strains both with and without S-9 mix. Negative controls were dosed with the vehicle, DMSO.

Results:

Rec-assay - The negative control caused inhibition in the H17 and M45 strains, and the positive control inhibited the M45 (rec-deficient) strain only. No inhibition was seen in the cultures dosed with FCR-1272 at doses as high as 10,000 ug/disk.

This study is ACCEPTABLE. Repeat studies should have been conducted to confirm the negative findings. The Report Number was not provided.

Reverse mutation assays - there were no increases in the number of revertant colonies in any strains dosed with FCR1272, with or without activation The

positive controls, AF-2, ENNG, 9-AA, and 2-NF induced reverse mutation in the absence of activation, and 2AA induced reverse mutation in the activated systems only.

This study is ACCEPTABLE. Repeat studies should have been conducted to confirm the negative findings.

REVERSE MUTATION INDUCTION ASSAY of FCR-1272

Litton Bionetics, Inc.; Report No. 2200; May, 1982

Protocol: In vitro cytotoxicity and reverse mutation assays were performed using Saccharomyces cerevisiae yeast cells. The S138 strain is a frame-shift mutant, and the S211 strain is a base-pair substitution mutant. Strain S211 cultures were dosed with 1.22-10,000 ug of FCR-1272/ml of DMSO in the cytotoxicity study and assessed after 3 days of incubation. A negative control was dosed with the vehicle, DMSO. In the reverse mutation induction assays, S211 and S138 cultures were dosed with 312.5-10,000 ug of FCR-1272/ml of DMSO. They were incubated for 3 days for population counts and 5-7 days for revertant counts. The assays were performed with and without S-9 mixture activation and assessed for the ability of both strains to revert to methionine prototrophy. The positive control compounds were sterigmatocystin (S138 and S211) for the activated systems, and quinacrine mustard (S138) and ethylmethane sulfonate (S211) for the nonactivated systems. The vehicle, DMSO, was used as the negative control.

Results:

Cytotoxicity Study - No cytotoxic effect was seen in the S211 cultures at doses as high as 10,000 ug of FCR-1272/ml of DMSO.

This study is ACCEPTABLE.

Reverse Mutation Induction Assay - The degree of survivability was similar in both strains with or without activation when compared to the negative controls. The number of S138 revertants was similar in all dosed cultures and negative controls, but significantly increased in the positive controls, particularly in the nonactivated positive controls. The assay performed with the S211 strain showed a moderate increase in revertants with and without activation, compared to the negative controls; the increase was not dose-related. A repeat of this study failed to show any increases in revertants. The positive controls in both S211 assays had significant effects on the number of revertants. Thus, FCR-1272 did not cause a mutagenic effect in the S138 and S211 Saccharomyces cerevisiae strains tested.

This study is ACCEPTABLE. The S138 assay should have been repeated to verify the negative findings in this strain.

RECOMBINATION AND CONVERSION Assays of FCR-1272

Litton Bionetics, Inc.; Report No. 2249; September, 1982

Protocol: The cytotoxicity study and the recombination and conversion assays were performed using Saccharomyces cerevisiae D_7 yeast cells. Doses used in the cytotoxicity study ranged from 1.22-10,000 ug FCR-1272/ml and the incubation period was 3 days. A negative control was dosed with the vehicle, DMSO. The recombination and conversion assays were performed by the method of Zimmerman et al (1975) and measured three parameters:

1. Mitotic gene conversion was detected by growth on tryptophan deficient media.
2. Mitotic recombination was assessed by calculating the total mitotic events per population scored.
3. Reverse mutation was measured by the growth of prototrophic colonies on isoleucine deficient media.

Incubation periods were 4-7 days. Assay doses ranged from 625-10,000 ug/ml. Negative controls were dosed with DMSO, and the positive controls were dosed with ethylmethanesulfonate (nonactivated systems) and sterigmotocystin (activated systems). All assays were performed with and without S-9 mixture activation.

Results:

Cytotoxicity test - No effect was seen in the D_7 cultures at doses as high as 10,000 ug FCR-1272/ml.

This study is ACCEPTABLE.

Recombination and Conversion Assays - The degree of survivability was similar in all populations dosed with FCR-1272 with or without activation when compared to the negative controls. Survivability was significantly decreased, however, in the activated positive controls. In the mitotic recombination assay, the number of crossovers in the dosed cultures with and without activation corresponded to the negative controls. In the mitotic gene conversion assay, the frequency of tryptophan convertants was similar in the dosed cultures and negative controls, both with and without activation. In the reverse mutation study, the dosed cultures had frequencies of isoleucine revertants comparable to the negative controls, both with and without activation. Thus, FCR-1272 did not cause a mutagenic effect in the Saccharomyces cerevisiae D_7 strain tested.

This study is ACCEPTABLE. Each assay should have been performed at least twice to verify the negative findings. Many portions of the report were occluded by confidential stamps which made reading difficult.

ADDENDUM

The following study was reviewed by Edwin R. Budd/Toxicology Branch.

FCR 1272 Chronic Toxicity to Dogs on Oral Administration (12-Months Feeding Study)

Bayer AG Institute of Toxicology: Report No. 11983; (Mobay Repot No. 86031): August 3, 1983. EPA Acc. No. 073256.

Study Design

The test material for this study was technical grade FCR 1272 (from several batches). As a 50% premix with Wessalon S, it was mixed in pulverized dog feed and presented to singly caged pure-bred male and female beagle dogs for 12 months. Analyses of the feed for content of active ingredient were performed at 1, 13, 26, 39 and 52 weeks. Six male and six female dogs per dosage level were treated at dosage levels of 0 (control), 40, 160 and 640 ppm.

The dogs were observed several times daily for appearance and behavior. Feed consumption was recorded daily. Body weights were determined weekly. Detailed general examinations (including reflex tests, body temperatures and pulse rates) were performed prior to administration of test material and at 5, 13, 26, 39 and 52 weeks. Ophthalmoscopic examinations were performed prior to administration of test material and at 5, 13, 29, 39 and 52 weeks

The following laboratory examinations (hematology, clinical chemistries and urinalyses) were conducted on all dogs prior to administration of the test material and at 6, 13, 26, 39 and 52 weeks.

Hematology:	hematocrit, hemoglobin, erythrocyte count, MCV, MCH, MCHC, thrombocyte count, reticulocyte count, thromboplastin time, blood sedimentation rate, leucocyte count and differential blood count.
Clinical Chemistries:	blood sugar, urea, creatinine, total protein, GOT, GPT, AP, bilirubin, cholesterol, GLDH, sodium, potassium, calcium and chloride.
Urinalyses:	volume, specific gravity, protein, glucose, blood, bilirubin, ketone bodies and pH. The urine sediment was also examined microscopically.

Gross necropsies were performed on all dogs at termination of the study. Organ weights were determined for heart, lung, liver, kidneys, spleen, thyroid, adrenals, prostate, brain, pancreas, testicles or ovaries. The following tissues/organs were microscopically examined for the control and high dosage level animals (only): heart, liver, lung, spleen, kidneys, brain, adrenals, thyroid, pituitary, testicles, epididymis, prostate, ovaries, uterus, parotid, esophagus, stomach, intestines, pancreas, gall bladder, skeletal muscle, urinary bladder, aorta, lymph nodes, thymus, mammary glands, eye, optic nerve, sciatic nerve, bone and bone marrow.

Results:

All dogs survived the 12-month treatment period. No biologically meaningful differences in appearance and/or behavior were observed between control and test dogs during the entire study except for the following:

1. Two high dosage level dogs, on a single occasion for each dog (at 36 weeks for one dog and at 37 weeks for the other dog), exhibited "slow and unsure movements" consisting more specifically of a "swaying, slightly clumsy gait primarily in the hind quarters." The animals were "reluctant to move, and walked or ran ---- generally stiffly."

2. At the highest dosage level, vomiting and pasty to liquid feces were observed considerably more frequently than in the control, low or mid dosage level dogs.

Both 1. and 2. (above) are considered by Toxicology Branch to be related to the administration of test material.

General examinations (including reflex tests, body temperatures and pulse rates) and ophthalmoscopic examinations were negative for effects due to the test material.

Mean feed consumption was reduced in the high dosage level male group, but this was due mostly to the poor eating habits of one single animal in this group. The decreased mean food consumption in this group was probably not related to the test material. Water consumption was unaffected by the test material.

Mean body weights of the high dosage level male group were consistently depressed below those of the control group throughout the entire 12-month study. This was interpreted by Toxicology Branch as an effect due to the test material. Mean body weights of females were unaffected. Increases in mean body weights from initiation of the study to termination of the study are presented below.

MEAN INCREASE IN BODY WEIGHT DURING STUDY

DOSAGE LEVEL	MALES	FEMALES
0 (control)	+ 3.7 kg	+ 3.4 kg
40 ppm	+ 4.2 kg	+ 3.4 kg
160 ppm	+ 4.8 kg	+ 3.6 kg
640 ppm	+ 2.6 kg	+ 3.8 kg

Results of hematological, clinical chemistry and urinalyses were all negative with respect to any biologically meaningful differences between control and test animals. Gross necropsies were similarly negative. Organ weights and organ/body weight ratios were also negative except for an increased spleen weight and spleen/body weight ratio for high dosage level females. Due to the high variability in spleen weights and the lack of any indicaton of effect on the spleen during gross necropsy and histopathology, it is likely that this observation was a random finding and not related to the administration of the test material.

The results of histopathological examination of tissues/organs from the control and high dosage level animals did not suggest any lesions attributable to treatment with the test material.

Conclusion:

This study is classified as CORE MINIMUM. The NOEL is 160 ppm. The LOEL is 640 ppm. At 640 ppm, slight "ataxia" was observed in two dogs on one occasion each. Increased vomiting, increased pasty to liquid feces, and decreased mean body weights in males were also observed at 640 ppm.

#jdl

EPA: 68-01-6561
TASK: 90
January 24, 1985

DATA EVALUATION RECORD

CYFLUTHRIN

Chronic Toxicity

CITATION: Suberg, H. and Loeser, E. FCR1272 (Cyfluthrin the active ingredient of Baythroid) chronic toxicity study in rats. (Unpublished report No. 11949 prepared by Bayer AG Institut Fuer Toxikologie for Mobay Chemical Corp., Agr. Chem. Div., Kansas City, MO., dated July 19, 1983.)

REVIEWED BY:

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APPROVED BY:

Edwin R. Budd
EPA Scientist

Signature: Edwin R. Budd
Date: January 31, 1985

DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity.

CITATION: Suberg, H. and Loeser, E. FCR1272 (Cyfluthrin the active ingredient of Baythroid) chronic toxicity study in rats. (Unpublished report No. 11949 prepared by Bayer AG Institut Fuer Toxikologie for Mobay Chemical Corp., Agr. Chem. Div., Kansas City, MO., dated July 19, 1983.)

ACCESSION NUMBER: 072365.

LABORATORY: Bayer AG Institut Fuer Toxikologie, Wuppertal, Federal Republic of Germany.

QUALITY ASSURANCE STATEMENT: Not present for this report.

TEST MATERIAL: The test material was identified as FCR1272, the active ingredient of Baythroid, an insecticide. It was a composite sample of batches received prior to the study and was available as a premix concentrate in Wessalon S, with 49.7 to 51.0% active ingredient. The purity of the technical material was not reported.

PROTOCOL:

1. Male and female Wistar SPF rats were obtained from Winkelmann, Borchen, Federal Republic of Germany. The rats were individually housed in Type II Makrolon cages in rooms maintained at 21-23° C and 50-60% humidity with 12 hour light/dark cycle. The rats were 5-6 weeks of age at the start of the study. Tapwater was available ad libitum.

   It was not reported whether the animals were acclimated to laboratory conditions prior to treatment. Animals were weighed prior to dosing and assigned to 4 groups with initial mean body weights of 80 g for males and 81 g for females.

2. The premix concentrate in Wessalon S, formulation 113, was mixed with pulverized feed to obtain the required concentrations of the active ingredient. The frequency of diet preparation throughout the study was not reported. The control group was fed the basal diet. The concentration, homogeneity, and stability of the diet was determined by gas chromotography at various intervals during the study.

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3. Groups of 65 males and 65 females were fed diets containing 0, 50, 150, and 450 ppm of test material. Dose selection was based on a subchronic feeding study.

4. Animals were observed for clinical signs twice daily and once a day on weekends and holidays.

   Individual body weights and group food consumption were determined weekly the first 26 weeks, bi-weekly during week 27 through 74, and then weekly until termination. Food consumption was determined by weighing the unconsumed feed and substracting this value from the amount of food offered.

   On day seven of the study 5 rats/sex/group were sacrificed and the activities of N-demethylase and O-demethylase as well as the concentration of cytochrome P_{450} in the liver were determined.

   Hematology, clinical chemistry, and urinalysis were performed on 10 rats/sex/group at 6, 12, 18, and 24 months of study. Serum protein electrophoresis was performed at 12 months of study. Blood samples were collected with a Pasteur pipette via the retroorbital venous plexus after ether anesthesia. Blood glucose determinations were performed on blood samples obtained from the tail vein without anesthesia. Blood for thromboplastin time was obtained by cardiac puncture. Urine samples were collected during 16 hr fasting periods.

   The following is a list of parameters analyzed: Hematology - erythrocyte count, hemoglobin, hematocrit, red cell indices (MCV, MCH, MCHC), total and differential leukocyte count and thrombocyte count. Clinical chemistry - alkaline phosphatase, SGOT, SGPT, creatinine, urea, glucose, cholesterol bilirubin, total protein, sodium, potassium, and calcium. Urinalyses - glucose, blood, protein, ketone, bilirubin, urobilinogen, pH, specific gravity and total volume.

   The fluoride content in bones and teeth of 5 males and 5 females from each group was determined at the 12-month interim and final sacrifices.

   Gross examination was performed on rats that died or were sacrificed moribund during the study, interim sacrifice animals, and on all survivors at termination. Rats were anesthetized with ether and sacrificed by exsanguination. At 12 months and termination, 5 rats/sex/group were perfused with 10% buffered formaldehyde, and then examined grossly.

   The following organs from each animal were weighed at the interim and terminal sacrifices: heart, testes, lung, liver, spleen, kidneys, adrenals and ovaries. The organs from perfused rats were not weighed.

The following tissues from all animals that died or were sacrificed moribund and all animals sacrificed at weeks 52 and 104, were fixed in 10% formaldehyde:

Aorta	Liver	Thymus (if present)
Eyes	Lung	Uterus
Intestine (duodenum, jejunum ileum, colon and in some cases cecum and rectum)	Lymph nodes	Gross Lesions
	Stomach	
	Spleen	
	Adrenals	
Femur enbloc with skeletal musculature and* sciatic nerve	Kidneys	
	Ovaries	
	Pancreas	
Brain	Prostate	
Urinary bladder	Spinal cord	
Heart	Seminal vesicles	
Testes	Sternum	
Pituitary	Thyroids, esophagus, and trachea enbloc	
Salivary glands		

Microscopic examination was performed on all the above tissues for each animal on the study.

5. Statistical Methods: The arithmetic mean and standard deviation (STD) for tabular data were calculated and the STD assessed at the 95 and 99% upper and lower confidence limits. The data for dosed groups were compared to the control groups with the significance test (U test) of Mann, Whitney and Wilcoxon at the 5 and 1% significance level. Fisher's exact test was used to compare the mortality of the dosed groups to the controls. An IBM subroutine package was used to generate randomization lists.

RESULTS:

Diet Analysis: There were no data presented or diet analyses for content, homogeneity, and stability of test material.

Clinical Signs: It was stated in the report that there were no differences noted among dosed and control animals in appearance, behavior, activity or condition of coat during the study. However, individual or group data were not presented. Ophthalmologic examinations were apparently not performed.

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* For perfused rats the sciatic nerve was isolated and fixed.

Mortalities: There were no differences in survival among dosed and control animals throughout the two-year study (Table 1).

TABLE 1. Percent Survival of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Month:	Percent Survival 18	24
Males			
Control		98(49/50)[a]	88(44/50)
50		98(49/50)	88(44/50)
150		100(50/50)	96(48/50)
450		96(48/50)	82(41/50)
Females			
Control		96(48/50)	86(43/50)
50		98(49/50)	90(45/50)
150		100(50/50)	90(45/50)
450		94(47/50)	82(41/50)

[a] Number of animals alive/number of animals in each group.

Body Weights: The mean body weights of males and females receiving the high-dose were significantly lower than control values throughout the study (Table 2). The mean body weights of males receiving the mid-dose was also significantly lower than the control group during the first year of the study, but the animals recovered thereafter. There were no effects on the body weights of animals receiving the low-dose.

Food Consumption: Food consumption was similar throughout the study among compound-treated and control groups (Table 3 and CBI Report Appendix, pp. 63-70). Based on mean food consumption and body weight data, it was reported that the average intake of test compound throughout the study was 2.02, 6.19, and 19.20 mg/kg/day in males and was 2.71, 8.15, and 25.47 mg/kg/day in females for the low-, mid-, and high-dose groups, respectively.

Hematology: There were a few isolated changes in certain hematologic parameters in compound-treated animals as compared to control values, at months 6, 12, 18, or 24 of the study, but none were dose- and/or time-related (CBI Report Tables 3-6). At the end of the study there was a significant decrease in leukocyte count in all dosed male groups.

TABLE 2. Mean Body Weights of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Week:	Body Weight (g) 0	13	26	51	78	104
Males							
Control		81	320	370	407	420	422
50		81	313	365	405	412	409
150		80	304**	356*	392*	407	407
450		80	295**	346**	378**	391**	382**
Females							
Control		81	199	221	239	261	266
50		81	197	219	238	259	267
150		81	195*	217	234	249*	257
450		81	189**	210**	221**	233**	239**

* Significanly different from control value $p < 0.05$.
** Significanly different from control value $p < 0.01$.

TABLE 3. Mean Food Consumption Data for Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Mean Food Intake (g/rat/day) at Week									
	1	7	13	20	26	39	51	65	78	104
Males										
Control	12.58	18.30	18.30	17.5	17.2	17.55	16.88	16.32	15.65	16.18
50	12.17	17.91	18.24	17.41	16.52	17.60	16.20	16.31	15.41	11.68
150	11.99	16.42	17.62	16.98	16.41	16.26	16.18	15.97	15.56	14.94
450	9.99	17.46	17.69	17.43	16.15	16.57	16.32	16.06	15.21	10.73
Females										
Control	11.23	13.06	13.44	14.81	13.79	13.47	12.41	13.29	13.34	14.78
50	10.39	12.53	13.85	13.11	12.69	13.26	13.18	13.17	12.77	13.61
150	11.09	12.36	13.36	13.06	12.23	13.59	12.16	13.21	12.42	13.25
450	10.60	12.04	13.43	12.70	12.15	12.57	11.47	13.04	12.65	13.87

Blood Chemistry: There were a few isolated changes in certain parameters in dosed animals as compared to control values, at months 6, 12, 18, or 24 of the study, but none were dose and/or time-related (CBI Report Tables 7-15). At the end of the study there was a significant decrease in plasma protein and cholesterol in females receiving the high-dose and in SGPT activity and calcium in males receiving the high-dose. At 12 months, the relative amounts of protein fractions in the serum were determined by electrophoresis. The results indicated a dose-related increased in alpha-1-globulins; there were no other differences noted between control and compound-treated animals.

Urinalysis: There were no dosed-related differences in urinalysis parameters between treated and control animals at months 6, 12, 18, or 24 of the study (CBI Report Appendix pp. 313-328).

Liver Enzyme Activities and Cytochrome P_{450} Content: The hepatic N- and O-demethylase activities and cytochrome P_{450} content in rats were determined one week after study initiation. There were no differences noted in N- or O-demethylase activities or cytochrome P_{450} levels in treated animals when compared to control values, except for a significant increase in N-demethylase activity in females receiving the high-dose (Table 4).

TABLE 4. Hepatic N-Demethylase Activity in Rats Fed Diets Containing Cyfluthrin for Two-Years

Group Dose (ppm)	N-Demethylase Activity (nmol/g/min) Male	Female
Control	107.8	59.3
50	107.7	69.1
150	108.7	71.3
450	135.4	103.8**

** Significantly different from control at $p < 0.01$.

Fluoride Content in Teeth and Bones: The fluoride content in teeth and bones of treated animals was similar to those of control values at month 12 of the study (CBI Report Table 17). Increased fluoride levels were noted in the teeth and bones of males receiving the high-dose, and in the bones of males receiving the mid-dose and females receiving the high-dose (Table 5).

Gross Examinations: Summary data for gross-findings were not presented. It was stated that "gross examination revealed no changes in any of the rats that could be attributed to treatment." (CBI report p 496 - 1177).

TABLE 5. Fluoride Content in Teeth and Bones of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Fluoride Content (mg/g ash)	
	Teeth	Bones
Males		
Control	0.097	0.464
50	0.125	0.503
150	0.113	0.514*
450	0.116**	0.560*
Females		
Control	0.144	0.654
50	0.144	0.665
150	0.140	0.698
450	0.164	0.779**

* Significantly different from control at $p < 0.05$
** Significantly different from control at $p < 0.05$

Organ Weights: At interim sacrifice, the mean liver weight (5 rats/sex/group) of males and females receiving the high-dose were significantly lower than control values. The liver to body weight ratios of treated male rats were similar to those of control, but the liver to body weight ratios of treated females were significantly lower than control values (Table 6). There were no other changes noted.

TABLE 6. Mean Organ Weight Data of Rats Fed Cyfluthrin for Two-Years

Group/Dose (ppm)	Body Weight (g)	Liver (g)	Liver:BW %	Kidney (g)	Kidney:BW %
		12 Month Sacrifice			
Males					
Control	435	15.61	3.58	2.37	0.543
50	418	14.83	3.55	2.43	0.582
150	385**	13.25	3.43	2.23	0.580
450	371**	12.90**	3.48	2.32	0.627
Females					
Control	234	8.36	3.57	1.54	0.658
50	235	7.31	3.10*	1.58	0.671
150	247	7.51	3.04**	1.58	0.643
450	208*	6.78**	3.26*	1.44	0.692
		24 Month Sacrifice			
Males					
Control	418	14.19	3.42	2.56	0.618
50	408	14.61	3.57*	2.66	0.655*
150	410	14.24	3.47	2.58	0.633
450	382**	12.98**	3.40	2.47	0.650**
Females					
Control	265	9.33	3.53	1.78	0.673
50	266	9.16	3.46	1.79	0.679
150	252*	8.51**	3.40	1.70*	0.679
450	237**	8.33**	3.53	1.65**	0.701

* Significantly different from control value $p < 0.05$.
** Significantly different from control value $p < 0.01$.

At final sacrifice, the mean liver weight of male rats receiving the high-dose was significantly lower than the control value (Table 6). Similarly, the mean liver and kidney weights in females receiving the mid- and high-dose were significantly lower than control values. However,

liver- and kidney-to-body weight ratios in both dosed males and dosed females were similar to control values. There was also an increase in lung- and adrenals-to-body weight ratios in females receiving the high-dose as compared to controls.

Histopathology: At the 12 month sacrifice, pituitary gland adenomas were found in one male receiving the low-dose, one male receiving the high-dose, and in two females receiving the mid-dose. Several non-neoplastic lesions were also observed in the interim sacrifice animals, but the incidences were similar among control and dosed rats. The neoplasms observed most frequently in animals that died or were sacrificed at study termination are summarized in Table 7.

The incidences of all neoplastic lesions observed in dosed animals were comparable to those observed in the control animals. Non-neoplastic lesions observed most frequently are summarized in (Table 8). There were increased incidences of the following histopathologic lesions in dosed animals when compared to controls: inflammatory foci of the kidneys of females receiving the mid- and high-doses; cortical hyperplastic nodules in the adrenals of males receiving the low- and high-doses and females receiving the high-dose; and medullary hyperplasia in the adrenals of males receiving the high-dose. The incidences of other histologic lesions were similar among control and dosed animals.

DISCUSSION:

The authors stated that the only compound-related effects observed in dosed rats were decreased body weights in males receiving the mid- and high-doses and females receiving the high-dose. They concluded that the NOEL was 50 ppm of test material in the diet.

Our evaluation of the data is in agreement with the authors statements, although we identified some additional compound-related histopathologic lesions. These effects include increased incidences of inflammatory foci of the kidneys of females receiving the mid- and high-dose; and cortical and/or medullary hyperplastic nodules in the adrenal gland of males and females receiving the high-dose. In addition, there was a significant increase in hepatic N-demethylase activity in females receiving the high-dose for 7 days, indicating enzyme induction by Cyfluthrin. Increased levels of fluoride in teeth and/or bones were also noted in males and females receiving the mid- and high-doses, but in the absence of metabolic studies the toxicological significance of these findings is unclear. We view effects on liver and kidney weights at the end of the study as being primarily due to decreased body weight, since the organ-to-body weight ratio were similar among control and treated animals. Finally, the incidences of neoplastic lesions in treated animals were similar to those observed in controls.

The following deficiencies were noted: individual clinical observations and eye examinations were not reported; no data were presented for diet analyses and stability.

TABLE 7. Summary of Neoplastic Lesions Most Frequently Observed in Rats Fed Cyfluthrin for Two Years

Lesion	Group:	Males				Females			
		0	50	150	450	0	50	150	450
Liver	N[a]	49	50	49	50	50	50	50	49
carcinoma		0	0	0	1	0	0	0	0
Kidneys	N	49	49	49	50	50	50	50	49
adenoma		0	0	1	0	0	0	0	0
Testes	N	49	49	49	50				
leydig cell tumor		3	5	5	3				
Uterus	N					50	50	50	49
polyp						14	7	20	17
adenocarcinoma						5	4	4	3
Pituitary gland	N	47	49	47	47	49	50	48	48
adenoma		10	11	19	6	14	23	10	12
Thyroid gland	N	49	48	47	48	49	48	49	47
adenoma		4	2	2	1	2	1	1	0
Adrenal glands	N	48	48	49	50	50	49	50	49
pheochromocytoma		4	3	5	6	0	2	1	1
Mammary glands	N					5	5	5	5
fibrosarcoma						5	3	3	3
Skin	N	1	2	0	5	4	10	4	4
fibrosarcoma		0	0	0	2	0	2	1	0

[a] The numbers of tissues examined microscopically.

TABLE 8. Summary of Non-Neoplastic Lesions Most Frequently Observed in Rats Fed Cyfluthrin for Two-Years[a]

Lesion	Group:	Males				Females			
		0	50	150	450	0	50	150	450
Heart	N	49	50	49	50	50	50	50	49
myocardial fibrosis		25	27	27	32	34	17	15	27
myocarditis		11	-	9	4	7	1	0	3
Trachea	N	49	50	47	50	49	49	50	48
chronic tracheitis		5	15	10	11	6	2	6	5
Lungs	N	49	50	49	50	50	50	50	49
macrophage		9	9	16	11	11	6	4	4
perivascular cuffing		18	22	16	9	8	13	10	9
Liver	N	49	50	49	50	50	50	50	49
inflammation		24	21	17	14	16	13	11	6
bile duct proliferation		31	34	32	29	14	8	8	13
clear cell foci		33	34	32	29	10	3	1	3
Kidneys	N	49	49	49	50	50	50	50	49
inflammatory foci		3	4	9	1	1	1	7*	7*
chronic nephropathy		38	43	45	38	29	35	34	17
Urinary bladder	N	48	48	49	50	50	49	48	49
cystitis		14	17	14	12	6	6	17	3
urothel. hyperplasia		2	1	2	2	0	2	2	4
Testes	N	49	49	49	50				
tubular atrophy		15	16	15	19				
leydig cell hyperplasia		8	11	12	7				
Prostate	N	49	49	49	50				
inflammation		4	3	2	2				
Ovaries	N					50	50	49	49
cyst						21	24	21	25
stromal hyperplasia						3	6	9	3
Uterus	N					50	50	50	49
cystic hyperplasia						10	9	10	5
Thyroid gland	N	49	48	47	48	49	48	49	47
follicular cyst		23	36	42	38	37	27	29	44
nodular hyperplasia		8	13	19	10	11	14	3	9
Adrenal glands	N	48	48	49	50	50	49	50	49
altered cell foci		23	23	23	17	10	24	30	14
cort. hyperpl. nodule		10	21*	14	20*	4	9	11	13*
medull. hyperplasia		4	8	8	14*	5	4	1	4
Spleen	N	49	48	49	50	50	50	50	49
hemopoiesis		28	14	15	18	33	23	17	23
Lymph nodes	N	49	49	46	50	50	47	48	49
hyperplasia		13	18	10	15	13	8	15	12
Eyes	N	49	47	49	50	49	49	47	49
retinal atrophy		16	13	9	14	23	15	16	25

* Statistically different from control value at $p < 0.05$.

[a] Statistical analyses conducted by the reviewers, using the Fisher Exact test.

CONCLUSIONS:

Under the conditions of this 2-year feeding study, Cyfluthrin was not oncogenic to male and female Wistar SPF rats. There was a compound-related effect on body weight of males receiving the mid- and high-doses and females receiving the high-dose. In addition, increased incidences of inflammatory foci of the kidneys of females receiving the mid- and high-doses and hyperplastic nodules of the adrenals of males and females receiving the high-dose were observed. There were no other effects noted except for increased levels of fluoride in teeth and/or bones of male and females receiving the mid- and high-doses and increased liver N-demethylase activity in females receiving the high-dose. Hence, the NOEL and LEL for chronic toxicity based on mean body weights of male rats were 50 and 150 ppm, respectively.

CORE CLASSIFICATION: Minimum for both chronic toxicity and oncogenicity.

EPA: 68-01-6561
TASK: 90
January 25, 1985

DATA EVALUATION RECORD

FCR1272 (CYFLUTHRIN)

Chronic Toxicity and Oncogenicity Study in Mice

CITATION: Suberg, H. and Loser, E. FCR1272 (Cyfluthrin) chronic toxicological study on mice. (Unpublished study No. 12035 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany for Mobay Chemical Corporation, Agr. Chem. Div., Kansas City, MO; dated August 24, 1983.)

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DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity and oncogenicity study in mice.

CITATION: Suberg, H. and Loser, E. FCR1272 (Cyfluthrir chronic toxicological study on mice. (Unpublished study No. 12035 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany for Mobay Chemical Corporation, Agr. Chem. Div., Kansas City, MO; dated August 24, 1983.)

ACCESSION NUMBER: 072366.

LABORATORY: Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

QUALITY ASSURANCE STATEMENT: Not present.

TEST MATERIAL: The test material was identified as an active ingredient sample designated as FCR 1272. It was received in batches as pre-mix concentrates in Wessalon S. The test compound content was 49.7 to 51.0% formulation 113. The common name of FCR 1272 is Cyfluthrin.

PROCEDURES:

1. Male and female SPF mice, strain CF1/W74, were obtained from Winkelmann, Borchen, Germany. The mice were 5-6 weeks of age at start of study and had mean weights of 27 g for males and 22 g for females. The animals were individually housed in cages in a room maintained at 21-23° C and 50-60% humidity on a 12-hour light/dark cycle. Food and tapwater were available ad libitum.

2. The test material was mixed with powdered feed to obtain the required concentrations. The active ingredient content and the test substance were verified at various intervals throughout the study.

3. Animals were randomly assigned to four dose groups which were fed diets containing 0, 50, 200, or 800 ppm. Each group consisted of 50 mice/sex.

4. Animals were observed twice daily (once a day on weekends and holidays) and changes and/or toxic symptoms were recorded when found. Individual body weights and group food consumption were determined weekly the first 15 weeks, every three weeks from week 18 to 66, and weekly thereafter. All surviving animals were sacrificed at 23 months of study.

Hematology and clinical chemistry were performed on 10 mice/sex/group at 6, 12, 18, and 23 months. Blood was collected via the retro-orbital venous plexus under ether anesthesia. The hematology parameters measured were erythrocyte count, hematocrit, hemoglobin, red cell indices (MCV, MCH and MCHC), total and differential leucocyte counts, thrombocyte count, and reticulocyte count. The clinical chemistry parameters measured were alkaline phosphatase, SGPT, creatinine, urea, cholesterol, and bilirubin. Urinalyses were not performed.

Fluoride content in the bones and teeth were determined on 5 mice/sex/group at 23 months of study.

Gross examination was performed on mice that died or were sacrificed when moribund. The organs and tissues were preserved for all animals. At 23 months all survivors were anesthetized with diethyl ether and sacrificed by exsanguination. The mice were grossly examined and the following organs were weighed: heart, testes, lung, liver, spleen, kidneys, and ovaries.

All animals that died or were sacrificed moribund and animals at termination had the following tissues preserved in 10% buffered formaldehyde solution for histological examination: aorta, eyes, intestine (duodenum, jejunum, ileum, colon, cecum, and rectum), femur en bloc with skeletal musculature and sciatic nerve, gallbladder, brain, Harderian glands, urinary bladder, skin, heart, testes, pituitary, salivary glands, liver, lung, lymph nodes (mesenteric and non-mesenteric), stomach, mammary glands, spleen, adrenals, kidneys, ovaries, pancreas, prostate, spinal cord, seminal vesicle, sternum, (thyroids, esophagus, and trachea en bloc), uterus, and gross lesions.

5. Statistical Methods: The mean and standard deviations of tabular data were assessed at the upper and lower confidence limits at levels of 95 and 99%. The data for dose groups were compared to the control group with the significance test (U test) of Mann, Whitney, and Wilcoxon, at the alpha 5 and 1% significance level. Fisher's exact test was used to compare the incidence of mortality in the dose groups and controls. An IBM subroutine package was used to generate randomization lists.

RESULTS:

Dietary Analyses: No analytical results were given for stability, homogeneity, or concentration of cyfluthrin in the diet.

Mortality: The incidence of mortality of male and female mice is summarized in Table 1. The incidence of mortality in the mid- and high-dose females was somewhat higher than controls throughout the study. However, only the mid-dose at termination was significantly different from controls. The mortality data are equivocal with respect to relationship to the test material.

Body Weight: Selected body weight data are given in Table 2. Male and female high-dose animals lost weight during the first week on study. The body weight of females remained significantly less than that of controls

TABLE 1. Mortality Incidence in Mice Fed Cyfluthrin

Dietary Level (ppm)	Incidence of Mortality at Week				
	26	52	64	78	99
Males					
0	4(92)[a]	13(74)	23(54)	34(32)	40(20)
50	3(94)	14(72)	20(60)	31(38)	39(22)
200	3(94)	13(74)	22(56)	33(34)	41(18)
800	5(90)	17(66)	19(62)	31(38)	44(12)
Females					
0	2(96)	6(88)	14(72)	20(60)	26(48)
50	1(98)	5(90)	13(74)	24(52)	30(40)
200	7(86)	15(70)	19(62)	29(42)	37(26)*
800	6(88)	12(76)	19(62)	27(46)	34(32)

[a] Numbers in parenthesis are the percent survival based 50 animal/sex/group.

* Significantly different from control value ($p \leq 0.05$).

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TABLE 2. Selected Mean Body Weight Data in Mice Fed Cyfluthrin

Dietary Level (ppm)	Mean Body Weight (g) at Week							Percent of Control at Week	
	0	1	13	27	51	78	99	13	99
Males									
0	26.7	27.9	35.0	39.5	43.0	42.9	40.2	100	100
50	26.4	28.2	34.7	38.8	40.9	41.0	38.3	99	95
200	27.0	28.3	35.0	38.4	41.9	40.5	36.0	100	90
800	27.3	26.7*	34.6	37.9	39.7*	39.1*	38.9	99	97
Females									
0	21.6	22.2	27.8	31.6	34.9	35.3	33.8	100	100
50	21.7	22.5	28.4	30.8	33.9	35.0	32.7	102	97
200	21.6	22.3	28.1	30.5	34.1	33.2	36.2	101	107
800	21.1	20.9**	27.6	30.0**	33.2*	32.2*	32.1	99	95

* Significantly different from control value ($p \leq 0.05$).
** Significantly different from control value ($p \leq 0.01$).

throughout the first 95 weeks of the study. The decreased mean body weight of high dosage level females (and possibly males) is likely to be related to the test material. At the mid dosage level, the data are equivocal. At 13 weeks and at termination, there were no significant differences in the mean body weight of treated animals as compared with controls.

Food Consumption: Selected food consumption and test compound intake data are given in Table 3. No significant differences between treated and control animals were noted for food consumption.

Hematology: Hematology results are summarized as follows:

6 Months - Male and female mice at 6 months exhibited no dose-related changes. In the male mice, there were sporadic significant differences in MCV and MCHC. (CBI page 13)

TABLE 3. Selected Food Consumption Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	Mean Food Consumed (g/mouse/day) at Week 1	54	99	Overall Average	Mean Compound Intake (mg/kg/day)
Males					
0	10	9	9	9	-
50	10	9	9	9	11.6
200	10	8	8	9	45.8
800	10	8	9	9	194.5
Females					
0	11	10	8	10	-
50	11	9	7	9	15.3
200	11	10	9	10	63.0
800	10	10	9	10	259.9

12 Months - No dose-related changes were noted in male or female mice. There was a significant increase in MCH and MCHC in male mice and sporadic significant differences in RBC and platelet count (CBI pg 017). In the females there was a significant increase in platelet counts and sporadic significant differences in RBC, Hgb, MCH, Hct, MCH, and MCHC.

18 Months - No dose-related changes were noted in male or female mice. There was a significant decrease in MCH and MCHC in the low-dose males (CBI pg 021). In the female mice, there was a significant increase in the segmented neutrophiles with corresponding decreases in the lymphocytes (CBI pg 024).

23 Months - No dose-related changes were noted in male or female mice. There was significant differences in Hct and MCHC in the low-dose male. (CBI pg. 025)

Clinical Chemistry: Significant differences noted in the liver enzyme activities are summarized in Table 4. Dose-related effects were most pronounced for alkaline phosphatase in males through 18 months. These effects were likely to have been related to the test material. No other differences were considered biologically relevant. Fluoride did not accumulate in teeth or bones.

Necropsy: Gross necropsies did not indicate any effects due to the test material.

Organ Weight: The absolute and relative organ weight data did not reveal any dose-related effects.

Histopathology: Frequently encountered non-neoplastic lesions are summarized in Table 5 and neoplastic lesions are given in Table 6. No dose-related differences were noted.

DISCUSSION:

According to Authors:

The only effect noted by the authors was decreased body weight in females fed 800 ppm as compared to controls. A target organ was not identified. They dismissed the alkaline phosphatase data since there was no significant finding for liver organ weight or histopathology data. Based on the body weight data, the NOEL for cyfluthrin in mice was 200 ppm and the LEL was 800 ppm.

According to This Review:

It appears that the effects of aging may have masked significant findings at termination of the study, especially in the alkaline phosphatase, body weight, and organ weight data.

In the body weight data, effects were noted throughout most of the study, but possibly due to mortality differences in all dosed groups of females and high-dose males as compared to their respective controls, the mean body weights of treated groups at termination were not significantly different from controls. Mean body weight differences were as high as 11% for mid- and high-dose males and 8% and 12% for mid- and high-dose females, respectively. Thus, the mid-dose (200 ppm) could be considered an effect level. This rationale also extends to mortality in females where excess mortality at termination was 8, 22, and 16% for the low-, mid-, and high-dose groups, respectively, as compared to controls. Excess mortality was 8% in the high-dose males at termination. Thus, the MTD may have been exceeded in this study.

In the clinical chemistry data, the dose-response of alkaline phosphatase activity in males was clearly evident at month 6, 12, and 18. At termination there was considerable evidence that many of the samples were hemolyzed, therefore leading to spurious results. The evidence is based on high concentrations of cholesterol and/or bilirubin. Enzyme activities

TABLE 4. Selected Clinical Chemistry Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	Alkaline Phosphatase (U/L) at Month 6	12	18	23	Glutamic-Pyruvic Transaminase (U/L) at Month 6	12	18	23
Males								
0	59	84	95	706[a]	35	55	33	637[a]
50	80*	115*	204*	238	32	35**	55	88
200	91**	120*	153*	106**	35	52	53	86
800	196**	146**	158**	371	45*	55	58**	192
Females								
0	155	163	162	431	39	31	35	135
50	124	122	193	310	33	30	34	65
200	120	150	259*	360	32	37	58*	56
800	154	117*	153	304	34	40	44	59

[a]Includes three animals with activities greater than 1200 U/L.
*Significantly different from control value ($p \leq 0.05$).
**Significantly different from control value ($p \leq 0.01$).

TABLE 5. Frequently Encountered Non-Neoplastic Lesions in Mice Fed Cyfluthrin

Organ/Finding	Males (ppm) 0	50	200	800	Females (ppm) 0	50	200	800
Heart	(47)[a]	(45)	(49)	(49)	(48)	(46)	(49)	(47)
myocardial degeneration	20	31	33	12	14	23	17	17
Trachea	(28)	(30)	(38)	(35)	(37)	(42)	(45)	(38)
round cell infiltration	7	5	8	16	22	11	16	11
Lungs	(46)	(44)	(49)	(45)	(48)	(45)	(48)	(47)
alveolar edema	11	10	20	6	2	2	8	7
Stomach	(38)	(38)	(45)	(46)	(47)	(44)	(44)	(46)
round cell infiltration	3	4	9	3	8	16	14	3
hermorrhagic erosion	3	4	2	8	3	2	2	10
Liver	(44)	(43)	(48)	(45)	(47)	(45)	(47)	(45)
lymphoid cell infiltration	5	11	5	1	6	15	11	7
Pancreas	(42)	(39)	(46)	(43)	(47)	(43)	(46)	(43)
lymphoid cell infiltration	2	8	8	1	10	12	11	5
atrophic acini	-	1	2	3	3	6	6	5
Kidney	(45)	(43)	(49)	(43)	(48)	(45)	(48)	(46)
tubular atrophy	26	19	29	28	22	13	17	19
calcification	15	17	19	15	1	3	1	-
glomerular cysts	14	17	16	12	7	5	1	3
degenerated tubuli	18	13	13	12	8	9	1	4
round cell infiltration	31	30	41	35	42	39	35	38
Testes	(46)	(42)	(49)	(47)				
tubular atrophy	9	10	9	8				
Ovaries					(48)	(44)	(48)	(46)
cyst(s)					22	17	11	16
Uterus					(48)	(45)	(48)	(40)
cystic hyperplasia					25	27	21	20

TABLE 5. Frequently Encountered Non-Neoplastic Lesions in Mice Fed Cyfluthrin (continued)

Organ/Finding	Males (ppm)				Females (ppm)			
	0	50	200	800	0	50	200	800
Adrenal Gland	(44)	(43)	(47)	(46)	(48)	(44)	(47)	(46)
A-cell proliferation	7	5	13	9	45	43	41	33
ceroid cell degeneration	2	1	-	3	30	26	25	19
Spleen	(44)	(41)	(47)	(43)	(48)	(44)	(47)	(45)
erythropoiesis	4	9	14	9	22	27	20	22
Lymph nodes	(42)	(37)	(45)	(37)	(48)	(43)	(48)	(33)
hyperplasia	16	11	8	5	23	21	21	19

[a] The numbers in parentheses are the number of tissues examined histologically.

TABLE 6. Frequently Encountered Neoplastic Lesions in Mice Fed Cyfluthrin

Organ/Finding	Males (ppm) 0	50	200	800	Females (ppm) 0	50	200	800
Lungs	(46)[a]	(44)	(49)	(48)	(48)	(45)	(48)	(47)
brochioalveolar tumor	10	13	11	8	16	5	11	12
Liver	(44)	(43)	(48)	(45)	(47)	(45)	(47)	(46)
adenoma, hepatocellular	-	2	3	4	3	2	4	-
carcinoma, hepatocellular	6	10	5	4	2	1	1	3
Uterus					(48)	(45)	(48)	(46)
stromal polyp					-	2	3	1
leiomyosarcoma					2	1	1	1
carcinoma					-	1	2	-
Pituitary	(40)	(33)	(42)	(39)	(44)	(41)	(43)	(37)
adenoma	-	-	1	1	4	1	2	1
Adrenal glands	(44)	(43)	(47)	(46)	(48)	(44)	(47)	(46)
cortical tumor, non-invasive	-	2	2	1	-	1	-	-
cortical tumor, invasive	4	2	2	2	1	1	1	-
Hemolymphoreticular System	(47)	(45)	(49)	(49)	(48)	(46)	(49)	(47)
malignant lymphoma	7	5	9	3	12	11	10	12

[a]Number in parenthesis is the number of animals in that group for which the organ was examined.

as well as bilirubin and cholesterol concentration are affected by hemolysis. Through 18 months, there were 2/120 bilirubin samples that were above 4.0 micromoles/liter and 2/120 cholesterol samples above 4.0 millimoles-liter (CBI pp. 214-225). However, at study termination 30/80 bilirubin samples and 25/80 cholesterol samples were above the same levels. For control males, 6/10 samples may have been hemolyzed based on cholesterol levels while 8/10 samples for control females may have been hemolyzed based on bilirubin concentration. Thus, the data for study based on the samples analyzed at termination were unacceptable. It is possible that the aging process increased the fragility of erythrocytes, however, fragility tests were not conducted.

There was no apparent reason to reject the alkaline phosphatase data in males. If a more conservative approach is used to assign biological significance i.e., when the means are two standard deviations above the control, then the mid- and high-dose results can be considered significant at 6 months; and it follows that all three treatment group means were significantly increased at 12 and 18 months. Since effects were observed at all doses, a no effect level could not be established for alkaline phosphatase activity.

For, organ weight data, all organs were included in the calculated means even if tissue masses were noted at necropsy. For those animals from which organ weights were taken, weight data are given in Table 7. The mean body weights at termination are different from those given in Table 2 because a number of animals were not included in the organ weight data. The reason for excluding these animals was not given. The standard deviations are included in the relative liver, spleen, and kidneys weight data. These large standard deviations are indicative of the wide variations in the data. Hence, an interim sacrifice might have provided usable data; however, the data at termination of the study were unacceptable for analysis.

Although the pathology data were adequate for this study, histopathology data did not confirm the liver as a target organ. The total number of tumors and the distribution of tumors within groups indicate that cyfluthrin is not an oncogen in mice.

CONCLUSIONS:

According to the Authors:

Cyfluthrin was not a carcinogen in mice, and the NOEL for the chronic study is 200 ppm while the LEL is 800 ppm based on body weight effects.

TABLE 7. Selected Weight Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	No. of Animals	Terminal Body Weight (g)	Percent of Control (%)	Relative[a] Liver Weight (%)	Relative[a] Spleen Weight (%)	Relative[a] Kidney Weight (%)
Males						
0	10	41.4	--	5.46 ± 1.43	0.23 ± 0.11	2.33 ± 1.36
50	11	38.4	93	6.32 ± 2.61	0.47 ± 0.59	2.26 ± 0.21*
200	9	36.7	89	4.65 ± 0.50	0.33 ± 0.23	2.35 ± 0.33*
800	6	38.2	92	6.02 ± 1.00	0.26 ± 0.07	2.43 ± 0.40
Females						
0	24	32.4	--	6.47 ± 2.75	0.87 ± 1.47	1.71 ± 0.28
50	19	32.7	101	6.19 ± 1.31	1.08 ± 1.05	1.75 ± 0.26
200	13	35.8	110	7.15 ± 4.64	1.02 ± 0.96*	1.72 ± 0.19
800	16	31.6	98	5.91 ± 1.06	0.79 ± 0.76	1.74 ± 0.15

[a]Relative to body weight.

*Significantly different from control value ($p \leq 0.05$).

According to the Review:

Cyfluthrin is not an oncogen in male or female mice under the conditions of this study. For chronic toxicity the LEL is 50 ppm based on an increased alkaline phosphatase activity in dosed males. The NOEL for cyfluthrin in male mice was not established.

CORE CLASSIFICATION: Core minimum for oncogenicity.
Supplementary for chronic toxicity.